of the N-end rule pathway are actively involved in the regulation of various cellular processes including proliferation, migration and apoptosis, which are hallmarks of cancer cells. Previously, we evaluated the four UBR ubiquitin ligases of the N-end rule as new targets for cancer treatment. UBRs can be effectively downregulated by siRNA embedded in lipid nanoparticles *in vitro* and *in vivo* and this negatively affects cell migration and proliferation as well as increases cell sensitivity to pro-apoptotic signals. Accurate ROS measurements showed that knockdown of UBRs leads to increased ROS production in hepatocarcinoma cells *in vitro*, while ROS levels in normal AML-12 hepatocytes were less affected. In this project we evaluate a novel approach for selective activation of ROS-sensitive cancer prodrugs by simultaneous downregulation of Ubrs of the N-end rule using siRNA. The work was supported by the NGP Skoltech-MIT program (validation of Ubr knockdown) and a grant from the Russian Science Foundation No. 19-44-04111 (ROS studies). *The authors marked with an asterisk equally contributed to the work.

Molecular biology of aging

P-31-001
Activity of human AP-endonuclease APE1 on damaged G-quadruplex structures

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Apurinic/apyrimidinic sites (AP-sites) are one of the most widespread DNA lesions. More than 95% of AP-sites arising in mammalian DNA are processed by AP-endonuclease 1 (APE1). Although canonical B-form is thought to be prevalent in human genome, DNA is able to adopt many noncanonical forms. Such DNA sites are often localized in genome regions having important biological significance. Some regions of such nature have an increased susceptibility to oxidative damage. In particular those are G-rich sequences observed in single-stranded telomeric repeats (TTAGGG in humans). The AP-sites occurring in such regions due to their being prone to create single-strand breaks in DNA are a threat to genomic stability. Left unrepaired such lesions can lead directly to shortening of telomeric regions which is known to result in premature aging and development of various diseases including neurodegeneration. At present the information about the ways and consequences of DNA repair in the telomeric region is insufficient. Therefore the main goal of this work was to elucidate mechanism of AP-sites processing by APE1 in TTAGGG tandem repeats. The model DNA-substrates forming G-quadruplex (G4) structures with single F-site (AP-site analogue) in core or loop regions were constructed. Their structures were proved by CD-spectroscopy. Analysis of product accumulation using gel-electrophoresis has shown that APE1 excises both types of G4. The process of DNA binding and catalysis was also monitored in the real-time by the stopped-flow method with detection of the FRET-signal. Taking together, obtained data revealed the ability of APE1 to excise AP-sites from different positions of G-quadruplex structures analogous to those in telomeric repeats. This work was supported by grants from the Russian Science Foundation (No 18-14-00135) and Russian Foundation for Basic Research (No 19-04-00012).

P-31-002
Muc17 functional maturation and expression in intestine is age-dependent

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Transmembrane mucin Muc17 is a dynamic glycoprotein expressed in apical membranes of intestinal epithelial cells (IECs). Muc17 extends up to 1 μm into the intestinal lumen, which makes Muc17 an ideal docking site for luminal gut bacteria. However, the Muc17 function is still unknown. Our aim is to determine the role of Muc17 in the small and large intestines. Muc17 and a panel of innate immunity components were analyzed in ileum and colon of mice 0, 3, 9 14 and 24 days after birth (P0, P3, P9, P14 and P24). Muc17 tissue localization was determined using immunofluorescence (IF), whereas gene expression of Muc17 and innate immunity components was assessed by RT-qPCR. Surprisingly, IF revealed that Muc17 resided intracellularly in ileum from P0 to P14 mice and was mobilized to IECs apical surface between P14 and P24, coinciding with weaning. Time-resolved gene expression analysis revealed a significant upregulation of Muc17 upon weaning that correlated with upregulation of cytokines such as Il-10 and Il-18 as well as antimicrobial proteins Reg3-β, Reg3-γ and Zg16. By contrast, Muc17 in the distal colon was intracellular from P0 to P3 and reached apical membrane of IECs by P9, corresponding to the period of early microbial colonization. Mobilization of Muc17 to apical membranes in colon was reflected in a significant upregulation of Muc17 gene expression, which coincided with upregulation of Toll-like receptors (TLRs) and the adaptors Myd88 and Trif. Our results suggest that the functional maturity of Muc17, hallmarked by apical expression, is age-dependent. In the ileum, Muc17 expression is trigged upon weaning and an adult-type microbiota through a TLR-independent signalling. By contrast, Muc17 expression in distal colon is TLR-dependent and triggered by the initial colonization of distal colon by gut microbiota. We suggest that Muc17 maturation depends on microbiota and plays a yet undefined role in microbial-host interactions.

P-31-003
A novel role for POLO kinase in the establishment of the non-random inheritance pattern of the spindle pole bodies in *Saccharomyces cerevisiae*

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In many cases cell divisions are asymmetric, and cellular components are differentially inherited by the resulting cells. The uneven distribution of these molecules constitutes a mechanism for the generation of cellular diversity that is essential during development, cell differentiation and aging. An interesting phenomenon associated to asymmetric cell division is the differential segregation of the spindle-associated microtubule-organizing centers (MTOCs). The budding yeast *Saccharomyces cerevisiae* represents an ideal model to study this process, since it displays a non-random inheritance pattern of the spindle pole bodies (SPB, the centrosome equivalent). Specifically, during budding yeast mitosis the old SPB inherited from the previous cell cycle is segregated to the bud, while the new one is retained in the mother cell. Remarkably, asymmetric inheritance of the centrosomes has been also described in higher eukaryotes, where the age of the

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