RADIATION-INDUCED ADHESIVENESS OF AORTIC ENDOTHELIUM IS IL-8 DEPENDENT

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Terrestrial radiation exposure is a well-established risk factor for cardiovascular disease. For example, coronary artery disease and stroke are both well-established adverse effects of therapeutic radiation, especially for breast and head-and-neck cancers. Similarly, atomic bomb survivors were significantly more likely to die of cardiovascular disease than their countrymen. Even radiation technologists, prior to 1950 (when regulations governing shielding and occupational exposure were less rigorous) had an increased risk of clinically significant atherosclerosis. Although the character of the radiation in interplanetary space is very different from that encountered on Earth, there is concern that exposure to this cosmic radiation might pose a similar risk for astronauts. However, perhaps partially due to the fact that so little is known about the mechanism of pro-atherogenic radiation effects, the current strategy to minimize risk from terrestrial radiation sources is to limit exposure. For astronauts on deep space missions, however, exposure to a significant amount of radiation will be unavoidable. An understanding of the mechanism of radiation-induced atherosclerosis will be essential in order to develop countermeasures.

One important pro-atherogenic effect of radiation is increased adhesiveness of vascular endothelium, leading to inappropriate accumulation of monocytes and other white blood cells, which can initiate a self-perpetuating inflammatory response. This vascular inflammation is an early event in atherosclerosis that can eventually lead to clinically significant cardiovascular events such as myocardial infarction and stroke. We showed earlier that x-rays, ^{56}Fe, and ^{28}Si all accelerate development of atherosclerosis in the apoE -/- mouse model. We also demonstrated that both x-rays and heavy ions increase adhesion of monocytic cells to vascular human aortic endothelial cells (HAECs) *in vitro* under conditions that mimic the shear stress in the bloodstream. These adhesiveness changes are independent of adhesion molecule expression levels, but are chemokine dependent. Here we identify the specific endothelial chemokine responsible for this radiation-induced adhesiveness. HAECs were grown as monolayers and exposed to 15 Gy x-rays, a dose that accelerates development of atherosclerotic plaques in the apoE -/- mouse model. X-irradiation increased IL-8 secretion almost 5-fold, while having little or no effect on expression of 15 other chemokines. Adhesiveness was then assayed under physiological shear stress using a flow chamber adhesion assay. Radiation significantly increased endothelial adhesiveness. The radiation-induced adhesiveness was specifically blocked by anti-IL-8 antibody, with no effect on baseline, radiation-independent adhesion. Addition of recombinant human IL-8 to un-irradiated HAECs was sufficient to increase adhesion to the same level as x-rays. Therefore, radiation-induced IL-8 signaling is both necessary and sufficient for radiation effects on aortic endothelial adhesiveness. This IL-8 induced adhesiveness may explain, at least in part, the pro-atherogenic effects of radiation and may suggest a new target for countermeasures.