

# In-depth analysis of the interplay between oncogenic mutations and NK cell-mediated cancer surveillance in solid tumors

Cecilia Pesini<sup>a,b,c,\*</sup>, Laura Artal<sup>a,d,\*</sup>, Jorge Paúl Bernal<sup>a</sup>, Diego Sánchez Martínez<sup>a,e,#</sup>, Julián Pardo<sup>a,b,c,#</sup>, and Ariel Ramírez-Labrada<sup>id a,b,#</sup>

<sup>a</sup>Aragón Health Research Institute (IIS Aragón), Biomedical Research Centre of Aragón (CIBA), Zaragoza, Spain; <sup>b</sup>Center for Biomedical Research in the Network of Infectious Diseases (CIBERINFEC), Carlos III Health Institute, Zaragoza, Spain; <sup>c</sup>Department of Microbiology, Radiology, Pediatrics and Public Health, University of Zaragoza, Zaragoza, Spain; <sup>d</sup>Institute of Carbochemistry (ICB-CSIC), Zaragoza, Spain; <sup>e</sup>Aragón I + D Foundation (ARAID), Government of Aragón, Zaragoza, Spain

## ABSTRACT

Natural killer (NK) cells play a crucial role in antitumoral and antiviral responses. Yet, cancer cells can alter themselves or the microenvironment through the secretion of cytokines or other factors, hindering NK cell activation and promoting a less cytotoxic phenotype. These resistance mechanisms, often referred to as the “hallmarks of cancer” are significantly influenced by the activation of oncogenes, impacting most, if not all, of the described hallmarks. Along with oncogenes, other types of genes, the tumor suppressor genes are frequently mutated or modified during cancer. Traditionally, these genes have been associated with uncontrollable tumor growth and apoptosis resistance. Recent evidence suggests oncogenic mutations extend beyond modulating cell death/proliferation programs, influencing cancer immunosurveillance. While T cells have been more studied, the results obtained highlight NK cells as emerging key protagonists for enhancing tumor cell elimination by modulating oncogenic activity. A few recent studies highlight the crucial role of oncogenic mutations in NK cell-mediated cancer recognition, impacting angiogenesis, stress ligands, and signaling balance within the tumor microenvironment. This review will critically examine recent discoveries correlating oncogenic mutations to NK cell-mediated cancer immunosurveillance, a relatively underexplored area, particularly in the era dominated by immune checkpoint inhibitors and CAR-T cells. Building on these insights, we will explore opportunities to improve NK cell-based immunotherapies, which are increasingly recognized as promising alternatives for treating low-antigenic tumors, offering significant advantages in terms of safety and manufacturing suitability.

## ARTICLE HISTORY

Received 6 May 2024  
Revised 7 July 2024  
Accepted 8 July 2024

## KEYWORDS

Cancer immunosurveillance; immunosurveillance; natural killer cells; oncogenes; tumor microenvironment; tumor suppressor genes

## 1. Introduction

### 1.1. Introducing natural killer cells





Natural killer (NK) cells play an essential role in antitumoral and antiviral responses, being the first line of defense against cancer and viral infections.<sup>1–3</sup> In humans, NK cells are identified by the expression of CD56 and the absence of CD3 surface markers.<sup>4,5</sup> Based on the expression level of two markers, CD56 and CD16, two conventional NK cell subsets have been described in humans: CD56<sup>bright</sup> CD16<sup>dim</sup> and CD56<sup>dim</sup> CD16<sup>bright</sup> (from now on referred as CD56<sup>bright</sup> and CD56<sup>dim</sup> NK cells, respectively).

Both subsets are phenotypically and functionally distinct. Whereas the first are mainly located in secondary lymphoid organs and tissues, the second group can predominantly be found circulating in peripheral blood.<sup>5</sup> In terms of cytotoxicity, CD56<sup>bright</sup> subset is less cytolytic. Indeed, since they are the predominant producers of immunoregulatory cytokines (e.g., interferon-gamma (IFN $\gamma$ ), tumor necrosis factor (TNF), granulocyte-macrophage colony-stimulating factor (GM-CSF),

IL-10 and IL-13), they are frequently known as pro-inflammatory NK cells.<sup>6</sup> On the other hand, CD56<sup>dim</sup> NK cells, while expressing high levels of cytotoxic molecules (perforin and granzyme B) as well as CD16a receptor (also known as IgG Fc receptor IIIA, Fc $\gamma$ RIIIA), exhibit lower cytokine production compared to CD56<sup>bright</sup> NK cells. Nonetheless, CD56<sup>dim</sup> NK cells are highly cytotoxic and proficient in performing Antibody-Dependent Cellular Cytotoxicity (ADCC).<sup>7</sup>

Finally, shared with some subsets of activated T cells (e.g., CD4-Th1 and  $\gamma\delta$ T cells), NK cells have a central role in the production of IFN $\gamma$ .<sup>8,9</sup> This pleiotropic cytokine regulates the expression of crucial genes implicated in regulated cell death (e.g., Bcl2-family proteins, caspases, or death receptors), inflammation, cell cycle regulation, and transcriptional activators' expression.<sup>10–12</sup>

Tumor cells have developed numerous highly sophisticated resistance mechanisms tied to cancer progression to avoid the multiple mechanisms of cancer immunosurveillance. These resistance mechanisms, defined by Hanahan and Weinberg as

**CONTACT** Ariel Ramírez-Labrada  [aramirezlabrada@yahoo.es](mailto:aramirezlabrada@yahoo.es)  Center for Biomedical Research in the Network of Infectious Diseases (CIBERINFEC), Carlos III Health Institute, Zaragoza, Spain; Julian Pardo  [pardojim@unizar.es](mailto:pardojim@unizar.es)  Aragón Health Research Institute (IIS Aragón), Biomedical Research Centre of Aragón (CIBA), Zaragoza, Spain

\*LA, and CP contributed equally to this work.

#ARL, JP, and DSM shared senior authorship.

© 2024 The Author(s). Published with license by Taylor & Francis Group, LLC.

This is an Open Access article distributed under the terms of the Creative Commons Attribution-NonCommercial License (<http://creativecommons.org/licenses/by-nc/4.0/>), which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited. The terms on which this article has been published allow the posting of the Accepted Manuscript in a repository by the author(s) or with their consent.

“hallmarks of cancer”, are significantly influenced by the activation of oncogenes.<sup>13</sup> Oncogenes are known for their ability to promote cell transformation, which provides malignant cells with survival and proliferation advantages. More recently, they have been shown to modify the cell niche establishing immunologically ‘cold’ tumor microenvironments (TMEs). Cold tumors seem not to generate adequate protective immune responses and do not present good responses to some types of immunotherapies, especially those related to antigen-specific responses.<sup>14,15</sup> Paradoxically, oncogenic changes would also be responsible for inducing an inflammatory microenvironment characterized by epithelial production of cytokines like IL23 and CCL9 shaping the TME toward conditions that will favor the development of certain tumors. This phenomenon operates through various pathways, including facilitating malignant cell proliferation and survival, promoting angiogenesis and metastasis, reprogramming stromal cells, and disrupting adaptive and NK cell immune responses.<sup>16–18</sup> In those cases, only malignant cells that adapt to the cellular stress imposed by oncogenesis and the TME will progress. During this phase of selective pressure, malignant cells with specific molecular alterations that confer immunoevasion are preferentially selected.<sup>15</sup>

Consequently, the identification and comprehensive understanding of these genes and their impact on the immune system’s response are paramount in the fight against cancer. Therefore, this review will focus on the major oncogenic driver mutations and how they modify the antitumoral potential of NK cells, with special emphasis on the regulation of NK cell recognition of tumor cells. Before that, we will briefly introduce the main mechanisms involved in NK cell-mediated control of cancer cells and tumor evasion strategies to understand better the potential impact of oncogenes in this process.

### 1.2. Dr. Jekyll: natural killer cells against cancer

In contrast to cytotoxic CD8+ T cells, NK cells do not require prior antigen exposure to mediate their antitumor function.<sup>4</sup> As shown in Figure 1a, NK cells possess several activating and inhibitory receptors. The balance between activating and inhibitory signals will determine whether NK cells will kill the target cells.<sup>19,20</sup>

As mentioned, NK cells are armed cytotoxic cells with high expression of perforin (PRF) and granzymes (GZMs), executors of granular exocytosis pathway. PRF is a protein that forms pores in the target cell membrane, permitting GZMs to enter inside the cell and inducing cell death.<sup>21–23</sup> GZMs are a family of serine-proteases comprised of (Figure 1b) five members in humans and ten in mice.<sup>24–26</sup> Among these, GZMB has the most potent cytotoxic activity mainly inducing apoptosis.<sup>27–29</sup> The cytotoxic activities of other GZMs remain controversial, but it is clear that GzmA, GzmM, or GzmK are involved in regulating the inflammatory response through extracellular mechanisms.<sup>26,30–36</sup>

Recently, it has been described that granular exocytosis pathway can be implicated in other types of regulated cell death, such as necroptosis and pyroptosis.<sup>37</sup> In addition to induce cell death, GZMs have been associated with additional biological functions, including inflammation, autoimmunity, extracellular matrix degradation, and related pathologies

including sepsis, cardiovascular disease, skin disorders, arthritis of ulcerative colitis among others.<sup>35,38,39</sup> However, a more detailed description of these serine-proteases is out of the scope of this review, and it has been the topic of recent excellent reviews.<sup>29,38,40,41</sup>

Besides granular exocytosis, NK cells can induce cell death by an additional mechanism based on death ligands, which are members of the TNF superfamily of proteins (see Figure 1c).<sup>42</sup> The most commonly expressed death ligands in NK cells are TNF $\alpha$  (Tumor necrosis factor), FasL (Fas Ligand), and TRAIL (TNF-related apoptosis inducing ligand).

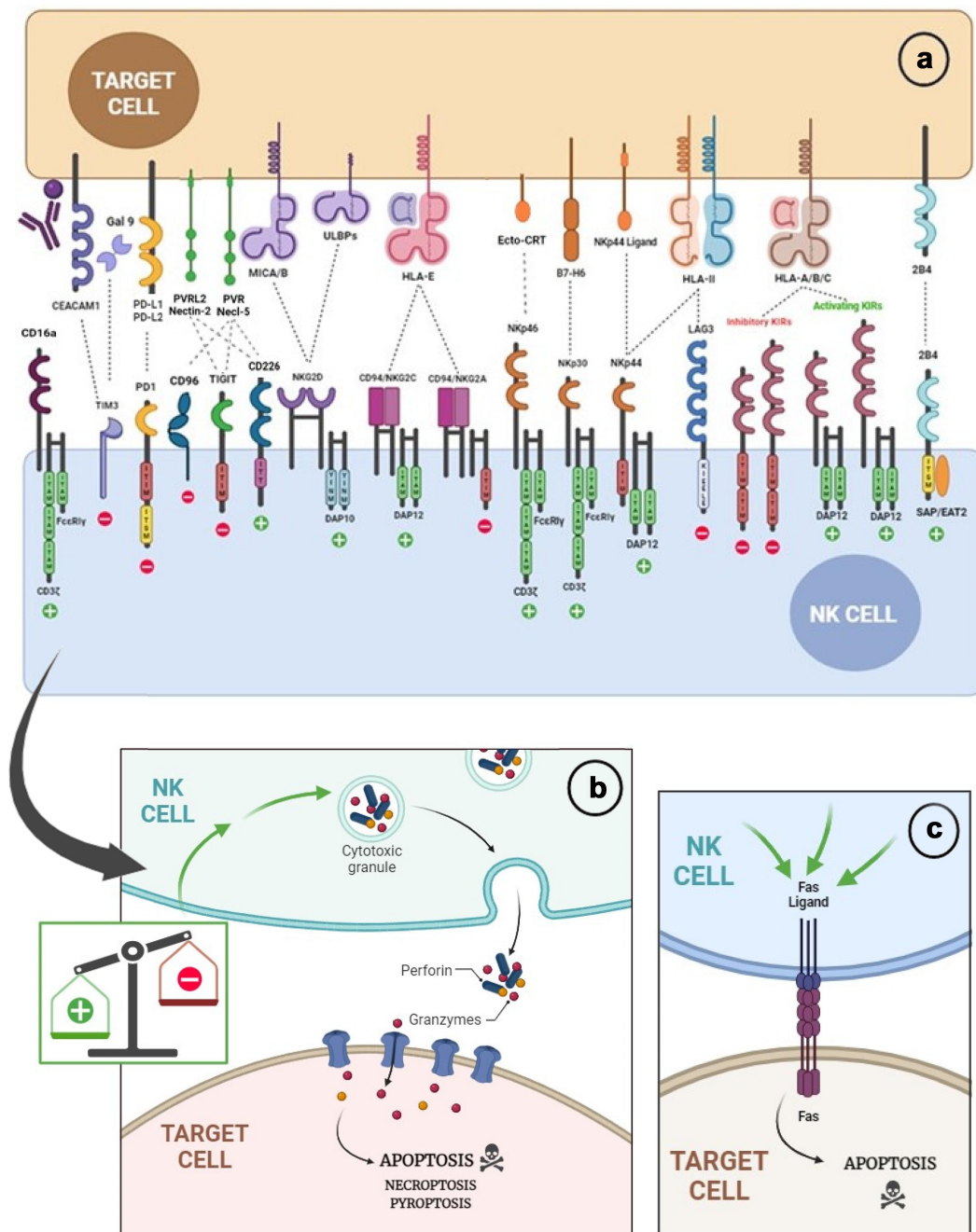
### 1.3. Mr. Hyde. Tumor immunoevasion from NK cell immunosurveillance

One of the primary functions of NK cells is to exert tumor-suppressive activity. Nonetheless, NK cells may paradoxically modulate tumor variants capable of evading NK cell immunosurveillance. In doing so, they inadvertently contribute to these tumor cells evading antitumoral mechanisms. These observations led to the development of the immunoeediting theory, which is divided into three phases “the three Es”: elimination, equilibrium, and escape.<sup>43,44</sup>

*Elimination* corresponds to immunosurveillance.<sup>45</sup> In this initial phase, NK cells play an essential role in eliminating emerging tumor cells due to their unique capacity to rapidly recognize and kill transformed cells. As cytotoxic cells of the innate immune system, they circulate with all the necessary molecules to recognize and eliminate tumor cells without prior antigen presentation.<sup>46,47</sup> In the emblematic study by Imai *et al.* (2000), it was observed that low NK cell activity was associated with an increased cancer risk during an 11-year follow-up period,<sup>48</sup> highlighting the importance of NK cells in the initial stages of tumor cell control.

However, some cells occasionally manage to evade the immune system, including NK cells,<sup>43</sup> initiating the second phase, *equilibrium*. During this period, immune cells, notably T cells, gain major relevance, continuing to target and eliminate tumor cells.<sup>49,50</sup> However, some tumor cells survive by entering a quiescent state and acquiring immunosuppressive properties, such as increasing the expression of anti-apoptotic molecules (e.g., Bcl-2)<sup>51</sup> and reducing antigen or major histocompatibility complex (MHC) class I expression, limiting T-cell recognition and subsequent killing of the cancer cells.<sup>52</sup> Here, NK cells play a crucial role because their ability to recognize tumor cells that have adapted to escape T-cell killing facilitated by the absence of MHC, the principal inhibitory ligand for NK cell receptors, enabling them to kill these ‘low immunogenic cells’ (Figure 1a). Notably, oncogenic transformation during these stages have been shown to modulate HLA-I expression, thus, contributing to recognition of cancer cells by NK cells.<sup>53,54</sup>

After a while, tumor cells begin to proliferate and divide massively again, the phase is considered the *escape* phase.<sup>45,55</sup> Again, NK cells play a pivotal role in metastasis control and tumor progression, as observed in small cell lung cancer, where evasion of NK cells by reduction of NKG2D-ligands reflects increased aggressiveness.<sup>56</sup>



**Figure 1.** NK cell-mediated cytotoxicity. NK cells express several receptors on their surface that will positively or negatively regulate their activity (A). NK cells possess two main mechanisms to induce the target cell death, granular exocytosis (B) and expression of death receptors (C). Figure created with BioRender.com.

Throughout this development, the tumor microenvironment (TME) is also established and shaped to promote cancer cell immunoevasion. This results in dampening NK cell function and altering their phenotype throughout the entire tumor progression process<sup>57,58</sup> which will be discussed in the next section.

## 2. The tumor microenvironment inhibits NK cell function

As aforementioned, an additional factor that strongly affects the modulation of NK cell responses is the TME. The TME encompasses all tumor components, including the different non-tumor cell populations: immune cells, fibroblasts, and cells that

comprise the blood vessels.<sup>59,60</sup> Within the TME, numerous complex interactions exist between extracellular matrix, non-immune, immune and cancerous cells, each having a clear impact on tumor progression, invasion, and metastasis.<sup>61</sup>

These interactions collectively generate an immunosuppressive environment that hinders effective immune responses, leading to poor trafficking and immune infiltration of tumors. The most relevant TME factors regulating NK cell activity are discussed below:

### 2.1. The TME architecture

TME architecture plays a crucial role in orchestrating both tumor immunity and therapeutic responses. Tumor initiation

and expansion depend entirely on the organization of the TME and physiological processes like angiogenesis, immune cell infiltration, and cancer cell proliferation.

In a ground-breaking study elucidating NK cell implications in mouse skin graft rejection, it was demonstrated that their migration to peripheral tissues elicits a distinctive dampening of their cytotoxic activity, mediated by the presence of collagens and elastin. This phenotypic alteration redirects NK cell functionality toward an augmented secretion of specific chemokines and cytokines like INF, CCL2, and CXCL10, thereby assuming a supportive role in T cell priming. This intriguing reprogramming of NK cell function provides a rationale for the selective loss of MHC-I expression observed in solid cancers but not leukemias.<sup>62</sup>

## 2.2. Nutrient deprivation

The effect of the tumor microenvironment (TME) on NK cell metabolism must also be taken into account as it is crucial for their function.<sup>63–65</sup> During tumor progression, cancer cells must adjust their metabolic activity to maintain the high biosynthetic rates required for rapid cell growth, despite low nutrient and oxygen availability. These adaptations are essential for cancer cell survival. Metabolic remodeling is believed to be a dynamic process that varies depending on the specific needs of the tumor. However, like other tumorigenic events, this metabolic adaptation is likely influenced by the actions of oncogenes and tumor suppressors.

Unlike normal cells, cancer cells preferentially utilize the glycolytic pathway over oxidative phosphorylation (OXPHOS) for glucose metabolism.<sup>66</sup> This preference reduces glucose availability and contributes to an acidic pH due to lactate production.<sup>67,68</sup> Moreover, hypoxia is observed due to limited oxygen availability, which reduces NK cell cytotoxic activity.<sup>69</sup> Specifically, hypoxia reduces NK cell activity by downregulating NK cell activating receptors and cytotoxic molecules like GZMB. Additionally, amino acid availability regulates NK cell functionality and signaling by maintaining important metabolic regulators like mTOR and c-Myc.<sup>70,71</sup>

## 2.3. Immunosuppressive cells

The main immunosuppressive cells in TME are tumor-associated macrophages (TAMs), Myeloid-derived suppressor cells (MDSCs), T regulatory cells (Tregs), tumor-associated neutrophils (TANs), and cancer-associated fibroblast (CAFs), with high capacity of immunosuppressive NK cells.<sup>59,61,72–81</sup> Notably, MDSCs are a group of myeloid-derived suppressor cells, precursors of dendritic cells, macrophages, and granulocytes, that have the ability to regulate immune response negatively.<sup>82–84</sup> Indeed, cancer-expanded MDSC can induce anergy of NK cells via membrane-bound TGF- $\beta$ 1.<sup>85</sup>

CAFs are another significant source of TGF- $\beta$  in the TME.<sup>86</sup> They play a pivotal role in ECM remodeling, as well as in cancer cell proliferation and invasion. CAFs modulate NK cells to an inactive phenotype through various mechanisms, including the recruitment of other immunosuppressive cells, such as M2 macrophages, as observed in colorectal cancer.<sup>87</sup> Notably, it has also been shown that oncogenes promotes

transformation of normal fibroblasts into CAFs.<sup>88</sup> They play a pivotal role in ECM remodeling, as well as in cancer cell proliferation and invasion.<sup>86</sup>

## 2.4. Cytokine profile

The influence of the TME on NK cell responses extends to its role in modulating the secretion of specific cytokines and factors by cancer cells. It is well known that cancer cells can modify the microenvironment in their vicinity by the secretion of specific cytokines or factors that directly or indirectly prevent NK cell activation or modulation to a less cytolytic phenotype (e.g., IL-6, IL-10, TGF- $\beta$ , prostaglandin E2 (PGE2), or indoleamine 2,3-dioxygenase (IDO)). Remarkably, TGF- $\beta$  is a master regulator of NK cell activity, promoting an immunosuppressive effect<sup>89</sup> galectin-9, highly expressed in many human cancers, can interact with TIM-3 on the surface of NK cells, limiting their cytotoxicity<sup>90,91</sup>; and the enzyme IDO which is widely present in tumors and contributes to the loss of NK cell cytotoxicity.<sup>92</sup> However, not all the signals block the antitumoral phenotype. Other molecules in the TME also help induce an antitumoral activity, like IL-15 mostly secreted by myeloid cells,<sup>93</sup> with an important role in NK cell survival, activation and proliferation.<sup>93,94</sup> Another activating signals in TME are the DAMPs (damage-associated molecular patterns) that trigger the production of type I IFNs, which increase NK cell antitumoral function.<sup>95</sup>

## 2.5. Receptor-ligand interactions

Some other relevant mechanisms described for NK cell immunosuppression are the modulation or release of NK cell receptor ligands by tumor cells to avoid receptor signaling.<sup>94,96–98</sup> For example, already in 2013, Reiners, KS. *et al.*, discovered that chronic lymphocytic leukemia patients were able to evade the antitumor activity of NK cells due to the secretion of the soluble ligand BAG6/BAT3 blocking the activating NK cell receptor Nkp30.<sup>78,97</sup>

Similarly, NKG2D ligands, such as MICA/B (MHC class I chain-related proteins A and B) and ULBPs, are often shed by tumor cells, which blocks the activating receptor NKG2D in NK cells.<sup>96</sup> This process will be discussed in detail later, focusing on how oncogenes affect these ligands. NKG2DL expression on cell membranes can be reduced through proteolysis by some metalloproteinases (ADAM9, ADAM10, ADAM17), and matrix metalloproteinase (MMP9, MMP14) to form soluble NKG2DL.<sup>99</sup> NKG2D is a major activating receptor of NK cells, and many independent studies have shown down-regulation of NKG2D surface expression on NK cells from patients with cancer. This effect was attributable to the presence of soluble NKG2D ligands (NKG2DL)<sup>100</sup> and linked to anergic NK cells in several tumors. These anergic NK cells present impaired degranulation capabilities, reducing the release of PFN, GZMs, and antitumor cytokines.<sup>85,101,102</sup>

On the other hand, the downregulation of MHC-I is a well-known immune evasion mechanism in cancer, exposing tumoral cells to NK cell attack, since MHC-I serves as their primary inhibitory ligand. MHC class I molecules represent a fundamental molecular framework that mediates the activation

and function of cytotoxic effector cells of both the adaptive and innate immune systems, such as CD8<sup>+</sup> T cells and NK cells. T cells are activated upon recognizing a tumor-associated neopeptide on an MHC I complex, eliminating the target cell. However, many tumors evolve to evade this recognition by downregulating MHC-I molecules on their surface. To counter this, the human immune system has developed specific killer cell immunoglobulin-like receptors (KIRs) and leukocyte Ig-like receptors (LIRs) expressed by NK cells that bind to MHC I molecules and inhibit NK cell activation. Consequently, if MHC-I expression is impaired, the inhibitory signal is reduced, facilitating the activation of the 'missing self' signaling pathway and resulting in the cytotoxic destruction of the target cell.<sup>52,62,103,104</sup>

MHC-I molecules are highly polymorphic, reflected by a high number of HLA-A, -B and -C alleles. Variations in MHC-I alleles pose challenges for NK cell surveillance, affecting directly their education and their ability to recognize aberrant cells.<sup>103–105</sup> Some alleles effectively engage inhibitory receptors, while others fail due to genetic differences. In HIV infections, individuals with poorly recognized alleles have been related to NK cell immunoevasion.<sup>105</sup> The diverse HLA-I repertoire influences NK cell surveillance efficiency and cancer susceptibility. Understanding the regulation of HLA-NK cell interactions is crucial for immune recognition mechanisms and design of effective NK cell-based targeted therapies.

In addition to classic MHCs, non-classical HLA (HLA-E and HLA-G) have an important role in cancer. HLA-E and HLA-G are peptide-dependent MHC I molecules with low levels of heterogeneity compared to classical MHC I molecules. Peptide-bound HLA-E serves as a dominant inhibitory ligand for the dimeric CD94/NKG2A receptor on NK cells and are frequently upregulated in many cancers, suggesting that this axis functions as an acquired resistance mechanism in the tumor microenvironment.<sup>106,107</sup>

The other non-classical HLA, HLA-G, present numerous isoforms, soluble or membrane-bound.<sup>108</sup> It modulates NK cell activity by engaging inhibitory receptors like KIR2DL1, KIR2DL2/3, KIR2DL4 or ILT2. HLA-G is poorly expressed on adult healthy tissues, and its expression is increased in tumor cells favoring immune-evasion.<sup>108,109</sup>

When discussing immunomodulatory receptors and ligands in cancer, the PD-1 and PD-L1/PD-L2 duo has gained significant attention due to their crucial clinical applications with antibodies designed to inhibit this pathway. It has been observed that both PD-1 and PD-L1 molecules are expressed in NK cells under different conditions and that these molecules regulate NK cell function. PD-1 is increased in degranulated-NK cells upon exposure to tumor cells,<sup>110</sup> as well as in the NK cells from cancer patients.<sup>111</sup> Similarly, PD-L1 expression is upregulated by IL-2 exposure,<sup>112</sup> highlighting the significance of this axis in NK cells, as observed during the elucidation of the anti-PD-1/PD-L1 therapies mechanism.<sup>113</sup> It is noteworthy that PD-1 expression in NK cells is much lower than in T cells and is not induced by stimuli such as cytokines<sup>112</sup> but interaction with target cells<sup>111</sup> which could lead to negative results when analyzing their membrane expression in NK cell cultures. Many studies still debate its expression, suggesting that it may be important to consider the models and controls used. This

controversy is highlighted by observations from two groups that conducted similar experiments using the CT26 cell line in mice to study PD-1 levels in NK cells. One study concluded that NK cells lack PD-1 expression, while the other observed remarkable expression.<sup>114,115</sup>

With all of these mechanisms, cancer cells manage to sculpt an immunosuppressive TME for NK cells. Consequently, adoptive cell therapies, whether T or NK cell-based, are currently ineffective in treating solid tumors.<sup>116,117</sup> Despite NK cells continuously combating transformed cells to prevent cancer development, they are highly susceptible to changes in their environment. These environmental changes can cause NK cells to switch from their antitumor or pro-inflammatory roles to behaviors that promote tumor formation, angiogenesis, and metastasis.<sup>118,119</sup>

A comprehensive understanding of the mechanisms involved in NK cell-mediated cancer immunosurveillance has paved the way for investigating the impact of various components within the TME on the elimination of cancer by NK cells. Recent evidence suggests that oncogenes and tumor suppressor genes not only influence the characteristics of tumor cells but also play a crucial role in enabling cancer cells to shape the TME to evade immune-mediated destruction. However, the specific links between these changes and NK cell function during cancer immunosurveillance and immunotherapy remain underexplored despite new studies in recent years. In the following lines, we will discuss current evidence and speculate how oncogenic-driven transformation might regulate NK cell antitumoral activity.

### 3. Oncogenes and tumor suppressor genes in NK cell immunoevasion

#### 3.1. A brief introduction to oncogenic transformation

Oncogenes and tumor suppressor genes are frequently mutated or modified during cancer progression. In healthy cells, there are some genes, commonly known as proto-oncogenes, which are necessary for cell growth regulation and differentiation, but when these genes, or their expression, are altered (at this point, they are termed oncogenes), they contribute to promoting cancer development.<sup>120</sup> The change from proto-oncogene to oncogene can result from mutations, chromosomal rearrangements, amplifications, or viral insertions. In most cases, this will likely result in uncontrollable tumor growth and apoptosis resistance.<sup>121,122</sup> On the other hand, tumor suppressor genes encode growth-inhibitory proteins, meaning that their loss would cause deregulation of cell proliferation. In contrast to passenger mutations, driver mutations frequently occur in cancer-related genes and are involved in oncogenic signaling pathways.<sup>123</sup> Most relevant and best-characterized oncogenes and tumor suppressor genes include transcription factors (Myc, fos, jun, rel), GTPases (Ras), kinases (Raf, PI3K, Stat3, Src, Syk, BTK, EGFR, VEGFR), Rb, and p53 (see [Figure 2](#)). Within the next sections, we will focus on the available evidence that links the oncogenic function of some of these genes to tumor cell evasion from NK cell function.

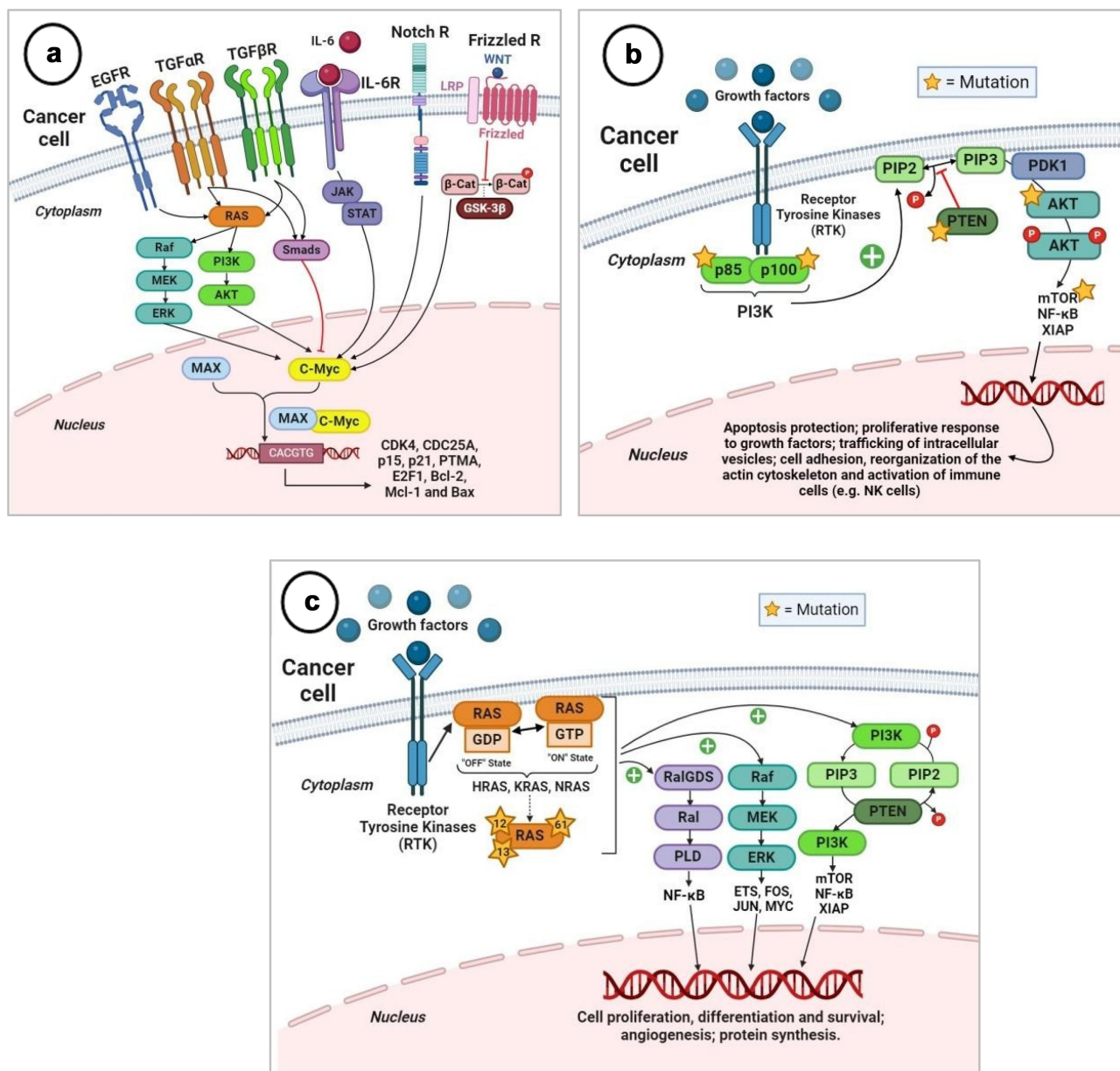


Figure 2. Oncogenic signaling pathways of myc (A), Ras (B), and PI3K (C). Figures created with BioRender.com.

### 3.2. Myc family

Myc alterations, including amplifications and activation, have been observed in over half of all cancer cases. Its pivotal role in regulating metabolic features, cell proliferation, growth, DNA replication, and numerous cellular processes tightly links it to multiple cancer hallmarks. It should be highlighted that similar to other oncogenes, Myc overexpression alone is usually insufficient for tumorigenesis induction.<sup>124–126</sup> The Myc family proteins comprise l-Myc (e.g., embryonic brains, kidney, and lung tissue), n-Myc (early developmental stages of neuronal tissues), and c-Myc (plenty of adult tissues).<sup>127</sup> As a transcription factor, Myc will form a dimer with Myc-associated factor X (MAX). Once they have dimerized, they will bind E-boxes (CACGTG) to the DNA within the enhancers and promoters of target genes. Those genes encode for proteins like CDK4 (Cyclin-dependent kinase 4), the phosphatase CDC25A, p15, p21, the oncoprotein prothymosin  $\alpha$  (PTMA), and

E2F1.<sup>128–130</sup> Myc is also known for being able to regulate the expression of anti-apoptotic (e.g., Bcl-2 and Mcl-1) and proapoptotic proteins (e.g., Bax).<sup>131</sup>

Of those three Myc isoforms, c-Myc has been shown to regulate carcinogenesis and progression in many cancers like breast, cervix, colon, stomach, lungs, and multiple myeloma.<sup>132,133</sup> For example, in lung cancer, c-Myc is frequently dysregulated and associated with unfavorable patient survival as it activates cell cycle-driving proteins and increases the expression of anti-apoptotic proteins like Bcl-2 and Mcl-1 that could affect NK cell cytotoxicity.<sup>134–136</sup> While the impact of c-Myc modulation on the tumor cell death machinery in NK cell immunosurveillance has not been explicitly examined, indirect evidence suggests that the relationship is more complex than initially anticipated. The role of anti-apoptotic proteins in impeding NK cell-mediated cancer elimination remains unclear. Studies employing specific protocols, combining stimulatory cells and cytokines, have

demonstrated that activated NK cells can effectively target cancer cells expressing these proteins.<sup>137</sup> Conversely, a recent report indicated that under conditions of limited NK cell activation and reduced numbers, overexpression of Bcl-XL or deficiency in Bak/Bax may aid tumors in evading NK cell-induced cell death.<sup>138</sup> Recently it was shown that Myc could inhibit the formation of RIPK1-RIPK3 complex which is required for initiation of necroptotic cell death,<sup>139</sup> although it is not known if NK cells activate necroptotic cell death in cancer cells. Consequently, the role of c-Myc modulation in the tumor cell death machinery, contributing to resistance against NK cells, remains ambiguous and necessitates further investigation.

MYC amplification can also alter the TME by modifying the metabolic characteristics of the cell. Although very little is known about the metabolic features of MYCN-amplified tumors, MYCN-amplified cells display enhanced expression of proteins and genes involved in glycolysis, OXPHOS, and ROS detoxification.<sup>140,141</sup> This enhances these metabolic pathways, leading to nutrient deprivation and acidification of the environment, contributing to impair NK cell activity.<sup>65,69,142</sup>

In addition to direct modulation of cancer cell machinery, cancer cell-associated c-Myc has been shown to influence the TME and viceversa. c-Myc, which is highly expressed in breast cancer cells, can regulate angiogenesis, the function of CAFs, and the response of immune cells, including NK cells.<sup>143</sup> Mezquita, P. *et al.*, found that c-Myc could increase VEGF (Vascular endothelial growth factor) expression, thus inducing angiogenesis.<sup>144</sup>

c-Myc can also increase the expression of miR-105 in tumor cells' vesicles, leading to up-regulation of c-Myc in CAFs, and reprogramming their metabolism toward a protumoral function.<sup>145</sup> Although these studies did not address the impact of these changes in NK cell activity, other evidence has shown that CAFs modulate NK cell function,<sup>59,61,72-81</sup> and, thus, pending of experimental validation, it could be speculated that c-Myc-mediated regulation of CAFs could impact NK antitumoral function as explained below.

CAFs have been identified as key players in neutralizing the NK cells' ability to eliminate cancer cells, employing a range of intricate mechanisms.<sup>61,72,81</sup> These include the secretion of soluble mediators like PGE2 and TGF- $\beta$ ,<sup>86</sup> which alter NK cell activation receptors such as NKG2D, NKp30, and NKp44 as well as cytotoxic molecule expression.<sup>146-148</sup> Moreover, CAFs can produce IDO. Therefore, they restrict not only NK cells' cytokine production but also their cytotoxicity.<sup>149</sup> The role of PGE2 and IDO as NK cell activation suppressors was already described by Li, T. *et al.*, in 2012. Based on their results, these two molecules suppress the activation of NK cells, thereby promoting tumor immune escape and creating favorable conditions for tumor progression.<sup>86</sup> Besides this, CAFs also up-regulate immune checkpoint molecules such as PD-L1.<sup>150</sup> Additionally, CAFs engage in synergistic interactions with other immune cells, contributing to the recruitment of M2 macrophages within the tumor environment and cooperating with them, which enhances inhibition of NK cell function.<sup>87</sup> In this line, c-Myc is overexpressed in CAFs and, after its activation by Wnt ligands from cancer cells, promotes M2 polarization and tumor cell progression, albeit the impact of immunosurveillance and NK cell function was not analyzed.<sup>143,151</sup>

Interestingly, once activated, c-Myc induces the expression of miR-17, which excludes immune cells such as NK cells due to the down-regulation of NKG2D ligands, MICA, and MICB and the up-regulation of CCL9 and IL-23.<sup>18,152</sup> Both cytokines, CCL9 and IL-23, are responsible for the rapid loss of T and B cells following Myc activation. However, while CCL9 alone is mainly required for the recruitment of PD-L1+ macrophages and angiogenesis, IL-23 alone is needed for the rapid exclusion of NK cells.<sup>18</sup> Since NK cells express the inhibitory checkpoint PD-1, their cytotoxic activity would be inhibited or down-regulated by the action of the recruited PD-L1+ macrophages.<sup>110</sup> However, the impact of the PD-1/PD-L1 axis and its alternative ligand PD-L2 on NK cell function remains controversial as discussed above. On the other hand, IL-23 has been related to NK cell-mediated control of tumor initiation and metastasis control in mouse cancer models. IL-23-deficient mice showed metastatic resistance mediated by NK cells, indicating that IL-23 can suppress NK cells' surveillance, antimetastatic and immunotherapeutic activity.<sup>153</sup>

As previously discussed, c-Myc can modify the expression of NKG2D ligands like MICA/B and ULBPs in chronic myeloid leukemia (CML) cells, reducing NK cell recognition.<sup>18,154</sup> Interestingly, inhibition of c-Myc by siRNA or chemical compounds restores ligand expression and NK cell killing potential confirming a causal effect of c-Myc in NK cell mediated recognition and elimination of CML cells. Myc oncogene is well known to drive T- and B-lymphoid malignancies, including Burkitt's lymphoma (BL) and Acute Lymphoblastic Leukemia (ALL).<sup>154</sup> Recently, it was shown that Myc overexpression altered the secretion of Type I IFNs from the T/B-lymphoblasts, causing a decrease in IL-15 and its receptor, which prevented NK cell maturation.<sup>155,156</sup> The effects of c-Myc on NK cell activity were shown to be enhanced by expression of oncogenic KRas<sup>G12D</sup>. In the KRas<sup>G12D</sup> mouse lung adenoma model, activation of Myc in this model induced more aggressive invasive adenocarcinomas by a mechanism depending on CCL9 and IL-23, which as indicated above, affected NK cell activity by recruiting PD-L1+ macrophages and depletion of NK cells.<sup>18</sup>

Despite all these findings, it should be noted that the role of Myc oncogene in the regulation of NK cell activity is intriguing since it has been shown that Myc activation in cancer cells triggered the up-regulation of NKG2D ligands and down-regulation of the MHC class I, both potent activating signals for NK-like cells.<sup>18,157-159</sup> A potential explanation for these apparently contradictory findings is that during the first stages of tumor development NK cells are prepared to eliminate cancer cells that have suffered oncogenic Myc transformation to avoid cancer progression, while, in more advanced stages, cancer cells have acquired the ability of using c-Myc to prevent NK cell action or by inducing NK cell anergy through chronic exposure to NKG2D ligands as discussed above. Further studies will be required to validate this hypothesis. Besides c-Myc, n-Myc amplification has also been established to affect the TME with potential impact on NK cell activity, although direct evidence for this is still unavailable. It was shown that n-Myc expression in neuroblastoma cells inhibited the expression of Th1-type chemokines such as CXCL9 and CXCL10, preventing the infiltration of T cells in tumors with a subsequent reduction

of IFN $\gamma$  and TNF $\alpha$ , creating a less pro-inflammatory microenvironment.<sup>125,160</sup> From these results, a reduction in NK cell infiltration could also be anticipated as CXCL9/10 are potent chemoattractants of NK cells,<sup>161,162</sup> albeit this speculation will require experimental validation.

Besides its direct impact on the resistance of cancer cells to NK cells and its role in shaping the TME to inhibit NK cell activity, Myc expression in immune cells can also influence NK cell function, contributing to cancer immunoevasion. One notable example is the promotion of immune-suppressive cells, such as Treg cells, which are well-established inhibitors of NK cell activity. Myc has been demonstrated to facilitate Treg cells' proliferation and functional activation by regulating their metabolism.<sup>163,164</sup> While the specific influence of Myc expression on Treg function and its consequent impact on NK cell inhibition have not been thoroughly investigated, recent research indicates that inhibiting Myc enhances the antitumoral activity of CD8+ T cells. This effect is achieved by suppressing Treg function, as demonstrated in a study where Myc inhibition led to increased CD8+ T cell activity.<sup>165</sup> These findings underscore the intricate interplay between Myc expression, Treg cells, and NK cell function in the complex landscape of cancer immunoevasion.

### 3.3. RAS

RAS proteins are essential components of signaling pathways coupled cell surface receptors. It is a GTPase protein, mutated in various cancers. About 20% of cancer patients carry a mutated version.<sup>166</sup> It belongs to a small GTPases superfamily composed of more than 150 members. This superfamily of proteins can be subclassified into RAS, RHO, RAB, and ARF families. Among them, the Ras family is encoded by three ubiquitously expressed genes: HRAS, KRAS (the most frequent mutated isoform), and NRAS. Usually, Ras aberrant functions in the context of cancer originate from single mutations at codons 12, 13, or 61 taking place in conserved sites, causing constitutive activation of Ras and its signaling pathways involving Raf/Mek/Erk, PI3K, and Ral GDS.<sup>167</sup>

The Ras-mutated protein form was reported to induce NKG2D ligand expression by a Raf-MAPK/MEK and PI3K signaling pathway and independently of the DNA damage sensors, which are usual triggers of NKG2D ligand expression after DNA damage and/or oxidative stress.<sup>86,168</sup> Furthermore, it is worth noting that the oncogene Ras has been documented to have a role in the context of non-small cell lung cancer, wherein the mutation of KRAS is associated with an elevation in the expression of PD-L1.<sup>169,170</sup> This finding has been associated with a better response to anti-PD-1 antibodies,<sup>170,171</sup> mainly due to CD8+sT cells, and the role of NK cells in these responses is still unclear.

Regarding the potential modulation of Ras mutations in cell death induced by NK cells, it should be noted that most of the studies that have directly addressed this question have found that NK cells are able to kill cancer cells using natural cytotoxicity or ADCC, irrespectively of mutations in Ras/Raf pathways.<sup>171</sup> Interestingly, it was found that colorectal cancer (CRC) cells with mutant KRAS showed resistance to perforin-independent ADCC in comparison with wild-type KRAS,

which was linked to KRAS-mediated resistance to death receptors.<sup>172,173</sup> However, when total cell death induced by NK cells was analyzed, no differences were observed between wt and mutant Ras, suggesting that only those tumor cells with mutations in Ras and, in addition, resistant to the PRF/GZM pathway, might acquire survival advantaged against NK cells. Although mutations that generate PRF resistance in cancer cells have not been described so far Ras mutated tumor cells overexpressing PI-9,<sup>174</sup> a GZMB serpin inhibitor, could be more resistant to NK cell mediated cell death. Additionally, mutated Ras tumor cells could be more resistant to NK cell serial killing a process in which PRF and FasL pathways seem to act sequentially for optimal elimination of cancer cells, at least in vitro.<sup>175</sup>

In 2020 Daia, E. *et al.*, demonstrated that KRAS<sup>G12D</sup> is packaged into exosomes that are engulfed by macrophages via AGER (advanced glycosylation end-product specific receptor) with the subsequent polarization of macrophages into an M2 tumor-promoting state.<sup>176</sup> As indicated above, M2 macrophages are able to suppress NK cells killing ability by different means including cooperation with CAFs, generation of anti-inflammatory cytokines and attraction of Treg cells.<sup>87,177,178</sup> However, the specific role of KRAS<sup>G12D</sup> endocytosed by macrophages on NK cell activity was not analyzed in that study.<sup>176</sup> Drawing insights from related studies, although not explicitly tested, one can speculate on the potential impact of oncogenic RAS variants on NK cell activity. This speculation is based on findings such as neutrophil attraction through KRAS-dependent IL-8 induction which could potentially influence NK cell activity through mechanisms like NETosis, a network extracellular trap made by DNA and proteins released by neutrophils under specific conditions.<sup>179–183</sup> Additionally, these RAS variants may affect NK cells by promoting the production of anti-inflammatory molecules (ARG1, ROS, NO, PGE2)<sup>184</sup> and facilitating IL-10/TGF- $\beta$ 1-dependent Treg infiltration.<sup>185</sup> Similarly, different studies have correlated the presence of KRAS mutations with the generation of immunosuppressive TME in CRC by recruiting MDSCs, which prevented T cell infiltration and activation, although NK cells were not analyzed.<sup>186,187</sup> This finding was also extended to lung adenocarcinoma.<sup>188</sup>

Mutations in Ras pathways have been linked to the modulation of cell death machinery, leading to an anti-apoptotic profile and HLA-I downregulation.<sup>189–191</sup> This alteration may potentially modulate NK cell-mediated antitumoral activity. However, the presence of Ras/Raf mutation did not affect the sensitivity of a panel of CRC cell lines to activated allogeneic NK cells; instead, it was mostly regulated by HLA-I levels independently of the driver mutation.<sup>171</sup>

### 3.4. PI3K (PIK3R1 and PIK3CA)

The phosphoinositide 3 kinase (PI3K) is a heterodimer composed of a regulatory subunit (p85), encoded by PIK3R1 gene, and a catalytic subunit (p100), encoded by PIK3CA gene. This signaling pathway responds to various extracellular signals through different tyrosine kinase-like receptors like ErbB family, or insulin-like growth factor 1 receptor (IGF1R)<sup>192,193</sup> generating the intermediate metabolite PiP3 by PiP2



phosphorylation that subsequently activates PKB/AKT/mTOR pathways. This pathway that is negatively regulated by the action of the PTEN phosphatase,<sup>194</sup> participates in several cellular processes including protection from apoptosis,<sup>195</sup> proliferative response to growth factors,<sup>196,197</sup> trafficking of intracellular vesicles, cell adhesion,<sup>198</sup> reorganization of the actin cytoskeleton<sup>199</sup> and activation of immune cells including NK<sup>200</sup> and T cells.<sup>201</sup> Notably, the PI3K-AKT-mTOR signaling pathway is the most frequently mutated in human cancer, being the following alterations the most common ones: PIK3CA, PIK3R1, PTEN, AKT, TSC1, TSC2, LKB1 (also known as STK11) and mTOR.<sup>202</sup> An example is breast cancer, where PTEN loss of or reduction in function is commonly found, allowing the constitutive activation of PI3K pathways, although the significance of this finding is still unclear.<sup>192,203,204</sup>

Like other oncogenes, the direct evidence linking mutations in the PI3K pathway to NK function is limited, with most connections being speculative. The hypotheses are primarily derived from observations of its impact on the TME and T cell function or infiltration. For instance, PI3KCA mutations have been associated with the presence of immunosuppressive molecules/cells in the TME, potentially influencing NK cell activity, although this aspect remains unexplored. Correlations have been observed, such as increased Treg, reduced T cell infiltration, increased PD-L1 expression and heightened resistance to immunotherapy in different cancer types linked to PI3KCA mutations.<sup>192,203</sup> In addition, similarly to Ras and Myc, speculations could be established from the studies relating PI3K mutation and regulation of cell death pathways in cancer cells, which could affect NK cell-mediated tumor cell death. For example, AKT inhibits pro-apoptotic caspase-9 and Bad and reduced expression of proapoptotic BH3-only proteins,<sup>205</sup> although, as indicated above, it is not clear yet the conditions at which these alterations can favor cancer immunoevasion of NK cell-mediated killing.<sup>137,138</sup>

While there are no studies specifically examining the influence of oncogenic mutations in the PI3K/AKT/TOR pathway on NK cell antitumoral activity, insights can be gleaned, and speculative observations can be made based on studies exploring the role of this pathway in the regulation of NK cell ligand expression. Several studies have analyzed the role of PI3K in the expression of inhibitory (classical and non-classical HLA-I) and activating (MIC, ULBP and Rae families) ligands in humans and mice. Independent studies using chemical inhibitors and activators found that activation of PI3K-AKT pathway inhibited HLA-I expression in cancer cells.<sup>206,207</sup> Another study found that placental-derived leptin enhanced inhibitory non-classical HLA-G molecule expression in trophoblasts by the MEK/Erk and PI3K-AKT pathways.<sup>208</sup> While the latter is not explicitly mentioned in a tumoral context, it is worth experimentally validating this extrapolation since, although potential differences are recognized, the interaction between mother and fetus bears notable similarities to the immune-cancer relationship. Indeed, with appropriate caution, regulating immunity at mother-fetus interface has inspired different discoveries in cancer immunoevasion.<sup>209</sup>

Regarding activating ligands, constitutive activation of PI3K pathways can increase the expression of various ligands from

the MIC, ULBP, and Rae families in cancer cells.<sup>210–213</sup> Although these ligands are typically defined as stress response ligands due to their association with cellular stress, the term “stress” is challenging to define, and the specific molecular pathways underlying their activation are complex. NKG2D ligands are regulated at multiple stages of biogenesis, including transcription, RNA stabilization, protein stabilization, and cleavage from the cell membrane. Ongoing in-depth studies have provided increasingly detailed insights into the specific pathways that modulate the expression levels of these proteins.<sup>213,214</sup>

For example, it has been shown that HER2 signaling induces the expression of MICA/B via the PI3K/AKT pathway in breast cancer cells, enhancing their susceptibility to NK cells.<sup>210</sup> Similarly, the EGFR tyrosine kinase inhibitor (TKI) gefitinib has been reported to downregulate the expression of MICB and ULBP-2/5/6 in non-small-cell lung cancer cells, likely through inhibition of the PI3K/AKT pathway.<sup>215</sup> However, other studies have shown that EGFR TKIs, such as erlotinib and gefitinib, can enhance the susceptibility of lung cancer cells to NK cell-mediated lysis by inducing ULBP1, attributing this increase to the inhibition of the PKC pathway.<sup>216</sup> It is important to note that these studies used different cell lines, which may exhibit varying expression of driver oncogenes or even different sensitivities to these drugs.

In addition, treatment with vorinostat or pterostilbene up-regulated MICA expression via the PI3K/AKT signaling pathway and improved the ability of NK cells to kill cancer cells.<sup>211,212</sup> Finally, BCR/ABL activation in chronic leukemia cells enhanced MICA expression and NK cell-dependent cytotoxicity by a pathway dependent on PI3K/mTOR.<sup>213</sup> Interestingly, BCR/ABL inhibition by Imatinib was shown to decrease MICA protein secretion, leading to increased susceptibility of cancer cells to NK cells. Thus, the efficacy of Imatinib in enhancing NK cell killing may not be attributed to an increase in MICA activation receptor expression, but rather to a decrease in soluble MICA levels.<sup>213</sup> All these findings are good examples of how drugs used in cancer treatment can affect NK cell antitumoral activity by regulating the activity of potential oncogenic proteins, providing the basis for the possible use of oncogenes as targets to enhance NK cell-based therapies.

It is worth mentioning a recent paper showing that IL-18 enhances MICA/B expression in dendritic cells favoring NK cell-DC interaction.<sup>217</sup> Although in a different context, since IL-18 is usually enhanced in some tumors, it is tempting to speculate on the implications of this finding in the recognition of cancer by NK cells.

As deduced from the preceding findings, PI3K activation seems to promote a shift toward NK cell activation and tumor recognition, seemingly indicating the tumor's strategy to evade T cells. However, as indicated above, additional mechanisms related to the immunosuppressive profile of TME, some of which are also regulated by the PI3K pathway, are likely to contribute to the immunoevasion of NK cell immunosurveillance. Thus, interfering with these immunosuppressive pathways like TGF- $\beta$  might present a chance to favor NK cell-mediated elimination of PI3K mutated tumors as mutations in this pathway appear to enhance cancer cell susceptibility to NK cells.

Beyond tumor mutations, recent findings suggest germline mutations in the PIK3CD gene can impair NK and CD8+ T cell cytotoxicity, leading to compromised immunity against herpesviruses and impaired tumor surveillance.<sup>218</sup>

### 3.5. STAT protein family: STAT3 and STAT5

STAT3, a member of the JAK-STAT signaling pathway, is constitutively activated in multiple cancers: colon, head and neck, pancreatic, breast, and hematological neoplasias.<sup>219–222</sup> It coordinates key cellular mechanisms like cell differentiation, proliferation, immune function, and apoptosis. However, it is also well known for its role in mediating tumor immune evasion.<sup>223,224</sup> For example, in multiple myeloma or CRC, STAT3 has been described to directly repress the transcription of NKG2D ligands (e.g. MICA) and therefore to inhibit the NK cell-mediated tumor surveillance. In those studies, the inhibition or knockdown of STAT3 led to a stronger NKG2D-dependent tumor cell death by NK cells.<sup>225,226</sup> An increase in other NK ligands (e.g. MICB or ULBP2) following STAT3 inhibition has also been reported.<sup>227,228</sup> Additionally, when STAT3 is constitutively active, it can trigger the release of immunosuppressive cytokines such as IL-10 or TGF- $\beta$  that will recruit immune cells (e.g. Tregs), which have an immunosuppressive effect on NK cells' cytotoxicity.<sup>229</sup>

Besides STAT3, another member of the STAT family is commonly activated in solid cancers, the STAT5 protein. Over the years, the constitutive activation of STAT5 has been associated with hematological malignancies (e.g. leukemia) and solid tumors (e.g. breast, lung, and colorectal cancer).<sup>230–233</sup> Nonetheless, the way in which it promotes tumor proliferation has been less described.<sup>234</sup>

### 3.6. Tumor suppressor genes

To finish this section, we will focus on tumor suppressor genes that have been shown to directly affect NK cell antitumoral activity, specifically the retinoblastoma (Rb) and p53 genes, which control different biological processes like cell death, cell cycle, and terminal differentiation, similarly to oncogenes (see Figure 3).

Rb is frequently inactivated in many human cancers, such as retinoblastoma, breast cancer, prostate cancer, and small cell lung cancer.<sup>235,236</sup> The canonical pathway whereby Rb exerts its tumor suppressive is through regulating the G1/S transition during cell cycle progression. For doing so, it modulates the activity of E2F transcription factors. In most cancers, alterations in this gene lead to a more aggressive tumor cell phenotype; it promotes tumor metastatic activity and drug resistance. Since uncontrolled cell proliferation and metastasis are hallmarks of cancer cells,<sup>13</sup> it has been postulated that genes acting as Rb function inhibitors (e.g., CCND1 and CDK4) are identified as oncogenes. Conversely, those promoting Rb functions (e.g., cyclin-dependent kinase inhibitors like CDKN1A, CDKN1B, and CDKN2A) are tumor suppressor genes.

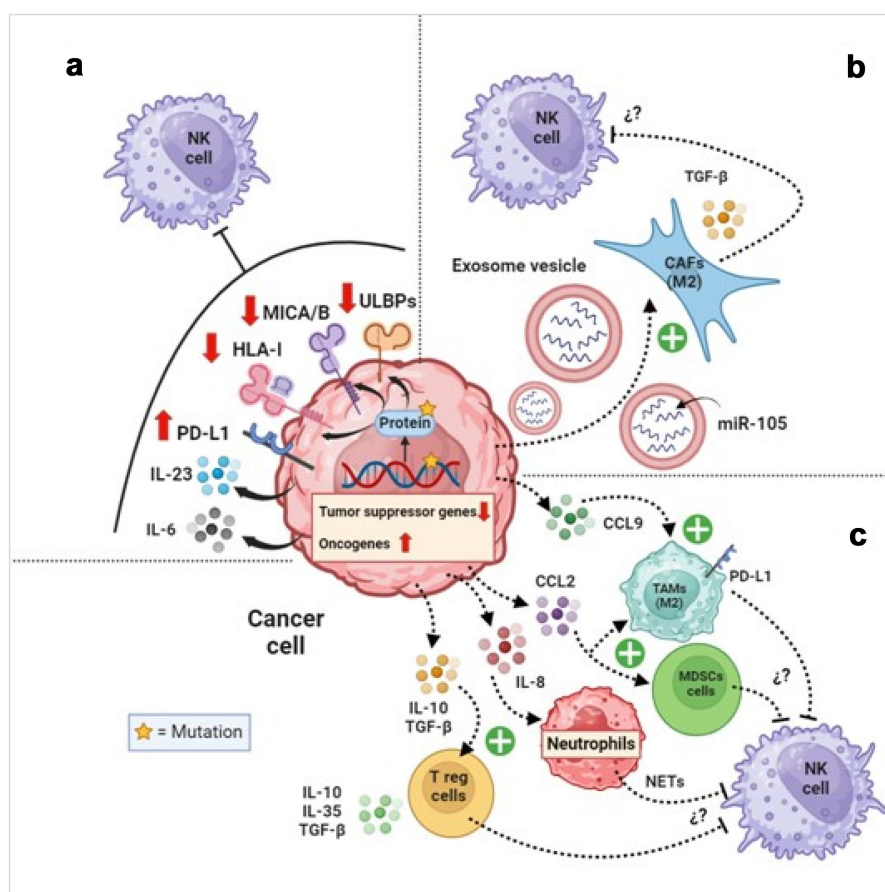
Again, most evidence on the role of Rb on NK cell activity is indirect from studies showing that suppression of Rb signaling affects immunomodulators involved in NK cell activity, including IL-6, CCL2, or prostaglandin-endoperoxide synthase 2

(PTGS2),<sup>237,238</sup> all of them negative regulators of NK cell activity by different means including direct action on NK cells or indirect regulation by promoting Treg, TAM and/or MDSCs infiltration (CCL2).<sup>239,240</sup> In 2015, the tumor suppressor gene Rb was established to negatively regulate NK cell cytotoxicity in mouse glioma. Deleting Rb was sufficient to enhance resistance to NK cell-mediated cytotoxicity, albeit the correlation with changes in activating and inhibitory ligands could not be well established as, apparently, deletion of Rb decreased activating ligands while increasing MHC-I.<sup>241</sup> Thus, further experiments will be required to analyze the mechanisms by which Rb mutations promote tumor resistance to NK cells.

p53 is a crucial tumor suppressor gene that is best known for maintaining genomic stability and inhibiting cell proliferation.<sup>242,243</sup> As a transcription factor, it regulates genes involved in cell cycle, apoptosis, DNA repair, and many others.<sup>244</sup> Loss of p53 function is frequently involved in cancer development.<sup>245</sup> Unlike other tumor suppressor genes (e.g. BRCA1 or Rb), which are usually inactivated by deletions or truncating mutations, most p53 mutations in cancers are missense mutations. p53 mutations origin full-length mutant p53 proteins (mutp53) with only one amino acid substitution.<sup>246,247</sup> These mutations present two principal effects. On the one hand, there is the loss of the wild-type p53 (wtp53) function, and on the other hand, mutp53 tends to promote tumorigenesis through the gain-of-function (GOF) mechanism. Plenty of GOF activities have been reported so far: cell proliferation promotion, metastasis, genomic instability, metabolic reprogramming, cell stemness, tumor microenvironment reshaping, immune suppression and resistance to therapy in cancer.<sup>247–249</sup>

The status of p53 within cancer cells profoundly influences the immune response, including regulation of PD-L1 and MHC-I expression, polarization of TAMs or inhibition of T and NK cell infiltration.<sup>250–252</sup> The loss of the wtp53 also has important effects on NK cell-mediated killing. In 2011 Textor, S. *et al.*, showed that NKG2D ligands expression (e.g. ULBP1 and ULBP2) are up-regulated at the transcriptional level by wtp53 but not mutp53. This transcription factor binds p53-responsive elements in the ULBP1/2 genes, leading to a higher expression of these NK cell ligands, thereby enhancing NK cell NKG2D-based cytotoxicity.<sup>253</sup> The same findings were confirmed in 2022 by Uddin, MB *et al.*, in a murine model, showing that the p53 missense mutant G242A, which corresponds to the human G245A mutation, plays a significant role in suppressing the activation of host NK cells. This suppression enables breast cancer cells to evade immune assault and avoid rejection by the immune system.<sup>254</sup>

Mutp53 is also recognized for its role in inhibiting apoptosis and autophagy, thus promoting the development of apoptosis resistance features.<sup>245,255</sup> Hence, the wtp53 protein is also relevant for regulating GZMB-mediated apoptotic pathways by cytotoxic T and NK cells.<sup>256</sup> In p53-mutated breast cancer cells, Chollat-Namy, M. *et al.*, showed that the reactivation of p53 transcriptional activity by a p53-stabilizing agent (CP-31398) increased their lysis by NK cells. They could not observe a modified expression of known p53 targets related to NK cell activity, but they clearly showed an autophagy promotion and triggered the sequestration of anti-apoptotic proteins (e.g. Bcl-XL and XIAP) in autophagosomes which potentiated GZMB-induced mitochondrial outer membrane permeabilization and caspase-3 cleavage; thus promoting GZMB-induced cell death.<sup>257</sup>



**Figure 3.** Effects of oncogenes and mutated tumor suppressor genes in NK cell immunosurveillance. (A) Tumor cells can directly inhibit NK cell function by secreting interleukins (e.g. IL-6 or IL-23) or by modulating the expression of NK cell receptor ligands (e.g. HLA-I, MICA/B or PD-L1). (B) Tumor cells can secrete exosome vesicles that contain specific microRNAs that will induce changes in other immune cells (e.g. TAMs or CAFs), inducing their transformation into a protumorigenic phenotype. (C) Tumor cells secrete multiple molecules (e.g. CCL9, CCL2, IL-8, IL-10 or TGF- $\beta$ ) that will recruit additional immune cells that have an immunosuppressive effect on the cytotoxicity of NK cells. The regular arrows show evidence already demonstrated while dotted arrows are hypothetical evidence that has not been proved yet. Figure created with BioRender.com.

This tumor suppressor gene is also well-known to regulate cell metabolism; however, how it affects metabolism-induced ligands' expression is not completely understood. Belkahla, S. *et al.*, showed that dichloroacetate (DCA) induced either OXPHOS in tumor cells and also the expression of NK ligands such as MICA/B, ULBP1, and ICAM-I in a wtp53-dependent mechanism (the opposite effect was observed in mutant or null p53). This all means that DCA can sensitize tumor cells but only those that are wtp53-expressing cells.<sup>258</sup>

Overall, these findings highlight the complex interplay between oncogenes and mutated tumor suppressor genes in the immune microenvironment and their effects on NK cell activating or inhibitory ligands, emphasizing the potential for targeted therapies in cancer treatment (See Table 1).

#### 4. Strategies to overcome oncogene-mediated NK cell immunosuppression

The overexpression of anti-apoptotic proteins, or conversely, the suppression of proapoptotic proteins, is a common outcome of oncogene activation.<sup>131</sup> Current therapeutic strategies exploring the combinations of specific inhibitors targeting the dysregulated proteins, typically Bcl-2 or Bcl-XL, along with

selectively activated NK cells, are being investigated,<sup>137,138</sup> proposing to establish a BH3 profile of the cancer cells to design specific trials to enhance the efficacy of adoptive NK cell therapy.<sup>137,138</sup> However, previous studies have proposed that a higher dose of expanded NK cells can overcome tumor resistance in hematological tumors, although this might present some limitations for patient treatment, especially in the case of solid tumors or with high tumoral burdens.<sup>137</sup>

However, reaching these higher doses might be plausible by designing specific trials to use NK cells as adjuvant therapy after stem cell transplant, chemotherapy, radiotherapy, or surgery to enhance tumor elimination and prevent recurrence.

KRAS and Myc alterations have also been strongly linked to the dysregulation of CDK4 activity. Besides, NK cell activation ligands were restored during the CDK4/6 inhibitor's treatment, observing an increase of ICAM1, MICA/B, and ULBPS.<sup>260</sup> The combination of protein inhibitors such as MEK and CDK4/6 inhibitors also induces senescence, possibly explaining the subsequent NK cell clearance, as NK cells play a crucial role in clearing cancer and senescent cells.<sup>260,261</sup> Therefore, the strategic use of CDK4/6 inhibitors such as palbociclib, ribociclib, and abemaciclib, in combination with NK cell adoptive therapy or with antibodies inducing NK cell-mediated ADCC, as well as with bispecific antibodies targeting NK cells, emerges as a promising strategy to enhance the

**Table 1.** Regulation of NK cell ligands' expression in tumor cells. CML (chronic myeloid leukemia); CRC (colorectal cancer); MM (multiple Myeloma); NSCLC (non-small cell lung Cancer); p53-RE (p53-responsive elements).

Oncogene	NK cell ligands	Tumor/Cell Type	Pathway	References
Myc	MICA/B ↓	CML	miR17	154
	MICA/B ↑	Lung cancer	Together with KRas <sup>G12D</sup>	18
	HLA-I	melanoma cell lines neuroblastoma cell line	mRNA ↓	158,159
Ras	NKG2D ↑	Ovarian and breast cancer	MAPK, PI3K, and DNA damage	168,259
PI3K	PD-L1 ↑	Lung cancer	MAPK and PI3K	170
	HLA-I ↓	Mesothelioma cell line	MAP kinase pathway	190,191
	HLA-I ↓	Head and neck carcinoma and colon cancer	PI3K-AKT	206,207
STAT3	MICA/B ↑	Breast cancer	Her2-PI3K-AKT	210
	MICA/B ↑	CML	cAbl-PI3K-mTOR	213
	MICA/B ↑	Cervical cancer and T-cell lymphoma	Vorinostat-PI3K-AKT Pterostilbene-PI3K-AKT	211,212
	MICA ↓	CRC cell line HT29 and MM CML cell line K562	STAT3 binding to the MICA promoter JAK/STAT3	225,226 227
	ULBP2 ↓	CML cell line K562		
P53	MICB ↓	Gastric adenocarcinoma		228
	ULBP1/2 ↑	NSCLC H1299 cell line	wtp53 binds to p53-RE	253
	PD-L1 ↑	Lung adenocarcinoma and breast cancer	mutp53 ⇒ PD-L1 mRNA ↑	252,254
	HLA-I ↑	colon cancer cell line HCT116	wtp53 ⇒ ERAP1 mRNA ↑ ⇒ HLA-I	250

eradication of tumor cells by NK cells. This innovative therapeutic approach offers an exciting prospect in the field of cancer immunotherapy, strengthening the potential for more effective tumor clearance and improved patient outcomes.

MICA/B and ULBPs are potent activator ligands for the NK cell receptor NKG2D. As indicated above their down-regulation has consistently been observed in numerous studies across various cancer contexts related to oncogenes or tumor suppressors genes.<sup>157,259</sup> Therefore, diverse approaches attempt to target the NKG2D axis for cancer immunotherapies. Additionally, in NKG2D ligand down-regulation, their cleavage and release as soluble forms also significantly influence NK cell activity. This impact is two-fold: not only does it directly result in the down-regulation of activation signals, but it also reshapes NK cells toward a pro-inflammatory phenotype. While membrane-bound NKG2D ligands boost NK cell cytotoxicity, soluble NKG2D ligands promote the expression of cytokines such as GM-CSF, IL-10, or CCL4, as well as the activation of pro-inflammatory signaling pathways like PKC- $\theta$  and ADAP.<sup>262</sup> In 2011, another study uncovered a possible new immunotherapy approach. Since ULBP1 and ULBP2 are direct p53 target genes, treating tumor cells with RITA (Reactivation of p53 and Induction of Tumor cell Apoptosis) would reactivate wild-type p53 and therefore would up-regulate the NKG2D ligands' expression. This novel design would enhance NK cell cytotoxicity.<sup>253</sup>

Considering that p53 inactivating mutations are frequently found in human tumors and the dependency of the GZMB-dependent apoptotic pathway of T and NK cells in the wtp53 protein, reactivating the function of p53 will be an interesting approach. Chollat-Namy, M. *et al.*, showed in their study that the pharmacological reactivation of a wt-like p53 function in p53-mutated breast cancer cells using a small molecule (CP-31398) increases their sensitivity to NK-mediated lysis.<sup>257</sup> This tumor suppressor gene is also well-known to regulate cell metabolism. However, due to the already described association between wtp53 and NK cell ligands, treatment with DCA, or similar drugs could decrease tumors with high proliferation as well as increase

the effectiveness of CAR NK cell or allogeneic NK cell therapies.<sup>258</sup>

The up-regulation of the immune checkpoint PD-L1 often occurs due to genetic alterations within cancer cells, including Ras and p53 mutations. Furthermore, the expression of PD-1 on NK cells has been documented, raising concerns about the capacity of PD-L1 engagement to attenuate NK cell function.<sup>110,111,113</sup> The development of immunotherapy has paved the way for a robust research focus on blocking the PD-1/PD-L1 inhibitory pathway, yielding remarkable results in various cancer types. Interestingly, the effectiveness of this therapy is not solely rooted in releasing the brake to the immune system; it also involves directing immune cells, primarily NK cells, by tagging the tumor with antibodies capable of inducing ADCC.<sup>115</sup>

As previously discussed, in some cancers tumor cells reduce the MHC-I expression to avoid T-cell recognition and their subsequent killing.<sup>52</sup> However, NK cells can recognize these "low immunogenic cells" and kill them. In a mouse model of carcinogen-induced Non-Small Cell Lung Cancer it was shown that knocking out STAT3 led to down-regulation of MHC I making those cells more susceptible to NK cell-mediated death.<sup>263</sup> Moreover, as already mentioned, tumors that harbor a constitutive activation of STAT3 release classical immunosuppressive cytokines (e.g. IL-10 and TGF- $\beta$ ), thus impairing tumor immune surveillance.<sup>229</sup> This is why STAT3 inhibitors are gaining increasing therapeutic interest.<sup>264</sup>

Beyond activation or inhibition ligands, NK cell activity is also modulated by chemokines. Modulating the secretion of chemokines, such as CXCL9 and CXCL10, can significantly impact NK cell tumor infiltration. Hence, the observed down-regulation of CXCL9 due to oncogenic activity is not only associated with reduced NK cell infiltration across various types of cancer<sup>265</sup> but also directly links the low number of infiltrated NK cells in CXCL9-deficient tumors to the worst prognosis in cholangiocarcinoma,<sup>161</sup> opening the door to immunotherapy by targeting the CXCL9/CXCR3 axis to promote lymphocyte infiltration.

Altered gene expression in tumor cells typically triggers adopting a migratory and invasive phenotype, collectively

known as epithelial-mesenchymal transition (EMT). During EMT, significant phenotypic changes occur in cancer cells, leading to highly invasive properties. Among these changes, the regulation of cell-cell adhesion markers, such as epithelial cadherin and cell adhesion molecule 1, is altered,<sup>266</sup> which can enhance NK cell cytotoxicity,<sup>267</sup> contributing to a better understanding of the pivotal role NK cells play in controlling metastasis.

The generation of reactive oxygen species (ROS) within tumors is a common characteristic resulting from the activation of oncogenes or the inactivation of tumor suppressors, such as the Rb gene. ROS directly suppresses NK cell activity. Various NK cell priming protocols have been explored to counteract NK cell ROS inactivation, yielding NK cells enriched in the ROS scavenger thioredoxin (Trx1). These Trx1-enriched NK cells exhibit protection against ROS, mirroring the observation of Trx1+ NK cells in lung cancer patients with ROS. According to this observation, when dividing these patients, smokers display higher ROS levels and worse prognoses compared to nonsmokers.<sup>268,269</sup>

## 5. Concluding remarks and future perspectives

In general, how mutations responsible for carcinogenesis shape the TME and modulate the antitumoral activity of NK cells remains largely unknown. The only clear fact is that NK cells have a genuinely complex regulation. Although they do not require prior antigen exposure, their antitumoral function relies entirely on different activating and inhibitory signals. Several NK cell ligands have been described; some potentiate NK cell activity, while others have an immunosuppressive effect. As already discussed here, the TME is crucial as it strongly affects NK cell cytotoxicity. Especially in an anti-inflammatory context, several cell populations (e.g. TAMs, MDSCs, Tregs or CAFs) and molecules (e.g. IL-6, IL-10, TGF- $\beta$ , PGE2 or IDO) are known for their negative impact on NK cell activity, thus promoting tumor progression. It is well known that several of those molecules have been secreted by cancer cells with the aim of modifying the microenvironment on their behalf.

It should be noted that NK cell functionality can also be altered by tumoral cell genetic components: oncogenes and tumor suppressor genes. During cancer progression, these genes are frequently mutated, ranging from loss of wild-type functions to overactivation of genes or acquisition of new functions. However, not everything is well understood. Some contradictions remain ambiguous and necessitate further investigation. For example, the activation of Myc in cancer cells has been proven to trigger the up-regulation of NKG2D ligands and down-regulation of MHC genes, both potent activating signals for NK-like cells. Why this is not enhancing NK cell activity is still not clear. We hypothesize that during the first stages of tumor development, NK cells are ready to eliminate cancer cells that have suffered oncogenic Myc transformation, while, in more advanced stages, cancer cells have acquired additional ability by using another oncogene to avoid NK cell action.

There is no doubt that oncogenes are capable of modulating NK cell death machinery. They can inhibit apoptosis (e.g.

increasing anti-apoptotic proteins, Bcl-2 or Mcl-1, or down-modulating pro-apoptotic proteins, caspase-9, Bad or BH3-only proteins); down-regulate NK cell activating ligands (e.g. MICA/B or ULBPs); up-regulate NK cell inhibitory ligands (e.g. PD-L1); generate resistance to the PRF/GZM pathway and promote immunosuppressive cytokines secretion (e.g. IL-10 or TGF- $\beta$ ); aiding angiogenesis and recruitment of negative regulators of NK cells. Nonetheless it is still not clear if this is enough per se to enhance resistance to NK cytotoxicity. In any case, whether the acquisition of cell death mutations due to oncogenic activation would enhance NK cell tumor escape in the context of other immunosuppressive factors such as TGF- $\beta$  or hypoxia remains to be analyzed.

In addition to the aforementioned, it should be highlighted that many of the studies conducted in this area are based on mouse models. Although these models have allowed important advances in the field of immunity and cancer, they are not perfect. Compared to humans, these models exhibit different ligand expression and regulation, which clearly limits their translation to human NK cell biology. There are also discrepancies in innate and adaptive immunity between the two species, which must be considered when using mice as pre-clinical models of human diseases.

It is also crucial to recognize that drugs designed to target oncogenes in cancer cells may inadvertently impact immune cell functions, including NK cells, due to shared characteristics with tumor cells, such as high proliferative rates and metabolic remodeling. This suggests that these drugs could influence the antitumor activity of immune cells, potentially inducing the opposite effect to what is desired, highlighting the intricate interplay between tumor cell genetics and immune cell responses, which underscores the need for comprehensive consideration of immune modulation in cancer therapy. Understanding the potential effects of these drugs on both cancer sensitivity to NK cells and the sensitivity of NK cells to the drugs themselves is crucial for optimizing treatment strategies and improving patient outcomes.

Despite the critical role of NK cells in antitumoral immunity, the direct impact of oncogenes on NK cell function has been largely overlooked in cancer research. While numerous studies have dissected the influence of oncogenes within the tumor microenvironment and on tumor cell death pathways, the focus has primarily been on T cells, leaving a significant gap in our understanding of NK cell biology. This disparity is evident in the limited number of papers exploring the direct effects of oncogenes on NK cell-mediated antitumoral responses, particularly within the context of the TME or tumor cell death mechanisms.

However, addressing this knowledge gap holds immense potential for enhancing cancer elimination strategies. By elucidating how oncogenes modulate NK cell activity, we can leverage this understanding to develop more comprehensive immunotherapeutic approaches that simultaneously target both T and NK cells. This integrated approach becomes increasingly crucial in light of the frequent tumor recurrences observed following CAR T cell-based immunotherapies. Moreover, emerging evidence suggests that while oncogenes may suppress T cell activity, they inadvertently render tumor cells more susceptible to NK cell recognition and elimination.

This paradoxical effect underscores the importance of exploiting the vulnerabilities of tumor cells to NK cell-mediated cytotoxicity. By capitalizing on strategies tumor cells employ to evade T cell surveillance, we can potentially enhance their visibility to NK cells, thus augmenting the overall antitumoral response.

In essence, unlocking the mechanisms by which oncogenes modulate NK cell function represents a promising avenue for refining cancer immunotherapy strategies. Through a concerted effort to investigate the direct impact of oncogenes on NK cells within the complex TME, we can pave the way for developing innovative therapeutic interventions that harness the synergistic capabilities of both innate and adaptive immune responses. By bridging the gap between T cell-centric research and the understudied realm of NK cell biology, we can aspire to achieve more durable and effective outcomes in the fight against cancer.

## Disclosure statement

No potential conflict of interest was reported by the author(s).

## Funding

Work in the laboratory is funded by CIBER -Consorcio Centro de Investigación Biomédica en Red- (CB21/13/00087), Instituto de Salud Carlos III, FEDER (Fondo Europeo de Desarrollo Regional), Gobierno de Aragón (Group B29\_23R), Ministerio de Ciencia, Innovación e Universidades (MICIU); and Agencia Estatal de Investigación (PID2020-113963RB-I00), ASPANOA, and Carrera de la Mujer de Monzón. DSM received funding from “Grant PID2022-136554OA-I00 funded by MICIU/AEI/10.13039/501100011033 and by “ERDF/EU”. Contrato Ramón y Cajal RYC2022-036627-I (AR-L), Predoctoral Grant from Fundación Científica Asociación Española Contra el Cáncer (CP) and Becas de introducción a la investigación JAEICU\_24\_00214 (LA).

## ORCID

Ariel Ramírez-Labrada  <http://orcid.org/0000-0002-3888-7036>

## References

- Orange JS, Ballas ZK. Natural killer cells in human health and disease. *Clin Immunol*. 2006 Jan 1;118(1):1–10. doi:10.1016/j.clim.2005.10.011.
- Vivier E, Tomasello E, Baratin M, Walzer T, Ugolini S. Functions of natural killer cells. *Nat Immunol*. 2008 Apr 18;9(5):503–510. doi:10.1038/ni1582.
- Cao Y, Wang X, Jin T, Tian Y, Dai C, Widarma C, Song R, Xu F. Immune checkpoint molecules in natural killer cells as potential targets for cancer immunotherapy. *Sig Transduct Target Ther*. 2020 Oct 29;5(1):1–19. doi:10.1038/s41392-020-00348-8.
- Lanier LL. Nk cell recognition. *Annu Rev Immunol*. 2004 Nov 11;23(1):225–274. doi:10.1146/annurev.immunol.23.021704.115526.
- Cooper MA, Fehniger TA, Caligiuri MA. The biology of human natural killer-cell subsets. *Trends Immunol*. 2001 Nov 1;22(11):633–640. doi:10.1016/S1471-4906(01)02060-9.
- Cooper MA, Fehniger TA, Turner SC, Chen KS, Ghaehri BA, Ghayur T, Carson WE, Caligiuri MA. Human natural killer cells: a unique innate immunoregulatory role for the CD56bright subset. *Blood*. 2001 May 15;97(10):3146–3151. doi:10.1182/blood.V97.10.3146.
- Ochoa MC, Minute L, Rodriguez I, Garasa S, Perez-Ruiz E, Inogés S, Melero I, Berraondo P. Antibody-dependent cell cytotoxicity: immunotherapy strategies enhancing effector NK cells. *Immunol Cell Biol*. 2017 Apr 1;95(4):347–355. doi:10.1038/icb.2017.6.
- Castro F, Cardoso AP, Gonçalves RM, Serre K, Oliveira MJ. Interferon-gamma at the crossroads of tumor immune surveillance or evasion. *Front Immunol*. 2018 May 4;9(MAY):1. doi:10.3389/fimmu.2018.00847.
- Arase H, Arase N, Saito T. Interferon gamma production by natural killer (NK) cells and NK1.1+ T cells upon NKR-P1 cross-linking. *J Exp Med*. 1996 May 1;183(5):2391–2396. doi:10.1084/jem.183.5.2391.
- Varela N, Muñoz-Pinedo C, Ruiz-Ruiz C, Robledo G, Pedrosa M, López-Rivas A. Interferon- $\gamma$  sensitizes human myeloid leukemia cells to death receptor-mediated apoptosis by a pleiotropic mechanism. *J Biol Chem*. 2001 Jan 25;276(21):17779–17787. doi:10.1074/jbc.M100815200.
- Fulda S, Debatin K-M. IFN $\gamma$  sensitizes for apoptosis by upregulating caspase-8 expression through the Stat1 pathway. *Oncogene*. 2002;21(15):2295–2308. doi:10.1038/sj.onc.1205255.
- Merchant MS, Yang X, Melchionda F, Romero M, Klein R, Thiele CJ, Tsokos M, Kontny HU, Mackall CL. Interferon  $\gamma$  enhances the effectiveness of tumor necrosis Factor-related apoptosis-inducing ligand receptor agonists in a xenograft model of Ewing’s sarcoma. *Cancer Res*. 2004 Nov 15;64(22):8349–8356. doi:10.1158/0008-5472.CAN-04-1705.
- Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discov*. 2022 Jan 1;12(1):31–46. doi:10.1158/2159-8290.CD-21-1059.
- Yum MK, Han S, Fink J, Wu SHS, Dabrowska C, Trendafilova T, Mustata R, Chatzeli L, Azzarelli R, Pshenichnaya I, et al. Tracing oncogene-driven remodelling of the intestinal stem cell niche. *Nature*. 2021 June 2;594(7863):442–447. doi:10.1038/s41586-021-03605-0.
- Petroni G, Buqué A, Coussens LM, Galluzzi L. Targeting oncogene and non-oncogene addiction to inflame the tumour microenvironment. *Nat Rev Drug Discov*. 2022 June 1;21(6):440–462. doi:10.1038/s41573-022-00415-5.
- Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436–444. doi:10.1038/nature07205.
- Coppé JP, Patil CK, Rodier F, Sun Y, Muñoz DP, Goldstein J, Nelson PS, Desprez P-Y, Campisi J. Senescence-associated secretory phenotypes reveal cell-nonautonomous functions of oncogenic RAS and the p53 tumor suppressor. *PLOS Biol*. 2008;6(12):2853–2868. doi:10.1371/journal.pbio.0060301.
- Kortlever RM, Sodir NM, Wilson CH, Burkhart DL, Pellegrinet L, Brown Swigart L, Littlewood TD, Evan GI. Myc cooperates with Ras by programming inflammation and immune suppression. *Cell*. 2017 Nov 11;171(6):1301–1315.e14. doi:10.1016/j.cell.2017.11.013.
- Culley FJ, Johnson M, Evans JH, Kumar S, Crilly R, Casasbuenas J, Schnyder T, Mehrabi M, Deonarain MP, Ushakov DS, et al. Natural killer cell signal integration balances synapse symmetry and migration. *PLOS Biol*. 2009 Jul;7(7):e1000159. doi:10.1371/journal.pbio.1000159.
- Vivier E, Nunès JA, Vély F. Natural killer cell signaling pathways. *Sci*. 2004 Nov 26;306(5701):1517–1519. doi:10.1126/science.1103478.
- Tschopp J, Masson D, Stanley KK. Structural/functional similarity between proteins involved in complement- and cytotoxic T-lymphocyte-mediated cytotoxicity. *Nature*. 1986;322(6082):831–834. doi:10.1038/322831a0.
- Catalfamo M, Henkart PA. Perforin and the granule exocytosis cytotoxicity pathway. *Curr Opin Immunol*. 2003 Oct 1;15(5):522–527. doi:10.1016/S0952-7915(03)00114-6.
- Voskoboinik I, Smyth MJ, Trapani JA. Perforin-mediated target-cell death and immune homeostasis. *Nat Rev Immunol*. 2006 Dec;6(12):940–952. doi:10.1038/nri1983.
- Kaiserman D, Bird CH, Sun J, Matthews A, Ung K, Whistock JC, Thompson PE, Trapani JA, Bird PI. The major human and mouse

- granzymes are structurally and functionally divergent. *J Cell Biol.* 2006 Nov 11;175(4):619–630. doi:10.1083/jcb.200606073.
25. Jenne DE, Tschopp J. Granzymes, a family of serine proteases released from granules of cytolytic T lymphocytes upon T cell receptor stimulation. *Immunol Rev.* 1988 June 1;103(1):53–71. doi:10.1111/j.1600-065X.1988.tb00749.x.
  26. Arias M, Martínez-Lostao L, Santiago L, Ferrandez A, Granville DJ, Pardo J. The untold story of granzymes in oncoimmunology: novel opportunities with old acquaintances. *Trends In Cancer.* 2017 June 1;3(6):407–422. doi:10.1016/j.trecan.2017.04.001.
  27. Jaime-Sanchez P, Uranga-Murillo I, Aguilo N, Khouili SC, Arias MA, Sancho D, Pardo J. Cell death induced by cytotoxic CD8+ T cells is immunogenic and primes caspase-3–dependent spread immunity against endogenous tumor antigens. *J Immunother Cancer.* 2020 Apr 1;8(1):e000528. doi:10.1136/jitc-2020-000528.
  28. Darmon AJ, Nicholson DW, Bleackley RC. Activation of the apoptotic protease CPP32 by cytotoxic T-cell-derived granzyme B. *Nat.* 1995 Oct 5;377(6548):446–448. doi:10.1038/377446a0.
  29. Pardo J, Bosque A, Brehm R, Wallich R, Naval J, Müllbacher A, Anel A, Simon MM. Apoptotic pathways are selectively activated by granzyme a and/or granzyme B in CTL-mediated target cell lysis. *J Cell Biol.* 2004 Nov 8;167(3):457–468. doi:10.1083/jcb.200406115.
  30. Afonina IS, Cullen SP, Martin SJ. Cytotoxic and non-cytotoxic roles of the CTL/NK protease granzyme B. *Immunol Rev.* 2010 May 1;235(1):105–116. doi:10.1111/j.0105-2896.2010.00908.x.
  31. Anthony DA, Andrews DM, Watt SV, Trapani JA, Smyth MJ. Functional dissection of the granzyme family: cell death and inflammation. *Immunol Rev.* 2010 May;235(1):73–92. doi:10.1111/j.0105-2896.2010.00907.x.
  32. Martínez-Lostao L, Anel A, Pardo J. How do cytotoxic lymphocytes kill cancer cells? *Clin Cancer Res.* 2015 Nov 15;21(22):5047–5056. doi:10.1158/1078-0432.CCR-15-0685.
  33. Turner CT, Lim D, Granville DJ. Granzyme B in skin inflammation and disease. *Matrix Biol.* 2019 Jan 1;75-76:126–140. doi:10.1016/j.matbio.2017.12.005.
  34. Wensink AC, Hack CE, Bovenschen N. Granzymes regulate proinflammatory cytokine responses. *J Immunol.* 2015 Jan 15;194(2):491–497. doi:10.4049/jimmunol.1401214.
  35. Santiago L, Castro M, Sanz-Pamplona R, Garzón M, Ramirez-Labrada A, Tapia E, Moreno V, Layunta E, Gil-Gómez G, Garrido M, et al. Extracellular granzyme a promotes colorectal cancer development by enhancing gut inflammation. *Cell Rep.* 2020 Jul 7;32(1):107847. doi:10.1016/j.celrep.2020.107847.
  36. Zhou Z, He H, Wang K, Shi X, Wang Y, Su Y, Wang Y, Li D, Liu W, Zhang Y, et al. Granzyme a from cytotoxic lymphocytes cleaves GSDMB to trigger pyroptosis in target cells. *Science.* 2020 May 29;368(6494):eaaz7548. doi:10.1126/science.aaz7548.
  37. de Miguel D, Ramirez-Labrada A, Uranga I, Hidalgo S, Santiago L, Galvez EM, Arias M, Pardo J. Inflammatory cell death induced by cytotoxic lymphocytes: a dangerous but necessary liaison. *FEBS J.* 2022 Aug 1;289(15):4398–4415. doi:10.1111/febs.16093.
  38. Garzón-Tituaña M, Arias MA, Sierra-Monzón JL, Morte-Romea E, Santiago L, Ramirez-Labrada A, Martínez-Lostao L, Paño-Pardo JR, Galvez EM, Pardo J. The multifaceted function of granzymes in sepsis: some facts and a lot to discover. *Front Immunol.* 2020 June 17;11:1054. doi:10.3389/fimmu.2020.01054.
  39. Zeglinski MR, Granville DJ. Granzymes in cardiovascular injury and disease. *Cell Signal.* 2020 Dec 1;76:109804. doi:10.1016/j.cell sig.2020.109804.
  40. Trapani JA. Granzymes: a family of lymphocyte granule serine proteases. *Genome Biol.* 2001;2(12):reviews3014.1. doi:10.1186/gb-2001-2-12-reviews3014.
  41. Richardson KC, Jung K, Pardo J, Turner CT, Granville DJ. Noncytotoxic roles of granzymes in health and disease. *Physiol (Bethesda).* 2022 Nov 1;37(6):323–348. doi:10.1152/physiol.00011.2022.
  42. Walczak H. Death receptor–ligand systems in cancer, cell death, and inflammation. *Cold Spring Harb Perspect Biol.* 2013;5(5):a008698–a008698. doi:10.1101/cshperspect.a008698.
  43. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity’s roles in cancer suppression and promotion. *Science.* 2011 Mar 25;331(6024):1565–1570. doi:10.1126/science.1203486.
  44. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity.* 2004;21(2):137–148. doi:10.1016/j.immuni.2004.07.017.
  45. Dunn GP, Bruce AT, Ikeda H, Old LJ, Schreiber RD. Cancer immunoediting: from immunosurveillance to tumor escape. *Nat Immunol.* 2002;3(11):991–998. doi:10.1038/ni1102-991.
  46. Orange JS. Natural killer cell deficiency. *J Allergy Clin Immunol.* 2013 Sep;132(3):515–525. doi:10.1016/j.jaci.2013.07.020.
  47. MacFarlane AW, Jilab M, Smith MR, Alpaugh RK, Cole ME, Litwin S, Millenson MM, Al-Saleem T, Cohen AD, Campbell KS, et al. NK cell dysfunction in chronic lymphocytic leukemia is associated with loss of the mature cells expressing inhibitory killer cell Ig-like receptors. *Oncoimmunol.* 2017 Jul 3;6(7):e1330235. doi:10.1080/2162402X.2017.1330235.
  48. Imai K, Matsuyama S, Miyake S, Suga K, Nakachi K. Natural cytotoxic activity of peripheral-blood lymphocytes and cancer incidence: an 11-year follow-up study of a general population. *The Lancet.* 2000 Nov 25;356(9244):1795–1799. doi:10.1016/S0140-6736(00)03231-1.
  49. Vesely MD, Kershaw MH, Schreiber RD, Smyth MJ. Natural innate and adaptive immunity to cancer. *Annu Rev Immunol.* 2011 Apr 23;29(1):235–271. doi:10.1146/annurev-immunol-031210-101324.
  50. Koebel CM, Vermi W, Swann JB, Zerafa N, Rodig SJ, Old LJ, Smyth MJ, Schreiber RD. Adaptive immunity maintains occult cancer in an equilibrium state. *Nature.* 2007 Dec 6;450(7171):903–907. doi:10.1038/nature06309.
  51. Beatty GL, Gladney WL. Immune escape mechanisms as a guide for cancer immunotherapy. *Clin Cancer Res.* 2015 Feb 2;21(4):687. doi:10.1158/1078-0432.CCR-14-1860.
  52. Hazini A, Fisher K, Seymour L. Deregulation of HLA-I in cancer and its central importance for immunotherapy. *J Immunother Cancer.* 2021 Aug 1;9(8):e002899. doi:10.1136/jitc-2021-002899.
  53. Miranda A, Funes JM, Sánchez N, Limia CM, Mesa M, Quezada SA, Pérez R, de León J. Oncogenic transformation can orchestrate immune evasion and inflammation in human mesenchymal stem cells independently of extrinsic immune-selective pressure. *Cancer Res.* 2015 Aug 1;75(15):3032–3042. doi:10.1158/0008-5472.CAN-14-3276.
  54. Fangazio M, Ladewig E, Gomez K, Garcia-Ibanez L, Kumar R, Teruya-Feldstein J, Rossi D, Filip I, Pan-Hammarström Q, Inghirami G, et al. Genetic mechanisms of HLA-I loss and immune escape in diffuse large B cell lymphoma. *Proc Natl Acad Sci U S A.* 2021 June 1;118(22):e2104504118. doi:10.1073/pnas.2104504118.
  55. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin.* 2021 Jan;71(1):7–33. doi:10.3322/caac.21654.
  56. Zhu M, Huang Y, Bender ME, Girard L, Kollipara R, Eglenen-Polat B, Naito Y, Savage TK, Huffman KE, Koyama S, et al. Evasion of innate immunity contributes to small cell lung cancer progression and metastasis. *Cancer Res.* 2021 Apr 1;81(7):1813–1826. doi:10.1158/0008-5472.CAN-20-2808.
  57. Bald T, Wagner M, Gao Y, Koyasu S, Smyth MJ. Hide and seek: plasticity of innate lymphoid cells in cancer. *Semin Immunol.* 2019 Feb 1;41:101273. doi:10.1016/j.simm.2019.04.001.
  58. Dean I, Lee CYC, Tuong ZK, Li Z, Tibbitt CA, Willis C, Gaspal F, Kennedy BC, Matei-Rascu V, Fiancette R, et al. Rapid functional impairment of natural killer cells following tumor entry limits anti-tumor immunity. *Nat Commun.* 2024 Dec 1;15(1):683. doi:10.1038/s41467-024-44789-z.
  59. Yang L, Zhang Y. Tumor-associated macrophages: from basic research to clinical application. *J Hematol Oncol.* 2017 Feb 28;10(1):58. doi:10.1186/s13045-017-0430-2.
  60. Von Ahrens D, Bhagat TD, Nagrath D, Maitra A, Verma A. The role of stromal cancer-associated fibroblasts in pancreatic cancer. *J Hematol Oncol.* 2017 Mar 28;10(1):76. doi:10.1186/s13045-017-0448-5.

61. Hinshaw DC, Shevde LA. The tumor microenvironment innately modulates cancer progression. *Cancer Res.* 2019 Sep 9;79(18):4557–4566. doi:10.1158/0008-5472.CAN-18-3962.
62. Bunting MD, Vyas M, Requesens M, Langenbucher A, Schiferle EB, Manguso RT, Lawrence MS, Demehri S. Extracellular matrix proteins regulate NK cell function in peripheral tissues. *Sci Adv.* 2022 Mar 1;8(11):3327. doi:10.1126/sciadv.abk3327.
63. Keppel MP, Topcagic N, Mah AY, Vogel TP, Cooper MA. Activation-specific metabolic requirements for NK cell IFN- $\gamma$  production. *J Immunol.* 2015 Feb 2;194(4):1954–1962. doi:10.4049/jimmunol.1402099.
64. Marçais A, Cherfils-Vicini J, Viant C, Degouve S, Viel S, Fenis A, Rabilloud J, Mayol K, Tavares A, Bienvenu J, et al. The metabolic checkpoint kinase mTOR is essential for IL-15 signaling during the development and activation of NK cells. *Nat Immunol.* 2014 Jun 29;15(8):749–757. doi:10.1038/ni.2936.
65. Donnelly RP, Loftus RM, Keating SE, Liou KT, Biron CA, Gardiner CM, Finlay DK. mTORC1-dependent metabolic reprogramming is a prerequisite for NK cell effector function. *J Immunol.* 2014 Nov 11;193(9):4477–4484. doi:10.4049/jimmunol.1401558.
66. Keibler MA, Wasylenko TM, Kelleher JK, Iliopoulos O, Vander Heiden MG, Stephanopoulos G. Metabolic requirements for cancer cell proliferation. *Cancer Metab.* 2016 Aug 18;4(1):1–16. doi:10.1186/s40170-016-0156-6.
67. Cong J, Wang X, Zheng X, Wang D, Fu B, Sun R, Tian Z, Wei H. Dysfunction of natural killer cells by FBP1-induced inhibition of glycolysis during lung cancer progression. *Cell Metab.* 2018 Aug 7;28(2):243–255.e5. doi:10.1016/j.cmet.2018.06.021.
68. Assmann N, O'Brien KL, Donnelly RP, Dyck L, Zaiatz-Bittencourt V, Loftus RM, Heinrich P, Oefner PJ, Lynch L, Gardiner CM, et al. Srebp-controlled glucose metabolism is essential for NK cell functional responses. *Nat Immunol.* 2017 Sep 18;18(11):1197–1206. doi:10.1038/ni.3838.
69. Ni J, Wang X, Stojanovic A, Zhang Q, Wincher M, Bühler L, Arnold A, Correia MP, Winkler M, Koch P-S, et al. Single-cell RNA sequencing of tumor-infiltrating NK cells reveals that inhibition of transcription factor HIF-1 $\alpha$  unleashes NK cell activity. *Immunity.* 2020 Jun 16;52(6):1075–1087.e8. doi:10.1016/j.immuni.2020.05.001.
70. Oberlies J, Watzl C, Giese T, Luckner C, Kropf P, Müller I, Ho AD, Munder M. Regulation of NK cell function by human granulocyte arginase. *J Immunol.* 2009 May 1;182(9):5259–5267. doi:10.4049/jimmunol.0803523.
71. Lamas B, Vergnaud-Gauduchon J, Goncalves-Mendes N, Perche O, Rossary A, Vasson MP, Farges M-C. Altered functions of natural killer cells in response to L-Arginine availability. *Cell Immunol.* 2012 Dec 1;280(2):182–190. doi:10.1016/j.cellimm.2012.11.018.
72. Schütz S, Solé-Boldo L, Lucena-Porcel C, Hoffmann J, Brobeil A, Lonsdorf AS, Rodríguez-Paredes M, Lyko F. Functionally distinct cancer-associated fibroblast subpopulations establish a tumor promoting environment in squamous cell carcinoma. *Nat Commun.* 2023;14(1):5413. doi:10.1038/s41467-023-41141-9.
73. Shaul ME, Fridlender ZG. Tumour-associated neutrophils in patients with cancer. *Nat Rev Clin Oncol.* 2019 Jun 3;16(10):601–620. doi:10.1038/s41571-019-0222-4.
74. Quail DF, Joyce JA. Microenvironmental regulation of tumor progression and metastasis. *Nat Med.* 2013 Nov 7;19(11):1423–1437. doi:10.1038/nm.3394.
75. Wang D, Yang L, Yue D, Cao L, Li L, Wang D, Ping Y, Shen Z, Zheng Y, Wang L, et al. Macrophage-derived CCL22 promotes an immunosuppressive tumor microenvironment via IL-8 in malignant pleural effusion. *Cancer Lett.* 2019 Jun 28;452:244–253. doi:10.1016/j.canlet.2019.03.040.
76. Liu C, Yu S, Kappes J, Wang J, Grizzle WE, Zinn KR, Zhang H-G. Expansion of spleen myeloid suppressor cells represses NK cell cytotoxicity in tumor-bearing host. *Blood.* 2007 May 5;109(10):4336–4342. doi:10.1182/blood-2006-09-046201.
77. Heier I, Hofgaard PO, Brandtzæg P, Jahnsen FL, Karlsson M. Depletion of CD4+ CD25+ regulatory T cells inhibits local tumour growth in a mouse model of B cell lymphoma. *Clin Exp Immunol.* 2008 May;152(2):381–387. doi:10.1111/j.1365-2249.2008.03642.x.
78. Kos K, Aslam MA, van de Ven R, Wellenstein MD, Pieters W, van Weverwijk A, Duits DEM, van Pul K, Hau C-S, Vrijland K, et al. Tumor-educated Tregs drive organ-specific metastasis in breast cancer by impairing NK cells in the lymph node niche. *Cell Rep.* 2022 Mar 1;38(9):110447. doi:10.1016/j.celrep.2022.110447.
79. Lainé A, Labiad O, Hernandez-Vargas H, This S, Sanlaville A, Léon S, Dalle S, Sheppard D, Travis MA, Paidassi H, et al. Regulatory T cells promote cancer immune-escape through integrin  $\alpha\beta$ -mediated TGF- $\beta$  activation. *Nat Commun.* 2021 Dec 1;12(1):6228. doi:10.1038/s41467-021-26352-2.
80. Manfroi B, Moreaux J, Righini C, Ghiringhelli F, Sturm N, Huard B. Tumor-associated neutrophils correlate with poor prognosis in diffuse large B-cell lymphoma patients. *Blood Cancer J.* 2018;8(7):66. doi:10.1038/s41408-018-0099-y.
81. Cheng Y, Li H, Deng Y, Tai Y, Zeng K, Zhang Y, Liu W, Zhang Q, Yang Y. Cancer-associated fibroblasts induce PDL1+ neutrophils through the IL6-STAT3 pathway that foster immune suppression in hepatocellular carcinoma. *Cell Death Dis.* 2018 Jan 1;9(4):422. doi:10.1038/s41419-018-0458-4.
82. Hegde S, Leader AM, Merad M. MDSC: markers, development, states, and unaddressed complexity. *Immunity.* 2021 May 5;54(5):875–884. doi:10.1016/j.immuni.2021.04.004.
83. Rodriguez PC, Quiceno DG, Zabaleta J, Ortiz B, Zea AH, Piazuelo MB, Delgado A, Correa P, Brayer J, Sotomayor EM, et al. Arginase I production in the tumor microenvironment by mature myeloid cells inhibits T-Cell receptor expression and antigen-specific T-Cell responses. *Cancer Res.* 2004;64(16):5839–5849. doi:10.1158/0008-5472.CAN-04-0465.
84. Srivastava MK, Sinha P, Clements VK, Rodriguez P, Ostrand-Rosenberg S. Myeloid-derived suppressor cells inhibit T cell activation by depleting cystine and cysteine. *Cancer Res.* 2010 Jan 1;70(1):68. doi:10.1158/0008-5472.CAN-09-2587.
85. Li H, Han Y, Guo Q, Zhang M, Cao X. Cancer-expanded myeloid-derived suppressor cells induce anergy of NK cells through membrane-bound TGF- $\beta$ 1. *J Immunol.* 2009 Jan 1;182(1):240–249. doi:10.4049/jimmunol.182.1.240.
86. Li T, Yang Y, Hua X, Wang G, Liu W, Jia C, Tai Y, Zhang Q, Chen G. Hepatocellular carcinoma-associated fibroblasts trigger NK cell dysfunction via PGE2 and IDO. *Cancer Lett.* 2012 May 28;318(2):154–161. doi:10.1016/j.canlet.2011.12.020.
87. Zhang R, Qi F, Zhao F, Li G, Shao S, Zhang X, Yuan L, Feng Y. Cancer-associated fibroblasts enhance tumor-associated macrophages enrichment and suppress NK cells function in colorectal cancer. *Cell Death Dis.* 2019 Mar 20;10(4):1–14. doi:10.1038/s41419-019-1435-2.
88. Lisanti MP, Martinez-Outschoorn UE, Sotgia F. Oncogenes induce the cancer-associated fibroblast phenotype: metabolic symbiosis and “fibroblast addiction” are new therapeutic targets for drug discovery. *Cell Cycle.* 2013 Sep 1;12(17):2723–2732. doi:10.4161/cc.25695.
89. Viel S, Marçais A, Guimaraes FSF, Loftus R, Rabilloud J, Grau M, Degouve S, Djebali S, Sanlaville A, Charrier E, et al. TGF- $\beta$  inhibits the activation and functions of NK cells by repressing the mTOR pathway. *Sci Signal.* 2016 Feb 16;9(415):ra19. doi:10.1126/scisignal.aad1884.
90. Bazhin A, Ganjalikhani Hakemi M, John Ralph S, Health G, Yasinska IM, Fasler-Kan E, Gonçalves Silva I, Mosimann M, Varani L, Bardelli M, et al. The Tim-3-Galectin-9 pathway and its regulatory mechanisms in human breast cancer. *Front Immunol.* 2019;10:1594. doi:10.3389/fimmu.2019.01594.
91. Sauer N, Janicka N, Szlasa W, Bartomiej S, Kołodzińska K, Dwernicka W, Oślizło M, Kulbacka J, Novickij V, Karłowicz-Bodalska K. TIM-3 as a promising target for cancer



- immunotherapy in a wide range of tumors. *Cancer Immunol Immunother.* 2023;72(11):3405–3425. doi:10.1007/s00262-023-03516-1.
92. Uyttenhove C, Pilotte L, Théate I, Stroobant V, Colau D, Parmentier N, Boon T, Van den Eynde BJ. Evidence for a tumoral immune resistance mechanism based on tryptophan degradation by indoleamine 2,3-dioxygenase. *Nat Med.* 2003 Oct;9(10):1269–1274. doi:10.1038/nm934.
  93. Santana Carrero RM, Beceren-Braun F, Rivas SC, Hegde SM, Gangadharan A, Plote D, Pham G, Anthony SM, Schluns KS. IL-15 is a component of the inflammatory milieu in the tumor microenvironment promoting antitumor responses. *Proc Natl Acad Sci U S A.* 2019 Jan 8;116(2):599–608. doi:10.1073/pnas.1814642116.
  94. Moreno-Nieves UY, Tay JK, Saumya S, Horowitz NB, Shin JH, Mohammad IA, Luca B, Mundy DC, Gulati GS, Bedi N, et al. Landscape of innate lymphoid cells in human head and neck cancer reveals divergent NK cell states in the tumor microenvironment. *Proc Natl Acad Sci USA.* 2021;118(28):e2101169118. doi:10.1073/pnas.2101169118.
  95. Garg AD, Agostinis P. Cell death and immunity in cancer: from danger signals to mimicry of pathogen defense responses. *Immunol Rev.* 2017 Nov 1;280(1):126–148. doi:10.1111/imr.12574.
  96. Maurer S, Kropp KN, Klein G, Steinle A, Haen SP, Walz JS, Hinterleitner C, Märklin M, Kopp H-G, Salih HR, et al. Platelet-mediated shedding of NKG2D ligands impairs NK cell immunosurveillance of tumor cells. *Oncoimmunol.* 2018 Feb 1;7(2):e1364827. doi:10.1080/2162402X.2017.1364827.
  97. Reiners KS, Topolar D, Henke A, Simhadri VR, Kessler J, Sauer M, Bessler M, Hansen HP, Tawadros S, Herling M, et al. Soluble ligands for NK cell receptors promote evasion of chronic lymphocytic leukemia cells from NK cell anti-tumor activity. *Blood.* 2013 May 2;121(18):3658–3665. doi:10.1182/blood-2013-01-476606.
  98. Bruno A, Focaccetti C, Pagani A, Imperatori AS, Spagnoletti M, Rotolo N, Cantelmo AR, Franzì F, Capella C, Ferlazzo G, et al. The proangiogenic phenotype of natural killer cells in patients with non-small cell lung cancer. *Neoplasia.* 2013 Feb 1;15(2):133–IN7. doi:10.1593/neo.121758.
  99. Chitadze G, Lettau M, Luecke S, Wang T, Janssen O, Fürst D, Mytilineos J, Wesch D, Oberg H-H, Held-Feindt J, et al. NKG2D- and T-cell receptor-dependent lysis of malignant glioma cell lines by human  $\gamma\delta$  T cells: modulation by temozolomide and a disintegrin and metalloproteases 10 and 17 inhibitors. *Oncoimmunol.* 2015 Dec 10;5(4):e1093276–e1093276. doi:10.1080/2162402X.2015.1093276.
  100. Cao W, Xi X, Hao Z, Li W, Kong Y, Cui L, Ma C, Ba D, He W. RAET1E2, a soluble isoform of the UL16-binding protein RAET1E produced by tumor cells, inhibits NKG2D-mediated NK cytotoxicity. *J Biol Chem.* 2007 June 29;282(26):18922–18928. doi:10.1074/jbc.M702504200.
  101. López-Soto A, Gonzalez S, Smyth MJ, Galluzzi L. Control of metastasis by NK cells. *Cancer Cell.* 2017 Aug 14;32(2):135–154. doi:10.1016/j.ccell.2017.06.009.
  102. Messaoudene M, Fregni G, Fourmentraux-Neves E, Chanal J, Maubec E, Mazouz-Dorval S, Couturaud B, Girod A, Sastre-Garau X, Albert S, et al. Mature cytotoxic CD56bright/CD16+ natural killer cells can infiltrate lymph nodes adjacent to metastatic melanoma. *Cancer Res.* 2014 Jan 1;74(1):81–92. doi:10.1158/0008-5472.CAN-13-1303.
  103. Horowitz A, Djaoud Z, Nemat-Gorgani N, Blokhuis J, Hilton HG, Béziat V, Malmberg K-J, Norman PJ, Guethlein LA, Parham P, et al. Class I HLA haplotypes form two schools that educate NK cells in different ways. *Sci Immunol.* 2016;1(3):eaag1672. doi:10.1126/sciimmunol.aag1672.
  104. Jonsson AH, Yang L, Kim S, Taffner SM, Yokoyama WM. Effects of MHC class I alleles on licensing of Ly49A+ NK cells. *J Immunol.* 2010 Apr 1;184(7):3424–3432. doi:10.4049/jimmunol.0904057.
  105. Hölzemer A, Thobakgale CF, Jimenez Cruz CA, Garcia-Beltran WF, Carlson JM, van Teijlingen NH, Mann JK, Jaggernath M, Kang S-G, Körner C, et al. Selection of an HLA-C\*03:04-restricted HIV-1 p24 gag sequence variant is associated with viral escape from KIR2DL3+ natural killer cells: data from an observational cohort in South Africa. *PLOS Med.* 2015 Nov 1;12(11):e1001900. doi:10.1371/journal.pmed.1001900.
  106. Braud V, Jones EY, McMichael A. The human major histocompatibility complex class II molecule HLA-E binds signal sequence-derived peptides with primary anchor residues at positions 2 and 9. *Eur J Immunol.* 1997;27(5):1164–1169. doi:10.1002/eji.1830270517.
  107. Borst L, van der Burg SH, van Hall T. The NKG2A-HLA-E axis as a novel checkpoint in the tumor microenvironment. *Clin Cancer Res.* 2021 Nov 1;26(21):5549–5556. doi:10.1158/1078-0432.CCR-19-2095.
  108. Li P, Wang N, Zhang Y, Wang C, Du L. HLA-G/sHLA-G and HLA-G-Bearing extracellular vesicles in cancers: potential role as biomarkers. *Front Immunol.* 2021 Nov 11;12:791535. doi:10.3389/fimmu.2021.791535.
  109. Lin A, Zhang X, Xu HH, Xu DP, Ruan YY, Yan WH. HLA-G expression is associated with metastasis and poor survival in the Balb/c nu/nu murine tumor model with ovarian cancer. *Int J Cancer.* 2012 Jul 1;131(1):150–157. doi:10.1002/ijc.26375.
  110. Pesini C, Hidalgo S, Arias MA, Santiago L, Calvo C, Ocariz-Díez M, Isla D, Lanuza PM, Agustín MJ, Galvez EM, et al. PD-1 is expressed in cytotoxic granules of NK cells and rapidly mobilized to the cell membrane following recognition of tumor cells. *Oncoimmunol.* 2022 Dec 31;11(1):2096359. doi:10.1080/2162402X.2022.2096359.
  111. Concha-Benavente F, Kansy B, Moskovitz J, Moy J, Chandran U, Ferris RL. PD-L1 mediates dysfunction in activated PD-1+ NK cells in head and neck cancer patients. *Cancer Immunol Res.* 2018 Dec 1;6(12):1548–1560. doi:10.1158/2326-6066.CIR-18-0062.
  112. Alvarez M, Simonetta F, Baker J, Morrison AR, Wenokur AS, Pierini A, Berraondo P, Negrin RS. Indirect impact of PD-1/PD-L1 blockade on a murine model of NK cell exhaustion. *Front Immunol.* 2020 Feb 11;11(7). doi:10.3389/fimmu.2020.00007.
  113. Benson DM, Bakan CE, Mishra A, Hofmeister CC, Efebera Y, Becknell B, Baiocchi RA, Zhang J, Yu J, Smith MK, et al. The PD-1/PD-L1 axis modulates the natural killer cell versus multiple myeloma effect: a therapeutic target for CT-011, a novel monoclonal anti-PD-1 antibody. *Blood.* 2010 Sep 9;116(13):2286–2294. doi:10.1182/blood-2010-02-271874.
  114. Judge SJ, Dunai C, Aguilar EG, Vick SC, Sturgill IR, Khuat LT, Stoffel KM, Van Dyke J, Longo DL, Darrow MA, et al. Minimal PD-1 expression in mouse and human NK cells under diverse conditions. *J Clin Invest.* 2020 June 1;130(6):3051–3068. doi:10.1172/JCI133353.
  115. Hsu J, Hodgins JJ, Marathe M, Nicolai CJ, Bourgeois-Daigneault MC, Trevino TN, Azimi CS, Scheer AK, Randolph HE, Thompson TW, et al. Contribution of NK cells to immunotherapy mediated by PD-1/PD-L1 blockade. *J Clin Invest.* 2018 Sep 9;128(10):4654–4668. doi:10.1172/JCI99317.
  116. Yin L, Wan Z, Sun P, Shuai P, Liu Y. Time to abandon CAR-T monotherapy for solid tumors. *Biochim Biophys Acta Rev Cancer.* 2023 Jul 1;1878(4):188930. doi:10.1016/j.bbcan.2023.188930.
  117. Habif G, Crinier A, André P, Vivier E, Narni-Mancinelli E. Targeting natural killer cells in solid tumors. *Cell Mol Immunol.* 2019 Mar 25;16(5):415–422. doi:10.1038/s41423-019-0224-2.
  118. Chiusa M, Hu W, Zienkiewicz J, Chen X, Zhang MZ, Harris RC, Dunworth M, Zhang H, Jaffee EM, Bader JS, et al. Cancer cells educate natural killer cells to a metastasis-promoting cell state. *J Cell Biol.* 2020 Sep 9;219(9):e202001134. doi:10.1083/jcb.202001134.
  119. Chan IS, Ewald AJ. The changing role of natural killer cells in cancer metastasis. *J Clin Invest.* 2022 Mar 3;132(6):e143762. doi:10.1172/JCI143762.
  120. Scully C. Oncogenes, onco-suppressors, carcinogenesis and oral cancer. *Br Dent J.* 1992 Jul 25;173(2):53–59. doi:10.1038/sj.bdj.4807936.
  121. Mohammad RM, Muqbil I, Lowe L, Yedjou C, Hsu HY, Lin LT, Siegelin MD, Fimognari C, Kumar NB, Dou QP, et al. Broad

- targeting of resistance to apoptosis in cancer. *Semin Cancer Biol.* 2015 Dec 1;35(8):S78–103. doi:10.1016/j.semcancer.2015.03.001.
122. Zahavi DJ, Weiner LM. Tumor mechanisms of resistance to immune attack. *Prog Mol Biol Transl Sci.* 2019 Jan 1;164:61–100.
  123. Greaves M, Maley CC. Clonal evolution in cancer. *Nat.* 2012 Jan 18;481(7381):306–313. doi:10.1038/nature10762.
  124. Dominguez-Sola D, Ying CY, Grandori C, Ruggiero L, Chen B, Li M, Galloway DA, Gu W, Gautier J, Dalla-Favera R. Non-transcriptional control of DNA replication by c-Myc. *Nat.* 2007 June 27;448(7152):445–451. doi:10.1038/nature05953.
  125. Packham G, Cleveland JL. Ornithine decarboxylase is a mediator of c-Myc-induced apoptosis. *Mol Cell Biol.* 1994 Sep;14(9):5741–5747. doi:10.1128/MCB.14.9.5741.
  126. Pusch O, Bernaschek G, Eilers M, Hengstschläger M. Activation of c-myc uncouples DNA replication from activation of G1-cyclin-dependent kinases. *Oncogene.* 1997;15(6):649–656. doi:10.1038/sj.onc.1201236.
  127. Brägelmann J, Böhm S, Guthrie MR, Mollaoglu G, Oliver TG, Sos ML. Family matters: how MYC family oncogenes impact small cell lung cancer. *Cell Cycle.* 2017 Aug 18;16(16):1489–1498. doi:10.1080/15384101.2017.1339849.
  128. Borzi C, Calzolari L, Ferretti AM, Caleca L, Pastorino U, Sozzi G, Fortunato O. c-Myc shuttled by tumour-derived extracellular vesicles promotes lung bronchial cell proliferation through miR-19b and miR-92a. *Cell Death Dis.* 2019 Oct 7;10(10):1–16. doi:10.1038/s41419-019-2003-5.
  129. O'Donnell KA, Wentzel EA, Zeller KI, Dang CV, Mendell JT. c-Myc-regulated microRNAs modulate E2F1 expression. *Nat.* 2005 June 9;435(7043):839–843. doi:10.1038/nature03677.
  130. Chang TC, Yu D, Lee YS, Wentzel EA, Arking DE, West KM, Dang CV, Thomas-Tikhonenko A, Mendell JT. Widespread microRNA repression by myc contributes to tumorigenesis. *Nat Genet.* 2008 Jan;40(1):43–50. doi:10.1038/ng.2007.30.
  131. Eischen CM, Woo D, Roussel MF, Cleveland JL. Apoptosis triggered by Myc-induced suppression of Bcl-XL or Bcl-2 is bypassed during lymphomagenesis. *Mol Cell Biol.* 2001 Aug 1;21(15):5063–5070. doi:10.1128/MCB.21.15.5063-5070.2001.
  132. Sowani A, Ong G, Dische S, Quinn C, White J, Soutter P, Waxman J, Sikora K. c-Myc oncogene expression and clinical outcome in carcinoma of the cervix. *Mol Cell Probes.* 1989 June 1;3(2):117–123. doi:10.1016/0890-8508(89)90022-4.
  133. Kim SS, Meitner P, Konkin TA, Cho YS, Resnick MB, Moss SF. Altered expression of Skp2, c-myc and p27 proteins but not mRNA after H. pylori eradication in chronic gastritis. *Mod Pathol.* 2006 Aug 5;19(1):49–58. doi:10.1038/modpathol.3800476.
  134. Chanvorachote P, Sriratanasak N, Nonpanya N. c-Myc contributes to malignancy of lung cancer: a potential anticancer drug target. *Anticancer Res.* 2020;40(2):609–618. doi:10.21873/anticancer.13990.
  135. Dammert MA, Brägelmann J, Olsen RR, Böhm S, Monhasery N, Whitney CP, Chalishazar MD, Tumbriink HL, Guthrie MR, Klein S, et al. MYC paralog-dependent apoptotic priming orchestrates a spectrum of vulnerabilities in small cell lung cancer. *Nat Commun.* 2019 Aug 2;10(1):1–11. doi:10.1038/s41467-019-11371-x.
  136. Kim YH, Girard L, Giacomini CP, Wang P, Hernandez-Boussard T, Tibshirani R, Minna JD, Pollack JR. Combined microarray analysis of small cell lung cancer reveals altered apoptotic balance and distinct expression signatures of MYC family gene amplification. *Oncogene.* 2006 Jan 5;25(1):130–138. doi:10.1038/sj.onc.1208997.
  137. Sánchez-Martínez D, Azaceta G, Muntasell A, Aguiló N, Núñez D, Gálvez EM, Naval J, Anel A, Palomera L, Vilches C, et al. Human NK cells activated by EBV+ lymphoblastoid cells overcome anti-apoptotic mechanisms of drug resistance in haematological cancer cells. *Oncoimmunol.* 2015;4(3):1–13. doi:10.4161/2162402X.2014.991613.
  138. Pan R, Ryan J, Pan D, Wucherpfennig KW, Letai A. Augmenting NK cell-based immunotherapy by targeting mitochondrial apoptosis. *Cell.* 2022 Apr 4;185(9):1521–1538.e18. doi:10.1016/j.cell.2022.03.030.
  139. Seong D, Jeong M, Seo J, Lee JY, Hwang CH, Shin HC, Shin JY, Nam YW, Jo JY, Lee H, et al. Identification of MYC as an anti-necroptotic protein that stifles RIPK1–RIPK3 complex formation. *Proc Natl Acad Sci USA.* 2020 Aug 1;117(33):19982–19993. doi:10.1073/pnas.2000979117.
  140. Oliynyk G, Ruiz-Pérez MV, Sainero-Alcolado L, Dzieran J, Zirath H, Gallart-Ayala H, Wheelock CE, Johansson HJ, Nilsson R, Lehtiö J, et al. MYCN-enhanced oxidative and glycolytic metabolism reveals vulnerabilities for targeting neuroblastoma. *iScience.* 2019 Nov 22;21:188–204. doi:10.1016/j.isci.2019.10.020.
  141. Tao L, Mohammad MA, Milazzo G, Moreno-Smith M, Patel TD, Zorman B, Badachhapa A, Hernandez BE, Wolf AB, Zeng Z, et al. MYCN-driven fatty acid uptake is a metabolic vulnerability in neuroblastoma. *Nat Commun.* 2022 June 28;13(1):1–17. doi:10.1038/s41467-022-31331-2.
  142. Harmon C, Robinson MW, Hand F, Almuaili D, Mentor K, Houlihan DD, Hoti E, Lynch L, Geoghegan J, O'Farrelly C. Lactate-mediated acidification of tumor microenvironment induces apoptosis of liver-resident NK cells in colorectal liver metastasis. *Cancer Immunol Res.* 2019 Feb 1;7(2):335–346. doi:10.1158/2326-6066.CIR-18-0481.
  143. Fyan G, Tong LX, Xu K, Tian WR, Guan XX. c-MYC mediates the crosstalk between breast cancer cells and tumor microenvironment. *Cell Commun Signal.* 2023 Jan 31;21(1):1–8. doi:10.1186/s12964-023-01043-1.
  144. Mezquita P, Parghi SS, Brandvold KA, Ruddell A. Myc regulates VEGF production in B cells by stimulating initiation of VEGF mRNA translation. *Oncogene.* 2004 Dec 6;24(5):889–901. doi:10.1038/sj.onc.1208251.
  145. Yan W, Wu X, Zhou W, Fong MY, Cao M, Liu J, Liu X, Chen C-H, Fadare O, Pizzo DP, et al. Cancer-cell-secreted exosomal miR-105 promotes tumour growth through the MYC-dependent metabolic reprogramming of stromal cells. *Nat Cell Biol.* 2018 May 1;20(5):597–609. doi:10.1038/s41556-018-0083-6.
  146. Castriconi R, Cantoni C, Della Chiesa M, Vitale M, Marcenaro E, Conte R, Biassoni R, Bottino C, Moretta L, Moretta A. Transforming growth factor  $\beta$ 1 inhibits expression of NKP30 and NKG2d receptors: consequences for the NK-mediated killing of dendritic cells. *Proc Natl Acad Sci M.* 2003 Apr 1;100(7):4120–4125. doi:10.1073/pnas.0730640100.
  147. Park A, Lee Y, Kim MS, Kang YJ, Park YJ, Jung H, Kim T-D, Lee HG, Choi I, Yoon SR. Prostaglandin E2 secreted by thyroid cancer cells contributes to immune escape through the suppression of natural killer (NK) cell cytotoxicity and NK cell differentiation. *Front Immunol.* 2018 Aug 9;9(AUG):363999. doi:10.3389/fimmu.2018.01859.
  148. Zaiatz-Bittencourt V, Finlay DK, Gardiner CM. Canonical TGF- $\beta$  signaling pathway represses human NK cell metabolism. *J Immunol.* 2018 June 15;200(12):3934–3941. doi:10.4049/jimmunol.1701461.
  149. Mao X, Xu J, Wang W, Liang C, Hua J, Liu J, Zhang B, Meng Q, Yu X, Shi S, et al. Crosstalk between cancer-associated fibroblasts and immune cells in the tumor microenvironment: new findings and future perspectives. *Mol Cancer.* 2021 Dec 1;20(1):131. doi:10.1186/s12943-021-01428-1.
  150. Kim DK, Jeong J, Lee DS, Hyeon DY, Park GW, Jeon S, Lee KB, Jang J-Y, Hwang D, Kim HM, et al. PD-L1-directed PIGF/VEGF blockade synergizes with chemotherapy by targeting CD141+ cancer-associated fibroblasts in pancreatic cancer. *Nat Commun.* 2022 Oct 22;13(1):1–19. doi:10.1038/s41467-022-33991-6.
  151. Yang Y, Ye YC, Chen Y, Zhao JL, Gao CC, Han H, Liu W-C, Qin H-Y. Crosstalk between hepatic tumor cells and macrophages via Wnt/ $\beta$ -catenin signaling promotes M2-like macrophage polarization and reinforces tumor malignant behaviors. *Cell Death Dis.* 2018 Jul 18;9(8):1–14. doi:10.1038/s41419-018-0818-0.
  152. Langowski JL, Kastelein RA, Oft M. Swords into plowshares: IL-23 repurposes tumor immune surveillance. *Trends Immunol.* 2007 May 1;28(5):207–212. doi:10.1016/j.it.2007.03.006.

153. Teng MWL, Andrews DM, McLaughlin N, Von Scheidt B, Ngiow SF, Möller A, Hill GR, Iwakura Y, Oft M, Smyth MJ. IL-23 suppresses innate immune response independently of IL-17A during carcinogenesis and metastasis. *Proc Natl Acad Sci U S A*. 2010 May 4;107(18):8328–8333. doi:10.1073/pnas.1003251107.
154. Lee Y, Heo W, Son C, Kang C, Park Y, Bae J. Upregulation of myc promotes the evasion of NK cell-mediated immunity through suppression of NKG2D ligands in K562 cells. *Mol Med Rep*. 2019;3301–3307. doi:10.3892/mmr.2019.10583.
155. Swaminathan S, Hansen AS, Heftdal LD, Dhanasekaran R, Deutzmann A, Fernandez WDM, Liefwalker DF, Horton C, Mosley A, Liebersbach M, et al. MYC functions as a switch for natural killer cell-mediated immune surveillance of lymphoid malignancies. *Nat Commun*. 2020 June 5;11(1):1–17. doi:10.1038/s41467-020-16447-7.
156. Montoya M, Schiavoni G, Mattei F, Gresser I, Belardelli F, Borrow P, Tough DF. Type I interferons produced by dendritic cells promote their phenotypic and functional activation. *Blood*. 2002 May 1;99(9):3263–3271. doi:10.1182/blood.V99.9.3263.
157. Morvan MG, Lanier LL. NK cells and cancer: you can teach innate cells new tricks. *Nat Rev Cancer*. 2015 Dec 23;16(1):7–19. doi:10.1038/nrc.2015.5.
158. Versteeg R, Noordermeer IA, Krüse-Wolters M, Ruiter DJ, Schrier PI. cMyc down-regulates class I HLA expression in human melanomas. *Embo J*. 1988;7(4):1023–1029. doi:10.1002/j.1460-2075.1988.tb02909.x.
159. Bernards R, Dessain SK, Weinberg RA. N-myc amplification causes down-modulation of MHC class I antigen expression in neuroblastoma. *Cell*. 1986 Dec 5;47(5):667–674. doi:10.1016/0092-8674(86)90509-X.
160. Layer JP, Kronmüller MT, Quast T, Van Den Boorn-Konijnberg D, Effern M, Hinze D, Althoff K, Schramm A, Westermann F, Peifer M, et al. Amplification of N-Myc is associated with a T-cell-poor microenvironment in metastatic neuroblastoma restraining interferon pathway activity and chemokine expression. *Oncogene*. 2017;36(6):e1320626. doi:10.1080/2162402X.2017.1320626.
161. Fukuda Y, Asaoka T, Eguchi H, Yokota Y, Kubo M, Kinoshita M, Urakawa S, Iwagami Y, Tomimaru Y, Akita H, et al. Endogenous CXCL9 affects prognosis by regulating tumor-infiltrating natural killer cells in intrahepatic cholangiocarcinoma. *Cancer Sci*. 2020 Feb 1;111(2):323–333. doi:10.1111/cas.14267.
162. Ghe R, Qing LY, Tian L, Zhang T, Mei YD, Hua YJ, Deng YC. Natural killer cell homing and trafficking in tissues and tumors: from biology to application. *Sig Transduct Target Ther*. 2022 June 29;7(1):1–21. doi:10.1038/s41392-022-01058-z.
163. Saravia J, Zeng H, Dhungana Y, Blanco DB, Nguyen TLM, Chapman NM, Wang Y, Kanneganti A, Liu S, Raynor JL, et al. Homeostasis and transitional activation of regulatory T cells require c-Myc. *Sci Adv*. 2020 Jan 1;6(1). doi:10.1126/sciadv.aaw6443.
164. Ma J, Hu W, Liu Y, Duan C, Zhang D, Wang Y, Cheng K, Yang L, Wu S, Jin B, et al. CD226 maintains regulatory T cell phenotype stability and metabolism by the mTOR/Myc pathway under inflammatory conditions. *Cell Rep*. 2023 Oct 31;42(10):113306. doi:10.1016/j.celrep.2023.113306.
165. Yang C, Liu Y, Hu Y, Fang L, Huang Z, Cui H, Xie J, Hong Y, Chen W, Xiao N, et al. Myc inhibition tips the immune balance to promote antitumor immunity. *Cell Mol Immunol*. 2022 Aug 12;19(9):1030–1041. doi:10.1038/s41423-022-00898-7.
166. Sealover NE, Kortum RL. Heterogeneity in RAS mutations: one size does not fit all. *Sci Signal*. 2022 Aug 8;15(746):eadc9816. doi:10.1126/scisignal.adc9816.
167. Prior IA, Lewis PD, Mattos C. A comprehensive survey of Ras mutations in cancer. *Cancer Res*. 2012 May 5;72(10):2457–2467. doi:10.1158/0008-5472.CAN-11-2612.
168. Gasser S, Orsulic S, Brown EJ, Raulat DH. The DNA damage pathway regulates innate immune system ligands of the NKG2D receptor. *Nature*. 2005 Jul 3;436(7054):1186–1190. doi:10.1038/nature03884.
169. Garon EB, Rizvi NA, Hui R, Leighl N, Balmanoukian AS, Eder JP, Patnaik A, Aggarwal C, Gubens M, Horn L, et al. Pembrolizumab for the treatment of non–Small-Cell lung cancer. *N Engl J Med*. 2015 May 21;372(21):2018–2028. doi:10.1056/NEJMoa1501824.
170. Coelho MA, de Carné Trécesson S, Rana S, Zecchin D, Moore C, Molina-Arcas M, East P, Spencer-Dene B, Nye E, Barnouin K, et al. Oncogenic RAS signaling promotes tumor immunoresistance by stabilizing PD-L1 mRNA. *Immunity*. 2017 Dec 12;47(6):1083–1099.e6. doi:10.1016/j.immuni.2017.11.016.
171. Lanuza PM, Alonso MH, Hidalgo S, Uranga-Murillo I, García-Mulero S, Arnau R, Santos C, Sanjuan X, Santiago L, Comas L, et al. Adoptive NK cell transfer as a treatment in colorectal cancer patients: analyses of tumour cell determinants correlating with efficacy in vitro and in vivo. *Front Immunol*. 2022 June 7;13:890836. doi:10.3389/fimmu.2022.890836.
172. Nakadate Y, Kodera Y, Kitamura Y, Shirasawa S, Tachibana T, Tamura T, Koizumi F. KRAS mutation confers resistance to antibody-dependent cellular cytotoxicity of cetuximab against human colorectal cancer cells. *Intl J Cancer*. 2014 May 1;134(9):2146–2155. doi:10.1002/ijc.28550.
173. Fenton RG, Hixon JA, Wrigh P, Brooks A, Sayers T. Inhibition of fas (CD95) expression and fas-mediated apoptosis by oncogenic ras. *Cancer Res*. 1998;58(15):3391–3400.
174. Medema JP, De Jong J, Peltenburg LTC, Verdegaal EME, Gorter A, Bres SA, Franken KLMC, Hahne M, Albar JP, Melief CJM, et al. Blockade of the granzyme B/perforin pathway through overexpression of the serine protease inhibitor PI-9/SPI-6 constitutes a mechanism for immune escape by tumors. *Proc Natl Acad Sci USA*. 2001 Sep 9;98(20):11515–11520. doi:10.1073/pnas.201398198.
175. Prager I, Liesche C, Van Ooijen H, Urlaub D, Verron Q, Sandström N, Fasbender F, Claus M, Eils R, Beaudouin J, et al. NK cells switch from granzyme B to death receptor-mediated cytotoxicity during serial killing. *J Exp Med*. 2019 Sep 9;216(9):2113–2127. doi:10.1084/jem.20181454.
176. Dai E, Han L, Liu J, Xie Y, Kroemer G, Klionsky DJ, Zeh HJ, Kang R, Wang J, Tang D, et al. Autophagy-dependent ferroptosis drives tumor-associated macrophage polarization via release and uptake of oncogenic KRAS protein. *Autophagy*. 2020 Nov 1;16(11):2069–2083. doi:10.1080/15548627.2020.1714209.
177. Wing JB, Tanaka A, Sakaguchi S. Human FOXP3+ regulatory T cell heterogeneity and function in autoimmunity and cancer. *Immunity*. 2019 Feb 19;50(2):302–316. doi:10.1016/j.immuni.2019.01.020.
178. Hayes ET, Hagan CE, Khoryati L, Gavin MA, Campbell DJ. Regulatory T cells maintain selective access to IL-2 and immune homeostasis despite substantially reduced CD25 function. *J Immunol*. 2020 Nov 11;205(10):2667–2678. doi:10.4049/jimmunol.1901520.
179. Sunaga N, Imai H, Shimizu K, Shames DS, Kakegawa S, Girard L, Sato M, Kaira K, Ishizuka T, Gazdar AF, et al. Oncogenic KRAS-induced interleukin-8 overexpression promotes cell growth and migration and contributes to aggressive phenotypes of non-small cell lung cancer. *Intl J Cancer*. 2012 Apr 15;130(8):1733–1744. doi:10.1002/ijc.26164.
180. Alfaro C, Teixeira A, Oñate C, Perez G, Sanmamed MF, Andueza MP, Alignani D, Labiano S, Azpilikueta A, Rodriguez-Paulete A, et al. Tumor-produced interleukin-8 attracts human myeloid-derived suppressor cells and elicits extrusion of neutrophil extracellular traps (NETs). *Clin Cancer Res*. 2016 Aug 1;22(15):3924–3936. doi:10.1158/1078-0432.CCR-15-2463.
181. de Andrea CE, Ochoa MC, Villalba-Esparza M, Teixeira Á, Schalper KA, Abengozar-Muela M, Eguren-Santamaría I, Sainz C, Sánchez-Gregorio S, Garasa S, et al. Heterogenous presence of neutrophil extracellular traps in human solid tumours is partially dependent on IL-8. *J Pathol*. 2021 Oct 1;255(2):190–201. doi:10.1002/path.5753.
182. Teixeira A, Garasa S, Ochoa MC, Villalba M, Olivera I, Cirella A, Eguren-Santamaría I, Berraondo P, Schalper KA, de Andrea CE, et al. IL8, neutrophils, and NETs in a collusion against cancer

- immunity and immunotherapy. *Clin Cancer Res.* 2021;27(9):2383–2393. doi:10.1158/1078-0432.CCR-20-1319.
183. Teijeira Á, Garasa S, Gato M, Alfaro C, Migueliz I, Cirella A, de Andrea C, Ochoa MC, Otano I, Etxebarria I, et al. CXCR1 and CXCR2 chemokine receptor agonists produced by tumors induce neutrophil extracellular traps that interfere with immune cytotoxicity. *Immunity.* 2020 May 19;52(5):856–871.e8. doi:10.1016/j.immuni.2020.03.001.
  184. Spiegel A, Brooks MW, Houshyar S, Reinhardt F, Ardolino M, Fessler E, Chen MB, Krall JA, DeCock J, Zervantonakis IK, et al. Neutrophils suppress intraluminal NK cell-mediated tumor cell clearance and enhance extravasation of disseminated carcinoma cells. *Cancer Discov.* 2016 Dec 1;6(6):630–649. doi:10.1158/2159-8290.CD-15-1157.
  185. Domvri K, Petanidis S, Zarogoulidis P, Anastakis D, Tsavlis D, Bai C, Huang H, Freitag L, Hohenforst-Schmidt W, Porpodis K, et al. Treg-dependent immunosuppression triggers effector T cell dysfunction via the STING/ILC2 axis. *Clin Immunol.* 2021 Jan 1;222:108620. doi:10.1016/j.clim.2020.108620.
  186. Liao W, Overman MJ, Boutin AT, Shang X, Zhao D, Dey P, Li J, Wang G, Lan Z, Li J, et al. KRAS-IRF2 axis drives immune suppression and immune therapy resistance in colorectal cancer. *Cancer Cell.* 2019 Apr 4;35(4):559–572.e7. doi:10.1016/j.ccell.2019.02.008.
  187. Petanidis S, Anastakis D, Argyraki M, Hadzopoulou-Cladaras M, Salifoglou A, Guan X-Y. Differential expression of IL-17, 22 and 23 in the progression of colorectal cancer in patients with K-ras mutation: ras signal inhibition and crosstalk with GM-CSF and IFN- $\gamma$ . *PLoS One.* 2013;8(9):e73616. doi:10.1371/journal.pone.0073616.
  188. Yuan B, Clowers MJ, Velasco WV, Peng S, Peng Q, Shi Y, Ramos-Castaneda M, Zarghooni M, Yang S, Babcock RL, et al. Targeting IL-1 $\beta$  as an immunopreventive and therapeutic modality for K-ras-mutant lung cancer. *JCI Insight.* 2022 June 6;7(11):e157788. doi:10.1172/jci.insight.157788.
  189. Kang J, Pervaiz S. Crosstalk between Bcl-2 family and Ras family small GTPases: potential cell fate regulation? *Front Oncol.* 2013 Jan 2;2(206):40650. doi:10.3389/fonc.2012.00206.
  190. Brea EJ, Oh CY, Manchado E, Budhu S, Gejman RS, Mo G, Mondello P, Han JE, Jarvis CA, Ulmert D, et al. Kinase regulation of human MHC Class I molecule expression on cancer cells. *Cancer Immunol Res.* 2016 Nov 1;4(11):936–947. doi:10.1158/2326-6066.CIR-16-0177.
  191. Lohmann S, Wollscheid U, Huber C, Seliger B. Multiple levels of MHC class I down-regulation by ras oncogenes. *Scand J Immunol.* 1996 May 1;43(5):537–544. doi:10.1046/j.1365-3083.1996.d01-73.x.
  192. Yang SX, Polley E, Lipkowitz S. New insights on PI3K/AKT pathway alterations and clinical outcomes in breast cancer. *Cancer Treat Rev.* 2016 Apr 1;45:87–96. doi:10.1016/j.ctrv.2016.03.004.
  193. Whitman M, Downes CP, Keeler M, Keller T, Cantley L. Type I phosphatidylinositol kinase makes a novel inositol phospholipid, phosphatidylinositol-3-phosphate. *Nat.* 1988;332(6165):644–646. doi:10.1038/332644a0.
  194. Stambolic V, Suzuki A, De la Pompa JL, Brothers GM, Mirtsos C, Sasaki T, Ruland J, Penninger JM, Siderovski DP, Mak TW, et al. Negative regulation of PKB/Akt-dependent cell survival by the tumor suppressor PTEN. *Cell.* 1998 Oct 2;95(1):29–39. doi:10.1016/S0092-8674(00)81780-8.
  195. Yao R, Cooper GM. Requirement for phosphatidylinositol-3 kinase in the prevention of apoptosis by nerve growth factor. *Science.* 1995;267(5206):2003–2006. doi:10.1126/science.7701324.
  196. Valius M, Kazlauskas A. Phospholipase C- $\gamma$ 1 and phosphatidylinositol 3 kinase are the downstream mediators of the PDGF receptor's mitogenic signal. *Cell.* 1993 Apr 23;73(2):321–334. doi:10.1016/0092-8674(93)90232-F.
  197. Gold MR, Duronio V, Saxenal SP, Schrader JW, Aebersoldll R. Multiple cytokines activate phosphatidylinositol 3-kinase in hemopoietic cells. Association of the enzyme with various tyrosine-phosphorylated proteins. *J Biol Chem.* 1994;269(7):5403–5412. doi:10.1016/S0021-9258(17)37701-3.
  198. Zell T, Hunt SW, Mobley JL, Finkelstein LD, Shimizu Y. CD28-mediated up-regulation of beta 1-integrin adhesion involves phosphatidylinositol 3-kinase. *J Immunol.* 1996;156(3):883–886. doi:10.4049/jimmunol.156.3.883.
  199. Ma AD, Metjian A, Bagrodia S, Taylor S, Abrams CS. Cytoskeletal reorganization by G protein-coupled receptors is dependent on phosphoinositide 3-kinase  $\gamma$ , a rac guanine exchange factor, and rac. *Mol Cell Biol.* 1998 Aug 1;18(8):4744–4751. doi:10.1128/MCB.18.8.4744.
  200. Jiang K, Zhong B, Gilvary DL, Corliss BC, Hong-Geller E, Wei S, Djeu JY. Pivotal role of phosphoinositide-3 kinase in regulation of cytotoxicity in natural killer cells. *Nat Immunol.* 2000;1(5):419–425. doi:10.1038/80859.
  201. Gringhuis SI, de Leij LFMH, Coffey PJ, Vellenga E. Signaling through CD5 activates a pathway involving phosphatidylinositol 3-kinase, Vav, and Rac1 in human mature T lymphocytes. *Mol Cell Biol.* 1998 Mar 1;18(3):1725–1735. doi:10.1128/MCB.18.3.1725.
  202. Janku F, Yap TA, Meric-Bernstam F. Targeting the PI3K pathway in cancer: are we making headway? *Nat Rev Clin Oncol.* 2018 Mar 6;15(5):273–291. doi:10.1038/nrclinonc.2018.28.
  203. Sobral-Leite M, Salomon I, Opdam M, Kruger DT, Beelen KJ, Van Der Noort V, van Vlierberghe RLP, Blok EJ, Giardiello D, Sanders J, et al. Cancer-immune interactions in ER-positive breast cancers: PI3K pathway alterations and tumor-infiltrating lymphocytes. *Breast Cancer Res.* 2019 Aug 7;21(1):1–12. doi:10.1186/s13058-019-1176-2.
  204. Collins NB, Al Abosy R, Miller BC, Bi K, Zhao Q, Quigley M, Ishizuka JJ, Yates KB, Pope HW, Manguso RT, et al. PI3K activation allows immune evasion by promoting an inhibitory myeloid tumor microenvironment. *J Immunother Cancer.* 2022 Mar 1;10(3):e003402. doi:10.1136/jitc-2021-003402.
  205. Chen X, Thakkar H, Tyan F, Gim S, Robinson H, Lee C, Pandey SK, Nwokorie C, Onwudiwe N, Srivastava RK. Constitutively active akt is an important regulator of TRAIL sensitivity in prostate cancer. *Oncogene.* 2001 Oct 9;20(42):6073–6083. doi:10.1038/sj.onc.1204736.
  206. Chandrasekaran S, Sasaki M, Scharer CD, Kissick HT, Patterson DG, Magliocca KR, Seykora JT, Sapkota B, Gutman DA, Cooper LA, et al. Phosphoinositide 3-kinase signaling can modulate MHC class I and II expression. *Mol Cancer Res.* 2019;17(12):2395–2409. doi:10.1158/1541-7786.MCR-19-0545.
  207. Mimura K, Shiraishi K, Mueller A, Izawa S, Kua L-F, So J, Yong W-P, Fujii H, Seliger B, Kiessling R, et al. The MAPK pathway is a predominant regulator of HLA-A expression in esophageal and gastric cancer. *J Immunol Author Choice.* 2013 Dec 12;191(12):6261–6272. doi:10.4049/jimmunol.1301597.
  208. Barrientos G, Toro A, Moschansky P, Cohen M, Garcia MG, Rose M, Maskin B, Sánchez-Margalet V, Blois SM, Varone CL, et al. Leptin promotes HLA-G expression on placental trophoblasts via the MEK/Erk and PI3K signaling pathways. *Placenta.* 2015 Apr 1;36(4):419–426. doi:10.1016/j.placenta.2015.01.006.
  209. Holtan SG, Creedon DJ, Haluska P, Markovic SN. Cancer and pregnancy: parallels in growth, invasion, and immune modulation and implications for cancer therapeutic agents. *Mayo Clin Proc.* 2009 Nov;84(11):985–1000. doi:10.1016/S0025-6196(11)60669-1.
  210. Okita R, Mougiakakos D, Ando T, Mao Y, Sarhan D, Wennerberg E, Seliger B, Lundqvist A, Mimura K, Kiessling R. HER2/HER3 signaling regulates NK cell-mediated cytotoxicity via MHC class I chain-related molecule a and B expression in human breast cancer cell lines. *J Immunol.* 2012 Mar 1;188(5):2136–2145. doi:10.4049/jimmunol.1102237.
  211. Xia C, He Z, Cai Y, Liang S. Vorinostat upregulates MICA via the PI3K/Akt pathway to enhance the ability of natural killer cells to kill tumor cells. *Eur J Pharmacol.* 2020 May 15;875:173057. doi:10.1016/j.ejphar.2020.173057.
  212. Li Z, Zhang J, You S, Zhang J, Zhang Y, Akram Z, Sun S. Pterostilbene upregulates MICA/B via the PI3K/AKT signaling pathway to enhance the capability of natural killer cells to kill

- cervical cancer cells. *Exp Cell Res.* 2024 Feb 15;435(2):113933. doi:10.1016/j.yexcr.2024.113933.
213. Boissel N, Rea D, Tieng V, Dulphy N, Brun M, Cayuela J-M, Rousselot P, Tamouza R, Le Bouteiller P, Mahon F-X, et al. BCR/ABL oncogene directly controls MHC class I chain-related molecule a expression in chronic myelogenous leukemia. *J Immunol.* 2006 Apr 15;176(8):5108–5116. doi:10.4049/jimmunol.176.8.5108.
  214. Raulet DH, Gasser S, Gowen BG, Deng W, Jung H. Regulation of ligands for the NKG2D activating receptor. *Annu Rev Immunol.* 2013 Mar;31(1):413–441. doi:10.1146/annurev-immunol-032712-095951.
  215. Okita R, Wolf D, Yasuda K, Maeda A, Yukawa T, Saisho S, Shimizu K, Yamaguchi Y, Oka M, Nakayama E, et al. Contrasting effects of the cytotoxic anticancer drug gemcitabine and the EGFR tyrosine kinase inhibitor gefitinib on NK cell-mediated cytotoxicity via regulation of NKG2D ligand in non-small-cell lung cancer cells. *PLOS One.* 2015 Oct 6;10(10):e0139809. doi:10.1371/journal.pone.0139809.
  216. Kim H, Kim SH, Kim MJ, Kim SJ, Park SJ, Chung JS, Bae J-H, Kang C-D. EGFR inhibitors enhanced the susceptibility to NK cell-mediated lysis of lung cancer cells. *J Immunother.* 2011 May;34(4):372–381. doi:10.1097/CJI.0b013e31821b724a.
  217. Brandstadter JD, Chen H, Jiang S, Huang X, Yang Y. IL-18-dependent NKG2D ligand upregulation on accessory cells is mediated by the PI3K/GSK-3 pathway. *J Leukoc Biol.* 2017 June 1;101(6):1317–1323. doi:10.1189/jlb.2A0816-342R.
  218. Edwards ESJ, Bier J, Cole TS, Wong M, Hsu P, Berglund LJ, Boztug K, Lau A, Gostick E, Price DA, et al. Activating PIK3CD mutations impair human cytotoxic lymphocyte differentiation and function and EBV immunity. *J Allergy Clin Immunol.* 2019 Jan 1;143(1):276–291.e6. doi:10.1016/j.jaci.2018.04.030.
  219. Neradugomma NK, Subramanian D, Tawfik OW, Goffin V, Kumar TR, Jensen RA, Anant S. Prolactin signaling enhances colon cancer stemness by modulating notch signaling in a Jak2-STAT3/ERK manner. *Carcinogenesis.* 2014;35(4):795–806. doi:10.1093/carcin/bgt379.
  220. Sen M, Pollock NI, Black J, DeGrave KA, Wheeler S, Freilino ML, Joyce S, Lui VWY, Zeng Y, Chiosea SI, et al. JAK kinase inhibition abrogates STAT3 activation and head and neck squamous cell carcinoma tumor growth. *Neoplasia.* 2015 Mar 1;17(3):256–264. doi:10.1016/j.neo.2015.01.003.
  221. Chen L, Zhou D, Liu Z, Huang X, Liu Q, Kang Y, Chen Z, Guo Y, Zhu H, Sun C, et al. Combination of gemcitabine and erlotinib inhibits recurrent pancreatic cancer growth in mice via the JAK-STAT pathway. *Oncol Rep.* 2018 Mar 1;35(3):1081–1089. doi:10.3892/or.2018.6198.
  222. Bagratuni T, Mavrianou N, Gavalas NG, Tzannis K, Arapinis C, Lontos M, Christodoulou MI, Thomakos N, Haidopoulos D, Rodolakis A, et al. JQ1 inhibits tumour growth in combination with cisplatin and suppresses JAK/STAT signalling pathway in ovarian cancer. *Eur J Cancer.* 2020 Feb 1;126:125–135. doi:10.1016/j.ejca.2019.11.017.
  223. Witalisz-Siepracka A, Klein K, Zdársky B, Stoiber D. The multifaceted role of STAT3 in NK-Cell tumor surveillance. *Front Immunol.* 2022 Jul 5;13:947568. doi:10.3389/fimmu.2022.947568.
  224. Kortylewski M, Yu H. Stat3 as a potential target for cancer immunotherapy. *J Immunother.* 2007 Feb;30(2):131–139. doi:10.1097/01.cji.0000211327.76266.65.
  225. Bedel R, Thierry-Vuillemin A, Grandclement C, Balland J, Remy-Martin JP, Kantelip B, Pallandre J-R, Pivot X, Ferrand C, Tiberghien P, et al. Novel role for STAT3 in transcriptional regulation of NK immune cell targeting receptor MICA on cancer cells. *Cancer Res.* 2011 Mar 1;71(5):1615–1626. doi:10.1158/0008-5472.CAN-09-4540.
  226. Fionda C, Malgarini G, Soriani A, Zingoni A, Cecere F, Iannitto ML, Ricciardi MR, Federico V, Petrucci MT, Santoni A, et al. Inhibition of glycogen synthase kinase-3 increases NKG2D ligand MICA expression and sensitivity to NK cell-mediated cytotoxicity in multiple myeloma cells: role of STAT3. *J Immunol.* 2013 June 15;190(12):6662–6672. doi:10.4049/jimmunol.1201426.
  227. Cai X, Lu X, Jia Z, Zhang X, Han W, Rong X, Ma L, Zhou M, Chen B. STAT3 contributes to NK cell recognition by modulating expression of NKG2D ligands in adriamycin-resistant K562/AO2 cells. *Int J Hematol.* 2015 Sep 19;102(5):536–543. doi:10.1007/s12185-015-1860-7.
  228. Garrido-Tapia M, Hernández CJ, Ascuri G, Kramm K, Morales M, Gárate V, Zúñiga R, Bustamante M, Aguillón JC, Catalán D, et al. STAT3 inhibition by STA21 increases cell surface expression of MICB and the release of soluble MICB by gastric adenocarcinoma cells. *Immunobiol.* 2017 Nov 1;222(11):1043–1051. doi:10.1016/j.imbio.2017.05.009.
  229. Kortylewski M, Yu H. Role of Stat3 in suppressing anti-tumor immunity. *Curr Opin Immunol.* 2008 Apr 1;20(2):228–233. doi:10.1016/j.coi.2008.03.010.
  230. Nieborowska-Skorska M, Wasik MA, Slupianek A, Salomoni P, Kitamura T, Calabretta B, Skorski T. Signal transducer and activator of transcription (STAT)5 activation by BCR/ABL is dependent on intact Src homology (SH)3 and SH2 domains of BCR/ABL and is required for leukemogenesis. *J Exp Med.* 1999 Apr 4;189(8):1229–1242. doi:10.1084/jem.189.8.1229.
  231. Funakoshi-Tago M, Tago K, Abe M, Sonoda Y, Kasahara T. STAT5 activation is critical for the transformation mediated by myeloproliferative disorder-associated JAK2 V617F mutant. *J Biol Chem.* 2010 Feb 2;285(8):5296–5307. doi:10.1074/jbc.M109.040733.
  232. Barash I. Stat5 in breast cancer: potential oncogenic activity coincides with positive prognosis for the disease. *Carcinogenesis.* 2012 Dec 1;33(12):2320–2325. doi:10.1093/carcin/bgs362.
  233. Halim CE, Deng S, Ong MS, Yap CT. Involvement of STAT5 in oncogenesis. *Biomedicines.* 2020 Sep 1;8(9):316. doi:10.3390/biomedicines8090316.
  234. Igelmann S, Neubauer HA, Ferbeyre G. STAT3 and STAT5 activation in solid cancers. *Cancers (Basel).* 2019 Oct 1;11(10):1428. doi:10.3390/cancers11101428.
  235. Burkhart DL, Sage J. Cellular mechanisms of tumour suppression by the retinoblastoma gene. *Nat Rev Cancer.* 2008 Sep;8(9):671–682. doi:10.1038/nrc2399.
  236. Knudsen ES, Knudsen KE. Tailoring to RB: tumour suppressor status and therapeutic response. *Nat Rev Cancer.* 2008;8(9):714–724. doi:10.1038/nrc2401.
  237. Kitajima S, Yoshida A, Kohno S, Li F, Suzuki S, Nagatani N, Nishimoto Y, Sasaki N, Muranaka H, Wan Y, et al. The RB-IL-6 axis controls self-renewal and endocrine therapy resistance by fine-tuning mitochondrial activity. *Oncogene.* 2017 May 8;36(36):5145–5157. doi:10.1038/ncr.2017.124.
  238. Kitajima S, Li F, Takahashi C. Tumor milieu controlled by RB tumor suppressor. *Int J Mol Sci.* 2020 Apr 1;21(7):2450. doi:10.3390/ijms21072450.
  239. Wu J, Gao FX, Wang C, Qin M, Han F, Xu T, Hu Z, Long Y, He X-M, Deng X, et al. IL-6 and IL-8 secreted by tumour cells impair the function of NK cells via the STAT3 pathway in oesophageal squamous cell carcinoma. *J Exp Clin Cancer Res.* 2019 Jul 19;38(1):1–15. doi:10.1186/s13046-019-1310-0.
  240. Li F, Kitajima S, Kohno S, Yoshida A, Tange S, Sasaki S, Okada N, Nishimoto Y, Muranaka H, Nagatani N, et al. Retinoblastoma inactivation induces a protumoral microenvironment via enhanced CCL2 secretion. *Cancer Res.* 2019 Aug 1;79(15):3903–3915. doi:10.1158/0008-5472.CAN-18-3604.
  241. Orozco-Morales M, Sánchez-García FJ, Golán-Cancela I, Hernández-Pedro N, Costoya JA, de la Cruz VP, Moreno-Jiménez S, Sotelo J, Pineda B. RB mutation and RAS overexpression induce resistance to NK cell-mediated cytotoxicity in glioma cells. *Cancer Cell Int.* 2015 June 5;15(1):1–11. doi:10.1186/s12935-015-0209-x.
  242. Bondar T, Medzhitov R. p53-mediated hematopoietic stem and progenitor cell competition. *Cell STEM Cell.* 2010 Apr 4;6(4):309–322. doi:10.1016/j.stem.2010.03.002.
  243. Cicalese A, Bonizzi G, Pasi CE, Faretta M, Ronzoni S, Giulini B, Brisken C, Minucci S, Di Fiore PP, Pelicci PG, et al. The tumor

- suppressor p53 regulates polarity of self-renewing divisions in mammary stem cells. *Cell*. 2009 Sep 18;138(6):1083–1095. doi:10.1016/j.cell.2009.06.048.
244. Zvezdaryk K, Sullivan D, Saifudeen Z. The p53/adipose-tissue/cancer nexus. *Front Endocrinol (Lausanne)*. 2018 Aug 14;9:457. doi:10.3389/fendo.2018.00457.
  245. Zhang C, Liu J, Xu D, Zhang T, Hu W, Feng Z, Lu H. Gain-of-function mutant p53 in cancer progression and therapy. *J Mol Cell Biol*. 2020 Sep 1;12(9):674–687. doi:10.1093/jmcb/mjaa040.
  246. Muller PAJ, Vousden KH. p53 mutations in cancer. *Nat Cell Biol*. 2013 Jan;15(1):2–8. doi:10.1038/ncb2641.
  247. Yue X, Zhao Y, Xu Y, Zheng M, Feng Z, Hu W. Mutant p53 in cancer: accumulation, gain-of-function and therapy. *J Mol Biol*. 2017 June 6;429(11):1595–1606. doi:10.1016/j.jmb.2017.03.030.
  248. Wang J, Li Q, Yin Y, Zhang Y, Cao Y, Lin X, Huang L, Hoffmann D, Lu M, Qiu Y. Excessive neutrophils and neutrophil extracellular traps in COVID-19. *Front Immunol*. 2020 Aug 18;11:2063. doi:10.3389/fimmu.2020.02063.
  249. Kogan-Sakin I, Tabach Y, Buganim Y, Molchadsky A, Solomon H, Madar S, Kamer I, Stambolsky P, Shelly A, Goldfinger N, et al. Mutant p53R175H upregulates Twist1 expression and promotes epithelial–mesenchymal transition in immortalized prostate cells. *Cell Death Differ*. 2010 Aug 6;18(2):271–281. doi:10.1038/cdd.2010.94.
  250. Wang B, Niu D, Lai L, Ren EC. p53 increases MHC class I expression by upregulating the endoplasmic reticulum aminopeptidase ERAP1. *Nat Commun*. 2013;4(1):2359. doi:10.1038/ncomms3359.
  251. Liu S, Liu T, Jiang J, Guo H, Yang R. p53 mutation and deletion contribute to tumor immune evasion. *Front Genet*. 2023;14:1088455. doi:10.3389/fgene.2023.1088455.
  252. Dong ZY, Zhong WZ, Zhang XC, Su J, Xie Z, Liu SY, Tu H-Y, Chen H-J, Sun Y-L, Zhou Q, et al. Potential predictive value of TP53 and KRAS mutation status for response to PD-1 blockade immunotherapy in lung adenocarcinoma. *Clin Cancer Res*. 2017 June 15;23(12):3012–3024. doi:10.1158/1078-0432.CCR-16-2554.
  253. Textor S, Fiegler N, Arnold A, Porgador A, Hofmann TG, Cerwenka A. Human NK cells are alerted to induction of p53 in cancer cells by upregulation of the NKG2D ligands ULBP1 and ULBP2. *Cancer Res*. 2011 Sep 15;71(18):5998–6009. doi:10.1158/0008-5472.CAN-10-3211.
  254. Uddin MB, Roy KR, Hill RA, Roy SC, Gu X, Li L, Zhang Q-J, You Z, Liu Y-Y. p53 missense mutant G242A subverts natural killer cells in sheltering mouse breast cancer cells against immune rejection. *Exp Cell Res*. 2022 Aug 1;417(1):113210. doi:10.1016/j.yexcr.2022.113210.
  255. Cordani M, Oppici E, Dando I, Butturini E, Dalla Pozza E, Nadal-Serrano M, Oliver J, Roca P, Mariotto S, Cellini B, et al. Mutant p53 proteins counteract autophagic mechanism sensitizing cancer cells to mTOR inhibition. *Mol Oncol*. 2016 Aug 1;10(7):1008–1029. doi:10.1016/j.molonc.2016.04.001.
  256. Meslin F, Thiery J, Richon C, Jalil A, Chouaib S. Granzyme B-induced cell death involves induction of p53 tumor suppressor gene and its activation in tumor target cells. *J Biol Chem*. 2007 Nov 9;282(45):32991–32999. doi:10.1074/jbc.M705290200.
  257. Chollat-Namy M, Ben Safta-Saadoun T, Haferssas D, Meurice G, Chouaib S, Thiery J. The pharmacological reactivation of p53 function improves breast tumor cell lysis by granzyme B and NK cells through induction of autophagy. *Cell Death Dis*. 2019 Oct 1;10(10):695. doi:10.1038/s41419-019-1950-1.
  258. Belkahlia S, Brualla JM, Fayd'herbe de Maudave A, Falvo P, Allende-Vega N, Constantinides M, Khan AUH, Coenon L, Alexia C, Mitola G, et al. The metabolism of cells regulates their sensitivity to NK cells depending on p53 status. *Sci Rep*. 2022 Dec 1;12(1):3234. doi:10.1038/s41598-022-07281-6.
  259. Liu XV, Ho SSW, Tan JJ, Kamran N, Gasser S. Ras activation induces expression of Raet1 family NK receptor ligands. *J Immunol*. 2012;189(4):1826–1834. doi:10.4049/jimmunol.1200965.
  260. Ruscetti M, Leibold J, Bott MJ, Fennell M, Kulick A, Salgado NR, Chen C-C, Ho Y-J, Sanchez-Rivera FJ, Feucht J, et al. NK cell-mediated cytotoxicity contributes to tumor control by a cytostatic drug combination. *Science*. 2018 Dec 12;362(6421):1416–1422. doi:10.1126/science.aas9090.
  261. Sagiv A, Biran A, Yon M, Simon J, Lowe SW, Krizhanovsky V. Granule exocytosis mediates immune surveillance of senescent cells. *Oncogene*. 2012 Jul 2;32(15):1971–1977. doi:10.1038/onc.2012.206.
  262. Dhar P, Basher F, Ji Z, Huang L, Qin S, Wainwright DA, Robinson J, Hagler S, Zhou J, MacKay S, et al. Tumor-derived NKG2D ligand sMIC reprograms NK cells to an inflammatory phenotype through CBM signalosome activation. *Commun Biol*. 2021;4(1):905. doi:10.1038/s42003-021-02440-3.
  263. Ihara S, Kida H, Arase H, Tripathi LP, Chen YA, Kimura T, Yoshida M, Kashiwa Y, Hirata H, Fukamizu R, et al. Inhibitory roles of signal transducer and activator of transcription 3 in anti-tumor immunity during carcinogen-induced lung tumorigenesis. *Cancer Res*. 2012 June 15;72(12):2990–2999. doi:10.1158/0008-5472.CAN-11-4062.
  264. Gotthardt D, Sexl V. STATs in NK-Cells: the good, the bad, and the ugly. *Front Immunol*. 2017 Jan 18;7:694. doi:10.3389/fimmu.2016.00694.
  265. Bronger H, Singer J, Windmüller C, Reuning U, Zech D, Delbridge C, Dorn J, Kiechle M, Schmalfeldt B, Schmitt M, et al. CXCL9 and CXCL10 predict survival and are regulated by cyclooxygenase inhibition in advanced serous ovarian cancer. *Br J Cancer*. 2016;115(5):553–563. doi:10.1038/bjc.2016.172.
  266. Hartsough EJ, Weiss MB, Heilman SA, Purwin TJ, Kugel CH, Rosenbaum SR, Erkes DA, Tiago M, HooKim K, Chervoneva I, et al. CADM1 is a TWIST1-regulated suppressor of invasion and survival. *Cell Death Dis*. 2019 Mar 25;10(4):1–15. doi:10.1038/s41419-019-1515-3.
  267. Chockley PJ, Chen J, Chen G, Beer DG, Standiford TJ, Keshamouni VG. Epithelial-mesenchymal transition leads to NK cell-mediated metastasis-specific immunosurveillance in lung cancer. *J Clin Invest*. 2018 Apr 2;128(4):1384–1396. doi:10.1172/JCI97611.
  268. Whiteside TL. NK cells in the tumor microenvironment and thioredoxin activity. *J Clin Invest*. 2020 Oct 1;130(10):5115–5117. doi:10.1172/JCI141460.
  269. Yang Y, Neo SY, Chen Z, Cui W, Chen Y, Guo M, Wang Y, Xu H, Kurzay A, Alici E, et al. Thioredoxin activity confers resistance against oxidative stress in tumor-infiltrating NK cells. *J Clin Invest*. 2020 Sep 9;130(10):5508–5522. doi:10.1172/JCI137585.