CAN CHROMOSOME INTEGRITY BE MAINTAINED ALWAYS AND EVERYWHERE?

Anna Genescà, Laura Tusell, Mariona Terradas, Laia Hernandez, David Soler, Marta Martín

Department of Cell Biology, Physiology and Immunology, Universitat Autònoma de Barcelona, 08193 Bellaterra, Spain

Genome integrity is known to be disturbed with age. This age-dependent impairment has been classically attributed to telomere length attrition. Telomeres shorten with age in proliferating cells of most human somatic tissues. Telomere dysfunction, which is known to influence both the structure and the number of chromosomes in cells, also affects DNA repair fidelity. Telomere function now emerges as a factor potentially contributing to increasing the sensitivity of aging human cells to DNA-damaging agents. Since eroded telomeres are sensed and act as DNA double strand breaks, they can interact with radiation-induced DNA breaks, thus sharply increasing the possibility of misrejoining and revealing itself as an important factor that definitely contributes to genomic instability and radiation sensitivity. In the light of more recent work carried out in our laboratory, it is clear that age-dependent radiation sensitivity and genomic instability is not only linked to telomere dysfunction but also to a progressive deterioration of DNA damage cell response. This is even more relevant when the malfunction of DNA-repair proteins has been observed in the scenario of low-dose radiation exposure. Concerned about the risks of mammography screening, our research group has analyzed the ability of human mammary epithelial cells to cope with mammogram-induced DNA damage. In a recent study, we show that the dose received by the breast surface per mammogram X-ray exploration induces increased frequencies of DNA double strand breaks to aged—but not to young—human mammary epithelial cells. This is consistent with recent IRCP published data that classifies breast tissues amongst those that are most sensitive to radiation and also with epidemiological studies that reveal increased carcinogenic risks of radiation exposures at older ages. When faced with low-dose radiation induced double strand breaks, aged mammary epithelial cells trigger a slow response, thus inducing increased amount of genetic damage. In this new scenario where telomere dysfunction and DNA repair impairment is produced by the sole act of proliferative cell aging, radiation sensitivity might acquire a temporal aspect: shortened telomeres and decreased repair efficiency in aged cells may potentially increase radiation sensitivity in elderly organisms.

Organisms are continuously exposed to DNA damaging agents, consequently, cells have developed an intricate system known as the DNA damage response to detect and repair DNA lesions. To restore genome integrity, the cell must overcome important hurdles in space and time so as to rapidly sense and initiate the correct signalling and repair programs. However, DNA damage response is not triggered with the same efficacy everywhere. Specifically, the micronuclear environment strongly hinders a proper DNA damage response. The almost total absence of DNA damage response factors recruitment to micronuclear DNA double strand breaks and helix-distorting base lesions indicate that micronuclei are almost incapable of generating an effective DNA damage response. Nuclear envelope defects have been identified as responsible for this defective micronuclear damage response. The data collected in this laboratory suggest that the DNA damage response machinery is not ready for action everywhere. Only the cell nucleus with intact envelope structure provides the adequate concentration of proteins for interacting with damaged DNA and triggering an efficient response. In the case of micronuclear DNA lesions, the chromatin encapsulated in micronuclei does not benefit from the intricate and efficient web of DDR players of the cell, and chromosome instability and radiation sensitivity would be favored under these circumstances when micronuclei is eventually incorporated into daughter nuclei. Thus micronuclei, which have mainly been considered as indicators of ongoing genomic instability, now emerge as a source of instability at the same time. Altogether, this reveals a new dimension in the significance of micronucleation within the carcinogenesis process.