Comment

Towards cancer mechanotherapy

Comment on "Mechanotransduction in tumor dynamics modeling" by B. Blanco, H.Gomez, J.Melchor, R. Palma, J. Soler, G. Rus

M. Doblare[a,b,c*], J. Ayensa-Jiménez[a,b], M. Perez-Aliacar[a]

a Aragón Institute of Engineering Research (I3A), University of Zaragoza, R&D Building, Block 5, 1st Floor, Mariano Esquillor s/n, 50018 Zaragoza

b Aragón Institute on Health Research (IIS Aragón), CIBA Building - Avda. San Juan Bosco, 13 50009 Zaragoza (Spain)

c Centro de Investigación en Red en Bioingeniería, Biomateriales y Nanomedicina (CIBER-BBN), Av. Monforte de Lemos, 3-5. Pabellón 11. Planta 0, 28029 Madrid (Spain)

Despite the huge investment made in research during the last decades, cancer remains as the leading cause of death in developed countries and the second in developing ones, with 10.0 million deaths worldwide in 2020 and 19.3 million new diagnoses. Moreover, cancer incidence is estimated to increase around 47% from 2020 to 2040 [1]. The main reason is that cancer is much more complex than initially thought. The old paradigm focused only on cells, genes, and internal molecular pathways has now been enlarged, considering the decisive influence of tumor microenvironment (TME). This multi-interactive and dynamic concept includes, among other, cell interactions at different organization levels, metabolism, chemical (oxygen, nutrients, …) and physical (mechanical, electrical, or magnetic, …) spatially dependent stimuli, that are produced and/or transmitted by cells and/or the extracellular matrix (ECM). Furthermore, tumor cells evolve differently within the same tumor, following different evolutionary paths, also influenced by the TME, which explains the high heterogeneity found in many types of cancer [2].

Since the pioneer work of Julius Wolff [3] who recognized the role of mechanical stresses on the characteristic structure of trabecular bone, the effect of mechanical properties and external forces on tissue and organ response and long-term evolution have been recognized as a fundamental feedback mechanism in many important biological processes. We can mention, among many other, homeostasis, morphogenesis, tissue formation and resorption, wound healing, tissue adaptation and long-term evolution of living organisms, as well as diseases as osteoporosis or cancer [4,5].

Cells can sense mechanical strains, pressure, or shear stresses, and probe the stiffness of the surrounding environment (mechanosensing) by means of several components like stretch channels, integrins, or focal adhesions through the talin-actin-vinculin pathway [6,7]. These mechanical signals are transduced to other biochemical cues (mechanotransduction) through various complex molecular and protein folding-unfolding mechanisms [8] like caveolae, nuclear shuttling proteins, or by signal integrators like the actin cytoskeleton [9] or the cell nucleus [10]. Finally, these new signals may be transmitted to other cells by direct gap junctions or through the surrounding ECM [11]. By these mechanisms, the mechanical environment may modify the spatial distribution of biochemical substances in the ECM and produce internal structural and functional rearrangements, changing cell functions as proliferation, migration, apoptotic or necrotic dead [12], and producing cell adaptation by epigenetic changes [13]. This interest on the role of mechanical cues on biological processes is easy to detect just looking at the number of papers and reviews on the field (280,377; 12,843 in the last year, entrances in Pubmed with the keyword mechanobiology).

Cancer evolution is also affected my mechanical strains (30,574; 2,787 in the last year, entrances in Pubmed with the keywords mechanobiology, cancer). For example, during metastasis, cells detach from the tumor and migrate through the stroma, remodeling the matrix around them [14]. There is evidence that certain types of tumors develop and become metastatic in specific mechanical environments while cancer cells and the surrounding tumoral tissue have mechanical properties distinct to those of the host healthy tissue [16]. Also, cells experience higher stresses during tumor growth which may gradually stop it [17].

Understanding the interaction between tumor cells and TME as well as the effect of external mechanical stimuli on such cells is therefore crucial. However, progressing in this understanding is difficult with only in vivo experiments. Despite these experiments being more realistic it is difficult in them to isolate effects or establish specific conditions, due to technical or ethical reasons. In vitro experiments permit better control of the variables, while reducing costly animal assays. However, the predictive power of currently available in vitro models is still poor in complex scenarios like cancer evolution due to the strong difficulties

in reproducing the structure and distribution of the different cell populations as well as the specific environmental conditions in which cells live, adapt, and react [18].

Complementarily, mathematical models provide capacities such as a strict separation and quantification of the effect of each mechanism or parameter. Besides, they allow to predict the outcome in "what if" situations, something sometimes impossible to achieve in in vitro and in vivo experiments [19, 20] due to technical and/or ethical reasons. However, the resulting mathematical models for complex cell environments are highly non-linear, with highly coupled multiphysic interactions, and with many parameters, usually difficult to measure and with important hidden correlations. Finally, there is a lack of data both for quantifying parameters and for validation purposes [21, 22]. Despite these limitations, mathematical models permit contrasting hypotheses, identifying global trends and designing new experiments, so they are now essential tools in biological research.

In their engaging review, Blanco et al. [23] provide an updated overview on the main mechanotransduction pathways, the mechanical properties of tumors, and their response to mechanical stimuli. A key issue in this topic is the accurate identification of the material constitutive behavior of tumors, establishing the differences with the surrounding healthy tissue. This is addressed in [18], showing the different growth pattern between "solid" and "fluid" tumors as well as the effect on growth of stiffness and viscosity. They also review the state of the art of mathematical models in cancer mechanobiology, as well as the fundamental formulation of the mechanical behavior of tumors. Moreover, a new model of the authors is briefly described that considers the main ingredients in cancer evolution as the effect of tumor growth on mechanical stress and on tumor cells and the effect of mechanotransduction.

This increasing knowledge on the effect of mechanical stimuli on tumor growth is opening new possibilities for mechanotherapy to partially control cancer evolution [24] (18; 8 in the last year, entrances in Pubmed with the keywords cancer, mechanotherapy). We could theoretically think in modifying the ECM stiffness or viscosity, or the inter-cellular forces by means of appropriate drugs as blebbistatin, or the TME internal stresses by means of ultrasounds, to modify the tumor evolution. Clinical trials have demonstrated that mechanical tissue disruption via high intensity focused ultrasound (HIFU) can ablate tumors and improve clinical outcomes in prostate, breast, liver, pancreas, bone, and brain tumors [25]. HIFU therapy also increases uptake of chemotherapeutical toxic drugs allowing for lower dosages [26] and can release cancer cell antigens inducing a systemic anti-neoplastic immune response [27]. However, HIFU's involves thermal ablation so it is not possible to discriminate between cancerous and normal tissue. Another possibility is using low-intensity pulsed ultrasound (LIPUS) instead. This technology, named as "Oncotripsy" [28], mechanically disrupts cancer cells while leaving healthy cells unharmed. This means a less invasive therapy, almost without side effects when compared more standard chemo or radiotherapy.

Taken together, the review and computational framework provided in [23] provides a comprehensive approach to better understand the complex scenario of mechanical strains and stresses in the cancer landscape and the avenues that this understanding opens for new therapeutical approaches. Mechanobiology is opening a new battle front in this apparently never ending fight against one of the main scourges of our times. However, many more experiments and basic knowledge are required. We still have more questions than answers. In the aim, Blanco's work is an important milestone.

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