Establishment of HindIIIG-1 Cell Line Obtained after Irradiation of Apoptosis Resistant HindIIIG Cells Characterizes by Genomic Instability, Altered DNA Repair Mechanisms, and Activation of Autophagy

Z. V. Chitikova[b, *], N. M. Yartseva[a], T. V. Bykova[a], S. G. Zubova[a], E. Yu. Kochetkova[a], V. A. Pospelov[a], and T. V. Pospelova[a]

[a] *Institute of Cytology, Russian Acsdemy of Sciences, Saint-Petersburg, 194064 Russia*

[b] *University of Geneva, Geneva, 1205 Switzerland*

**e-mail: zhanna.chitikova@gmail.com*

Genomic instability and genetic heterogeneity are among key features of cancer cells that allow their survival under environmental stress. A rapid accumulation of a great number of mutations in a single event due to a massive rearrangement of fragmented chromosomes termed chromothripsis favors cancer progression and resistance to therapy. Complex chromosomal rearrangements caused by chromothripsis are associated with a random ligation of multiple chromosome fragments by an error prone non-homologous end joining (NHEJ) DNA repair. Here we studied the activation of DNA damage response (DDR) and NHEJ as markers of genomic instability in non-irradiated HindIIIG-1 cells obtained after depolyploidization of irradiated HindIIIG cells resistant to apoptosis. The implication of chromothrypsis and autophagy in establishment of novel HindIIIG-1 cell line has been also investigated. Our results demonstrate that non-irradiated HindIIIG-1 cells characterize by high genomic instability, persistent activation of DDR and NHEJ. Chromosome fragmentation in irradiated HindIIIG and non-treated HindIIIG-1 cells taken together with the activation of NHEJ suggest the implication of chromothrypsis-like mechanism in the establishment of HindIIIG-1 cell line. Unlike HindIIIG cells, HindIIIG-1 acquired such features as adhesion-independent cell growth and migration through the pores of Matrigel-coated membrane that may indicate their metastatic potential. Degradation of damaged DNA, nuclei and micronuclei by autophagy in HindIIIG and HindIIIG-1 cells suggests its role in genome maintenance, cell survival and death.

Keywords: apoptosis resistance, autophagy, chromosome fragmentation, chromotripsis, chromosomal instability, DNA damage response, DNA repair