Ectopic cellular senescence induced by ionising radiation of varying quality in endothelial human 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 leading to death or terminal differentiation that it resembles, is not unambiguously linked with telomere length attrition and can be reversed. Thus, it is possible that SIPS, while representing an escape from radiation-induced death, may be enacted by damage-response pathways and lead ultimately to genome instability and hence transformation. In vivo accumulation of prematurely senescent cells in a normal tissue can impact its performance and accelerate degenerative effects. In order to study the dependence of SIPS upon radiation quality and to examine its mechanistical link with reduced telomere length, we exposed a widely used model system (human vein endothelial cells) to the GSI carbon ion beam 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 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 do their unirradiated counterparts, exhibiting a complex dependence upon increasing LET values and a non-linear correlation with telomere length reduction.

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