Contribution ID: **233** Type: **poster preferred**

TGF-β and the Radiation Bystander Effect in Human Peripheral Blood mononuclear cells –preliminary results and potential applications

Wednesday, 17 October 2012 16:17 (1 minute)

The radiation bystander effect, whereby cells not directly exposed to ionizing radiation exhibit characteristic signs of radiation damage was first observed twenty years ago and remains an active area of research within radiobiology. This effect has since been demonstrated in a number of experimental systems; the literature confirms the relevance of the bystander effect to human peripheral blood lymphocytes, which are routinely harvested for the monitoring of radiation workers. Recently attempts have been made to connect the bystander effect to another potential factor for the assessment of low-dose risk, the radioadaptive response.
One of the signal molecules, widely mentioned in the context of the bystander effect is TGF-β, a secretable protein factor implicated in apoptosis via the SMAD pathway, and cell cycle regulation via p15 and p21. When secreted, TGF-β has been proven to act as an autocrine signaling factor and to interact with the immune system, preventing the activation of lymphocytes, and colocalizing with inflammation sites.
Seeing the potential to produce a bystander effect in the systems we routinely use in our laboratory, we have conducted two preliminary experiments with peripheral blood mononuclear cells (PBMCs) pooled from 8 and 21 donors, respectively, in which we irradiated PBMCs in the presence or absence of serum with 3.3 Gy of 60Co γ-rays and incubated non-irradiated cells with medium taken from irradiated ones. The preliminary results seem to confirm the presence of a bystander effect in our system, with cellular viability dropping off some 7-8% 24h after irradiation and more significantly (~25%) in the cells which were irradiated in the presence of serum; medium transfer had similar observable effects to irradiation in the absence of serum. TGF-β levels also remained relatively constant when PBMCs were irradiated in the absence of serum, but increased sharply with irradiation plus serum. Subsequent experiments will aim to confirm the presence of a bystander effect through analyzing the following parameters: cellular viability, apoptosis, DNA damage (comet test-neutral and alkaline), micronuclei, SCEs, intracellular ROS, γH2AX foci, and quantification of TGF-β and SMAD-3. In case a bystander effect is solidly established, we will continue with our experiments, potentially using an occupationally exposed cohort in order to screen for an adaptive response, or observing the effects of proteasome inhibitors on the system.

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Session Classification: Poster Session 2

Track Classification: Non-Targeted Effects of Radiation