Maria Widel

Systems Engineering Group, Department of Automatics, Electronics and Informatics,
Silesian University of Technology

E-mail: maria.widel@polsl.pl

Mutual signaling between ionizing radiation exposed and non-exposed cells: potential impact on cancer radiotherapy

Intercellular communication in organism is important for homeostasis phenomenon, the physiological regulatory processes that keep the constant state of the internal environment. Each disease can interfere with internal equilibrium of organs and cells, which is further disrupted by different therapies. Malignant diseases are usually treated by highly aggressive methods, among them is radiotherapy which affects not only tumor cells but also normal cells included in radiation field. For a long time it was generally accepted that ionizing radiation affects the cells via direct ionization or via indirect effects of water radiolysis products which induce damage, mainly in DNA [9]. Indeed, DNA damage such as chromosomal aberrations, micronuclei, sister chromatid exchange, mutagenesis result from ionization of cells. These all types of damage, if unrepaired can lead to cell death, or if misrepaired can lead to genomic instability and carcinogenesis. However, in the two last decades the growing number of studies describes the phenomenon termed "radiation-induced bystander effect" (RIBE) [5, 6]. RIBE is a non-targeted effect where the molecular signal(s) produced by the directly irradiated cells can elicit subsequent responses in non-irradiated neighbors. These responses include a variety of damage-inducible stress responses resembling that observed in directly hit cells. Furthermore, molecular signals secreted by hit cells can be carried far apart, possibly affecting distant targets. Signaling molecules in bystander effect are diverse. In addition to short living oxygen and nitrogen free radicals, the long-living radicals, interleukin 8, TGF-β and other can be involved [7, 8]. Some data indicates that bystander effect is also present in vivo [2, 3]. Furthermore, recent studies show that, when irradiated cells are incubated in the vicinity of the non-irradiated cells, the two populations of cells interplay. Thus, the signals are sent not only by irradiated cells leading to changes in non-radiation ones, but the non-hit cells answer the directly irradiated ones [1, 4, 10]. It is possible that the impact of bystander effect on responses of cancer and healthy tissues to radiation is more relevant than is believed at present. The bystander effect may be a potentially harmful (in vivo damage of neighboring normal cells), or even useful event in radiotherapy (the elevation of damage to tumor cells not directly hit by radiation or the initiation of tumor cell differentiation), both leading to modulation of the therapeutic ratio. The paper will show a comprehensive review of the various aspects concerning

the radiation induced bystander effect with special stress on mutual interplay of irradiated and non-irradiated cells based on existing knowledge and the personal results.

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