Studies of bystander effects in human artificial 3D tissues after charged particle microbeam irradiation

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The universality of the target theory of radiation-induced effects is challenged by observations of non-targeted effects such as bystander effects. Essential features of bystander effects are that they do not require direct nuclear exposure by radiation and they are particularly significant at low doses. Radiation effects at the tissue level under normal conditions prove that individual cells cannot be considered as an isolated functional unit within most tissues of a multicellular organism. Therefore the radiation response is not simply the sum of cellular responses as assumed in classical radiobiology, predominantly from studies using cell cultures. Experimental models, which maintain tissue-like intercellular cell signalling and three-dimensional (3D) structure, are essential for proper understanding of bystander effects. The tissue microenvironment is also important for proper manifestation of non-targeted effects. Extracellular signalling in normal tissues plays a crucial role in initiation and perpetuation of both bystander effect and genomic instability. The main rationale for our research is that the bystander effect is likely to be natural phenomena which should be studied in an in vivo like multicellular system with preserved 3D tissue microarchitecture and microenvironment. This necessitates moving from in vitro cell culture systems to tissue-based systems. Our current work relates to human artificial epidermal (EpiDerm) and trachea-bronchial (AirWay) 3D tissue systems. Charged particle microbeams are a powerful tool for investigating mechanisms of bystander effects. Microbeams are facilities that allow irradiation of individual cells or cell regions with a precise numbers of charged particles with micrometer precision. In our studies we were using counted $^{3}He^{2+}$ and proton exposures. We demonstrated strong bystander induced apoptosis and premature differentiation after very low dose irradiation, which propagates up 1000 micrometers from irradiated spot. Our theory is that the main function of the bystander effects is to decrease the risk of transformation in a multicellular organism exposed to radiation by removing potentially damaged cells is via apoptosis and irreversible differentiation. A better understanding of non-targeted effects may have important consequences for health risk assessment and, consequently, on radiation protection. Non-targeted effects may contribute to the estimation of cancer risk from occupational, medical and environmental exposures. In particular, they may have implications for the applicability of the Linear-No-Threshold (LNT) model in extrapolating radiation risk data into the low-dose region. Further research is required to determine if these effects, typically measured in vitro, are applicable in tissue level, whole animals, and ultimately in humans.

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