

Mast cells in colo-rectal damage following radiation exposureK. Bliando^a, F. Milliat^a, M. Benderitter^a, I. Martelly^b and A. François^a^a*IRSN, BP 17, 92262 Fontenay-aux-Roses, France;* ^b*Laboratoire CRRET-UMR7149, Université Paris XII - Val de Marne, IUT de Créteil, 61 avenue du Général de Gaulle, 94010 CRETEIL CEDEX, France**karl.bliando@irsn.fr*

Radiation therapy, alone or in combination with chemotherapy and/or surgery, is used in more than half of cancer treatments and contributes to increased number of cancer survivors. However radiation exposure is associated with toxicity in non malignant tissues, and represents a strong limitation in the use of this therapeutic tool. The intestine is one of the most radio-sensitive organ and may be comprised in the irradiation field in most of the treatment schedules for pelvic cancers such as prostatic tumors. The irradiated healthy colorectum appears inflamed and is accompanied by acute pain and bleeding in 80% of patients. For 5 to 10% of them, chronic tissue fibrosis may lead to organ dysfunction and require surgical resection. Mast cell hyperplasia has been observed in many fibrotic disorders comprising renal failure, asthma, liver cirrhosis and Crohn's disease. The ability of mast cells to liberate a wide range of neutral protease, cytokines and fibrogenic mediators, together with their localisation close to the endothelium, mucosa and nervous system make them putative key regulators of the response of the different tissue compartments to radiation exposure. Human tissues were obtained from surgical resections 6 weeks post-radiotherapy for rectal adenocarcinoma. Radiation damage, and especially vascular dystrophy, was associated with mast cell hyperplasia, as revealed by tryptase and c-kit immunostaining, both mast cell specific antigens. To evaluate the exact role of mast cells in inflammatory and fibrotic injury following radiation exposure, we used a model of mouse radiation rectocolitis induced by a localized single dose exposure of 27Gy. Radiation injury is characterized by acute apoptosis in the stem cell compartment (1 and 3 days), strong inflammatory reaction with mucosal ulcerations (14 days) and progressive tissue fibrosis until 14 weeks post-exposure. These observations are consistent with tissue damage observed in human rectal radiation injury. At the molecular level, mRNA analysis revealed increased expression of two mast cell proteases: mouse chymase and mouse carboxypeptidase A-3, with respective maximum increases of 9.7 and 2.7 fold. Moreover, relative PAI-1 expression, a fibrogenic mediator known to be secreted by activated mast cells, was up-regulated from day 1 to 14 weeks post irradiation. These preliminary data confirm the interest to study the role of mast cells in radiation enteropathy. Studies on ongoing to compare molecular and histological changes induced by radiation exposure in mast cell deficient mice versus congenic wild type mice to elucidate mast cell implication in radiation enteritis and fibrosis.