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Localised Synchrotron Radiation In Mice Induces Persistent Systemic Genotoxic Events Mediated By The Functional Immune System

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The discovery of the radiation-induced bystander effect (RIBE) (1) has expanded knowledge of radiobiological mechanisms beyond the scope of the central dogma of radiation biology, i.e. that only cells that absorbed a dose of ionising radiation (IR) are affected and the response is dose-dependent. The RIBE is now a well-established phe-nomenon comprising cyto- and genotoxic effects in out-of-field cells associated with irradiated cells. A counterpart in vivo phenomenon, a change in an organ or tissue distant from the irradiated region, was termed the radiation-induced abscopal effect (RIAE) (2). The mechanisms of the RIAE are only beginning to be understood, however the immune system has been proposed as the main mediator.
It is not known how radiation settings affect non-targeted normal tissues and therefore the risk of radi-ation-related adverse abscopal effects. At the Imaging and Medical Beamline (IMBL), the Australian Synchrotron, we examined systemic effects of microbeam radiotherapy (MRT) and broad beam (BB) configurations, in mice that were locally exposed to a very short pulse of a high dose-rate X-ray synchrotron beam (49 Gy/sec). We determined how radiation volume and dose impact the RIAE. We associated the propagation of these systemic effects with the induction of innate and adaptive immune effector responses and with modulations of plasma cytokine concentrations. Finally, we compared the RIAE in mice with the functional immune system and in immune-deficient mice. C57BL/6 mice were irradiated with 10 or 40 Gy incident dose of MRT or BB in an 8x8, 8x1, or 2x2-mm area of the right hind leg. For irradiation with MRT, a collimator produced beam widths of 25 μm and microbeam centre-to-centre spacings of 200 μm. The absorbed doses of incident and scattered radiation were measured with the radiochromic EBT3 and XRQA2 films. Blood samples, irradiated skin and a variety of normal unirradiated tissues were collected for DNA damage analysis of double-strand breaks (DSBs) quantified as gamma-H2AX foci in tissue sections and oxidatitive clustered DNA lesions (OCDL) measured by constant field gel electrophoresis of genomic DNA treated with pyrimidine- and abasic site-specific enzymes. We also measured the systemic immune response (plasma cytokine concentrations) and the local immune response (in-situ quantification of immune cells). The 10 Gy 8x8 mm MRT irradiation experiment was repeated in immune-deficient mice; (i) NOD SCID gamma (NSG), (ii) CCL2/MCP1 knock-outs, and (iii) in C57BL/6 mice treated with anti-CSF1R ASF98 antibody which effectively depletes macrophages.
OCDLs elevated in a wide variety of unirradiated normal tissues. In out-of-field duodenum, a trend for elevated apoptotic cell death was observed under most irradiation conditions, however DSBs elevated only after exposure to lower doses (10 Gy peak dose, but not 40 Gy). These genotoxic events were accompanied by changes in concentrations of MDC, CCL2/MCP1, Eotaxin, IL-10, TIMP-1, VEGF, TGFβ-1 and TGFβ-2 plasma cytokines and by changes in frequencies of macrophages, neutrophils and T-lymphocytes in duodenum. Overall, systemic radiation responses were dose-independent (3). Strikingly, these effects and the abscopal innate and adaptive immune effector responses were completely or partially abrogated in the mice with various immune deficiencies (4), highlighting the role of the functional immune system in propagation of systemic genotoxic effects of localised irradiation.
These findings have implications for the planning of therapeutic and diagnostic radiation treatment to reduce the risk of radiation-related ad-verse systemic effects.

References:

1. KM Prise & JM O'Sullivan, Nature Reviews. Cancer. 9:351-360 (2009).
2. S. Siva et al, Cancer Letters 356:82-90 (2015).
3. J. Ventura et al, Cancer Research 77:6389-6399 (2017).
4. P. Lobachevsky et al, IJROBP (under review).

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