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After the bomb drops: A new look at radiation-induced multiple organ dysfunction syndrome (MODS)

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Abstract

Purpose—There is increasing concern that, since the Cold War era, there has been little progress regarding the availability of medical countermeasures in the event of either a radiological or nuclear incident. Fortunately, since much is known about the acute consequences that are likely to be experienced by an exposed population, the probability of survival from the immediate hematological crises after total body irradiation (TBI) has improved in recent years. Therefore focus has begun to shift towards later down-stream effects, seen in such organs as the gastrointestinal tract (GI), skin, and lung. However, the mechanisms underlying therapy-related normal tissue late effects, resulting from localised irradiation, have remained somewhat elusive and even less is known about the development of the delayed syndrome seen in the context of whole body exposures, when it is likely that systemic perturbations may alter tissue microenvironments and homeostasis.

Conclusions—The sequence of organ failures observed after near-lethal TBI doses are similar in many ways to that of multiple organ dysfunction syndrome (MODS), leading to multiple organ failure (MOF). In this review, we compare the mechanistic pathways that underlie both MODS and delayed normal tissue effects since these may impact on strategies to identify radiation countermeasures.

Keywords

MODS; normal tissue delayed effects; combined injury

Normal tissue effects following a nuclear or radiological incident

The United States (US) Government has long been aware of the potential risk from an attack involving nuclear or radiological weaponry, but the threat level for such an incident has risen significantly since the events of 2001 (Poston 2005). Described in reports issued by the US Department of Homeland Security, the ‘best guess’ scenarios for such an event have fallen into five possible categories (Homeland Security Council 2005): (i) An attack on a nuclear power plant; (ii) the use of a simple radiological device; (iii) the use of a dispersal device, aka a ‘dirty bomb’; and, finally, the use of either (iv) an improvised or (v) sophisticated nuclear weapon. Interestingly, in the initial aftermath of ‘9/11’, the principal threat seemed to be from the use of a dirty bomb, a device that would lead to the terrorists’

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goal of increasing public terror, although it would be unlikely to result in many physical casualties (Gonzalez 2005). However, partly as a result of developments in Korea, Pakistan, and Iran over the past few years, the more recent 15 all-hazards planning scenarios that have been developed by the Federal interagency community include not only the detonation of a dirty bomb, but also the detonation of a 10-kiloton nuclear device. Other contemplated threats have included radioactive contamination of food and water supplies. Such scenarios involve a high probability of mass casualties that may have been exposed to external ionising radiation (neutrons, gamma) and/or external and internal contamination (Homeland Security Council 2009).

With this increased concern over US national security has come the realisation that, since the Cold War era, there has been very little progress regarding medical response efforts in the event of either a radiological or nuclear incident. Of deepest concern, only a limited number of agents are approved for mitigation or treatment of radiation injury, and few would be available in sufficient quantities to deal with circumstances involving mass casualties. To address this issue, the National Institute for Allergy and Infectious Disease (NIAID) has initiated a research program that has emphasised the development of countermeasure agents for use in the National Strategic Stockpile and, as a component of this effort, has established a network of Centers for Medical Countermeasures against Radiation (CMCR) (Department of Health and Human Services USA 2005), a collaborative network of academic institutions that has the primary goal of accelerating the identification, development and deployment of new medical countermeasures to be used in the aftermath of an event.

As part of the approval process for agents that may be used following such a catastrophic nuclear or radiological incident, however, one of the items of evidence that is required by the Food and Drug Administration (FDA) is a mechanistic understanding of the targeted disease; that is, an evidence-based biological explanation must be provided for the mechanism(s) leading to radiation-induced pathophysiology (Food and Drug Administration USA 2002). Fortunately, much is known about the immediate (or acute) consequences that are likely to be experienced by an exposed population, i.e., the acute radiation syndrome (ARS). The term ARS encompasses three types of 'radiation sicknesses': The so-called bone marrow, gastrointestinal (GI), and cardiovascular/central nervous system (CNS) syndromes (Andrews 1967, Hall and Giaccia 2006). Our mechanistic understanding of these syndromes comes from the well-documented observations of personnel following the detonation of nuclear weapons in Japan (Gilbert and Ohara 1984, Pierce et al. 1996) or exposed during weapons testing, the availability of records from radiation industrial accidents such as Chernobyl and Goiânia (International Atomic Energy Agency [IAEA] 1988, United Nations Scientific Committee on the Effects of Atomic Radiation [UNSCEAR] 2000, Mettler et al. 2007), as well as the large literature on the signs and symptoms seen in patients undergoing cancer therapy using total body irradiation (TBI) (Vriesendorp et al. 1994, West and Mitchell 2004). The syndromes are named according to the organ or tissue presenting with the most prominent signs and symptoms and are predicated on the relative radiation sensitivities of critical cell populations, in particular the stem/progenitor cells in the hematopoietic system and gastrointestinal villi, while the CNS syndrome reflects early onset endothelial cell damage and vascular leak. The severity and occurrence of each of the syndromes are, therefore, dose-related although the time to onset is related to the turnover rate of the critical cell population. In general, the associated dose ranges of each syndrome are highly predictive, with the proviso that an accelerated 'hematopoietic death' can occur at higher doses and, therefore, may be confused with 'GI death' (Mason et al. 1989, Rotolo et al. 2009). As a result, because any one tissue can contain more than one 'critical' subpopulation with varying radiosensitivities, the timing of a radiation response cannot be used as an absolute guide to what tissue is failing.

Because of the potential risk for overwhelming numbers of casualties suffering from ARS following a large-scale accident or terrorist event, federal attention initially focused on the development of treatment(s) for acute radiation injury and the critical need for 'after-the-fact' dosimeters and biomarker assays. Considerable progress has been made in these areas (Amundson et al. 2004, Epperly et al. 2008, Paul and Amundson 2008, Fu et al. 2009, Georges et al. 2009) and, although much work remains, the probability of survival from the immediate hematological crises after TBI has improved (Baranov et al. 1994, Vlasov and Kvacheva 1996, Hirama et al. 2003, Stone et al. 2004, Drouet and Hérodin 2010). As a result, focus has begun to shift towards later, more down-stream effects, seen in such organs as the GI, skin, and lung. The importance of these delayed responses is exemplified by the unfortunate deaths of accidentally exposed Japanese workers, who, despite heroic efforts made by the medical community, nonetheless succumbed to a mixture of chronic hematological and late-onset non-hematological complications (Endo and Yamaguchi 2003, Hirama and Akashi 2005). Indeed, a diverse range of delayed radiation-induced pathologies is now known to be associated with survival of acute high dose radiation exposure (Miller 1995, Preston et al. 2003, Kusunoki and Hayashi 2008). Unfortunately, with regard to the requirements of the FDA, our relative understanding of the mechanistic pathogenesis of delayed radiation-induced effects (versus acute) is far from clear, despite decades of research in the area of late effects. Additional radiobiological, physical and biological factors, such as tissue physiology (e.g., functional units, hierarchical composition), inherent wound repair responses (e.g., pro- and anti-inflammatory response or fibrosis pathways), radiation factors (e.g., dose rate, volume, radiation quality, heterogeneity of exposure, etc.) and extrinsic factors (e.g., physical or microbial damage) all appear to play a role in the development and progression of both delayed and late normal tissue responses to radiation. Indeed, the biological complexity of the responses means that damage can be manifested in many different ways and at different times.

A further complication is the fact that much of our understanding of specific late organ effects *per se* follows localised irradiation. Very little is known about the development of delayed effects in the context of whole body exposures, when it is likely that systemic perturbations may alter tissue microenvironments and homeostasis. However, although the patterns of delayed radiation-induced pathology are complex, the sequence of organ failures observed after near-lethal TBI doses is similar to that of multiple organ dysfunction syndrome (MODS) that can lead to multiple organ failure (MOF). In this respect, radiation is not dissimilar to injuries such as mechanical and thermal trauma, pancreatitis, sepsis, and shock (Meineke and Fliedner 2005, Monti et al. 2005). Furthermore, it is worth noting that the timeline of progression and the final outcomes seen following a number of accidental exposures bear considerable similarity to the progression of late pneumonopathies and/or nephropathies that can be seen in patients receiving TBI as part of cancer therapy for hematological disorders (Kal and van Kempen-Harteveld 2006, Oya et al. 2006, Carver et al. 2007, Cheng et al. 2008, Schneider et al. 2008).

These observations clearly suggest that the understanding of radiation pathologies seen after whole or extensive body exposure and, more importantly, their mitigation may be best considered as involving multiple, rather than individual, organs; in other words, the timing of onset and dose relationships following a catastrophic nuclear or radiological event may not relate to those dictated by classical radiobiological concepts. Indeed, with reference to the current literature, in general, MODS is considered as the final stages in a continuum of events associated with uncontrolled inflammatory responses and loss of vascular homeostasis. The syndrome can be caused by, or can contribute to, multiple primary events, including infection or release of bacterial products across damaged epithelial surfaces, hypoxia resulting from massive cell death, extensive burns and wound damage, and immune deficiency. Given the similarity between these symptoms and those that are

characteristically seen during ARS, the subsequent development of a MODS-like syndrome appears highly probable.

Multiple organ dysfunction syndrome as a model for radiation-induced multiple organ failure (RI-MOF)

In the same way that radiation-induced normal tissue late effects have emerged from successful cancer therapies, the history of physicians' recognition of multiple organ dysfunction syndrome is intimately related to progress in the support and treatment of acutely injured personnel (Mizock 2009). For example, in the Second World War, physicians observed that the provision of whole blood transfusions reduced the incidence of shock from wounds compared with the levels reported in the First World War, although some surviving patients developed post-traumatic renal failure. In more recent combat situations, treatments for the renal condition (i.e., the use of fluid resuscitation) allowed the incidence of subsequent respiratory failure (e.g., Da Nang lung) to become evident (Pearce and Lyons 1999). Gradually, it became apparent that, as medical technologies continued to enhance delivery of care, a new clinical syndrome was emerging that consists of a pattern of sequential failure in multiple organs, and this syndrome follows similar temporal progressions irrespective of the initial cause of injury (Skillman et al. 1969, Tilney et al. 1973, Baue 1975). In 1991, the term 'multiple organ dysfunction syndrome' was coined as a descriptor for this condition (Anonymous 1992), with one of its most recent definitions being "the development of potentially reversible physiologic derangement in 2 or more organs ... arising in the wake of a potentially life-threatening physiologic insult" (Marshall 2001), a definition that inherently allows for the development of MODS from multiple, both infectious and non-infectious, sources, i.e., including radiation injury.

Recent observations demonstrate a similar pattern of multi-organ failure subsequent to radiation injury. A late consequence of accidental radiation exposure in the form of the progressive and sequential impairment(s) in critical organs and tissues has been observed following the apparent recovery from the ARS that, despite medical efforts, nonetheless leads to delayed morbidity; this condition has been defined by some as *radiation-induced* multi-organ failure (Meineke and Fliedner 2005, Monti et al. 2005). As mentioned previously, one of the most spectacular examples of such a response occurred with the criticality accident at Tokai-mura in Japan in 1999 (Endo and Yamaguchi 2003, Hirama and Akashi 2005). In this incident, three employees, working for a company that manufactured nuclear fuel for power plants, were mixing batches of uranyl nitrate in the final steps of producing uranium for a fast reactor. In the course of trying to facilitate a speedier production process, the workers used a larger-than-normal container, but they exceeded its mass limit, resulting in criticality. All three of the employees were exposed to high doses of neutrons and g-rays and two of them rapidly exhibited a severe form of ARS as a result of the lethal radiation doses received by their bone marrow and skin (Hirama et al. 2003). During the course of the prompt and efficient medical interventions that were delivered, all three of the victims received intensive supportive care. In addition, the two employees exhibiting severe ARS were treated with hematopoietic stem cell transplantation and one subsequently demonstrated successful engraftment and bone marrow recovery (Nagayama et al. 2002). However, neither of these two personnel ultimately recovered: One developed respiratory failure, severe skin lesions and gastrointestinal bleeding, dying of MOF on day 82, whilst the second patient, the one who had shown evidence of a successful stem cell transplantation, developed severe skin lesions, which evolved into MOF with gastrointestinal bleeding and infectious complications, culminating in death on day 210 (Hirama et al. 2003).

The Tokai-mura incident offers dramatic examples of RI-MOF; other, less morbid outcomes include such symptoms as persistent bone marrow suppression and cutaneous effects (e.g., dermatofibrosis, radiation ulcers), all of which have been documented in surviving emergency personnel from Chernobyl (Gottlober et al. 2001, Konchalovsky et al. 2005) and have, therefore, been described as examples of radiation-induced multiple organ dysfunction syndrome (RI-MODS). Such outcomes were particularly evident under circumstances where there were significant levels of acute total or sub-total radiation burn due to beta exposure. Chronic radiation ulcers also were seen in soldiers exposed to whole body gamma doses alone from abandoned cesium and radon sources at Lilo Training Center in Georgia (Scherthan et al. 2007). Interestingly, other late effects that were observed in these latter individuals included persistently altered T-cell ratios, increased intracellular adhesion molecule (ICAM)-1 and β 1-integrin expression, and aberrant bone marrow cells and lymphocytes, suggesting that such delayed effects may involve a systemic inflammatory and/or immune injury in conjunction with the documented superficial radiation burns.

These findings corroborate the necessity for developing mitigators and/or treatments in the context of systemic radiation injury rather than simply expanding on strategies targeted at known late normal tissue effects in individual organs. But to strategically and successfully design and assess such agents requires an understanding of the mechanisms underlying RI-MOF or RI-MODS in order to both focus on potential targets for intervention as well as provide the requisite information for FDA approval (Food and Drug Administration USA 2002). The relatively low number of detailed and relevant cases of RI-MODS and RI-MOF could confound such attempts; fortunately, several of the key concepts that facilitate physicians' understanding of MODS coincide with current hypotheses that offer explanations for the underlying mechanisms that lead to radiation-induced delayed/late normal tissue effects. It is therefore possible to make use of the MODS literature and its attendant hypotheses, integrating these into classic radiation biology concepts to form a series of inter-connected pathways that provide a mechanistic explanation for the development of RI-MODS and RI-MOF (Figure 1).

Pathways to RI-MODS and RI-MOF

Classically, radiation biologists have believed that radiation-induced late effects were the downstream consequence of direct cell kill of critical target populations in the injured parenchyma leading to repopulation in the form of tissue remodeling. Therefore, it was thought that the length of time it took for symptom appearance was a result of the slower cell turnover time of critical cells in late responding tissues combined with a greater capacity for DNA repair (Withers et al. 1980). However, over the past 2–3 decades, such thinking has been modified so that the mechanisms underlying late-effect progression are believed to involve a continuum of more nuanced and complex responses that includes the induction and modification of normal reparative and restorative processes, changes in the tissue microenvironment, particularly in the cytokine milieu, and the influx of inflammatory cells prior to the development of the chronic tissue injury (Zhao and Robbins 2009). It is logical to assume that this complexity would increase further following systemic injury, when it is likely that the level of cross-talk between damaged organs and tissues would be expanded. Integrating both classical and modern radiobiological hypotheses into some of the concepts proposed for MODS induction, we hypothesise that the initiation and development of RI-MODS and RI-MOF involves three inter-connected pathways.

Pathway 1

Inflammation, immunity, and chronic Reactive Oxygen Species (ROS)

Pathway 1 includes both the acute and chronic development of inflammation and their associated cytokines, components that have been considered critical by many of the researchers looking at radiation-induced late effects for the past few decades and, thus, have formed the focus of many of the on-going mitigation efforts (Kaanders et al. 1999, Denham and Hauer-Jensen 2002). However, some investigators now have begun to expand on this field of research to suggest a greater role for an altered immune response in normal tissue injury (Schaue and McBride 2010). Alternatively, as a means of providing an explanation for the persistence of the aberrant wound-healing response seen in individual organs following radiation injury, other groups have examined the role played by chronic oxidative stress in late effect progression, in particular the contributions made by the production of reactive oxygen species in the mitochondria (Alsbeih et al. 2009). The inter-relationship of these three processes has led us to place them in a single pathway, although each individual process ultimately may provide targets for mitigation.

(a) Role of inflammation—There has been a classically held belief that MODS is the result of an excessive systemic inflammatory response to an initiating injurious trigger (Goris et al. 1985). A strong body of evidence in radiation biology similarly supports a role for acute and/or chronic inflammation in the development of normal tissue late effects and, therefore, in RI-MODS. We and others have shown that the immediate (i.e., within 1–24 hours) response to radiation injury in the lung following TBI is associated with an acute neutrophil infiltration (Johnston et al. 2009). Similar immediate responses, in the form of inflammatory cell migration and activation, have been observed by numerous investigators, not only in the lung (Franko et al. 1997, Hong et al. 1999), but also in other normal tissues, including brain (Hong et al. 1995, Olschowka et al. 1997, Kyrkanides et al. 1999), GI (Langberg et al. 1994), and skin (Xiao et al. 2006). However, this immediate inflammatory response is generally self-limiting and, therefore, may be considered to be part of normal canonical wound healing pathways. Indeed, coincident negative regulation also has been shown to occur through the expression of anti-inflammatory mediators, such as interleukin (IL)-10, transforming growth factor (TGF)-beta, and the prostaglandins (Kyrkanides et al. 2002, Moore et al. 2004).

Intuitively, a causal link between the acute inflammation and chronic outcomes appears unlikely because of the significant temporal delay between these events, particularly following low dose injury and the extended ‘latent period’. However, over the days, weeks, and months following irradiation, periods of increased pro-inflammatory molecular expression have been shown to recur in a cyclical fashion in irradiated normal tissues (Chiang et al. 1997), producing a pattern that was originally described as a ‘perpetual cytokine cascade’ (Rubin et al. 1995). The repetitive pattern of increases in expression levels of cytokines (Johnston et al. 1996, Randall and Coggle 1996, Peng et al. 1998, Daigle et al. 2001), chemokines (Johnston et al. 1998, 2002), prostaglandins (Ts’ao et al. 1983, Kyrkanides et al. 2002, Moore et al. 2004), and adhesion molecules (Hallahan and Virudachalam 1997a, 1997b) have been demonstrated in many normal tissues. It is interesting to note that such cyclical events also were observed in, and even proposed as a mechanism for, MODS as long ago as the 1980s (Cerra 1987). It is also worth noting that in the Tokai-Mura incident, the so-called ‘latent period’ was not particularly evident in the two more severely injured personnel, indicating that there may indeed be a quasi-continuum between the immediate inflammatory period and later events when part of RI-MODS.

Although it has not been proven conclusively that these ‘waves’ of cytokines have a functional link with the pathologic endpoint, nonetheless observations in the lung, for

example, support this hypothesis. During the acute radiation-induced phase, when there is significant upregulation of both pro-inflammatory cytokines and chemokines, inflammation is the predominant histological and physiologic feature, taking the form of macrophage infiltration into the air spaces and focal accumulations of mononuclear cells and mast cells found peribronchially, perivascularly, and in alveolar walls (Penney et al. 1982, Johnston et al. 2004, Haston et al. 2007); these events are accompanied by a decline in pulmonary function (Thomas et al. 2001, Hernberg et al. 2002). Interestingly, the specific subset of macrophages that is associated with the early pneumonitic period appears to express high cytokine levels and may, therefore, form a critical component of the pathogenic wave (Hong et al. 2003).

Such findings also hold true for the development of radiation-induced effects in other normal tissues. For example, associations between inflammation and cytokine expression have been suggested in the skin. In classic clinical studies performed by Turesson and co-workers, erythema was reported as appearing in 'waves', in keeping with the cyclical expression of the inflammatory mediators (Turesson and Notter 1986, Turesson et al. 1996). The erythema that was observed persisting after radiation treatment had been halted, was not restricted to the treatment field, and could be mitigated using anti-inflammatory agents (Simonen et al. 1998), supporting the possibility of a relationship between cytokine expression, inflammation and prolonged or delayed effects. In addition, in radiation models of brain injury, investigators have demonstrated periodic upregulation of a number of different cytokines (Kyrkanides et al. 1999, Daigle et al. 2001), cytokine receptors, cell adhesion molecules (Olschowka et al. 1997), and, although not correlated with specific inflammatory cells or inflammation events, nonetheless these appear to be related to the development of late neurological abnormalities (Chiang et al. 1997).

This non-specific, yet broad-based correlation between inflammation and normal tissue late effects has led many to investigate limiting the inflammatory reaction as a mitigating or preventative approach, particularly in light of the beneficial effects from both glucocorticosteroids and non-steroidal anti-inflammatory drugs that have been seen in irradiated organs and tissues (Michalowski 1994, Belkacemi et al. 1999, Magana and Crowell 2003, Kosaka et al. 2006, Sekine et al. 2006). For example, investigators have looked at the efficacy of an anti-inflammatory approach by modifying monocyte recruitment through the use of the multi-targeted agent, lovastatin (Merck and Co., Inc., West Point, PA, USA), a non-specific inhibitor of the chemokine, monocyte chemoattractant protein-1. Statin-treated animals demonstrated a statistically significant reduction in both macrophage and lymphocyte populations in the lung compared with radiation alone, as well as improved rates of survival (Williams et al. 2004). Similarly, while groups have demonstrated the upregulation of proinflammatory mediators in the brain following irradiation (Olschowka et al. 1997, Kyrkanides et al. 1999, Moore et al. 2005), others have shown that blockade of such inflammation restores late neurogenic dysfunction (Monje et al. 2003), further suggesting that inflammation plays a prominent role in the pathophysiology of delayed effects, both with respect to the individual organs and in the context of systemic injury.

Importantly, variations in pro-inflammatory cytokine expression have been reported between different tissues, although these appear to be related to magnitude and timing, rather than being of a qualitative nature (Vegesna et al. 1995, Johnston et al. 1996, 1998, Olschowka et al. 1997, Daigle et al. 2001). It is likely that this variability in response results from differences in models or targets and, therefore, might be related to either physical properties (i.e., radiation delivery factors) or biological factors (i.e., the relative cellular composition of individual tissues and genetic polymorphisms in cytokine-related genes and pathways). Thus, the number and functional status of the major cellular source(s) of the predominant cytokines (frequently macrophages) may characterise the overall expression of

cytokines and therefore have a major impact on tissue response. However, the receptor profiles of each tissue will likely determine which cells respond to the signaling molecules and, consequently, will define the tissue specificity of the final outcome (McBride et al. 2004).

In general, most cytokines act locally and influence cells only in their immediate vicinity. Few find their way into the circulation under normal circumstances and their half-lives there tend to be variably short. The presence of high levels of circulating pro-inflammatory cytokines, such as tumour necrosis factor (TNF)-alpha, and interleukins IL-1, IL-6, IL-8, etc., is an indication of ongoing pathogenic events; the clearest example of this is seen during life-threatening sepsis, which is one cause of MODS. It is not clear at this time how different organs respond to these systemic signals and how this influences their response to mitigators, but it is likely that there will be significant variation from organ to organ, especially when considering that many cytokines are multifunctional in nature and can induce both beneficial and detrimental effects. Perhaps the best-studied effect of the systemic activation of this cytokine network is through the hypothalamo-pituitary-adrenocortical axis (HPA) that results in neuroendocrine and behavioural effects. The link between inflammation and the neurological changes during infection is well known, but similar effects can be observed during irradiation or elicited by other causes of MODS. Less is known about responses of other organs.

(b) Role of immunity—In parallel with the hypothesis that inflammation is an intimate component of radiation-induced late effects, some investigators have suggested that immune dysregulation plays a more critical role than was previously thought. It has been proposed that the observed organ failure results from the loss of homeostasis between systemic inflammation and the counter-balancing anti-inflammatory responses (McBride et al. 2004, Demaria et al. 2005, Lugade et al. 2008, Schaeue and McBride 2010); immune dysregulation also has been proposed as being a critical player in the development of MODS (Mizock 2009). Both of these hypotheses, for radiation-induced effects and MODS, respectively, have evolved out of the infection and immunity literature, in particular from the concept that the body responds to ‘danger’ signals elicited by injured, dead, or dying cells. Even more tellingly, under conditions of chronic immune inflammation, antigens and, in particular, autoantigens, are thought to drive waves of pro-inflammatory responses, which may be brought under temporary control only to escape periodically (Atassi and Casali 2008), thereby providing an explanation for the observed cyclical waves of cytokines seen during the progression to radiation-induced late effects.

As part of the generation of an immune response, it has been demonstrated that mononuclear phagocytes (monocytes, tissue macrophages) and mast cells in the body recognise infection and trauma via pathogen-associated or damage-associated molecular patterns, respectively (Carta et al. 2009, Sato et al. 2009), through their surface Toll-like receptors (TLR) or other pattern response receptor families (Mogensen 2009). As part of MODS initiation, for example, TLR binding is a critical triggering step that ultimately leads to systemic activation of inflammation through signal amplification by cytokines and other mediators (Mizock 2009). Interestingly, recent studies have shown that airway innate immune response is dependent on radioresistant TLR5-expressing cells (Janot et al. 2009) and, therefore may provide an explanation for the observation that, following lung irradiation, TNFalpha, IL-1alpha, and IL-1beta are induced within hours of injury and these cytokines differentially persist until the development of pneumonitis and fibrosis (Johnston et al. 1995, 1996, Rubin et al. 1995). More recent work has demonstrated that this early upregulation can be seen even at doses that are below the threshold for pulmonary late effect induction (Johnston et al. 2009). Similarly, it has been shown that there is an early (within days) and robust

upregulation of TNF α and IL-1 β expression in microglia following CNS irradiation (Kyrkanides et al. 1999).

However, although there is a correlation between injury and the immediate proinflammatory cytokine response, both for the MODS trigger and the radiation damage, interestingly it is less clear how the body actually recognises and differentiates radiation damage *per se*. One clue may be offered by older literature, which indicates that both lipopolysaccharide and IL-1 provide significant levels of radiation protection (Stevenson et al. 1981, Neta 1997), strongly supporting the involvement of the TLR-IL-1 R superfamily in the radiation response. Such findings have led to a number of groups pursuing upregulation or stimulation of TLR as a potential radiation protective mechanism; for example, there are indications that the administration of flagellin (a molecular sub-unit purified from *Salmonella* flagellin), a TLR5 agonist that preferentially activates epithelial cells, may be useful for protecting against radiation injury in the gastrointestinal tract (Burdelya et al. 2008, Vijay-Kumar et al. 2008). More intriguing in respect to recent interests in mitigation rather than radioprotection is the intimate connection between inflammation and immunity, particularly through the activation and maturation of antigen-presenting cells (APC). The most powerful APC are dendritic cells and, for example, Lord and colleagues investigated the responses of epidermal (Langerhans cells) and interstitial dendritic cells to irradiation, demonstrating that there is a dose-related depletion of cutaneous dendritic cells following irradiation, with both populations sharing similar migratory kinetics following injury (Cummings et al. 2009). Furthermore, the group showed that the immunostimulatory cytokine, IL-12 (BD Biosciences, San Jose, CA, USA), mediated these effects. Such findings are significant since dendritic cells can belong to either macrophage or plasmacytoid lineages, so that late disruption of hematopoietic progenitors may affect dendritic cell responses, not only in the skin, but in many normal tissues of interest.

Finally, the revelation that dendritic cells are critical for the generation of cluster of differentiation (CD)-8 $^{+}$ cytolytic and CD4 $^{+}$ helper T cells (Banchereau and Steinman 1998) may have implications with regard to the significant T-cell infiltrations that have been identified as part of the late pathology in irradiated lung and brain, respectively. However, it is interesting to note that, in irradiated mouse brain, at least one study has shown no evidence for the expression of immune cytokines, such as IL-2, IL-4 or IL-12 (Hong et al. 1995), which may reflect the privileged nature of the brain and, therefore, may result in differential responses, with immune mechanisms assuming greater importance in other tissues, such as lung and skin. Despite these findings, it is known that a considerable degree of cross-talk exists between the central nervous system and the immune system (Tracey 2007) and, indeed, there has been speculation that MODS may be the result of autonomic dysfunction through the ‘uncoupling’ of neurally-mediated organ interactions (Godin and Buchman 1996). Such findings may have significance beyond the field of countermeasures given the current interest in low dose TBI for the treatment of some cancers (Safwat 2000, Feinendegen et al. 2007).

(c) Role of reactive oxygen species (ROS)—In addition to the concept of a ‘perpetual’ cycle of inflammation and cytokines that has been proposed as being critical to the process of progression in normal tissue radiation injury, a number of investigators have focused on the generation of reactive oxygen/nitrogen oxide species (RNOS) by the abnormally upregulated inflammatory cells (Zhao and Robbins 2009). Of course, it is widely appreciated that the immediate (indirect) damage that is seen as a result of ionising radiation exposure is principally due to a robust, though extremely transient, production of ROS (Travis 2001, Hall and Giaccia 2006). However, the observed downstream patterns of inflammatory cell recruitment and cytokine generation (Rubin et al. 1995, McBride et al. 2004) themselves may lead to the generation of chronic pathological levels of ROS/RNOS,

and so these potentially harmful species have been hypothesised as additional contributors to the progression towards tissue deficits. Indeed, indirect data suggest that ROS, released by nicotinamide adenine dinucleotide phosphate (NADPH) oxidase, xanthine oxidase, and nitric oxide (NO) synthase activity, are the products of a radiation-induced dysfunctional mitochondrial respiratory chain. Thus chronic ROS production may play a pivotal role in delayed normal tissue injury since it has been seen in normal tissues in the weeks to months following radiation injury (Kergonou et al. 1981, Cruthirds et al. 2003, Gutierrez et al. 2006), including in brain (Di Toro et al. 2007, Rola et al. 2007), skin (Benderitter et al. 2007), and bone marrow (O'Brien et al. 2008). Interestingly, similar links between mitochondrial dysfunction and the pathogenesis of MODS also have been identified (Ozawa et al. 1983, Exline and Crouser 2008), with studies showing correlations between NO overproduction, antioxidant depletion, mitochondrial dysfunction, and reduced adenosine triphosphate concentrations with MOD-associated organ failure and other adverse outcomes (Brealey et al. 2002, Singer et al. 2004). However, more importantly, the existence of a functional link between oxidative stress and radiation damage has been suggested, particularly in the lung, as a result of the successful use of radical scavengers in reducing late effects (Epperly et al. 1998, 1999, Rabbani et al. 2005, 2007).

Pathway 2

Barrier integrity

It long has been presumed by many radiation biologists that the effect of radiation on blood vessels has profound implications on late normal tissue radiobiology. Indeed, for decades, there were two principal and opposing hypotheses that were used to explain normal tissue late effects: one which assumed that the target cells for late tissue injury were stem cells in critical populations in the parenchyma (cell loss leading to repopulation and/or tissue remodeling) (Casarett 1964), whilst the other assumed that the critical target cells were the vascular endothelial cell population (Hopewell 1979), so that the fundamental underlying cause of late effects was dysfunction in the microcirculation. The more recent approach to the mechanisms underlying late radiation injury modifies the earlier emphasis on target cells *per se*; however, the hypothesised roles played by the immune response, hypoxia, and cellular infiltration in late effect progression returns scientific focus not only to the vascular system, but also to barrier integrity.

A significant volume of work from investigators such as Fajardo and colleagues has described the effects of radiation on the endothelial cell population (Archambeau et al. 1984, Fajardo 1989, Fajardo et al. 2001). Furthermore, the radiation-induced increase in the expression of genes associated with inflammatory and coagulation processes, including the specific upregulation of adhesion molecules (Van der Meeren et al. 2003), and the demonstrated association between a reduction in coagulation proteins through the use of thrombopoietin and reduced mortality following TBI (Van der Meeren et al. 2004) supports the critical role played by the endothelial cells in radiation-associated inflammatory and thrombotic processes. Such studies have increased our understanding of endothelial cell function, demonstrating that these cells do not simply act as the barrier lining of blood vessels, but also are involved in multiple homeostatic processes, including providing functional elements in inflammation and immunity, coagulation and angiogenesis (Tilki et al. 2009). Importantly, radiation injury appears to disrupt many if not all of these functions and exacerbation is a likely result from high dose TBI.

Early pathologic lesions can be detected in endothelial cells in the form of swelling of the cytoplasm, irregularities in the plasma membrane leading to the formation of pseudopodia, which together with the swollen cytoplasm, can lead to vessel blockage, resulting in areas of tissue hypoxia (Vujaskovic et al. 2001). Physiologically, loss of cells through direct cell

killing can result in breakdown in vessel wall integrity, leading to alterations in vascular permeability that have been seen both preclinically and clinically following irradiation (Etiz et al. 2000, Yuan et al. 2006). Again, although such changes have not yet been linked directly to the waves of expression of 'danger' signals discussed earlier, endothelial cells express receptors for TNF and IL-1 and other cytokines and may respond directly to their presence. Alternatively, radiation-induced vascular damage may allow cytokines to penetrate the barrier and enter tissues from the circulation. TNF and vascular endothelial growth factor (VEGF), in particular, are known to precipitate progressive changes in the hemostatic balance and alterations in blood flow in the microvasculature even in the absence of radiation damage, and this is likely exacerbated at varying times after exposure. In this context, an initiating vascular lesion could be sufficient to stimulate further vascular dysfunction or parenchymal cell proliferation and radiation-induced cell death, leading to organ failure with an accelerated time course.

Changes in vascular function have been observed in many normal tissues, including the lung (Osterreicher et al. 2004), skin (Schwint et al. 1990), and brain after irradiation. For example, cerebrovascular dysfunction, characterised by compromise of the blood-brain barrier, is commonly seen after localised, high dose brain irradiation, and the resultant acute development of cerebral edema may contribute to the later effects of vascular collapse, hypoxia, and white matter necrosis. Further, investigators have previously identified that early radiation-induced changes in vascular permeability in the brain, leading to edema, are dependent upon cyclooxygenase (COX)-2 activity (Moore et al. 2004), suggesting a potential role for inflammation in vascular dysfunction. Other investigators have indicated that there are distinct and radiation-specific changes in the blood-brain barrier involving a size-dependent increase in permeability, affecting paracellular transport via an upregulated ICAM-1 pathway (Yuan et al. 2003). The critical role that the bone marrow vascular niche plays in hematopoiesis, both as a conduit to the peripheral circulation and as a site for hematopoietic progenitor differentiation (Kopp et al. 2005), suggests a link between damage to the vasculature and both ARS and RI-MODS.

Overall, the relationship between inflammation and vascular permeability in all normal tissues may be 'a chicken or the egg' question; endothelial hyperpermeability appears to be a significant component in vascular inflammation associated with trauma including irradiation, ischaemia-reperfusion injury, sepsis, adult respiratory distress syndrome, diabetes, thrombosis, and cancer (Kumar et al. 2009). Inflammatory stimuli, such as radiation injury, activate neutrophils (Johnston et al. 2009) as well as upregulate such factors as VEGF and TNF α (Fleckenstein et al. 2007). These factors can cause dissociation in the cell-cell junctions between endothelial cells, leading to a widened intercellular space that facilitates transendothelial flux, and this effect would be compounded further by direct or indirect radiation-induced endothelial cell kill. Mechanistically, the downstream structural changes in the endothelial barrier are initiated through agonist-receptor binding, followed by activation of intracellular signaling molecules, including protein kinase C, tyrosine kinases, and small Rhoguanosine triphosphate (GTP)ases; these kinases and GTPases then phosphorylate or alter the conformation of different subcellular components that control cell-cell adhesion, resulting in the observed paracellular hyperpermeability (Yuan et al. 2003); such pathways may offer targets for mitigation.

However, the vasculature is not the only barrier in the body and, furthermore, it is not the only barrier affected by radiation. For example, radiation-induced loss of crypt cells can lead to a breakdown in the complex intestinal environment, in particular in the epithelial mucosal layer, with the result that infection is a major cause of death as part of the ARS (Mettler and Upton 1995). Numerous studies have compared conventionally housed and germ-free mice with respect to the lethal effects of TBI doses in the ranges that result in death from bone

marrow and gut functional insufficiency (6–13 Gy). In all cases, the lethal dose, whether for gamma- or X-rays (Wilson 1963, McLaughlin et al. 1964, 1971) or neutrons (Jervis et al. 1971), was lower in conventionally housed mice. These differences are often attributed solely to immune deficiency, but also probably include radiation-induced failure of the dynamic epithelial interface where commensals compete with acquired pathogens (Macdonald and Monteleone 2005) leading to bacterial translocation. Infection was also the primary cause of death in those patients who died from large area beta burns at Chernobyl (Mettler et al. 2007), suggesting that skin integrity may play as important a role in homeostasis following TBI injury as does the gastrointestinal tract. In general, the response to wounds involves mobilisation of phagocytes and precursor endothelial cells from the bone marrow; after TBI, this response may be compromised and the presence of microbial products could activate any cells that are recruited to produce high systemic levels of pro-inflammatory cytokines leading to RI-MODS so that elimination or control of micro-organisms may reduce late effects (Kaanders et al. 1999).

Pathway 3

Stem/progenitor cell loss

The most basic and fundamental consequence of radiation injury is cell death as a result of macromolecular damage, most importantly in the DNA. Injured cells ‘choose’ to die through a number of pathways, for example, by apoptosis or through mitotic catastrophe: apoptosis takes place within hours of the initial injury, although there may be downstream secondary waves of apoptotic death (Blagosklonny 2007, Mora and Regnier-Vigouroux 2009), whereas mitotic catastrophe requires, as the name implies, passage through the mitotic phase of the cell cycle and, therefore, may take days or even weeks to occur. In the clinical literature, the characteristic description of acute radiation sensitivity is frequently associated with a pro-apoptotic phenotype; for example, immediately following irradiation, lymphocytes upregulate such pro-apoptotic genes as FAS (TNF receptor superfamily, member 6), B-cell lymphoma-2 (BCL2)-associated X (BAX), and caspase-3, whilst down-regulating members of the BCL2 family, leading to extensive radiation-induced apoptosis within hours of injury (Drouet et al. 1999, Tannock et al. 2005). However, it has been observed that, in general, only 10–15% of cells will die via an apoptotic form of death, with the majority of cells dying through mitotic catastrophe-related mechanisms.

Classically, it was believed that hematopoietic and GI stem cells were highly radiosensitive since they were in areas that displayed radiation-induced apoptosis (Hall and Giaccia 2006), whilst loss of critical stem cells, particularly from the parenchyma, that were stimulated to express damage while dividing to replace lost cells provided the mechanism for late effect development. Certainly, the kinetics of the bone marrow syndrome, i.e., the observed progressive symptoms of granulocytopenia, thrombocytopenia and anemia, can be explained by transit time and time to depletion of the more functional cell compartments. It is important to note that acute systemic injury of the hematopoietic system also has been observed following internal contamination, by either inhalation or ingestion, and therefore may be seen following detonation of a dirty bomb or as a result of inhalation or ingestion from fallout (Vogel 2007, Jefferson et al. 2009). However, in recent years, the scientific community has become increasingly aware that stem cells, including those in the hematopoietic system, reside within protected ‘stem cell niches’. The principal function of these niches is to preserve stem cell proliferative potential and multipotency, assuring controlled stem cell renewal and activation for tissue regeneration (Porter and Calvi 2008, Raymond et al. 2009). Niche regulation, particularly in the bone marrow, requires establishing a balance between self-renewal and differentiation, with this balance becoming critical during times of injury.

Many groups have helped to characterise the bone marrow stem cell niche(s) (Adams et al. 2007, Frisch et al. 2008, Porter and Calvi 2008, Raymond et al. 2009) and, in terms of regulation, have shown that it occurs through cells within the bone marrow microenvironment, an environment that includes, for example, the osteoblasts (Calvi et al. 2003), osteoclasts (Kollet et al. 2006), and endothelial cells (Porter and Calvi 2009), and is likely maintained through cell-cell and cell-extracellular matrix interactions. With respect to radiation injury specifically, some investigators have shown that the bone marrow stem cell niche is relatively hypoxic (Parmar et al. 2007) and since the stem cells appear to exist in a quiescent or very slowly cycling state (Harrison and Astle 1982, Schaniel and Moore 2009) they are therefore, relatively radio-resistant. As a result, the subsequent observed loss of blood cell elements may be due to the sensitivity of the less quiescent hematopoietic stem cell (HSC) niches, i.e., that of the 'short-term' HSC (Huang et al. 2008) and/or the multi-potent daughter/progenitor cell populations. Indeed, mitigation using antiapoptotic cytokines targeting CD34+ cells, a heterogeneous compartment of short-term HSC and progenitor cells, has been shown to improve survival and accelerate recovery from TBI (Drouet et al. 1999). In addition, there are indications that there are significant and differential changes in stem cell and progenitor populations during the acute response period (Peslak et al. 2010). As a consequence, subsequent recovery and reconstitution of the hematopoietic system following TBI would occur through the mobilisation and differentiation of the undamaged or more protected HSC (Quesenberry et al. 2005, Greenberger and Epperly 2009), offering an explanation for the successes seen through the use of conservative care alone (Baranov et al. 1995, Georges et al. 2009). Importantly, strategies are being developed that specifically target the bone marrow niche, for example by either reducing cell loss through antiapoptotic therapies (Hérodin et al. 2007) or assisting with regeneration (Himburg et al. 2010) that may provide further mitigation in the higher dose ranges, although the role that such strategies may play with respect to delayed or late damage is less certain.

In addition to its acute response to radiation, there are indications from earlier literature that there may be long-term expression of damage in the bone marrow compartment (Hendry 1985, Bierkens et al. 1989). This is supported by more recent data showing evidence of significant late injury to the hematopoietic system following both external irradiation and internal contamination, with the most striking findings being a significant decrease in short-term HSC numbers and function (Peslak et al. 2010). The chronic changes (particularly in the context of internal contamination, which results in a persistent low-dose systemic irradiation) are consistent with previous observations by other investigators (Seed et al. 2002a, 2002b, Simonnet et al. 2009). These findings, together with the contributions that hematopoietic progenitor cells make to ongoing recruitment and activation of inflammatory and immune cells and the known disruption of the bone marrow microenvironment (Gevorgyan et al. 2007, Schultz-Hector and Trott 2007), suggest that the delayed normal tissue injuries seen in the context of total body exposures may involve long-term effects on hematopoiesis and dysfunction of HSC, as well as support the concept of cross-talk taking place between all three of the proposed pathways. Importantly, such disruptions may have both indirect and direct downstream consequences on delayed effects in other tissues and organs as a result of alterations in the inflammatory and immune cell responses; for example, there have been suggestions by some that bone marrow-derived progenitor cell populations could play a role in wound healing as well as late radiation fibrosis in different tissues (Kotton et al. 2001, Krause et al. 2001, Hess et al. 2002, Epperly et al. 2003). Also, as described earlier, disruption of the bone marrow microenvironment can affect the differentiation of immune cells, such as murine dendritic cells into osteoclasts, through the interaction between bone and the immune system (Wakkach et al. 2008).

Finally, classic radiobiological theory suggests that changes in stem cell content and disruption of the individual functional subunits that form the structural organisation of these

tissues are critical events in homeostatic dysregulation. In addition to the bone marrow, stem cell niches exist in other organs, including the nervous system and skin (Raymond et al. 2009). Indeed, research has shown that the stem cells in the subgranular zone of the adult brain are sensitive to radiation, with injury and cell loss affecting neurogenesis and, potentially, cognitive function (Fike et al. 2009); these changes have been related to the redox and inflammatory states (Monje et al. 2003, Limoli et al. 2007, Rola et al. 2007). Since neurotransmitter signalling is a part of host defence and repair mechanisms, the physiological interactions between the nervous, immune, and hematopoietic systems are an important endpoint (Spiegel et al. 2008) and, again, may have relevance beyond the field of countermeasures.

Additional considerations

One final hypothesis regarding the promotion of post-traumatic MODS is known as the 'two-hit' model (Mizock 2009). This theory suggests that the first hit or injury 'primes' the responding leukocytes, so that a subsequent, apparently minor insult (the 'second hit') generates the excessive inflammatory response that ultimately leads to MODS. Similarly, the biomedical consequences of radiation exposure have been shown to be significantly exacerbated by concurrent trauma and disease (Pellmar and Ledney 2005). In vitro studies have shown that irradiation has more of a priming effect on pro-inflammatory cytokine production than directly promoting high levels of secretion; an additional lipopolysaccharide stimulus, however, results in very high levels (Chiang and McBride 1991). These findings are significant given the likelihood of combined injury in a radiological or nuclear event (DiCarlo et al. 2008). In a recent publication by Kiang et al. (2010), the investigators suggest that, as hypothesised previously, radiation promotes an imbalance between pro-inflammatory and anti-inflammatory cytokines, leading to immunological dysfunction. This results in the combined injury aggravating the initial traumatic injury, further disturbing homeostasis (Jiao et al. 2009). Indeed, exacerbation in the pulmonary response to an additional injury, whether bacterial (Manning et al. 2009), viral (Manning et al. 2010), or fungal (Downing et al. 2009), has been shown; the increased response occurs not only when the two traumatic events are delivered concurrently, but also when there is a delay between the events. Finally, the evident breakdown in the barrier integrity of the skin following trauma with respect to wound healing has long been known to be affected by radiation (Benderitter et al. 2007, Hao et al. 2009). Overall, such findings are not novel (Gruber et al. 1985). They indicate that the body has evolved efficient mechanisms to deal with local failure within tissues and organs but has minimal ability to cope with failure of systems that are common to multiple tissues and that can be affected by multiple causes. The resulting disturbance of homeostasis can result potentially in life-threatening situations due to MOF. They provide further support for consideration of systemic effects when pursuing countermeasures for radiation exposure. Indeed, the complexity of the underlying mechanisms suggests that mitigation of any single pathway or process is unlikely to provide full amelioration of the damage and that a combined approach will be required.

On a final note, to date the cases where RI-MODS and RI-MOF have been observed and described have involved TBI doses that have been in excess of the accepted dose that leads to 50% lethality within 30 days of exposure (the LD_{50/30} exposure level) for humans, but where the symptoms associated with ARS were successfully treated. However, it is worth noting that, in general, the calculated doses received were below the accepted threshold levels for the individual therapy-related late effects seen in many of the involved normal tissues. Although dose heterogeneity may account for some of this differential, the observation supports the complexity of the underlying mechanisms RI-MODS and RI-MOF, but, more importantly, the role of systemic injury in exacerbating the individual response of each organ leading to the development of the delayed syndrome. Indeed, work from one of

our own groups has shown that immediate cytokine expression in the lung is greater following TBI versus thoracic irradiation alone, even when the lung is exposed to an identical dose in each case (Johnston et al. 2009), and TBI exposure was associated with more robust late events. However, a significant issue, which is yet to be resolved, is the relative 'weight' played by each of the proposed putative pathways or individual processes in the delayed syndrome or whether the systemic involvement is predicated on greater injury in one or more critical organs or tissues; heterogenous dose exposure would add a further confounding element. Of note, a recent report (Fliedner et al. 2009) supported METREPOL (Medical Treatment Protocols for Radiation Accident), which grades the severity of response in the neurovascular, hematopoietic, gastrointestinal systems, and skin, and provides a multiorgan assessment; however, this is currently applicable only to the acute response (Gorin et al. 2006).

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Figure 1.

Stylised overview of the proposed mechanisms leading to radiation-induced multiple organ dysfunction syndrome (RI-MODS) or RI-multiple organ failure (MOF) following total body irradiation. We have hypothesised that the initiation and development of RI-MODS and RI-MOF involves three inter-connected pathways, all of which have their roots in fundamental radiobiological principles: Pathway 1 identifies the inter-relationship between radiation-induced alterations in both localised and systemic inflammatory and immune status, and the potential role played by chronic reactive oxygen species (ROS) production in these changes; Pathway 2 suggests a greater, more integrative role may be played in the development of delayed radiation effects by the disruption in barrier integrity, particularly at the vascular level, including the blood-brain barrier (BBB); Pathway 3 highlights the tissue deficit that may occur due to stem/progenitor cell loss. Without mitigation, the outcome for any single survivor of the acute radiation syndrome will be the result of the severity and deficits experienced in any or all of these related pathways.