Low Dose Gamma Radiation-Induced Early Responses in the Heart and BM-derived EPCs: Implications for Long-Term Cardiovascular Risks

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Previous epidemiologic data demonstrated that cardiovascular (CV) morbidity may occur within months and years and CV mortality may occur within decades after initial radiation exposure. Echocardiographic measurements obtained from astronauts after space mission revealed a 19-23% lower stroke volume, associated with a 15-23% reduction in cardiac size post-mission compared to pre-mission. MRI measurements obtained from four astronauts following a 10-day space mission revealed ~12% decrease in left ventricular mass. Coronary angiogenesis will be enhanced during the restoration of cardiac size and function (and skeletal muscle growth) facilitated by a post-mission exercise program. This will be accompanied by significant growth of vascular network and will likely involve mobilization of bone marrow (BM)-derived EPCs that are critical for endothelial maintenance and repair. Hence, EPC dysfunction could contribute to the pathogenesis of ischemic vascular diseases and for maintenance of normal vascular homeostasis in the heart during normal aging. Neither data on BM-derived EPC survival or mobilization, recruitment and incorporation during and after space flights, nor DNA damage responses of EPCs to space radiation, are known. Intracellular Ca2+ plays a fundamental role in numerous signaling pathways and serves as a mediator of pathological processes in muscle and non-muscle diseases. A Ca2+-dependent process known as Excitation-Contraction (EC) coupling regulates cardiac muscle contraction and force generation. Radiation may cause deleterious effects on cytoplasmic Ca2+ handling, RyR Ca2+ release and potentially cause mitochondrial alterations due to increased accumulation of Ca2+ within mitochondrial matrix. These alterations may lead to severe reduction in cardiomyocyte contractility. To assess the effect of low-dose radiation in BM-derived EPCs we evaluated the effect of a full-body single dose 1 Gy γ-irradiation [low linear energy transfer (LET) type of radiation] on the formation of γ-H2AX foci (all γ-H2AX results were confirmed using p53BP1 staining) in BM-derived EPCs and in the heart in C57/B16J mice. Our studies revealed that within 24 hrs the decay of γ-H2AX foci is slow in mouse EPCs, which may be indicative of inefficient or delayed DNA DSB repair. There was an increase in the % of BM-derived EPCs with N γ-H2AX foci and increase of γ-H2AX per cell over 7 days post-radiation, indicating a possibility of significant radiobiological bystander responses in EPCs. In media transfer experiments BM-derived EPCs exhibit significant bystander responses in vitro. We found significant γ-H2AX foci decay in irradiated mouse heart resident endothelial cells (EC) and non-EC cells, indicating considerable DNA DSB repair, however with slower than usual Repair kinetics reported for other primary cells, i.e., fibroblasts, leukocytes. We also found that radiation-induced increase in cytoplasmic [Ca2+]i concentration was sustained for longer periods of time. This was accompanied by a partial loss of mitochondrial membrane potential (ΔΨm), which most likely resulted from mitochondrial calcium overload and subsequent activation of the permeability transition (PT) pore. Moreover, full body 1 Gy radiation led to a substantial loss of mitochondrial membrane potential for at least seven days, suggesting that if sustained for longer periods of time this may alter mitochondrial membrane integrity. We conclude that longitudinal studies using low-dose proton and heavy ion (HZE) radiation studies are warranted to determine space radiation-induced long-term Excess Relative Risks (ERR) for cardiovascular diseases.