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Potential Targets for Intervention in Radiation-Induced Heart Disease

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Abstract

Radiotherapy of thoracic and chest wall tumors, if all or part of the heart was included in the radiation field, can lead to radiation-induced heart disease (RIHD), a late and potentially severe side effect. RIHD presents clinically several years after irradiation and manifestations include accelerated atherosclerosis, pericardial and myocardial fibrosis, conduction abnormalities, and injury to cardiac valves. The pathogenesis of RIHD is largely unknown, and a treatment is not available. Hence, ongoing pre-clinical studies aim to elucidate molecular and cellular mechanisms of RIHD. Here, an overview of recent pre-clinical studies is given, and based on the results of these studies, potential targets for intervention in RIHD are discussed.

Keywords

Radiation; heart; animal models; transforming growth factor-beta; renin-angiotensin system; mast cells; endothelin system; sensory nerves

INTRODUCTION

There currently are millions of cancer survivors worldwide. In the Western world, about 40% of cancer survivors are at least 10 years past their cancer diagnosis. The number of long-term cancer survivors continues to grow worldwide with ongoing improvements in cancer therapy [1, 2]. Late side effects of cancer therapy, including secondary cancers and non-tumor tissue injury from radiation- and chemo-therapy, are a significant clinical problem among long-term cancer survivors. One of these late side effects of therapy, radiation-induced heart disease (RIHD) may occur after radiotherapy of thoracic and chest wall tumors whenever all or part of the heart was situated in the radiation field. The pathogenesis of RIHD is largely unknown, and a treatment is not available. Hence, ongoing pre-clinical studies aim to elucidate molecular and cellular mechanisms of RIHD and thereby identify potential targets for intervention. This review describes recent advances in the field of experimental RIHD.

CLINICAL SIGNIFICANCE OF RADIATION-INDUCED HEART DISEASE

RIHD is a late, relatively common and potentially severe side effect of radiotherapy of thoracic and chest wall tumors whenever all or part of the heart was included in the radiation field. RIHD presents clinically several years after irradiation and manifestations include

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accelerated atherosclerosis, pericardial and myocardial fibrosis, conduction abnormalities, and injury to cardiac valves [3, 4]. The disease is progressive and its incidence and severity increase with several factors, such as a higher radiation dose volume, younger age at the time of radiotherapy, a greater time elapsed since treatment, concomitant use of certain chemotherapeutic agents such as anthracyclines, obesity, and hypertension.

Many studies illustrate the clinical significance of RIHD, as reviewed by others [3, 5, 6]. In short, among patients treated with thoracic radiotherapy in the ’70s and ’80s a more than twofold increase in cardiovascular mortality is reported, both when compared with patients who did not receive radiotherapy and when compared with the general population [7, 8]. Although radiotherapy reduced the risk of recurrent cancer among breast cancer patients treated in this era, this benefit was offset by an increase in cardiac mortality [9–11]. Among breast cancer patients treated in the ’80s and ’90s a significant increase in the incidence of heart disease is found in left-sided breast cancer patients versus patients treated for right-sided breast cancer, indicating a significant adverse effect of radiation on the heart [12, 13].

Radiotherapy planning has improved over time, leading to reduced cardiac dose exposures during the last decades. However, recent studies indicate that problems persist; for instance, patients with Hodgkin’s Disease, lung cancer, esophageal and proximal gastric cancer may still receive a high dose of radiation to a small part of the heart or a lower dose of radiation to the whole heart [14–20]. In addition, adjuvant tangential radiotherapy, the common treatment of breast cancer in most parts of the world and in the recent past also in the western world, is known to expose small parts of the heart to doses >20 Gy in about 50% of left-sided breast cancer patients [21]. Although long-term effects of recent radiotherapy techniques cannot yet be determined [22], a high incidence of treatment-induced left ventricular perfusion defects is found in the first months to years after tangential radiotherapy for breast cancer [6, 23–25], indicating that the heart continues to be an organ at risk in certain groups of long-term cancer survivors. Moreover, although there is increasing use of concomitant therapies, the extent to which these therapies enhance the effects of radiation on normal tissues is not yet known.

Although RIHD is widely acknowledged as an impedement to quality of life for certain long-term cancer survivors, the pathogenesis of RIHD is largely unknown, and treatment is not yet available. As a means to identify potential targets for intervention strategies, several ongoing pre-clinical studies seek to unravel the molecular and cellular mechanisms of RIHD.

Pre-Clinical Models of Radiation-Induced Heart Disease

Studies on molecular and cellular mechanisms of RIHD in pre-clinical animal models are ongoing [26–31]. While transgenic mouse models are being used to study radiation-accelerated atherosclerosis [32, 33], rodents are usually not atherosclerosis-prone. Hence, few studies have used rat models to investigate radiation-induced coronary artery disease [34, 35]. The rat model of local heart irradiation, on the other hand, has been used successfully in pre-clinical studies of radiation-induced cardiomyopathy [36–39]. Localized heart irradiation in rats, both with a single dose and with a fractionated irradiation protocol, leads to reduced ventricular ejection fraction and restrictive diastolic filling as measured *in vivo* [40] and reduced cardiac output and increased diastolic stiffness when measured *ex vivo* [40–42]. Histopathological changes including myocardial degeneration (myocardial necrosis, accompanied by inflammation) and fibrosis. Radiation fibrosis and restrictive diastolic filling are commonly described in humans, although mainly after exposures with relatively high doses of radiation [4, 43–46]. The incidence of these alterations after lower dose exposures is not yet known. Data on dose-response relationships of RIHD in animal models are reviewed elsewhere [31, 47].

New technological advances have brought more detailed and minimally invasive methods to study cardiovascular changes in small laboratory animals. Techniques such as high-resolution ultrasound, magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT) are currently in use to assess cardiac structural and functional changes after exposure to radiation in small animals and will undoubtedly contribute to the progress made in the field of experimental RIHD in the coming years.

Below we outline the results obtained from pre-clinical studies designed to uncover mechanisms of RIHD. Studies have addressed the roles of endothelial injury, transforming growth factor-beta (TGF-β), the renin-angiotensin system (RAS), mast cells, the cardiac sensory nervous system, and endothelin-1 (ET-1) in experimental RIHD.

POTENTIAL MECHANISMS OF RIHD: REVIEW OF PRE-CLINICAL STUDIES

Endothelial Injury

Endothelial dysfunction has been shown to play an important role in the pathogenesis of normal tissue radiation injury, as reviewed elsewhere [48, 49]. Endothelial dysfunction is associated with a loss of thromboresistance and increased expression of chemokines and adhesion molecules and may lead to a pro-fibrotic and pro-inflammatory environment, all likely contributors to manifestations of radiation injury. Several studies suggest that endothelial dysfunction is occurring in RIHD, as experimental RIHD is associated with histopathological signs of microvascular injury and reduced myocardial capillary density [50], focal loss of endothelial alkaline phosphatase [27, 51], and increased expression and deposition of von Willebrand factor [52]. A recent study suggests that altered lipid profiles or other circulating factors may affect radiation-induced changes in the myocardial microvasculature [53]. Hence, although not yet tested in experimental models, pharmacological modifiers of endothelial function, such as statins and certain beta-blockers that are of benefit in many cardiovascular disease states may potentially reduce manifestations of RIHD.

TRANSFORMING GROWTH FACTOR-BETA

TGF-β is a pluripotent growth factor that controls many functions including cell proliferation and differentiation in many cell types. TGF-β plays an important role in cardiac hypertrophy and fibrosis [54, 55] and is considered a central growth player in radiation-induced normal tissue fibrosis [56–58] and radiation-induced vascular injury [59, 60]. Previous studies showed upregulation of TGF-β, both at the mRNA and the protein level, after local heart irradiation in the rat [61–63].

A TGF-β–inducing compound was used to investigate the role of TGF-β in RIHD in the rat. Radiation induced a significant increase in collagen deposition, which was more severe after TGF-β induction (unpublished data). To further analyze the role of TGF-β in RIHD, studies involving TGF-β signaling inhibition are being undertaken.

THE RENIN-ANGIOTENSIN SYSTEM

The RAS is a major regulatory system of cardiovascular and renal functions, regulating blood volume and vascular resistance. In addition to the first discovered circulatory RAS, recent evidence has shown that local tissue RAS plays a significant role in tissue homeostasis and the response to injury [64]. Angiotensin II (Ang II) is a small peptide formed in the RAS after the initial conversion of angiotensinogen to angiotensin I (Ang I) by the enzyme renin. The role of Ang II in cardiac pathophysiology is well known, having been the subject of numerous reviews [65–67]. Ang II can be generated from Ang I by several

proteases, of which angiotensin converting enzyme (ACE) and mast cell chymase are the main converters [68]. Mast cell chymase seems of particular importance in the local extravascular generation of Ang II [69]. Interestingly, the local cardiac RAS interacts with many other systems in the heart, including the cardiac nervous systems and the endothelin system, and locally generated Ang II appears to contribute to cardiac hypertrophy and fibrosis [70, 71].

The role of RAS in radiation injury in organs other than the heart has been studied extensively and reviewed elsewhere [72, 73]. ACE inhibitors and antagonists of angiotensin type 1 receptors reduce experimental radiation injury in organs such as kidney, lung and brain [74–76]. Studies are emerging that show an upregulation of mediators of the cardiac RAS after local heart irradiation in animal models [77]. However, although the ACE inhibitor captopril reduced radiation injury in kidney, lung, and skin of rats [76, 78, 79], captopril did not prevent cardiac function loss in a rat model of RIHD [80]. Captopril, on the other hand, did reduce myocardial fibrosis and prevented left ventricular capillary density loss after local heart irradiation. However, these effects were suggested to be caused by properties of captopril other than ACE inhibition [80]. The role of RAS in cardiac radiation injury and the potential intervention in RIHD by pharmacological modification of RAS or by Ang II receptor inhibitors need further investigation.

MAST CELLS

As reviewed in detail elsewhere, mast cells are cells that derive from hematopoietic progenitor cells that release a wide range of cellular mediators, both via a mechanism that involves mast cell degranulation and via a constitutive pathway that does not involve degranulation [81]. Mast cells are resident to the heart and several lines of evidence support a role for mast cells in cardiac remodeling. For instance, mast cell hyperplasia is a common feature in human conditions associated with coronary atherosclerosis and myocardial fibrosis [82, 83] and in many animal models of heart disease [84], including RIHD [80, 85]. Increased mast cell numbers coincide with myocardial radiation injury, suggesting that mast cells may be involved in the development of RIHD.

Mast cell-deficient animal models have provided extensive insight into the role of mast cells in biological responses *in vivo* [86, 87]. Both mast cell development and maturation depend on the c-kit receptor, the protein-tyrosine kinase receptor that is specific for stem cell factor. Hence, several mast cell-deficient models are based on a mutation in the c-kit receptor or the stem cell factor gene [88–90]. Our laboratories have made use of the mast cell-deficient Ws/Ws rat model. Ws/Ws animals originate from a rat of the brown-Norway (BN)/*f*Mai strain with a spontaneous 12-base deletion in the white spotting (Ws) gene locus encoding for the c-kit receptor [91]. As a result of their homozygous c-kit mutation, Ws/Ws rats lack functional mast cells, as well as melanocytes and interstitial cells of Cajal in the intestine, while their wildtype (+/+) litter mates show no abnormalities for these cell types [92]. Because the 12-base c-kit deletion is highly localized, Ws/Ws rats do not suffer from anemia and hematopoietic abnormalities characteristic of some of the mast cell-deficient mouse models [93, 94].

Ws/Ws rats and their +/+ litter mates were used to examine the role of cardiac mast cells in RIHD. Although the absence of mast cells diminished radiation-induced myocardial inflammation and degeneration, adverse changes in *in vivo* cardiac dimensions, myocardial fibrosis and *ex vivo* measures of myocardial stiffness were exacerbated at 6 months in the absence of mast cells [42]. These studies suggest that mast cells, in contrast to what had been the prevailing assumption, play a predominantly protective role in RIHD. Several studies have obtained similar results in other cardiac disease models [95, 96].

Mast cells interact with many cellular systems in the heart through their plethora of cellular mediators. Together with a reduction in radiation-induced cardiac function loss, mast cells were shown to be involved in cardiac radiation-induced upregulation of ET-1 and the sensory neuropeptide calcitonin gene related peptide (CGRP) [97], suggesting that mast cells may mediate their protective effects *via* interacttion with the endothelin system and/or the sensory nervous system.

CARDIAC SENSORY NERVOUS SYSTEM

Neuroimmune interactions are now widely accepted as important modulators of tissue homeostasis and injury. Mast cells are one of the main cell types involved in these neuroimmune interactions [98]. Mast cells are found in close proximity to nerve terminals or axons in many organs, including the heart [99, 100]. Moreover, mast cells may interact with neurons via specific adhesion molecules [101]. Interactions between mast cells and nerves on the molecular level have been extensively described and reviewed elsewhere [98, 102].

The interactions between mast cells and the cardiac nervous system are two-directional. While cardiac nerves influence mast cell function, mast cells in turn may affect nerve function. Mast cells express α- and β-adrenergic receptors [103, 104]. In normal rat myocardium, β-blockade is associated with increased mast cell degranulation and decreased collagen deposition [105]. In addition, sensory neuropeptides such as CGRP, substance P, and neuropeptide Y are able to induce mast cell degranulation [106–111], or enhance mast cell degranulation as induced by a second stimulus [112, 113]. Other neuropeptides, including somatostatin and vasoactive intestinal peptide, have been shown to inhibit mast cell degranulation [114, 115].

While cardiac nerves affect mast cell function, as described above, influence also occurs in the other direction. For example, mast cells produce nerve growth factor [116], an important factor in survival, growth, and differentiation of sensory and sympathetic neurons [117, 118]. Mast cell-derived proteases affect neuronal function via activation of proteinase-activated receptor-2 on the surface of neurons [119, 120]. Mast cell mediators, such as histamine and serotonin, influence the release of acetylcholine and norepinephrine from the autonomic nerve system [121], while mast cell enzymes can cleave certain sensory neuropeptides [122–124].

Albeit not intuitive, increasing evidence supports an important role for the sensory nervous system in the regulation of cardiac function. Cardiac sensory nerves act as detectors of myocardial ischemia and changes in potassium levels and pH. Hence, cardiac sensory denervation in diabetes mellitus patients contributes to silent myocardial ischemia [125, 126]. Cardiac sensory nerves play an additional protective role in the heart *via* the release of both nitric oxide and neuropeptides such as CGRP [127, 128]. CGRP is a potent vasodilator, but also has beneficial effects in the heart by local downregulation of tumor necrosis factor-alpha (TNF-α) and upregulation of insulin-like growth factor-1 (IGF-1) [129, 130]. Hence, CGRP plays a protective role in myocardial injury such as from ischemia-reperfusion and doxorubicin [131, 132]. Interestingly, both downregulation of TNF-α and upregulation of IGF-1 have also been shown to be protective in normal tissue radiation injury in organs other than the heart [133, 134].

The roles of the two sensory neuropeptides CGRP and substance P have been studied extensively in a rat model of radiation enteropathy [135]. Small intestine mRNA levels of both neuropeptides were upregulated after local irradiation. Administration of CGRP ameliorated radiation-induced intestine injury in rats, while a CGRP antagonist exacerbated injury, suggesting that CGRP played a protective role. Opposing results were obtained from the administration of substance P and a substance P receptor antagonist, suggesting that

substance P played an aggravating role in intestinal radiation injury [135]. Considering the mast cell involvement in radiation-induced upregulation of CGRP in experimental RIHD and the known protective roles of CGRP in experimental radiation enteropathy and in myocardial injury from other causes, the role of this neuropeptide in RIHD deserves further investigation.

ENDOTHELIN SYSTEM

ET-1 is a 21-amino acid peptide that was first discovered as a potent vasoconstrictor but also has pro-inflammatory and pro-fibrotic properties [136, 137]. ET-1 is generated from its precursor, big endothelin, by several endothelin-converting enzymes and by mast cell-derived proteases [138]. ET-1 exerts its effects *via* two receptors, ET_A and ET_B, which are expressed by a wide variety of cell types in the heart [137, 139]. The role of ET-1 in cardiovascular pathology has been studied extensively [140, 141]. Short-term up-regulation of ET-1 and its receptors may serve as a mechanism to maintain cardiac function in certain cardiovascular diseases [142, 143]. Long-term up-regulation of the endothelin system, on the other hand, may have detrimental effects due to the vasopressor, pro-hypertrophic, and profibrotic properties of ET-1 [139, 144].

In vivo and *in vitro* evidence has demonstrated interacttions between mast cells and the endothelin system; however, the relationship between mast cells and the endothelin system is complex. Mast cells have been shown to both produce and degrade ET-1 [145–147]. The mast cell protease responsible for cleaving ET-1 and thereby protecting against ET-1 toxicity [40] may be carboxypeptidase A [148]. In addition, mast cells express ET_A, which upon activation by ET-1 induces mast cell degranulation [149]. Mast cells contain proteases that can activate matrix metalloproteinase (MMP) [150, 151]. In the rat heart, ET-1 increases MMP activity by inducing cardiac mast cell degranulation [152].

In a rat model of chronic volume overload induced by an aortocaval fistula, dual inhibition of ET_A and ET_B prevented mast cell degranulation and the associated increase in cardiac MMP levels, interstitial collagen degradation, and ventricular dilatation [153]. On the other hand, dual inhibition of ET_A and ET_B in a rat model of RIHD did not alter radiation-induced functional or structural cardiac changes [97]. Moreover, selective ET_A inhibition led to an increase in the number of sclerotic vessels in a rat model of localized intestine irradiation [154]. Dosing of receptor antagonists and opposing cardiovascular effects of the ET_A and ET_B receptors [155, 156] warrant further studies to clarify the role of ET-1 and its two receptors in RIHD.

CONCLUSIONS: CLUES TO POSSIBLE DRUG TARGETS

Experimental models of local heart irradiation have shed light on the pathogenesis of RIHD. Modifiers of endothelial injury, TGF-β, RAS, cardiac sensory nerves, and the endothelin system may potentially modify manifestations of RIHD. Nevertheless, many mechanisms of this disease may still be unknown.

ABBREVIATIONS

ACE	Angiotensin converting enzyme
AngII	Angiotensin II
CGRP	Calcitonin gene related peptide
ET-1	Endothelin-1

IGF-1	Insulin-like growth factor-1
MMP	Metalloproteinase
MRI	Magnetic resonance imaging
PET	Positron emission tomography
RAS	Renin-angiotensin system
RIHD	Radiation-induced heart disease
SPECT	Single photon emission computed tomography
TGF-β	Transforming growth factor-beta
TNF-α	Tumor necrosis factor-alpha
Ws	White spotting gene

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