Exposure to Heavy Ion Radiation Induced Persistent Oxidative Stress in Mouse Intestine

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Abstract: Ionizing radiation-induced oxidative stress is attributed to generation of reactive oxygen species (ROS) due to radiolysis of water molecules and is short lived. Persistent oxidative stress has also been observed after radiation exposure and is implicated in the late effects of radiation. The goal of this study was to determine if long-term oxidative stress in mouse intestinal epithelial cells (IEC) is dependent on radiation quality at a dose relevant to fractionated radiotherapy. Mice (C57BL/6J; 6 to 8 weeks; female) were irradiated with 2 Gy of γ-rays, a low-linear energy transfer (LET) radiation, and intestinal tissues and IEC were collected 1 year after radiation exposure. Intracellular ROS, mitochondrial function, and antioxidant activity in IEC were studied by flow cytometry and biochemical assays. Oxidative DNA damage, cell death, and mitogenic activity in IEC were assessed by immunohistochemistry. Effects of γ radiation were compared to ^{56}Fe radiation (iso-toxic dose: 1.6 Gy; energy: 1000 MeV/nucleon; LET: 148 KeV/micron), we used as representative of high-LET radiation, since it's one of the important sources of high Z and high energy (HZE) radiation in cosmic rays. Radiation quality affected the level of persistent oxidative stress with higher elevation of intracellular ROS and mitochondrial superoxide in high-LET ^{56}Fe radiation compared to unirradiated controls and γ radiation. NADPH oxidase activity, mitochondrial membrane damage, and loss of mitochondrial membrane potential were greater in ^{56}Fe-irradiated mice. Compared to γ radiation oxidative DNA damage was higher, cell death ratio was unchanged, and mitotic activity was increased after ^{56}Fe radiation. Taken together our results indicate that long-term functional dysregulation of mitochondria and increased NADPH oxidase activity are major contributing factors towards heavy ion radiation-induced persistent oxidative stress in IEC with potential for neoplastic transformation.