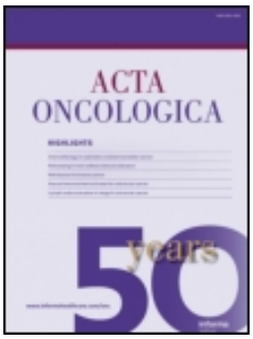

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EDITORIAL

Radiation-induced bystander effects

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Ionizing radiation is an important part of cancer therapy and at the molecular and cellular level it is generally believed that damage to the DNA within the cell nucleus is the major cause of reproductive cell death. This classical view also assumes that the cell killing effect is closely related to the amount of energy deposited in the DNA of the cell traversed by the radiation. In the last decade several newly recognized findings have suggested so-called non-targeted responses where unirradiated cells may respond when their neighbors are irradiated. This phenomenon is generally referred to as the bystander effect and the response in unirradiated cells may include cell killing, genomic instability or delayed death, DNA damage, chromosomal aberrations, altered gene expression or mutations [1].

The term bystander has previously been used in gene therapy where bystander effects are described as when the gene product of a transfected DNA travels from the transfected cell into neighboring cells. Upon radiation-exposure the bystander effect is so far mainly identified using *in vitro* cell cultures. Mothersill and Seymour [2] found that medium from low-LET irradiated cell cultures could reduce the survival of non-irradiated cells. The effect was cell-type dependent and recognized already at low radiation doses with no further effect at higher doses. Earlier studies with different experimental design showed that high-LET alpha particles induced chromosomal damage in 30% of the cells even if only 1% of the cell population was traversed by an alpha particle [3]. Several other studies have confirmed these results and more recent studies also involve irradiation of tissue explants with a charged particle microbeam [4].

Clearly, these findings challenge the conventional notion that damage to the DNA/genome is only induced by ionizing events in the irradiated cell. A critical question is of course how the bystander effect influences the therapeutic outcome, e.g. its impact on tumor cell killing, normal tissue response, and radiation-induced cancer. Studies on both early and late responses in normal and tumor cells, preferably *in vivo* or in more complex *in vitro* models could help to resolve these questions.

In this issue of Acta Oncologica, Djordjevic and Lange [5] present experimental indications of a bystander cell killing effect identified when three-dimensional spheroids of different constitutions of cell populations are used. In this system, primarily developed to evaluate radiation response of fresh tumor biopsy material without interference from overgrowing normal fibroblasts, they recognize bystander-like responses when mixing test cells with heavily irradiated feeder cells. Thus the presence of irradiated cells in a 3D spheroid co-culture system brings the clonogenicity down. Somewhat surprising, this bystander response was obtained at relatively high doses and it is possible that other factors could influence the response. However, this study pinpoints critical aspects on the use of appropriate *in vitro* tests of radiation sensitivity, and ultimately, predictive assays for use in tumor therapy.

What do we know about the mechanism transferring the signals from an irradiated cell to an unirradiated bystander cells? The results so far implicate extracellular factors that are transferred to bystander cells, either directly via gap junctions between adjacent cells, or indirectly via autocrine or paracrine factors (reviewed in [6]). Clearly the signals and responses are cell-type dependent and irradiation of cells have been found to initiate a bystander response involving cytokines (e.g. tumor necrosis factor α or interleukin 8), reactive oxygen

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species (e.g. hydrogen peroxide) or nitric oxide [7]. Furthermore, increased stress response in terms of p21 (CDKN1A) expression or increased phosphorylation of p53 has been found in neighboring, unirradiated cells. This effect is believed to involve signaling via the cell membrane since treatment of cells with lindane, or other agents that inhibits gap junction intercellular communication, reduced the stress response in the bystander cells. Adding to the complexity of bystander response, recent results provide evidence that the COX-2-related pathway, which is essential in mediating cellular inflammatory response, is a critical signaling link for the bystander phenomenon [8].

Basic understanding of the underlying molecular pathways in bystander signaling and its potential role in different tissues is of great scientific and clinical interest. But how should this knowledge be implemented into clinical practice and does this then affect the standard response models that are used? In another study in this issue, Tomé et al. [9] ask the question if local bystander effect necessitate revision of tumor control probability (TCP) models based on observed clinical data. The authors discuss the role of bystander effect, on the microscopic scale, on the macroscopic assumptions for determining TCP. If present in radiation therapy, bystander-mediated cell killing in inhomogeneously irradiated tumors could violate the standard assumption that "clonogens are non-interacting and cell killings are uncorrelated events". From the hypothesis that the bystander effect could have impact on the overall tumor response to radiation, the authors suggest that these strong assumptions in current TCP models can be replaced by weaker ones, allowing for clonogens to be partly interacting and cell killings to be correlated event on the microscopic level.

Bystander response detected *in vitro* seems essentially to be a low-dose phenomenon and the effect seems to saturate at doses above 0.1 Gy. The bystander effect could well contribute to tumor cell killing at much higher doses, although its relative importance is probably reduced. Thus, the vast majority of tumor cells exposed to conventional radiation therapy are probably killed by ionizing tracks directly interacting with the cell. However, in situations with low dose-rate radiation, e.g. radionuclide therapy, the bystander effect could have a different impact on the tumor cell survival and, in addition, killing of bystander cells might compensate for heterogeneous dose-distributions.

There has been an enormous progress in our understanding of DNA repair and signaling response to radiation damage [1]. Still we do not fully understand the complex intracellular responses to radiation damage on DNA and how neighboring cells communicate bystander signals. More knowledge about these molecular processes could ultimately contribute towards improvement of radiation therapy.

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