

Lethal Total Body Irradiation is accompanied by endotoxemia and is reduced by an endotoxin inhibitor

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Total body irradiation (TBI) is used to treat a variety of malignancies but is associated with a number of toxicities. There has also recently been heightened concern regarding mass population radiation exposure that is either accidental (e.g., nuclear plant leak) or intentional (war/terrorism). There is therefore an unmet need for research into the mechanisms of radiation toxicity and potential mitigating agents. Acute radiation toxicity is characterized by damage to the intestinal tract, potentially resulting in leakage of bacterial endotoxin or lipopolysaccharide (LPS) to the peripheral circulation, in the setting of concomitant damage to the bone marrow. The hematopoietic damage impedes neutrophil-dependent mechanisms to combat bacterial infection, and neutralize bacterial toxins, thereby contributing to pathological activation of the innate immune system. The purpose of the study is to determine whether endotoxemia and endotoxin-directed innate immunity play roles in total body irradiation (TBI) - induced morbidity and mortality. In experiments studying antibiotic free adult C57BL6 mice, TBI dose-dependent mortality ranged from 30-90% across 13-30 days at doses under 9 GY to rapid 100% mortality by 6 days at 16GY (N =10 mice per group; difference between 8 and 16GY significant at $p < 0.0001$). TBI at 8-16GY induced substantial endotoxemia (10-1,000 EU/mL; N = 4-5). Quantitative real-time PCR microarray analysis of liver total RNA (N = 1 mouse at each TBI dose 0, 6, 8, 10 and 16GY) revealed TBI dose-dependent up-regulation of endotoxin receptor components including CD14 and LPS-binding protein (LBP), as well as key pro-inflammatory (TNF, IL1) and counter-regulatory (IL-10) cytokines. The addition of an oral fluoroquinolone antibiotic (enrofloxacin) reduced mortality at TBI doses of < 9 GY but not at higher TBI doses. Our results raise the possibility that TBI-induced endotoxemia may contribute to TBI-induced pathology, and that endotoxin antagonists might reduce TBI-induced-toxicity.