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Proteomic Evaluation of Sex Differences in the Plasma of Non-human Primates Exposed to Ionizing Radiation for Biomarker Discovery

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Abstract : Radiation exposure results in dose-dependent and time-dependent multi-organ damage. Drug development of medical countermeasures (MCM) for radiation-induced injury occurs under the FDA Animal Rule because human efficacy studies are not ethical or feasible. The FDA Animal Rule requires the representation of both sexes and describes several uses for biomarkers in MCM drug development studies. Currently, MCMs are limited and there is no FDA-approved biomarker for any radiation injury. Sex as a variable is essential to identifying biomarkers and developing effective MCMs for acute radiation exposure (ARS) and delayed effects of acute radiation exposure (DEARE). These studies aim to address the death of information on sex differences that have not been determined by studies that included only male, single-sex cohorts. Studies have reported differences in radiosensitivity according to sex. As such, biomarker discovery for radiation-induced damage must consider sex as a variable. This study evaluated the plasma proteomic profile of Rhesus macaque non-human primates after different exposures and doses, as well as time points after radiation. Exposures and doses included total body irradiation between 5-7.5 Gy and partial body irradiation with 5% bone marrow sparing at 9, 9.5 and 10 Gy. Timepoints after irradiation included days 1, 3, 60, and 180, which encompassed both acute radiation syndromes and delayed effects of acute radiation exposure. Bottom-up proteomic analyses of plasma included equal numbers of males and females. In the control animals, few proteomic differences are observed between the sexes. In the irradiated animals, there are a few sex differences, with changes mostly consisting of proteins upregulated in the female animals. Multiple canonical pathways were upregulated in irradiated animals relative to the control animals when subjected to pathway analysis, but differential responses between the sexes are limited. These data provide critical baseline differences according to sex and establish sex differences in non-human primate models relevant to drug development of MCM under the FDA Animal Rule.

Keywords : ionizing radiation, sex differences, plasma proteomics, biomarker discovery
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