Understanding Radiation-Induced Vascular Disease*

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Radiation injury of blood vessels was originally described more than a century ago and remains a contemporary clinical problem, despite dramatic advances in the field of radiation oncology (1). Clinical studies indicate that patients who have previously undergone radiation therapy for various malignancies—such as lymphoma, breast cancer, and head and neck cancer—are at increased risk for developing vascular disease (2). The consequences are significant; depending upon the study, the relative risk of suffering a clinical cardiovascular event (i.e., myocardial infarction, stroke) related to radiation therapy ranges from approximately 1.5- to 4.0-fold, and this risk is further amplified in the presence of traditional cardiovascular risk factors (3,4).

Most cardiovascular events occur >10 years after completing radiotherapy, so demonstrating causality has proven difficult (5). An estimated 50 million cancer survivors worldwide have been treated with radiation therapy; accordingly, clinicians must be aware of the potential cardiovascular risk and manage risk factors appropriately. Moreover, research into the mechanisms of radiation-induced vascular disease is paramount to understanding and potentially modifying the disease process. The study by Martin et al. (6) in this issue of the Journal is welcome, because it sheds new light on the pathogenesis of radiation-induced vascular disease in humans.

Experimental studies in animals have firmly established a causal relationship between irradiation and vascular disease. Lethal total-body irradiation of atherosclerosis-prone mice followed by bone marrow transplantation noticeably altered lesion composition and stability (7,8). Nonlethal irradiation of atherosclerosis-prone mice did not change systemic indicators of inflammation or cholesterol levels but dramatically altered lesion composition long after treatment (9). There were no changes in the atherosclerotic lesions of “out-of-field” arteries, consistent with a local rather than systemic effect of radiation. Irradiated arteries 22 to 34 weeks after treatment were highly enriched with macrophages, which accounted for the majority of the lesion area. Also, intraplaque hemorrhage was restricted to and commonly observed in irradiated arteries. These studies, however, did not identify a molecular mechanism to explain the observations.

Studies to address radiation-induced vascular disease in humans have largely been descriptive in nature. From the histological perspective, lesions in medium-sized to large vessels (>100 μm in diameter) exhibit typical features of atherosclerosis, including lipid accumulation, inflammation, and thrombosis (3). Increases in intimal thickness and connective tissue content are also prominent features (2). From the angiographic perspective, the lesions are longer than traditional atherosclerotic lesions, and the regions of maximal stenosis tend to be at the ends of the lesions (10). Treating these lesions via open surgical procedures is often problematic, due to extensive soft tissue scarring; hence, percutaneous approaches are usually preferred (5).

How does a course of radiotherapy initiate a chronic vascular process that eventually leads to clinical events many years after treatment? Experimental studies in vitro and in vivo indicate that radiation therapy causes acute up-regulation of pro-inflammatory cytokines and adhesion molecules in endothelium that recruits inflammatory cells to sites of vascular injury (11). It is unlikely, however, that this acute insult per se is sufficient to produce long-term occlusive atherosclerotic disease. Thus, late effects of radiation therapy are more likely responsible. In this regard, induction of chronic oxidative stress is increasingly being implicated in radiation-induced late tissue injury (12). In addition to the rapid burst of free radicals produced acutely by ionization of water molecules, radiation increases chronic free radical production and oxidative stress in the affected tissues. Oxidative stress up-regulates numerous pathways pertinent to vascular disease, including matrix metalloproteinases, adhesion molecules, pro-inflammatory cytokines, and smooth muscle cell proliferation and apoptosis, while inactivating vasculoprotective nitric oxide. Considerable evidence suggests that the nuclear transcription factor NF-κB serves as a molecular link between oxidative stress and chronic inflammation (13).

The nuclear factor-kappa B (NF-κB) family of transcription factors includes 5 members: p50, p52, p65, RelB, and c-Rel. The NF-κB is involved in numerous pathological and physiological conditions, including cellular function (i.e., proliferation, differentiation, and survival), tumorigen-

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directly or indirectly modulate NF-κB, agents, such as aspirin, omega-3 fatty acids, and statins, ameliorate the disease process? Several commonly used agents, such as aspirin, omega-3 fatty acids, and statins, directly or indirectly modulate NF-κB activity; whether these medications could ameliorate radiation-induced vascular disease remains to be determined. Also, inhibitors of NF-κB are being tested for a variety of inflammatory states and might eventually make their way into clinical medicine (13,14). Perhaps such therapy could be employed to treat radiation-induced vascular disease. Alternatively, the pathways responsible for up-regulated oxidative stress might be targeted. In this regard, activation of the angiotensin II-aldosterone system has been hypothesized to play a key role in propagating oxidative stress after radiation therapy (12,15). Thus, pharmacotherapy directed against this pathway could potentially be efficacious against radiation-induced vascular disease.

In conclusion, Martin et al. (6) have made an important contribution to the field of radiation-induced vascular disease by demonstrating local and sustained up-regulation of NF-κB in irradiated human blood vessels. The expression profiles suggest that NF-κB contributes to the pathology by inducing pro-inflammatory genes. Further research is needed to determine the clinical significance of their findings and to investigate whether currently available and/or emerging therapies can modulate the disease process.

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