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EDITORIAL

Tissue toxicity induced by ionizing radiation to the normal intestine: Understanding the pathophysiological mechanisms to improve the medical management

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At the present time, more than one-half of all cancer patients are treated with radiation therapy. Despite a good therapeutic index, radiotherapy can disable normal tissue injury to normal tissues in long-term cancer survivors. Thus, an important challenge to modern radiation therapy is to increase the tolerance of normal tissues, in order to improve the quality of life of the patients, and to enhance local tumor control using dose escalation and/or new biological radiosensitizers[1]. The recent progress made by 3D-conformal and intensity-modulated radiation therapy has reduced radiation-induced complications especially in dose-limiting organs like the intestine[2]. Yet, acute intestinal complications do occur but are generally transient, whereas low and mild grade chronic gastrointestinal side effects continue to influence the patient's quality of life. Because the clinical evolution of delayed intestinal toxicity is progressive and inevitable, these complications are of much concern in clinical practice and further improvement in the management of such patients is required.

The current serie published in the *World Journal of Gastroenterology* contains several articles reviewing the most recent research in the field of radiation-induced intestinal toxicity the current therapeutic advances according to the patient's symptoms as well as constructive proposals for the improvement of the medical management of such patients. The proposed improvements depend upon the development of reliable diagnostic tests that are able to identify the underlying causes of the symptoms. The contribution by Lutgens *et al*[3] provides evidence that citrullinemia can be used in clinical and experimental settings as a biomaker of epithelial cell loss. The review by Kruse *et al*[4] addresses the recent advances in the use of micro array for the prediction of radiosensitivity and damage to normal tissues as well as their main limitations.

The physiopathological, cellular and molecular mechanisms of radiation-induced toxicity have been discussed according to the cellular compartments of the intestine and their implication to acute and chronic intestinal toxicity. Tissue exposure to ionizing radiation stimulates the local production of reactive oxygen species which induce replicative and apoptotic death of epithelial and microvascular endothelial cells of the intestinal mucosa. However, the intestinal response to radiation injury cannot be restricted to a simple cell-killing process but depends upon continuous and integrated pathogenic processes involving cell differentiation and crosstalk between the various cellular components within the extracellular matrix. Otterson[5] reviews the impact of irradiation on gastrointestinal motility with special emphasis on the enteric nervous system. Molla *et al*[6], Wang *et al*[7] discuss the role of radiation-induced vascular damage in the acute and delayed intestinal response to ionizing radiation. The radiation-induced alterations of intracellular signaling pathways lead to the transactivation of specific target genes such as genes coding for paracrine factors including vasoactive factors, thrombogenic agents, pro/anti inflammatory mediators and growth factors. The review by Verrechia *et al*[8] focuses on the role of TGF-β1 in fibrogenesis. TGF-β1 is a potent fibrogenic growth factor that triggers alterations in the resident cell phenotypes that subsequently modify cell to cell interactions and tissue composition. Finally, the extracellular matrix itself may contribute to the self-perpetuation of these wound healing signals by the release of growth factors and by constant activation of cell phenotype *via* membrane-associated receptors. The long-term persistence of these phenotypical alterations may have an impact on the activity of neighboring cells (mesenchymal, endothelial, epithelial or immune cells) and may lead to a possible amplification of the wound healing signals that perpetuate fibrosis. This aspect has been well

discussed by Haydont *et al*[9].

It is clear from these articles that the normal intestinal response to radiation injury cannot be restricted to a simple cell-killing process. Therefore, the previous concept of a primary cell target in which a single-cell type (whether it is epithelial or endothelial cell) dictated the whole tissue response to radiation injury should be replaced by the concept of coordinated multicellular response that may lead to either tissue recovery or to the development of complications[10]. The recent advances in this field should lead in the near future to the development of biologically-based therapeutic strategies which can be used clinical practice. These strategies would also be applicable to treat radiation injury in the event of radiation accidents or acts of terrorism and would help to improve the therapeutic management of other chronic intestinal diseases.

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