Bystander Effect and Radiation Risk: a theoretical approach

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The concept of dose-response linearity has been in practice for risk assessment of chemical carcinogens and ionising radiation for the past 30 years. But in recent years the evidence from cancer mortality studies and new radiobiological phenomena such as genomic instability, the bystander effect and adaptive response have challenged this accepted hypothesis - questioning whether low dose linearity is also appropriate for low dose risk assessment. Generally, the linear-no-threshold model (LNT) implies: that cancer is a stochastic process; that the dose response for a particular effect is additive; that the genomic instability is of no relevance to cancer; and that ionising radiation is not a unique carcinogen. These assumptions are generally not supported by experimental data - which are mainly carried out at relatively large doses, neither by theoretical considerations.

Undoubtedly, although radiation biology over the past half-century has made great advances in providing a detailed description of radiation action in the cell, the progress has been slow, uncertain, intuitive and largely descriptive. In order to achieve real insights into and understand the controls and processes involved in biological phenomena, mathematical and computational methods could provide the precise tool needed to design appropriate experiments. Useful mathematical-biology models contain a high level of predictive power and are not just simulations of experimental data. And indeed, a question frequently asked whether it is ever going to be feasible describing biological and cancer problems in terms of mathematics? Unlike the more exact sciences such as physics, most biological quantities, which are heterogeneous and subject to many complex and interacting factors, are highly descriptive and entities are not easily expressed as a set of invariant quantities. Despite such difficulties, in the recent past there has been a rapid surge in mathematical theories and biophysical models along with the advances in laboratory and clinical cancer research to provide predictive descriptions, for example, observations on population and dynamics in tumour growth, diffusion processes, protein regulations and the role of kinase pathways in human diseases. In order to formulate a more realistic radiation risk model, the model should incorporate all the influencing phenomena operative at low doses such as bystander-effect and adaptive-response. This paper presents a biophysical model (BSDM) of radiation-induced bystander effect\(^1\) and some preliminary results on possible potential impact of bystander effect on radiation risk calculations.

The principle aim of the bystander model is to establish whether bystander signal can be associated with low molecular weight factors which are transmitted by diffusion type processes in the medium surrounding the recipient cells. Cell inactivation and induced oncogenic transformation by microbeam and broad beam irradiation systems were considered. The biophysical model postulates that the oncogenic bystander response observed in non-hit cells originates from specific signals received from inactivated cells. The bystander signals are assumed to be protein-like molecules spreading in the culture media by Brownian motion. The bystander signals are assumed to switch cells into a state of cell death (apoptotic/mitotic/necrosis) or induced oncogenic transformation modes. The bystander cell survival observed after treatment with the irradiated conditioned medium using broad-beam and the micro-beam irradiation modalities were analysed and interpreted in the framework of the BSDM model. The model predictions for cell inactivation and induced oncogenic transformation frequencies agree well with observed data from micro-beam and broad-beam experiments. In the case of irradiation with constant fraction of cells, transformation frequency for the bystander effect increases with increasing radiation dose. The BSDM model predicts that the bystander effect cannot be interpreted solely as a low-dose effect phenomenon. It is shown that the bystander component of radiation response can increase with dose and can be observed at high doses as well as low doses. The validity of this conclusion is supported by analysis of experimental results from high-LET micro-beam experiments.