

**Ectopic Cellular Senescence Induced by Ionising Radiation of Varying Quality in Human Endothelial Cells**

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Non-cancer biological effects of ionising radiation exposure are of relevance for estimating normal tissue damage arising from radiotherapy as well as for space radiation protection. In particular, as ion-based radiation treatment of cancer is looking increasingly promising, it is necessary to investigate whether charged particles such as carbon ions, whose increased biological effectiveness at causing early cytotoxicity in the form of clonogenic death is well known, are also more effective than photons at inducing late effects, thereby obscuring their beneficial anti-cancer potential. Aside from neoplastic transformation, one such late effect is cellular senescence, which has been shown to be inducible in vitro by a variety of stressors, including ionising radiation at sub-lethal doses. Such a response, termed stress-induced premature senescence (SIPS), manifests itself as a senescent-like phenotype but, unlike physiological loss of reproductive ability, which serves as a tumour repressor mechanism leading to death or terminal differentiation, is not unambiguously linked with telomere length attrition. In fact, SIPS, while enabling the damaged cell to escape radiation-induced death, can be enacted by damage-response pathways. This may ultimately lead to genome instability and hence transformation. In vivo, accumulation of prematurely senescent cells in a normal tissue can impact its performance and accelerate its degeneration. In order to study the dependence of SIPS upon radiation quality and to examine whether it is mechanistically linked with reduced telomere length, we exposed a model system (human vein endothelial cells) to the GSI carbon ion beam, used for therapeutic purposes, at both the LET values incurred by normal (plateau region) and tumour (spread-out Bragg Peak) cells. X-ray irradiation was used as a reference. The onset of cellular senescence was studied by beta-galactosidase expression in the progeny of irradiated or control cells and related to measurements of telomere length. The latter was performed by means of an automated system that allows recognition of interphase cells labelled by a pan-telomeric fluorescent probe and a centromere-directed probe (IQ-FISH). Relative telomere length was obtained by the fluorescence intensity ratio between the two markers. Our data suggest that ionising radiation causes surviving descendants to enter senescence earlier than their sham-irradiated counterparts, exhibiting a complex dependence upon LET and a non-linear correlation with telomere length reduction.