Toland A.E., Ravichandran K., Riethman H., Naber S.P., Näär A.M., et al. 2015. Haploinsufficiency for BRCA1 leads to cell-type-specific genomic instability and premature senescence. Nat. Commun. V. 6. P. 7505.

Shmulevich R., Krizhanovsky V. 2021. Cell Senescence, DNA damage, and metabolism. Antioxid. Redox Signal. V. 34. P. 324.

Takai H., Smogorzewska A., de Lange T. 2003. DNA damage foci at dysfunctional telomeres. Curr. Biol. V. 13. P. 1549.

The Tabula Muris Consortium. 2020. A single-cell transcriptomic atlas characterizes ageing tissues in the mouse. Nature. V. 583. P. 590.

Vignard J., Mirey G., Salles B. 2013. Ionizing-radiation induced DNA double-strand breaks: a direct and indirect lighting up. Radiother. Oncol. V. 108. P. 362.

Yousefzadeh M., Henpita C., Vyas R., Soto-Palma C., Robbins P., Niedernhofer L. 2021. DNA damage-how and why we age?. Elife. 10: e62852. https://doi.org/10.7554/eLife.62852

Zampetidis C., Galanos P., Angelopoulou A., Zhu Y., Karamitros T., Polyzou A., Mourkioti I., Lagopati N., Mirzazadeh R., Polyzos A., Garnerone S., Gusmao E.G., Sofiadis K., Pefani D.E., Demaria M., et al. 2021. Genomic instability is an early event driving chromatin reorganization and escape from oncogene-induced senescence. BioRxiv preprint. https://doi.org/10.1101/2020.12.20.423639

Zhang P., Kishimoto Y., Grammatikakis I., Gottimukkala K., Cutler R.G., Zhang S., Abdelmohsen K., Bohr V.A., Misra Sen J., Gorospe M., Mattson M.P. 2019. Senolytic therapy alleviates Ab-associated oligodendrocyte progenitor cell senescence and cognitive deficits in an Alzheimer's disease model. Nat. Neurosci. V. 22. P. 719.

Zhu Y., Armstrong J.L., Tchkonia T., Kirkland J.L. 2014. Cellular senescence and the senescent secretory phenotype in age-related chronic diseases. Curr. Opin. Clin. Nutr. Metab. Care. V. 17. P. 324.

Reduced Efficiency of DNA Repair and Antioxidant Defense Promote the Accumulation of DNA Damage During Cell Senescence

P. I. Deryabin[a] and A. V. Borodkina[a, *]

[a] *Institute of Cytology Russian Academy of Scienses, St. Petersburg, 194064 Russia*

**e-mail: borodkina618@gmail.com*

The accumulation of senescent cells within the organism positively correlates with age and is considered as one of the risk factors for an age-dependent increase in the incidence of cancer. The tumor-promoting role of senescent cells is commonly considered to be realized via the paracrine effects of the senescence-associated secretory phenotype on the cellular microenvironment. However, according to recent research, neoplastic transformation may also be due to the genetic instability of senescent cells resulting from accumulating DNA damage. The present study aimed to unravel the intracellular molecular causes that can mediate the occurrence and accumulation of DNA damage during cell senescence. Here we applied replicative and stress-induced senescence of human endometrial stromal cells (ESCs) as models of cell senescence. We revealed that both types of ESCs senescence were accompanied by the formation of persistent DNA damage foci. We detected a decrease in the effectiveness of antioxidant defense in senescent ESCs using the genetically encoded HyPer biosensor. At the same time the level of endogenous reactive oxygen species (ROS) significantly increased in senescent cells, which may mediate the formation of the DNA damage foci. Further accumulation of DNA damage foci can be associated with a decrease in the efficiency of the repair systems in senescent ESCs, as evidenced by both transcriptomic analysis and the results reflecting the dynamics of DNA damage repair caused by oxidative stress or ionizing radiation. Thus, the accumulation of DNA damage in senescent ESCs is, on the one hand, mediated by the ineffective antioxidant protection and increasing ROS levels, and on the other hand, by a low efficiency of damage repair.

Keywords: cell senescence, genetic instability, DNA damage, DNA repair, reactive oxygen species, HyPer, human endometrial stromal cells