Induction and persistence of an immune intestinal imbalance by intestinal y-irradiation in the rat

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During radiotherapy for pelvic or abdominal cancer, the intestine is a critical dose-limiting organ. Despite precautions in treatment (planning and delivery), patients develop radiation-induced bowel injury during and for several months after treatment. Radiation enteropathy therefore remains an important obstacle to the radiocurability of abdominal tumors continues to impair patients' quality of life. An inflammatory process associated to immune imbalance has been hypothesized for the development of chronic radiation enteritis. The development of delayed radiation effects involves a continuous process starting immediately at the time of irradiation. The chronic inflammatory reactions are typically characterized by a large infiltrate of immune cells (macrophages, lymphocytes). The balance of cytokines production is crucial to immune response to disease prevention and CD4+ T cells play a prominent role in the disease progression. The persistence of disease susceptibility and resistance depends on the profiles of the cytokines secreted by Th1 and Th2 cells. In the early time, we showed that abdominal single irradiation (10Gy) or fractionated colorectal ?-irradiation (4Gy/fractions, 3 fractions/week and total dose 52Gy) modified the Th1 and Th2 cytokines expression characterized by Th1 cytokines (IFN-gamma/IP10) repression. The Th2 shift occurred via regulation of the level of cytokine-mediators through transcriptional modulation and STAT signaling. During the acute phase, the immune imbalance is associated to an infiltration of macrophages and neutrophiles. This Th1/Th2 imbalance may be attributed to a different radiosensitivity (Th1 more radiosensitive than Th2) and the secretion of a feed-back inhibitor of Th1 polarization potentiating the Th2 profile. In long term (6 months after radiotherapy) the intestinal response may be also driven by the Th2- type responses. The molecular mechanism of this immune imbalance persistence remained unknown. Interestingly, irradiation created an immunosuppressive effect characterized by IL10/STAT3 pathway repression, the pathway known to regulate Th1/Th2 balance. A decrease of the CD4+CD25+FOXP3+ regulatory T cells (Tregs) frequency in the mesenteric lymph nodes may be at the genesis of the IL-10 repression. These results raise the question of whether the Th2 polarization post-irradiation (acute and delayed time) in the intestine involve a highway code of the T cell trafficking induced by a homeostastatic differential chemokines and an alteration of the microvasculature. The assumed loss of tolerance induced by reduced frequency of Treg may be deleterious for Th inactivation and antibacterial responses. These findings suggest the importance to reduce irradiation effects during and after radiotherapy based on immune deviation.

Article published by EDP Sciences and available at http://www.radioprotection.org or http://dx.doi.org/10.1051/radiopro:2008562