Unpredictable sporadic and large SPEs may occur several times during the eleven-year solar cycle and pose serious health risks for manned exploratory missions beyond Low-Earth Orbit. These events acutely could cause the prodromal syndrome – a transient period of anorexia, nausea and vomiting that starts within a few hours, and may compromise crew performance. At expected doses, acute effects could be due to direct damage to intestinal mucosa as well as the effect of injury responses that involve intercellular signalling. Ionizing radiation (IR) activates a complex network of stress responses that affect cellular functions and cellular viability, and triggers altered expression of variety of cytokines and other intercellular messengers. Many of these signaling events can impinge on processes associated with inflammatory responses. Many studies show after IR a general over-expression of pro-inflammatory markers.
Task Description:

systemically and in tissues such as the intestine. A major mediator of inflammatory signaling is p38 MAP kinase (p38), which is upstream, and sometimes downstream, of key cytokines including TNF-a, IL-6, and IL-1β, as well as other key mediators like COX-2 and p53. In the case of the prodromal syndrome, inflammatory signaling may impact on intestinal function either directly by damage to the mucosa, by local production of inflammatory cytokines, or by systemic effects of inflammatory cytokines on the gut. My principal hypothesis is that inflammatory signaling contributes to the prodromal syndrome and can affect the gut by systemic cytokine signaling. I am using a genetic approach in a defined mouse model system to study inflammatory signaling after space radiation exposure with emphasis on SPS, and the effects of such signaling on cellular and molecular parameters in the intestine. By blocking p38 signaling with dominant-negative p38 mutant, we are able to assess the potential advantages of anti-inflammatory therapy to treat the prodromal syndrome.

Rationale for HRP Directed Research:

Radiation-induced prodromal syndrome is a distressing and clinically important adverse outcome inpatients undergoing radiotherapy. Moreover, also in the case of individuals involved in radiological accidents the same symptoms may appear within few hours of the exposure. Although patients receiving TBI are at greatest risk, prodromal syndrome is also seen following partial body irradiation and abdominal irradiation. Missing effective prophylaxis and/or treatment, affected patients experience various complications, including dehydration, electrolyte imbalance and malnutrition, which all may delay disease management and hamper quality of life in these subjects. The incidence, severity and onset of symptoms, such as nausea and vomiting, depend on site of irradiation, dose, and size of targeted field. Although the molecular and cellular mechanisms underlying the prodromal syndrome are still unclear, both gastrointestinal effects and central effects are likely to be involved. Our research is aimed to contribute not only in the prevention and/or management of acute space radiation effects, but also in the treatment of prodromal syndrome in patients undergoing radiotherapy or in individuals involved in radiological accidents. The tryptophan derivative 5-hydroxytryptamine (5-HT, or serotonin) is an important signaling molecule in the brain and periphery. The GI tract is where 95% of the total body serotonin is produced and stored. Upon radiation exposure, enterochromaffin-like cells in the intestine release serotonin and this event triggers nausea and vomiting via peripheral and central mechanisms involving 5-HT3 receptors, visceral afferent fibers and chemoreceptor trigger zone (CTZ). In vitro evidence suggests that p38 MAPK is involved in serotonin transport through activation of serotonin transporters (SERTs). Studies employing multiple p38 MAPK activators (ansomycin, H2O2 and UV radiation) showed an elevation of 5-HT transport parallel with p38 MAPK phosphorylation, as well as suppression of anisomycin stimulation by p38 MAPK siRNA treatments. We hypothesize that p38 MAPK is a critical component in up-regulation of serotonin transport in the intestine and that may contribute to onset of prodromal syndrome. Therefore, we are interested in investigating the joint effect of radiation exposure and p38 activity on serotonin release and transport both locally in the GI tract and at a systemic level. The identification of molecular determinants of the prodromal syndrome will importantly contribute in development of pharmacological treatment to be employed not only for space risk countermeasures, but also on Earth in clinically and accidentally exposed individuals.

Research Impact/Earth Benefits:

Overall, during the course of the period of funding we have made substantial progress for both Aims of our study. Our principal hypothesis is that p38 dependent inflammatory signaling contributes to the prodromal syndrome and can affect intestinal status either by local signaling events and/or by systemic cytokine signaling. The main focus of this research is early alteration of oxidative stress, cytokine signaling and intestinal proliferation and immune in both the small and large intestine following exposure to gamma-rays vs. space radiation. - In wt mice, dose- and radiation-type dependent increase in ROS level was observed that suggests pro-oxidant inflammatory-like response is more accentuated for space radiation than for gamma-rays. - We have observed a central role of p38 in inflammation-associated signaling after IR exposure for both gamma-rays and space radiation: inflammation and cytokine associated genes show attenuated responsiveness compared to wt by expression profiling. - Staining for proliferation markers, such as PCNA, indicates a role of p38 MAPK kinase in cellular proliferation as early as 24 hr after radiation exposure. Effect is pronounced and stable also several months after exposure in both small intestine and colon. As we want to identify both mechanisms responsible for acute radiation response locally in the intestine, and systemic biomarkers of such response, we have also performed a metabolomics study in serum and urine of wt and p38DN/+ mice exposed to either gamma rays or 1 GeV/n protons. For metabolomics analysis, serum and urine were collected from animals exposed to doses between 0.5 and 3 Gy at 6, 24 hr and 1, 2, 4 weeks after irradiation; in vivo changes were measured by UPLC/TOFMS in order to identify metabolic signatures associated with the acute response to high-energy protons exposure in wt compared to p38DN/+ animals. We are now working on correlating metabolite profiles with intestinal effects such as the ones we described above. Overall, we have found that urine metabolome is differentially regulated in wt and p38DN/+. Several metabolites have been found that were up- or down-regulated in p38DN/+ mice compared to wt littermates after radiation exposure and that may represent biomarkers of p38-dependent systemic or intestinal response induced by exposure to gamma rays and/or high-energy protons.

Task Progress:

Bibliography Type:

Description: (Last Updated: 02/23/2017)

Abstracts for Journals and Proceedings


Articles in peer-reviewed Journals


Articles in peer-reviewed Journals

| Awards | Trani D. "1st Place Award in the Postdoc Poster Competition, 22nd Annual NASA Space Radiation Investigators' Workshop, League City, TX, September 2011." Sep-2011 |