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Modifying Radiation Damage

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Abstract

Radiation leaves a fairly characteristic footprint in biological materials, but this is rapidly all but obliterated by the canonical biological responses to the radiation damage. The innate immune recognition systems that sense “danger” through direct radiation damage and through associated collateral damage set in motion a chain of events that, in a tissue compromised by radiation, often unwittingly result in oscillating waves of molecular and cellular responses as tissues attempt to heal. Understanding “nature’s whispers” that inform on these processes will lead to novel forms of intervention targeted more precisely towards modifying them in an appropriate and timely fashion so as to improve the healing process and prevent or mitigate the development of acute and late effects of normal tissue radiation damage, whether it be accidental, as a result of a terrorist incident, or of therapeutic treatment of cancer. Here we attempt to discuss some of the non-free radical scavenging mechanisms that modify radiation responses and comment on where we see them within a conceptual framework of an evolving radiation-induced lesion.

Keywords

TBI; cytokines; RDS; inflammation; NF-κB

> “Biological research workers should listen for “nature’s whispers” and stop telling her what to do.”
>
> Peyton Rous

INTRODUCTION

The military use of atomic power during World War II and the subsequent development of the nuclear industry spurred efforts to find agents for the prophylaxis, mitigation, and treatment of radiation injury; efforts that have been reintensified recently by an increased threat of terrorist use of radiation sources. In the 1960s and 1970s considerable research effort went into the discovery of thiol agents that would protect against radiation, working from the knowledge that the cytotoxic effects of ionizing radiation were elicited in large part via production of reactive oxygen species (ROS) such as superoxide and hydroxyl radicals. Many free radical scavengers were studied, none more than WR2721, which became the drug Amifostine. In fact, Amifostine is a prodrug that is converted to the active free aminothiol WR1065 *in vivo* by alkaline phosphatase, which helps to decrease thiol toxicity, but does not eliminate it [1]. Radio-protection by thiols is thought to reduce initial radiation-induced DNA damage [2], which means that they have to be present at the time of

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irradiation. This limits their usefulness, but Amifostine has been used to prevent xerostomia in head and neck cancer radiation therapy (RT) [3].

Another important finding from the 1960s was that endotoxin could enhance survival of mice receiving total body irradiation (TBI) [4]. This was of obvious relevance to the leakage of bacterial products across an irradiated gut, but seemed to have limited potential in terms of a useful product for modifying radiation effects given its toxicity. However, the advent of recombinant materials brought a reassessment of this work and the finding that the cytokines interleukin-1 (IL-1) and tumor necrosis factor alpha (TNF-α) were most likely responsible for the endotoxin-mediated radioprotection [5] spawned numerous studies of other cytokines. This research forged a link between the immune system and radiation-induced normal tissue damage that allows radiation effects to be placed within an appropriate biological context. TNF-α and IL-1 were most active if given 18 hrs before TBI, although significant mitigation was achieved with a single dose of IL-1 administered within 3 h after a lethal dose ($LD_{95/30}$) of TBI [6]. In contrast, granulocyte colony-stimulating factor (G-CSF), stem cell factor, and granulocyte macrophage colony-stimulating factor (GM-CSF) are most effective if given post-exposure as they accelerated recovery of the hematopoietic system (reviewed in [2,7]). Human G-CSF, GM-CSF, pegylated G-CSF, and IL-11 are currently approved by FDA for treating acute myelosuppression (reviewed in [8]).

The revolution in biology that has happened since these seminal findings were made has brought considerable understanding of the importance of molecular pathways activated by DNA damage to cellular responses leading to DNA repair, cell cycle arrest and/or cell death - giving a molecular explanation for these classic hallmarks of radiation exposure. The conceptual message is that DNA damage is not the only factor that determines life and death of the irradiated cell, but how the damage is sensed and dealt with is of critical importance.

It soon became clear that genes encoding these DNA damage response pathways were prime candidates for cancer-causing mutations and transfer of such genes often altered intrinsic cellular radiosensitivity, not because the cells were transformed, but because processes relating to cell proliferation and cell death/survival were affected. Since modifications of the internal molecular signaling network could affect cellular responses to radiation, it was not surprising that various cytokines and cytokine gene transfers had similar effects [9] and that compounds that activate or block these same pathways could be used to modify radiation responses, something that has been exploited clinically with the use of anti-EGFR to improve the outcome of radiation therapy in head and neck cancer patients [10], although care must be taken in the extrapolation from responses of cancer cells to normal ones. It is possible to conclude that cells make integrated responses to radiation damage coordinated through DNA repair, cell cycle, and cell death pathways

In the same vein, in recent years there has been considerable progress in our understanding of the coordinated tissue damage response to radiation and the mechanisms by which external “danger” is sensed by the body [11]. The conceptual basis stems largely from studies of innate immunity to pathogens showing that canonical wound healing pathways are activated. In a tissue where cells may be seriously compromised by a large amount of latent radiation-induced DNA damage, the canonical pathways may be disrupted leading to waves of molecular responses with time, similar to a chronic inflammatory lesion, with damage persisting and recurring due to failed efforts at healing [11]. Within this framework, the balance of pro-oxidant/anti-oxidant molecules, pro-inflammatory/anti-inflammatory cytokines, and growth promoting and inhibitory factors, along with involvement of mobilized bone marrow-derived precursor cells affords ample opportunity for intervention aimed at mitigating or treating radiation-damaged tissues, with recognition that the status of

the network of molecular processes in a cell and of the cellular interactions within and between tissues has genetic and organ-specific components.

In this review we will discuss classes of agents other than the direct free radical scavenging thiols that modify radiation responses and will comment on how they might fit a conceptual framework of DNA, cell, and tissue responses to radiation damage. We will argue that the best approach to modifying radiation responses may be to promote natural host cytoprotective mechanisms and that by listening to "nature's whispers". With this, we may better address the dearth of agents with robust, prolonged efficacy, broad specificity, and minimal toxicity that could protect a large population in the event of a radiological emergency, or that could increase the radiotherapeutic benefit of cancer treatment.

DNA REPAIR AND CHROMATIN MODIFICATION

We will not deal with the "classic" radioprotective mechanisms of thiols here, but it is worth pointing out that there are many agents that affect DNA repair that are not free radical scavengers, and that many thiols may also radioprotect by other mechanisms. One factor affecting DNA repair is chromatin structure. The extent of chromatin condensation has long been known to influence DNA repair and cellular radiosensitivity [12,13]. Direct visualization of chromatin domains showed that genetically inactive condensed heterochromatin is much less susceptible to radiation-induced DSBs than transcriptionally active, open chromatin [14], presumably because free radicals are less able to penetrate condensed structures. On the other hand, DNA DSB repair was more efficient in euchromatin, presumably in large part because the multiple components of the repair machinery have easier access. The mechanisms linking DNA repair to chromatin remodeling are clearly complex, but there are examples of radioprotection that can be attributed to these mechanisms.

After DNA DSB formation, a prominent change at the chromatin level is the increase in histone H2A.X phosphorrylation (γH2A.X), which elicits recruitment of many effecttor proteins to the site, where the complex interplay of docking and activation events occurs that is essential for DNA repair. One of the binding partners is the tumor suppressor histone acetylase transferase (HAT) Tip60, which binds to DSBs in particular in heterochromatin [15–18], which have a greater requirement for ATM in their repair and which is a slower process than in euchromatin. The finding that Tip60 is activated by histone H3 trimethylated on lysine 9 (H3K9me3), and targeted there by the Mre11–Rad50–Nbs1 (MRN) repair complex, suggests that methylation status of histones will be important in this repair process [19]. Tip60 causes chromatin relaxation by acetylating histone H4, which allows more efficient loading of repair factors and more efficient DSB repair [20]. Acetylation may also be a requirement for dephosphorylation of critical proteins such as -H2AX, which is a required step for efficient recovery from DNA damage checkpoint arrest [21]. Tip60 can also acetylate ATM (ataxia telangiectasia mutated) kinase, which plays so important a role in the DNA repair and damage response that its mutated form represents the poster child for a radiation sensitivity syndrome. In this way, Tip60 can link chromatin remodeling to DNA DSB repair and through ATM to downstream responses like cell cycle arrest and apoptosis. Furthermore, Tip60 activation can repress STAT3 activation with anti-inflammatory and immunosuppressive consequences [22,23]. Obviously, while allowing access of repair factors, chromatin relaxation prior to, as opposed to after, radiation exposure could also allow better access of radiation-induced free radicals, increasing the extent of DNA damage [24,25] and the timing of interventions aimed at modifying chromatin structure must be considered if DNA repair is to be enhanced.

Indeed, exclusion of free radicals by chromatin compacttion is a mechanism proposed to account for the radioprotective effects of the DNA minor groove-binding ligand Hoechst 33342 on DNA and intact cell nuclei [26,27], as well as on cells from cytogenetic damage and death, and on mice from lethality after TBI [28,29]. Radioprotection by DNA-compaction was also reported for oligolysine-treated DNA [30] and spermine treatment of plasmid or viral DNA and viral minichromosomes, but not native chromatin[31,32]. RH-3 (an herbal preparation of Hippophae rhamnoides) also causes chromatin compaction [33] and protects mice when given 30 min before lethal TBI [34,35]. Like many of these agents, RH3 has in fact multiple effects, including acting on death pathways, the immune system, and stem cells [36] that may also affect outcome.

In contrast, tetracycline and ciprofloxacin have been recently shown to activate Tip60 HAT *in vitro*, presumably by intercalating in DNA, and to aid radiation-induced DNA repair if given before or 1 hr after cell irradiation [37]. These antibiotics also modified cell viability if given after, as well as before, radiation, and tetracycline was an effective mitigator of lethal TBI damage in mice even if given 24 hrs after exposure. This suggests that examination of the effects of agents on post-transcriptional histone modifications may be a useful way to profile the pathways by which they may work. A similar intercalating mechanism was proposed for the radioprotective action of the anti-malaria drug chloroquine, which, unlike the antibiotics, activated ATM [38], suggesting the involvement of different pathways. This profiling may also explain why some DNA intercalating agents, such Hoechst 33342, are mutagenic while others that enhance DNA repair are not. Obviously, not all chromatin remodeling agents intercalate, for example TLK1B, a spliced mRNA variant of the TLK1 kinase, protects cells from the genotoxic effects of radiation [39–41] by promoting chromatin remodeling concurrent with improved repair of DNA damage. Further evidence for the importance of chromatin structure in radiation responses is the finding that histone deacetylase inhibitors may prevent lethality of mice if given 24 hrs before or 1 hr after TBI [42], although they also frequently radiosensitize tumor cells. Clearly, as the role of chromatin structure in the DNA repair and damage response becomes better understood and the tools for its analysis improve, there will be an increase in the number of agents that will use this as a target for intervention in radiation responses.

ANTIOXIDANT PATHWAYS

Cells have powerful innate anti-oxidant defenses. Obviously, these have not evolved to combat radiation-induced ROS but rather the damaging effects of ROS generated in large part through the mitochondrial respiratory chain and oxygen metabolizing enzymes, such as NADPH oxidases, myeloperoxidases, cyclooxygenase and lipoxygenase, and hypoxanthine/xanthine that are notably activated during inflammatory responses. ROS directly produced by radiation-induced ionization events are quantitatively relatively minor in comparison, although the deposition of energy within 2 nm of the DNA and the efficiency of free radicals so produced to cause DNA DSB gives an importance to radiation-induced ROS that transcends their meager quantity. However, the ROS generated through ionization events following irradiation are greatly supplemented by the effects of radiation in causing leakage of ROS from mitochondrial membranes and in generating inflammation. In this way, radiation effects overlap considerably with innate immune mechanisms that cause cell and tissue damage during host responses to other “danger” signals. Importantly, ROS and reactive nitrogen species (RNS) act as second messengers, regulating numerous cellular processes by directly altering protein structures with redox-sensitive cysteines resulting in activation of EGFR, PDGR, and other kinases [43,44], inactivation of phosphatases such as Cdc25, stimulating NF-κB, JNK, and AP-1 pathways, and affecting ion channel functions [45]. The full spectrum of redox-sensitive proteins is still unknown, but many critical signaling molecules can be categorized in this way and, as a result, altering the redox

balance in a cell can have profound effects on radiosensitivity. It is not possible to cover all the anti-oxidant systems here but some examples of the genre will be discussed.

NF-κB and AP-1 are redox-sensitive transcription factors that play critical roles in integrating ROS signaling with cellular response to infectious agents and innate and adaptive immunity. Exposure of mice to TBI induces NF-κB activation that in the spleen, lymph nodes, bone marrow and the intestinal epithelial (GI) cells consist mainly of NF-κB p50/RelA heterodimers, [46,47]. Genetic mouse models indicate the physiological importance of NF-κB as a survival mechanism in the radioprotection of GI tissue. $P50^{-/-}$ mice have elevated levels of apoptosis in intestinal epithetlial cells, decreased survival of the small intestinal crypts, and increased GI radiosensitivity [48]. Conditional GI cell-specific IkappaB-kinase beta (IKKβ) knockout mice also display a significant increase in radiation-induced epithelial cell apoptosis, indicating that the IKKβ dependency of NF-κB activation, which has been attributed to increased expression and activation of p53 and decreased expression of anti-apoptotic Bcl-2 family proteins[49]. The anti-oxidant caffeic acid phenethyl ester (CAPE) inhibits NF-κB activation [50] and reduces the radiation-induced inflamematory responses in the lung, including IL-1, IL-6, TNF-α, and TGF-β, as well as radiation-induced interstitial pneumonitis. Other free radical scavenging agents such as disulfide metabolites of amifostine (WR-33278), N-acetyl-cysteine, mesna, captopril, and dithiothreitol (DTT) also activate NF-κB although only WR-1065 and WR-33278 displayed immediate activation of NF-κB suggesting direct action on redox-sensitive components [51,52].

MnSOD (SOD2) is a component of the mitochondrial antioxidant defense system that converts superoxide to hydrogen peroxide, which is in turn reduced by glutathione (GSH) to water and alcohols. It is in the front line of inducible antioxidant defenses being generated through NF-κB-dependent pathways in response to changes in mitochondrial permeability and ROS release. Since ionizing radiation can induce NF-κB, it is no surprise it can induce MnSOD [53]. Although the MnSOD gene promoter contains binding motifs for a number of transcription factors other than NF-κB, it is this that naturally links it to the pro-oxidant tissue destructive activities of pro-inflammatory cytokines such as TNF-α [54] and IL-1 [53]. This is an important mechanism for the radioprotective effects of these cytokines [55,56] and of other agents. Even thiols such as amifostine [57,58] and N-acetyl cysteine [59] can induce delayed cytoprotection independent of their direct free radical scavenging abilities through this mechanism. Also, overexpression of heat shock protein HSP25 (HSPB1) induces MnSOD through activating NF-κB [60] and/or Bcl2 expression [61]. Clearly, MnSOD induction could be a common end pathway for many radioprotective agents that activate NF-κB, however it is not the only possible final effector pro-survival mechanism for this pathway and many other downstream molecules could increase radiation resistance, such as bcl-xl, iNOS, and A20, perhaps acting in unison.

Perhaps the most direct evidence that MnSOD can radioprotect cells comes from overexpression of the MnSOD gene in normal cells and tissues. Intratracheal injection of MnSOD plasmid prior to thoracic irradiation of C57B6/6J mice protected the lung and esophagus from damage [62,63], overexpression in the small intestine protected against radiation enteritis [64], and a single subcutaneous injection of adeno-associated virus expressing MnSOD significantly mitigated acute skin injury following a single dose of 30–35 Gy [65]. Recently, a new mini-circle MnSOD plasmid with improved delivery characteristics was found to be as efficacious as full-length MnSOD plasmid in protecting mice against lethality after TBI [66]. Interestingly, MnSOD-deficient mice, which have a shortened life span and display a multifaceted phenotype [67], showed less radiation-induced neurogenesis defects than wild type mice [68], indicating that compensatory mechanisms might come into play. Radioprotection may not be the outcome for MnSOD

gene transfer into tumors, which often have low basal MnSOD levels [53] and even MnSOD gene silencing. Indeed, certain tumors may be radiosensitized by MnSOD overexpression [69] through overproduction of hydrogen peroxide [70] and failure of its scavengers pyruvate or 2-deoxyglucose [71] to remove the high levels. Where tested, the presence of the mitochondrial leader sequence for expressed MnSOD seemed to be essential for radioprotection [72] confirming that MnSOD is normally used largely to control mitochondrial ROS.

As a result of these studies, numerous synthetic SOD mimics with low molecular weight and good membrane permeability have been developed as antioxidant therapies, and some seem to protect against radiation exposure. For example, MnTE-2-PyP^{5+}, a MnPorphyrin, is an effective radioprotector that scavenges ROS/RNS and reduces DNA oxidative damage [73,74]. Administration of MnTE-2-PyP^{5+} reduces pulmonary injury and blocks activation of TGF-β and HIF-α in Fischer rats when given daily for 2 weeks after 28 Gy hemithorax irradiation [75]. MnTnHex-2-PyP^{5+}, an analogue of MnTE-2-PyP^{5+} that has more lipophilic properties, also ameliorated lung damage, although it was not as effective at reducing expression of TGF-β and other key molecules. On the other hand, MnTnHex-2-PyP^{5+} was more effective than MnTE-2-PyP^{5+} in protecting against radiation-induced apoptosis and DNA damage in human lymphoblastoid cells [76]. EUK-189, a MnSalen compound, also possesses SOD-like activity and protects from and mitigates against radiation injury. A subcutaneous injection at − 24, − 1, +1, or +6 h relative to lethal TBI enhanced 30 d survival with a dose reduction factor (DRF) of 1.15 [77].

Although antioxidant molecules often display a degree of specialization that may be reflected in the location in which they are expressed, they do not appear to operate in isolation but rather as a coordinated system. MnSOD induction appears to be an early response to ROS production. Haton [78] found that irradiation induced MnSOD and thioredoxin 2 expression in the gut by 6 hours after abdominal exposure, but by 4 days the response had waned and a second level of induced antioxidant genes were expressed including glutathione peroxidases and metallothioneins. Pardo found that overexpression of MnSOD stabilized the antioxidant pool including glutathione and total thiols leading to production of hemeoxygenase-1, glutamate-cysteine ligase, and NF-E2-related factor-2 (Nrf2)[79].

Nrf2 is a transcription factor that binds to the anti-oxidant response element (ARE). Under basal conditions, association of Nrf2 with the redox-sensitive CUL3 adaptor protein Keap1 [80] causes rapid Nrf2 ubiquitylation and degradation. Under oxidative stress Nrf2 is stabilized and acts as a master regulator of multiple cytoprotective pathways such as manganese-superoxide dismutase (MnSOD), glutathione transferases, heme oxygenase-1 (HO-1), and NAD(P) H: quinone oxidoreductase-1 (NQO-1) [81,82]. Inhibition of 26S proteasome function, which is very sensitive to oxidative stress and leads to increased ROS production perhaps through failure of constitutively produced Bax-beta to be degraded [83], seems intimately linked to Nrf2 levels, which in turn transcriptionally activates genes of certain proteasome subunits [84].

In spite of its obvious relevance, the role of the Nrf2-ARE system in radiation responses is not clear. Nrf2 knockout cells and mice are more sensitive to radiation lethality suggesting that the basal level of anti-oxidants it controls are critical in moderating radiation responses (McDonald, submitted). Irradiation does induce Nrf2 expression, as might be expected, but only after a considerable delay (McDonald, submitted), which is in keeping with the observation of Haton that glutathione peroxidases were produced only 4 days after gut irradiation [78]. This may be in keeping with the need for a level of pro-oxidant/pro-inflammatory response to proceed before the redox balance is restored and a reflection of the

involvement of the system in combating prolonged oxidative stress and promoting tissue regeneration. It may also be a reflection of the fact that many Nrf2 products are expressed at high levels and depletion is needed prior to induction. The radioprotective effect of Podophyllum hexandrum (REC-2000) involves up-regulation of the Nrf2 downstream effector HO-1 and is via hemopoietic system stimulation [85]. HO-1 seems to be required for hematopoiesis since bone marrow cells from mice lacking one allele of HO-1 had dramatically compromised ability to rescue lethally irradiated wild-type recipients and HO-1 deficiency disrupted the response of stem cells and progenitors to acute stress [86].

The metallothioneins (MTs) also seem to be induced fairly late after irradiation [78]. These are a group of intracellular metal-binding proteins with high cysteine content that can detoxify heavy metals and protect cells or tissues from oxidative damage by scavenging hydroxyl and superoxide radicals. Heavy metals, glucocorticoids, interferon and other cytokines, free radicals, and certain antitumor drugs will induce MTs, as well as ionizing radiation [87]. Thus, pre-treatment of mice with Zn, Cd, or Mn induce MT synthesis in the liver prior to IR and decrease mortality [88–90]. Bismuth nitrate treatment protected irradiated mice from bone marrow, but not gut, death and increased the number of endogenous spleen colonies [91]. However, overexpression of mouse MT in Chinese hamster ovary cells did not alter cell survival following irradiation [92] and MT pre-induction by cadmium chloride in mice liver did not protect against the lethal effects of combined radiation injury, such as 7 Gy TBI plus thermal burn [93]. Mice deficient in MTs show some effect on radiation sensitivity of bone marrow-derived cells at low doses [94], but the exact role of this system in radiation protection is still not fully clear and, as with all anti-oxidants, it may vary with the cell type, intracellular location, and level of expression.

CELL DEATH

Many modulators of normal tissue radiation responses affect cell death either directly or indirectly. The NF-κB pathway that is so intimately linked to redox control, often promotes cell survival while the AP-1 transcription factor, which is also redox-sensitive, seems more pre-occupied with cell death, although this varies with the cell and tissue type and with genetics [95]. The same is true for the prime sensor of radiation-induced DNA damage, p53, with which NF-κB appears at times to have a mutually antagonistic relationship [49,96]. Tissues containing cell populations with a high proliferative capacity tend to have strong evidence of rapid p53-mediated apoptosis following even moderate doses of radiation, as cells do not explore the possibility of repair (reviewed in [97]). This may be because cell death is a recurring event in such tissues and of generally little consequence, as in lymphocytes of the hematopoietic system, hair follicles [98], oligodendroblasts of spinal cord, and progenitor cells for epithelial surfaces. On the contrary, normal fibroblasts respond to irradiation predominantly by irreversible p53-dependent growth arrest[99] which is in keeping with their role in tissue replacement. There have been a lot of efforts to suppress p53 activity via pharmacological means in order to reduce p53-dependent radiation-induced rapid apoptosis in normal tissues. Komarov identified a small molecule pifithrin α (PFTα), which was able to temporarily and reversibly suppress p53 *via* inhibiting p53-mediated transactivation of target genes [96,100]. Consistently, p53-deficient mice survived doses of radiation that cause lethal hematopoietic syndrome in wild-type animals. However, p53 deficiency also resulted in sensitization of mice to higher doses of radiation, causing lethal GI syndrome [101]. Continuous cell proliferation in p53-deficient epithelium crypts without growth arrest correlated with accelerated death of damaged cells followed by rapid destruction of villi and accelerated lethality. This was also observed in p21-deficient mice indicating that p53/p21-mediated growth arrest plays a protective role in the epithelium of small intestine after high radiation doses.

P53 can induce apoptosis by transcriptional target gene regulation or transcription-independent signaling [102,103]. Strom *et al*. took an approach to target non-transcriptional activity of p53; selective inhibition of the mitochondrial branch of the p53 pathway [104]. P53 translocates to the mitochondria where it can directly interact with Bcl2 family members, as can its downstream colleague PUMA, resulting in permeabilization of the outer mitochondrial membrane. They identified a small molecule pifithrin-μ (PFTμ) that inhibits p53 binding to mitochondria reducing its affinity to anti-apoptotic proteins Bcl-xL and Bcl-2 without any effect on p53-dependent transcriptional activation. PFTμ has a high specificity for p53 and rescued primary mouse thymocytes from p53-mediated apoptosis caused by irradiation and protected mice from lethal TBI. Furthermore, suppressing PUMA by antisense oligonucleotides provided significant radioprotection of intestinal progenitor cells reducing the GI syndrome [105].

Modulation of radiation-induced apoptosis has been implicated as a mechanism of action for a number of radioprotectors. A dietary supplement consisting of L-selenomethionine, vitamin C, vitamin E succinate, α-lipoic acid and N-acetyl cysteine significantly increased the 30 day survival of mice when given prior to, or after, lethal TBI [106]. This was associated with increased Bcl2 and decreased Bax, caspase 9 and TGF-β1 mRNA expression in the bone marrow after irradiation. Similar molecular changes accompanied the protective effect of dietary flaxseed against pulmonary fibrosis, inflammation, and oxidative lung damage [107]. Clearly, it is logical that modifying cell death pathways would affect radiation responses and there are numerous examples to support this view, however care must be taken not to compromise the effects of such death pathways in tissue homeostasis and regeneration.

ADENOSINERGIC PATHWAYS

Purine nucleosides, like adenosine, have been shown to enhance DNA repair in irradiated leucocytes and repeatedly to radioprotect [108–113] to mitigate lethality in mice receiving TBI [114–116]. The Chinese herbal medicine Cordyceps sinesis that is an effective radioprotector and accelerates bone marrow recovery when given after TBI [117,118] was recently found to be 3′ adenosine [119]. Mice treated with adenosine and its analog inosine following 12 Gy TBI had increased survival [116], and drugs that elevate extracellular adenosine are known to accelerate myelorecovery of mice when given starting even 3 days after WBI and mobilizing hematopoietic progenitor cells [115,120–122].

Adenosine is one of nature’s tissue protectants and the production of extracellular adenosine is a primordial homeostatic “danger” signaling mechanism. Its production is enhanced by hypoxia and anti-oxidant stimuli to generate an anti-inflammatory and immunosuppressive milieu. Nucleotides such as ATP that are released in sites of damage are catabolized extracellularly by ectonucleotidases to produce adenosine, which has long been known to play a critical and non-redundant role in the protection of normal tissues from collateral damage during inflammation [123–125]. The exact mechanism of tissue protection is unknown, but classic cytoprotective mechanisms that are involved probably include the production of hypoxia and of the cytokine interferon-alpha (IFN-α). Activating of ectonucleotidases leads to production of adenosine, the anti-inflammatory cytokines interleukin-10 (IL-10) and TGF-β [119,126], and an anti-oxidant milieu that promotes hematopoiesis, angiogenesis, tissue regeneration, and wound healing [127,128]. Importantly, IFN-α has recently been shown to activate hematopoietic stem cells [129] and may provide a link between adenosinergic stimuli and hematopoiesis. In addition to controlling immune function, anti-inflammatory adenosinergic pathways also aid enteric function following gut damage [130]. Extracellular adenosine regulates many physiologic functions through four known G-protein coupled receptors (GPCR): A_1, A_{2a}, A_{2b}, and A3 that appear to have

distinct functions. The available data suggest that agonists of A_1 receptors inhibit adenylate cyclase to exert pro-inflammatory effects that attract macrophages to the site of damage but inhibit the bone marrow recovery process, whereas A_2 and A_3 receptor agonists are anti-inflammatory, act on lymphocytes (largely A_2R), and stimulate bone marrow regeneration and progenitor mobilization (largely A_3R) [120,131]. In the future, these drugs will help elucidate the role of the adenosinergic pathways in the tissue response to damage and may offer new reagents for modifying such responses.

TOLL LIKE RECEPTOR (TLR) ACTIVATION AND CYTOKINES

TLRs recognize molecular patterns associated with microbial “non-self” (pathogen-associated molecular patterns, or PAMPs) and “damaged self” (damaged-associated molecular pattern molecules, or DAMPs) to initiate acute inflammation and to combat the “danger” inherent in pathogen invasion or pathological cell death, as is caused by irradiation. To do so effectively, they must be closely linked with the adenosinergic system and again INF-α and NF-κB pathways are critical players. There are currently about 12 members of the TLR subfamily in mice, 10 in humans [132], plus nucleotide-binding oligomerization domain (NOD)-like and retinoic acid-inducible gene (RIG)-like receptors [133], and C-type lectins [134], all of which can recognize PAMPS and/or DAMPS. The ligands for some TLRs have yet to be identified, but TLR4/MD2 dimers are particularly important in the response to PAMPS like lipopolysaccharide (LPS), whereas TLR2 can form heterodimers with TLR1 or TLR6 to respond to lipopeptide components of Gram-positive and -negative bacteria, while TLR5 recognizes bacterial flagellins [135]. In contrast to these cell surface dimers, TLR3, TLR7, and TLR9 are intracellular receptors that sense mainly RNA and DNA, as do NOD- and RIG-like receptors (reviewed in [136]).

DAMPs include the high mobility group box-1 (HMGB1) proteins that bind within the minor DNA groove and are released by damaged cells, including following irradiation. They share with LPS the ability to activate TLR4/MD2 but may also activate TLR2 [137]. Other DAMPs include heat shock proteins, degradation products of extracellular matrix (surfactant protein A, fibronectin extra domain A, and hyaluronan fragments), and other damage-associated proteins, such as beta defensin, uric acid, S100, minimally modified low-density lipoprotein (LDL), and possibly ROS-damaged proteins [138]. In spite of their complexity, all TLRs essentially signal through the adapter proteins, MyD88 and/or TRIF [139], to activate primarily the transcription factors NF-κB, AP-1, and interferon regulatory factor (IRF) 3 or 7.

Radioprotection conferred by LPS pretreatment [4] is presumed to operate through TLR4 and similar receptors to activate NF-κB to give pro-inflammatory cytokines that generate radioprotective, anti-oxidant responses, such as MnSOD, as described above. However, there are other stimuli and pathways associated with these “danger” signaling systems that give different outcomes. Gudkov’s group attempted to suppress radiation-induced apoptosis in the hematopoietic and gut systems by flagellin-induced NF-κB activation. They developed CBLB502, a polypeptide derived from *Salmonella* flagellin that binds to TLR5 and activates NF-κB without triggering systemic inflammation [140]. Systemic treatment of mice with purified flagellin protected mice if given between 2 h before to 4 h after exposure to lethal WBI and required TLR5 and the TLR signaling adaptor MyD88 [141]. Flagellin-elicited radioprotection was, in part, mediated via effects on bone marrow but without a pronounced rescue of radiation-induced anemia or leukopenia. Again, the TLR system appears to offer some hope of modifying radiation-induced tissue damage responses.

While these innate immune systems provide critical tools for modifying radiation responses, it is still not clear how best to use them in a given situation. The complexity of the responses

can be illustrated by IL-1, which is much studied and clearly an excellent radioprotector if given 18 hrs before TBI, although toxic in humans. It acts to generate anti-oxidant defenses such as MnSOD, but also metallothionein, scavenging acute-phase proteins, and GSH, as well as production of hematopoietic growth factors [142–144]. The IL-1 receptor is critical in radioprotection suggesting a role for stromal cell activation [145] and since anti-IL-1 type 1 receptor antibody sensitizes mice to TBI, IL-1 is thought to have intrinsic radioprotective activity [146]. In spite of this effect on hematopoiesis and modest GI radioprotective activity [147] that can be attributed to decreased jejunal progenitor cell apoptosis [148], it has little activity if given after whole body TBI. In general, TNF-α has radioprotective activities that seem to overlap with those of IL-1, as might be expected [6,142,149,150].

In contrast to IL-1 and TNF-α, stem cell factor (SCF), which stimulates primitive multipotential hematopoietic stem cells [151] and more rapid hematopoietic recovery when given after TBI [152], did not induce hematopoietic CSFs, IL-6 or MnSOD [153] and had radioprotective effects against GI death if given after TBI [154]. SCF significantly reduced radiation-induced apoptosis in murine cell lines transfected with the SCF receptor, c-kit [155]. The zinc-finger transcription factor Slug was reported to be a target of c-kit mediated radioprotection [156] since Slug could complement the hematopoietic failure c-kit-deficient mice receiviung TBI, while SCF/c-kit could not return the complement in Slug-deficient radiosensitive animals. Mono-or dual therapy with GM-CSF and/or IL-3, or the human GM-CSF/IL-3 fusion protein (PIXY321), has been shown to decrease the respective periods of neutropenia and thrombocytopenia in sublethally irradiated rhesus monkeys. In mice, the extent of radioprotection seemed to vary with the strains and conditions [142,157–160], but clearly accelerating bone marrow recovery is an important part of enhancing recovery from TBI. Tissues may however vary in their responses to cytokine intervention. Thus, the immune cytokine IL-12 radioprotected mice when given 18 to 24 h prior to TBI, but sensitized B6D2F1 (12 Gy) and C3H/HeJ (9 Gy) to GI damage increasing circulating TNF and IL-6 levels to LPS through an INF mechanism [153,161,162].

A critical aspect of understanding cytokine involvement is realization that these systems work in a coordinated manner and that the balance between pro-inflammatory, pro-oxidant cytokines and their anti-oxidant, anti-inflammatory counterparts affects the hematopoietic system. When given before radiation exposure, the anti-oxidant/pro-oxidant balance seems critical to outcome, while after exposure the ability to generate cellular regeneration becomes more relevant.

CELL PROLIFERATION AND THE HEALING PHASE

One would hope that following radiation exposure the final phase of healing is reached, which involves cell proliferation, angiogenesis, fibrogenesis, and re-epithelialization that aim to limit damage and repair tissue, and that these processes also would offer targets for therapeutic intervention. The triggers for this phase include free radicals [45], ligands for ARs and TLRs [163], and such growth factors as fibroblast (FGF), epithelial (EGF), vascular endothelial (VEGF), and platelet derived (PDGF), acting on epithelial cells, endothelial cells, and fibroblasts. While such responses are generally beneficial, in irradiated tissues the stimulus to proliferate can unmask latent DNA damage and cause a vicious cycle of further cell death or carcinogenesis. Some years ago we proposed a unifying concept: that factors promotive of cell growth are cytoprotective and increase cellular radioresistance [164,165].

As an example of what appears to be a common paradigm, EGFR is thought to confer tumor resistance to radiation through the activation of survival and cell proliferation pathways, and radiation-induced rapid EGFR activation to confer protection through the activation of the

PI3K/AKT pathway [166–168], although how this may differ from ligand-induced EGFR activation is unknown [169–171]. Recent studies identified more a direct role for EGFR in repair of radiation-induced DNA damage. Radiation induces the ligand-independent translocation of the EGFR into the nucleoplasm in a free radical dependent process [172] where it can interact with the catalytic subunit of DNA-dependent protein kinase and the regulatory subunit Ku70 to promote nonhomologous end-joining DNA repair [173]. A few radioprotectors including Bowman-Birk proteinase inhibitor and O-phosphotyrosine have been reported to assist DNA repair via EGFR phosphorylation and nuclear transport [174–176]. It is important to note that induced cytoprotective responses have an inherent risk of producing persisting genomic instability that might drive carcinogenesis since they involve cells that might otherwise have been eliminated by cell death.

Another important family contains the fibroblast growth factors (FGFs) that participate in the control of growth and differentiation of endodermal and mesodermal structures during embryonal development, induce angiogenesis, and facilitate wound healing. Various members have been shown to protect against acute and late radiation damage of normal tissues. Acidic (aFGF, FGF-1) and basic (bFGF, FGF-2) myeloprotect mice from TBI, with FGF2 showing more effect and giving more rapid recovery of hematopoietic cells and peripheral white and red cells, and platelets [177]. FGF1 and FGF2 are radioprotective for small bowel when given 24 h before or 1 h after irradiation [178]. FGFs also promote bone growth and may prevent radiation-induced pneumonitis [2,179]. Part of the radioprotective effect of FGF2 may be in preventing endothelial cell apoptosis [180], which may how it protected mice from radiation-induced crypt damage and the GI syndrome [181]. FGF1:FGF2 chimeric protein (FGFC) which presents universal FGF receptor specificity, better stability and biological activity than FGF1 or FGF2 has been developed for clinical applications. It stimulated keratinocyte proliferation more effectively than FGF2 alone and enhanced the survival of small intestine crypts [182]. FGF-4 is a radiation-inducible, heparin-binding growth factor whose expression by adenoviral delivery protects mice from bone marrow and GI damage after TBI [183,184], inhibiting radiation-induced apoptosis of the crypt cells. Prophylactic administration of FGF-20 prior to lethal TBI significantly increased mouse survival, perhaps by activating Nrf2, MnSOD, and the ERK/Akt pathway [185]. FGF7 and FGF10, or keratinocyte growth factors (KGF) 1 and 2, are more epithelial cell-specific than are other FGFs. KGFs could prevent radiation toxicity to the abdomen or pelvis [186] and lung [187], and other epithelial tissues. Palifermin (KGF-1) reduced mucositis in a phase III trial with non-Hodgkin's lymphoma patients undergoing bone marrow transplantation consisting of 12 Gy TBI [188]. It also showed improved the severity of mucositis and less salivary toxicity among head and neck cancer patients receiving hyperfractionated radiation [189].

Fibrosis is a common outcome of tissue irradiation that is considered to be an attempt by the body to replace damaged tissue with ground substance. A major profibrotic cytokine is transforming growth factor (TGF)-β, which regulates many aspects of wound repair including inflammation, chemotaxis, and deposition of extracellular matrix [190] with synthesis of collagen I, III and IV, repression of degrading enzymes, such as MMP-1, and up-regulation of integrin surface receptors, such as α2β1, leading to myofibroblast differentiation and constrictive fibrosis [191]. TGF-β1 levels, and the most important signaling receptor TGF-β R2, are increased in irradiated mouse skin [192,193] and the rat ileal muscularis layer even on day 1 after irradiation [47]. Signaling leads to increased nucleoplasmatic shuttling of active Smad2/3 and induction of TGF-β1 target genes in fibrotic healing, which is mainly due to decrease in cytoplasmatic levels of the inhibitory Smad7 in irradiated tissue [194]. At the same time, the anti-proliferative and anti-inflammatory action of TGF-β on primitive hematopoietic progenitors sensitizes mice to radiation-induced hematopoietic lethality [162]. A direct role of TGF-β1 in radiation fibrosis

was reported using Smad3 knockout (S3KO) mice that had decreased wound widths and enhanced epithelialization that correlated with increased neutrophil migration [195,196]. S3KO fibroblasts had increased phosphorylation of ERK-MAPK, p53 and H2A.X, and decreased profibrotic gene expression after irradiation [197]. In the lung, anti-TGF-β antibody decreased radiation-induced lung injury [198] and this system has become a popular target for modification of radiation-induced lung injury.

Finally, blockers of the renin-angiotensin system (RAS) have been very successful in ameliorating late radiation tissue injury. The decapeptide angiotensin (Ang) I produced by the RAS is biologically inactive and cleaved to the active AngII by the angiotensin-converting enzyme (ACE) in blood and endothelial cells. AngII, a potent vasoconstrictor, functions by binding to the type 1 (AT_1) or type 2 (AT_2) receptor. However, recent studies found more complex pathways for the formation/metabolism of Ang peptides and their mediators (reviewed in [199]). Treatments with the RAS blockers are well tolerated and effective against radiation-induced injury to kidney, lung and brain.

In kidney, Moulder and others established that captopril, first generation thiol-containing ACE inhibitor could prevent and treat experimental radiation nephropathy [200–203]. Further studies revealed that a non-thiol ACE inhibitor enalapril as well as AT_1R and AT_2R antagonists reduced the severity of nephropathy, whole other anti-hypertensive drugs had no effect [204–208]. AT_1 blockers such as L-158,809 are superior to ACE inhibitors for prevention/mitigation, while they are equally effective in treatment [209,210]. Blocking AT_2R augments the effect of AT_1R antagonists on mitigation of nephropathy while it has no effect on treatment, suggesting potentially different mechanism [211].

In lung, Captopril administered to rats after lung irradiation ameliorated pulmonary endothelial dysfunction and fibrosis [212,213]. Non-thiol ACEIs and L-158809 were equally effective, as was the AT_1R blocker, affirming the role of AngII in modulation of lung fibrosis [214,215]. In rat brain, chronic administration of ramipril (an ACE inhibitor) started 2 weeks after a 30 Gy dose reduced optic neuropathy [216] and administration of L-158,809 in drinking water prior to 40 Gy fractioned TBI and continued for the duration of experiment prevented cognitive impairment in rats at 6 and 12 months [217].

The mechanisms by which RAS blockers act to mitigate radiation-induced late tissue injuries are not known. However, it has been suggested that they exert their activity by modulating chronic oxidative stress and inflammation [199,218]. AngII plays a key role in regulating blood pressure and fluid homeostasis under physiological conditions and has mitogenic, pro-inflammatory, and pro-fibrotic properties. Lowering blood pressure does not however seem to be important for modification of radiation-induced late effects [218]. Its effects in upregulating TGF-β and MMP-2, and in altering activity of the fibrinolytic system [219–222], or in generating ROS through NADPH oxidase [223] or aldosterone signaling, which can lead to EGFR transactivation and MAPK activity [224,225] remain as possible mechanisms.

COMMENTARY

The most obvious conclusion to be drawn from this incomplete review is that numerous agents can modify radiation damage by numerous processes. Indeed, perhaps all radiation response modifiers affect multiple aspects of biology that are of possible relevance to the outcome. Nowhere is the level of integration more striking than when a single agent is found to affect DNA damage and repair, redox regulation, multiple cell signaling pathways, and tissue regeneration. Yet, radiation biologists have long been familiar with the integration of DNA damage and repair with cell cycle arrest and cell death that speak to common

coordinated responses and should not be surprised by the spatial and temporal integration of the molecular and cellular networks that contribute to tissue homeostasis.

In thinking of mechanism of action of agents, it is perhaps more useful to consider the procession of events that are initiated by radiation damage. While different types of radiation may leave slightly different footprints in biological material, these are rapidly obliterated by the biological responses to damage that conform to canonical pathways of wound healing that in a heavily radiation damaged tissue results in wave-like oscillations in molecular markers of events that unfold over what may be a considerable time period (Fig. 1). Little is known about the control mechanisms that operate to dampen these oscillations and damaging sequelae of inflammation but they appear to be under genetic and tissue-specific control. It follows that DNA damage with repair or misrepair, cellular damage with death or survival, and tissue damage with regeneration or replacement are not unique to radiation, except in that the tissue may be compromised by latent radiation damage that is expressed only when cells are stimulated to divide and respond with mitotic death or sensecence.

In an evolutionary sense, these mechanisms have arisen to allow multi-cellular, multi-tissue structures with considerable specialization of organ function. Damage to these structures whether from pathogen or non-pathogen sources is sensed by innate immune recognition mechanisms that respond accordingly. This integrated scenario is much more complex than simply direct radiation-induced cell kill resulting in tissue damage. Host defenses are activated involving pro-inflammatory cytokines and cells that cause vascular leak and initially amplify the damage through production of high levels of ROS. The exact role of these free radicals in cell killing due to radiation is uncertain but cell death receptors and associated molecules activated following radiation generally enhance cell death and are reasonable targets for intervention, as are other molecules responsible for this collateral damage and the cell death process itself. Little is known of the importance of chromatin structure in this scenario, but radiation-induced cell kill is clearly not a random process and this is one factor that can affect it. One can imagine this system as being critical with a day or so of exposure and its manipulation could be of considerable benefit.

Damage sensors, such as the adenosinergic and toll-like receptor systems, play critical roles in sensing the extent of damage and limiting it. The development of cytoprotective hypoxia in concert with activation of cells surrounding the lesion by cytokines and growth factors shifts their molecular balance towards resisting cell death and microbial invasion and protective pathways are induced to limit damage through transcription factors such as NF-κB and Nrf2 that increase anti-oxidant levels. It follows that LPS and the pro-inflammatory cytokines like TNF-α and IL-1 that generate these conditions, if delivered before radiation exposure will be protective. The timing of agents that generate level 1 induced anti-oxidants may differ somewhat from those acting more on level 2 systems, but there may be some crosstalk. The pro-inflammatory, pro-oxidant nature of the initial destructive response to LPS and similar agents is likely to counter any beneficial effects if they are given after irradiation. Since the nature of the adenosinergic and toll-like receptors that are activated can dictate the nature of the subsequent cytokines that are produced, this is another balancing act that critically determines outcome and that needs further investigation. Importantly, after TBI these systems may be bombarded by PAMPS from microorganisms liberated through a radiation-damaged intestine. The nature of the microbiota and the extent to which TLRs expressed on epithelial cells generate innate local immunity are likely to be critical factors.

Importantly, this scenario must change into one where there is angiogenesis and cell proliferation leading to a regenerative response. Proliferative regeneration that follows

irradiation has been the subject of numerous normal tissue studies but little is known of the checks and balances that control it. Inherent in this phase are the factors that decide between tissue regeneration and tissue replacement, such as fibrosis. Ongoing inflammation would seem to be a negative factor in this process and the rapid transition to an anti-inflammatory, anti-oxidant milieu that also stimulates angiogenesis would seem of most benefit. However, while it is easy to use words “anti-inflammatory milieu” multiple factors contribute to each situation making a unique blend that is likely to require further more precise definition before fully understanding its consequences. What is known is that there is a time lag before normal tissues start to regenerate following irradiation that can be days, weeks, or months and this is of obvious relevance to interventions aimed at amplifying or prolonging this phase, or at removing negative influences. There is remarkably little research been conducted on how best to achieve these goals, in spite of recognition that recovery of the stem/progenitor cell populations must be critical for fully functional tissue repair.

Finally, the most promising aspect of these scenarios is that the need to restore homeostasis at many levels within multiple tissue systems, suggests multiple distinct targets for mitigation efforts that may be initiated days, weeks, or even months and years after exposure so as to rebalance deranged tissues. DNA repair processes, redox action, cytokines, ARs, TLRs, and stem/progenitor cells obviously serve as potential targets. In addition to tissue-specific targets, the fact that the innate immune system plays a key role not only in sensing “danger” but also in integrating repair efforts and in directing mesenchymal and epithelial cells to restore tissue function offers a wealth of new possibilities for intervention. Understanding how to direct this molecular and cellular orchestra will lead to more informed discovery of novel modifiers of radiation responses and their more extensive use.

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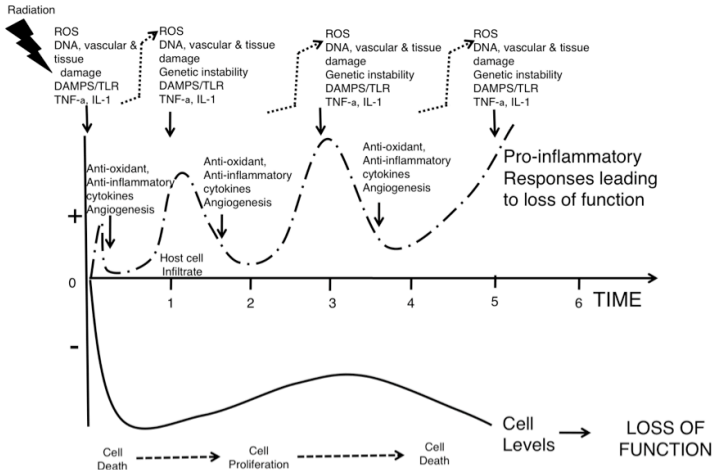

Fig. 1.

Cartoon showing waves of molecular and cellular pro-oxidant/anti-oxidant and pro-inflammatory/anti-inflammatory events leading to cell death, proliferation, and more cell death with functional loss of homeostasis in a tissue after irradiation.