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Abstract 5723: Inhibition of angiogenesis in the mouse heart by ionizing radiation

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Abstract

The heart is a critical dose-limiting organ during radiotherapy. In patients treated for breast cancer or Hodgkin's disease, regions of the heart can receive radiation doses in excess of 40 Gy. More recently, epidemiological and clinical studies suggested that even moderate to low radiation doses increase the risk of cardiovascular disease that can present years after the initial exposure. Radiation can cause cardiac microvascular damage but the mechanisms of pathogenesis of radiation-induced heart disease have not been clearly defined. Cardiac injury triggers repair processes in the myocardium requiring neovascularisation. Here, we investigated latent effects of ionizing radiation on angiogenic responses in the mouse heart. We also assessed the effects of radiation on cardiac endothelial responses and angiogenesis in vitro. The hearts of C57BL/6 and ApoE-/- mice were locally irradiated with 0.2 to 16 Gy and animals were sacrificed at 20, 40 and 60 weeks post-irradiation. Formation of angiogenic sprouts was assessed in ventricular heart explants embedded in fibrin gels. The angiogenic capacity of irradiated hearts was also assessed through a novel fibroblast-endothelial “self-assembling assay” we developed. Mouse hearts were enzymatically digested into a single cell suspension and cultured for 10 days. Within 5 to 7 days, endothelial cells began to form capillary-like structures surrounded by fibroblasts and pericytes, modeling the angiogenic process. Cardiac endothelial cells were also irradiated in vitro and effects on migration and capillary-tube formation on a fibroblast bed were established. Radiation caused a dose-dependent inhibition of endothelial sprout formation in explants from both mouse models. Significant changes were observed at 8 and 16 Gy after 20 weeks and at ≥2 Gy after 40 or 60 weeks post irradiation. Irradiation also significantly reduced the adherence and growth of extracted cardiac cells and inhibited the quantity and quality of the capillary-like structures formed in the “self-assembling” model. In vitro, irradiation (≥0.2 Gy) inhibited the migration of cardiac endothelial cells in scratch wound assays and capillary-like formation on a fibroblast bed. Our data show that radiation causes persistent and progressive vascular damage and suppresses angiogenic activity in the heart. Angiogenesis was inhibited at doses likely to be delivered during thoracic radiation in cancer patients. Impairment of the angiogenic response

could lead to further ischemia and degeneration in the myocardium and contribute to the development of heart disease.