Long-term differential changes in mouse intestinal metabolomics after γ and heavy ion radiation exposure

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Abstract: Tissue consequences of radiation exposure are dependent on radiation quality and high linear energy transfer (high-LET) radiation, such as heavy ions in space is known to deposit higher energy in tissues and cause greater damage than low-LET γ radiation. While radiation exposure has been linked to intestinal pathologies, there are very few studies on long-term effects of radiation, fewer involved a therapeutically relevant γ radiation dose, and none explored persistent tissue metabolomic alterations after heavy ion space radiation exposure. Using a metabolomics approach, we report long-term metabolomic markers of radiation injury and perturbation of signaling pathways linked to metabolic alterations in mice after heavy ion or γ radiation exposure. Intestinal tissues (C57BL/6J, female, 6 to 8 wks) were analyzed using ultra performance liquid chromatography coupled with electrospray quadrupole time-of-flight mass spectrometry (UPLC-QToF-MS) two months after 2 Gy γ radiation and results were compared to an equitoxic ^{56}Fe (1.6 Gy) radiation dose. The biological relevance of the metabolites was determined using Ingenuity Pathway Analysis, immunoblots, and immunohistochemistry. Metabolic profile analysis showed radiation-type-dependent spatial separation of the groups. Decreased adenine and guanosine and increased inosine and uridine suggested perturbed nucleotide metabolism. While both the radiation types affected amino acid metabolism, the ^{56}Fe radiation preferentially altered dipeptide metabolism. Furthermore, ^{56}Fe radiation caused upregulation of 'prostanoid biosynthesis' and 'eicosanoid signaling', which are the two interlinked events related to cellular inflammation and have implications for nutrient absorption and inflammatory bowel disease during space missions and after radiotherapy. In conclusion, our data showed for the first time that metabolomics can not only be used to distinguish between heavy ion and γ radiation exposures, but also as a radiation-risk assessment tool for intestinal pathologies through identification of biomarkers persisting long after exposure.