ELECTRON THERAPY HORMESIS IN INFLAMMATORY VASCULAR DISEASE

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Introduction

Hormesis dose response is actively debated and not fully accepted as a biologic biphasic response to an exposure of increasing amounts of a chemical or energy such as ionizing radiation. Low levels of externally delivered ionizing radiation has been shown to produce stimulatory effects, generally in the range of 1 to 50 cGy of low linear energy transfer radiation stimulatory effects may result in therapeutic effects on a cell or to an organism. We show the low-level effects of internally delivered electron energy (Auger and conversion electrons) from Sn-117m in an inflammatory animal cardiovascular disease model that produced a radiation hormesis effect.

Description of the Work

Sn-117m emits monoenergetic conversion electrons (significant energies 127-158 keV; emission probability 113%) and imageable gamma radiation (159 keV, 86% abundant) and accompanying low energy emissions are Auger electrons (<21 keV) and X-rays (<29 keV). The half-life is 14 days.

***Animal Studies*: In the study, genetically modified Apo-E mice were fed a Harlan Western Rodent Diet to induce arterial vulnerable plaque. At 18 ± 1 weeks of age, a [Sn-117]-DOTA-annexin V or a saline single venous injection was administered into 4 groups of mice – control (saline), low dose (1.7 µCi), medium dose (16.7 µCi), and high dose (83.3 µCi), and sacrificed at 30 days following injection. Histologically, the best therapeutic effect was seen at the low dose of 1.7 µCi. A follow-on Apo-E mouse study injected [Sn-117]-DOTA-annexin V or saline into 4 groups of mice – Group 1 (control using saline), Group 2 (1.0 µCi), Group 3 (1.7 µCi) and Group 4 (3.4 µCi) with 12 mice per group.**

The study results indicated that all these low doses of Sn-117m-DOTA-annexin had a statistically significant effect on vulnerable plaque, a plaque stabilizing effect with no indication of toxicity and with induced apoptosis in macrophages.

***Human Studies*: The human imaging trials using corresponding low dose Sn-117m-DOTA-annexin (i.e., 3 mCi systemically delivered) were able to image large collections of unstable plaque in aneurysms. These same doses were highly localized to CD-68 macrophages in the unstable plaque as observed by a comparison of optical (stained) tissue and autoradiography images (Fig. 1). The doses used in these trials were determined to be below traditional therapeutic radiation effects for fracturing DNA/RNA and are ~100 times lower than typical therapeutic doses used in oncology. The observed doses were well below the level traditionally needed to kill a significant fraction of the targeted cells. This, together with the observations of the animal studies, suggests that some non-lethal, radiation-induced mechanism is involved in the observed plaque response[1].**

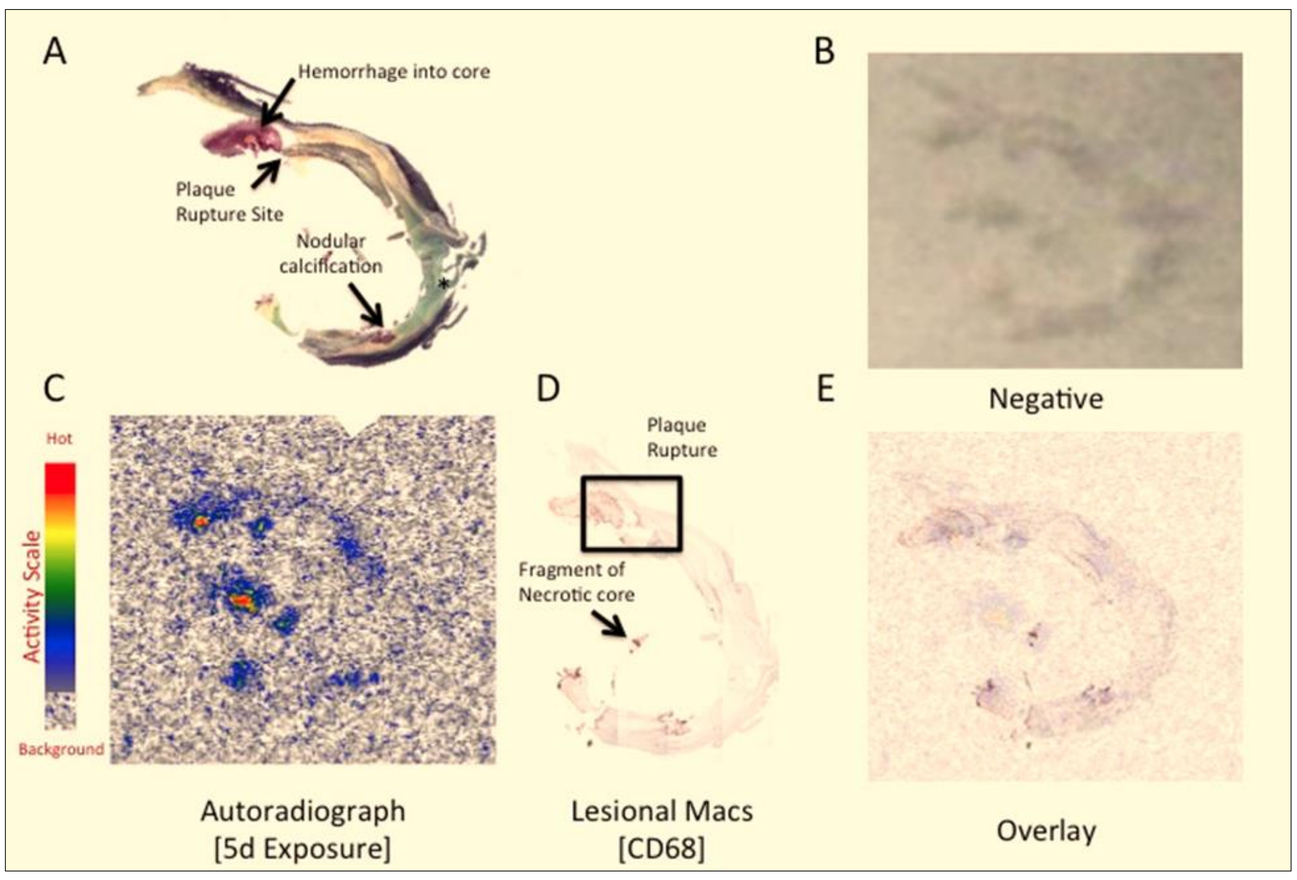

Figure 1. Corresponding microscopic and autoradiographic images of a carotid plaque post imaging with tin-117m. The lesion in the upper left at the first level of the bifurcation is consistent with plaque rupture with hemorrhage and focal collections of macrophages (CD68 staining – reddish-brown color). The autoradiographic image shows focal hotspots particularly in the fibrous cap/necrotic core near the rupture site. The center of the plaque shows a fragment of necrotic core, which also shows a strong intensity for tin-117m. The lower right 'Overlay' panel represents an autoradiographic image (shown in the lower left) superimposed on the CD68 stain.

Conclusions

The novel therapeutic effects described, if further validated, could change the way internally delivered medical isotopes are utilized due to the very low level of energy employed ("internal electron therapy").

References

1. G. Sgouros, Dosimetry Report (June 2013), Clear Vascular Inc.

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