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Controversy Section : What causes the radiation GI syndrome?

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The arguments in this controversy are about whether the radiation GI syndrome is caused by death of the endothelial cells lining the blood vessels of the villi and crypts of the jejunum, or whether it is caused by radiation killing of the epithelial cells in the crypts. Perhaps an arcane issue to some, but in fact the issues debated here are of fundamental importance as they underlie the basic mechanism by which normal tissues are damaged by irradiation.

Let's put this controversy in context. For many years now, following the pioneering studies of Rod Withers in the early 1970's, the prevailing and universally accepted hypothesis has been that the radiation GI syndrome is caused by killing of the cells of the crypts of Lieberkühn. These cells divide rapidly and provide a continuous supply of cells that move up the villi, differentiating as they do so until they are sloughed off at the top of the villi. Because proliferating cells die most rapidly after radiation, generally by a mitotically linked death, it is the cells of the crypts that are depleted by a radiation dose of 10 to 15 Gy (the dose at which the GI syndrome is important in mice). With time the differentiated cells of the villi continue to be sloughed off but because of the depletion of cells of the crypts they are not replaced so the villi become shorter and shorter and if the dose is sufficiently high, are totally lost leading to death of the animal. Rod Withers' seminal contribution was to show that the survival of the cells of the crypt could be measured using a colony forming assay and that the sensitivity of the cells was similar to that of other mammalian cells of both normal and tumor origin (1). This hypothesis of sterilization by radiation of the stem cells of a normal tissue leading eventually to loss of the differentiated cell forms the basis for our understanding of radiation effects on other rapidly dividing tissues such as skin and testes. It is the explanation you will see in any textbook of radiobiology (2).

This textbook model received a significant challenge in 2001 in a Science paper from the joint lab of Zvi Fuks and Richard Kolesnik (3). This influential publication argued that the endothelium within the intestinal mucosa is the actual target of radiation damage, with stem cell dysfunction as a consequence. Thus in one series of elegant experiments Fuks and Kolesnik suggested that it was the microvascular endothelial cells not the epithelial cells of the crypts that were the primary target leading to the radiation GI syndrome and also that apoptosis as opposed to mitotically linked death was the mechanism of cell killing. Needless to say these challenges to the accepted dogma have important mechanistic and practical consequences for chemotherapy or radiotherapy.

The present controversy section stems from a recent publication in this journal from Shuller and colleagues at MIT who reported that even direct irradiation of endothelial cells in blood vessels using an ingenious technique using epithermal neutrons in combination with boronated liposomes that are restricted to blood vessels did not produce apoptosis of the endothelial cells

of the GI tract (4). They also gave whole body radiation doses above and below those needed from the GI syndrome and again reported few if any endothelial cells undergoing apoptosis. They concluded that their data did not support the hypothesis that vascular endothelial cell apoptosis is the cause of the GI syndrome.

This brings us up to date. Readers can now examine the three letters of this Controversy section and the following publication from the Fuks/Kolesnick laboratory (Rotolo et al, this issue). The letters are from Hendry and colleagues, who generally support the finding of lack of apoptosis in endothelial cells, from Gudkov and Gleiberman who report that they also see endothelial cell apoptosis as suggested by Fuks and Kolesnik, and a response to both letters from the the Coderre lab at MIT.

The interested reader should also read the important paper that follows the Controversy section from Rotolo and colleagues in the Fuks/Kolesnik laboratory (Rotolo et al, this issue). These authors show that mice with genetic knockout of the pro-apoptotic proteins Bax and Bak prevented endothelial cell apoptosis in the GI tract and protected against death from the GI syndrome. This again supports the idea that a component at least of the GI syndrome is caused by endothelial cell apoptosis. However, the authors also determined the effect of Bax and Bak knockout on the survival of crypt cells using the classic crypt survival assay developed by Withers and colleagues. They show that lack of Bax and Bak (which abrogated endothelial cell apoptosis) protects the crypts from radiation killing, but only by a dose modification factor (DMF) of roughly 1.15.

So what is one to make of this controversy? Coderre and colleagues and Fuks/Kolesnik agree on one thing: that there are major technical difficulties and potential artifacts of measuring apoptosis in tissue sections. This is one take home message. The other comes from the paper following the Controversy section (Rotolo et al, this issue). Data in this publication (Fig.3) show that inhibiting endothelial cell apoptosis does not prevent death of crypt cells by radiation using a clonogenic assay, but rather, adds a modest protection (by a DMF of 1.15). Thus, the issue appears not to be a black and white one: both cell types could be involved, with radiation inducted death of the crypt epithelial cells being the most important target and apoptosis of vascular endothelial cells perhaps a modifier of the direct radiation killing of crypt epithelial cells.

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