Effects of Radiation on Adaptive Immunity: Contact Hypersensitivity Model

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It has long been appreciated that cells of the immune system are radiosensitive and use apoptosis as the primary mechanism of cell death following injury. The hypervariability of the immunoglobulin superfamily of genes expressed in lymphoid cells also led to the appreciation of the nonhomologous end joining mechanism of DNA repair. Clinically, whole body irradiation is used in treatment of some lymphomas and as an immunosuppressive agent for bone marrow transplants. Inflammation at sites of radiotherapy is a common side effect. Many studies with radiation have addressed the changes in cell populations following radiation exposure and have shown a reproducible pattern of relative sensitivities amongst different lymphocyte classes and *in vivo* culture of cells derived from irradiated animals have addressed functional capacity in terms of spontaneous and stimulated mitogenesis and their specific profiles of cytokine production. However, many fewer studies have examined the coordinated responses of an irradiated immune system in terms of responses to challenge by a foreign antigen or organism. This is especially true in the dose regime below 1 Gray. We are trying to understand the functional capacity of the murine immune system in terms of adaptive cellular immunity following low dose whole body exposures to gamma rays using chemical contact hypersensitivity as an adaptive immunity model. In the context of low level radioactive waste handling and contamination remediation, exposure to chemical antigens may interact with low level radiation exposure to determine health risks.

Contact hypersensitivity (formally, Type IV delayed-type hypersensitivity) is an inflammatory response of the skin following repeated exposure to a chemical agent. Its underlying mechanisms are related to those of normal responses to parasite infection, and inappropriately regulated responses leading to asthma. We induce contact hypersensitivity (CH) by painting the abdominal skin of C57BL/6 mice with fluorescein isothiocyanate (FITC) in a suitable solvent system. The low molecular weight, lipophilic FITC reacts as a hapten with proteins (carriers) of the skin to create complete antigens. These FITC-protein conjugates are processed by antigen presenting cells which migrate to regional lymph nodes and "present" antigens to naïve T lymphocytes. FITC-peptide specific T cells are then activated and differentiate into several T cell subclasses including T memory cells that redistribute to distal skin and lymphoid sites. This is the sensitization phase of the CH response. After several days or weeks, FITC is applied to the ear of a sensitized mouse where, after 24 to 48 hours, a local inflammatory reaction takes place causing the ear the swell due to infiltration of immune cells (including eosinophils, a unique FITC-induced response). This is the elicitation phase of the CH response. The magnitude of the ear swelling can be quantified as a measure of the strength of the inflammatory response. A specific pattern of cytokine expression (T_{H2}) along with production of immunoglobulin E serve as biomarkers. The FITC-associated fluorescence allows distribution of antigen and antigen presenting cells to draining lymph nodes to be monitored. We irradiate animals with doses from 10 to 200 cGy of ^{60}Co gamma rays at various times relative to the sensitization and elicitation phases of the CH response to determine whether an immune memory is properly established and maintained. We will briefly review previous observations on immune function with low doses and then present our results to date, which have concentrated on the sensitization phase of the CH response. In the course of our study we will also examine the elicitation phase and quantify the critical processes in the systems-level response to antigen challenge.