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Ionizing Radiation: The Good, the Bad, and the Ugly

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Abstract

Skin changes from ionizing radiation have been scientifically documented since 1902 (Hymes *et al.*, 2006). Ionizing radiation is a widely accepted form of treatment for various types of cancer. Despite the technological advances, radiation skin injury remains a significant problem. This injury, often referred to as radiation dermatitis, occurs in about 95% of patients receiving radiation therapy for cancer and ranges in severity from mild erythema to moist desquamation and ulceration (McQuestion, 2011; Salvo *et al.*, 2010). Ionizing radiation is not only a concern for cancer patients, but also a public health concern due to the potential for and reality of a nuclear and/or radiological event. Recently, the United States has increased efforts to develop medical countermeasures to protect against radiation toxicities from acts of bioterrorism, as well as cancer treatment. Management of radiation dermatitis would improve the therapeutic benefit of radiation therapy for cancer and potentially the mortality expected in any “dirty bomb” attack (Benderitter *et al.*, 2010; Muller and Meineke, 2010). Currently, there is no effective treatment to prevent or mitigate radiation skin injury. This review summarizes “the good, the bad and the ugly” of current and evolving knowledge regarding mechanisms of and treatments for radiation skin injury.

Current Understanding: Perception of Radiation Skin Injury

Radiation Exposure

Radiation injury involves morphological and functional changes that occur in noncancerous or “normal” tissue as a direct result of ionizing radiation (Mendelsohn *et al.*, 2002). Beta radiation can penetrate several centimeters into the skin, whereas gamma radiation can penetrate through skin and into the human body (Wolbarst *et al.*, 2010). The degree of radiation injury is related to the total radiation dose, proportion of body irradiated, volume of tissues irradiated, and the time interval of received radiation dose (Cox and Ang, 2010; Hall and Giaccia, 2006). The most radiosensitive cells in the body are those which are highly proliferative and sufficiently oxygenated. The most radiosensitive organ systems are bone marrow, reproductive and gastrointestinal systems, skin, muscle, and brain (Cox and Ang, 2010; Hall and Giaccia, 2006). Organ systems are more tolerant of low dose radiation exposure over a long period of time, as used in fractionated radiotherapy, compared to high local radiation exposure or total body irradiation (Cox and Ang, 2010; Hall and Giaccia, 2006). For example, radiotherapy for breast cancer involves fractionated radiation doses of ~2 Gy for six weeks for a total radiation dose of ≥50 Gy. A total body irradiation dose of 100 Gy would result 100% chance of death within hours of radiation exposure (Cox and Ang, 2010; Hall and Giaccia, 2006). The total body irradiation dose in which death will occur in 50% of individuals (LD_{50}) is 3-4 Gy (Cox and Ang, 2010; Hall and Giaccia, 2006). Although the kinetics of the clinical signs of radiation exposure may differ between cancer

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radiotherapy and a “dirty bomb” attack, the symptoms and syndromes in exposed organ systems are similar (Williams and McBride, 2011).

Radiation Skin Injury

The main function of skin is to establish an effective physical and immunological barrier against the surrounding environment. The epidermis, the outermost layer of the skin primarily composed of stratifying layers of keratinocytes, functions as the primary barrier and biosensor to the external environment. The dermis is immediately underneath the epidermis providing the skin's structural strength. It is primarily composed of connective tissue produced by dermal fibroblasts. Skin is susceptible to radiation damage because it is a continuously renewing organ containing rapidly proliferating and maturing cells. The basal keratinocytes, hair follicle stem cells, and melanocytes are highly radiosensitive (McQuestion, 2011; Mendelsohn *et al.*, 2002). Radiation skin injury involves immediate damage to basal keratinocytes and hair follicle stem cells, followed by a burst of free radicals, irreversible double-stranded breaks in nuclear and mitochondrial DNA and inflammation (Eide and Weinstock, 2005; Hymes *et al.*, 2006; Lopez *et al.*, 2005; McQuestion, 2011; Mendelsohn *et al.*, 2002). During radiation therapy, the first fractionated dose of radiation destroys a percentage of basal keratinocytes, resulting in a disruption in the self-renewing property of the epidermis (McQuestion, 2011). These repeated exposures do not allow time for cells to repair tissue or DNA damage. Although the remaining keratinocytes are stimulated to proliferate, these cells are continually destroyed with each fractionated radiation treatment. Therefore, it is not surprising that cancer patients undergoing radiation therapy experience skin reactions, as well as other symptoms (Hickok *et al.*, 2005). Radiation skin injury occurs in about 95% of patients receiving radiation treatment for cancer (McQuestion, 2011; Salvo *et al.*, 2010). Radiation skin injury has also been reported in over 70 cases of fluoroscopically guided procedures due to the lack of awareness of radiation exposure to skin during the procedure (Brown and Rzucidlo, 2011). Reported entrance doses from fluoroscopically guided procedures have ranged from 2 - 58 Gy (Brown and Rzucidlo, 2011). Radiation skin toxicities can negatively affect the quality of a patient's life due to pain and premature interruption of radiation treatment which, in turn, may impair control of disease (Duncan *et al.*, 1996; McQuestion, 2011; Robertson *et al.*, 1998; Salvo *et al.*, 2010). Despite substantial improvements in radiation technology, such as intensity-modulated radiation therapy (IMRT), radiation skin injury is still a concerning problem (McQuestion, 2011; Pignol *et al.*, 2008; Salvo *et al.*, 2010).

Radiation skin injury can be categorized as acute or late (*i.e.*, chronic) injuries (Table 1). Acute injury occurs within hours to weeks after radiation exposure, whereas late injury presents months to years after radiation exposure (McQuestion, 2011; Mendelsohn *et al.*, 2002; Salvo *et al.*, 2010; Wolbarst *et al.*, 2010). Individuals who experience severe acute injury are not more susceptible to severe late injury (Meyer *et al.*, 2011). Acute radiation skin injury primarily involves cellular alterations and inflammation in the epidermis and the dermis. Acute effects begin with erythema, edema, pigment changes, and depilation. Even though, histological analyses of irradiated skin show hyperproliferation of the epidermis and thickening of the stratum corneum; transepiderml water loss (TEWL), a measure for skin barrier integrity, is significantly increased (Jensen *et al.*, 2011; Schmuth *et al.*, 2001). Severe radiation injury results in complete loss of the epidermis and persistent fibrinous exudates and edema. Reepithelialization begins within 10-14 days after radiation exposure in the absence of infection (McQuestion, 2011). About a year after radiation exposure, the skin is thin, hypovascularized, tight, and susceptible to trauma or infection (Mendelsohn *et al.*, 2002). Chronic radiation skin injury includes delayed ulcers, fibrosis, and telangiectasias that present weeks to years after radiation exposure (Bridges and al., 2007; Brown and Rzucidlo, 2011; Mendelsohn *et al.*, 2002).

For many years, radiation burns (i.e., radiation skin injury) have been treated using the same therapeutic measures applied to thermal burns. However, the pathophysiology of radiation burns differs from thermal burns in three major ways (Bey *et al.*, 2010; Lataillade *et al.*, 2007). First, radiation burns have a dose-dependent clinical pattern, which includes dry desquamation at 12-20 Gy, moist desquamation at ≥20 Gy, and necrosis at >35 Gy (Bey *et al.*, 2010; Brown and Rzucidlo, 2011; Hymes *et al.*, 2006; Mendelsohn *et al.*, 2002; Wolbarst *et al.*, 2010). Secondly, radiation burns are associated with opiate-resistant chronic pain (Bey *et al.*, 2010; Lataillade *et al.*, 2007). The most complicating factor of radiation burns is the unpredictable successive inflammatory waves occurring weeks to years after radiation exposure (Bey *et al.*, 2010; Lataillade *et al.*, 2007). These uncontrolled inflammatory waves make it difficult to delineate the radiation-injured tissue from non-injured tissue. Conventional treatment for severe radiation burns combines surgical excision of damaged tissue and reconstructive surgery, such as full-thickness skin grafts (Bey *et al.*, 2010; Lataillade *et al.*, 2007). However, successive inflammatory waves often lead to impairment and necrosis of the newly grafted skin. Therefore, the majority of severe radiation burns require successive surgical excisions and reconstructions, as well as amputation (Bey *et al.*, 2010; Lataillade *et al.*, 2007). Overall, the healing of radiation burns is extensive and unpredictable.

Risk Factors

Both treatment- and patient-related factors can contribute to risk of developing severe radiation skin injury. Technical factors with radiotherapy that influence the degree of radiation skin injury include: radiation dose to skin, irradiation site, fractionation timing, total exposure time, and angle of radiation beam (Brown and Rzucidlo, 2011; McQuestion, 2011). The dose of radiation at the skin is directly related to the severity of injury. Different skin areas of the body have different sensitivities to radiation. The most sensitive skin regions of the body are the anterior of the neck, extremities, chest, abdomen, and face (Brown and Rzucidlo, 2011). Additionally, hair follicles on the scalp and breast tissue are both radiosensitive compared to other regions of the body (Brown and Rzucidlo, 2011). Patient-related factors include preexisting conditions, obesity, age, gender, chronic sun exposure, smoking (Brown and Rzucidlo, 2011; Hymes *et al.*, 2006; McQuestion, 2011; Salvo *et al.*, 2010). Individuals with ataxia telangiectasia (AT) and hereditary nevoid basal cell carcinoma syndrome (Gorlin Syndrome) require dose alterations or avoidance of radiation exposure (Hymes *et al.*, 2006). Individuals with AT, a rare autosomal-recessive disorder resulting in mutations in the ATM gene, are highly susceptible to severe radiation dermatitis. Irradiation of individuals with Gorlin Syndrome could produce widespread cutaneous tumors. Other disorders that increase risk of radiation skin injury include connective tissue disorders (lupus; scleroderma), chromosomal breakage syndromes (Fanconi's anemia; Bloom syndrome), xeroderma pigmentosa, Gardner's syndrome, hereditary malignant melanoma, and dyplastic nevus syndrome (Hymes *et al.*, 2006). Patients that are older and female have increased risk of radiation skin injury (Brown and Rzucidlo, 2011; Hymes *et al.*, 2006; McQuestion, 2011; Salvo *et al.*, 2010). A recent study in head and neck cancer patients reported that females were at higher risk for acute and late radiation-induced toxicities (OR= 1.72 and OR = 3.96, respectively) compared to males (Meyer *et al.*, 2011).

Other risk factors for severe radiation skin injury are increased TEWL and infiltration of pathogens or bacteria into the skin (Elliott *et al.*, 1990; Hill *et al.*, 2004; Ledney *et al.*, 1991; Martin *et al.*, 2010). Severe radiation dermatitis for localized radiation has previously been linked to *Staphylococcus aureus* infection (Hill *et al.*, 2004). Host antimicrobial defenses are severely compromised by radiation and/or skin trauma combined with radiation (Ledney *et al.*, 1991). Even mice exposed to sublethal total body radiation have increased susceptibility

to bacterial infections in wounds (Elliott *et al.*, 1990; Konchalovsky *et al.*, 2005; Ledney *et al.*, 1991; Williams and McBride, 2011). It appears that ionizing radiation damage in the skin is somewhat similar to atopic dermatitis. Atopic dermatitis (AD), a common form of eczema, affects up to 20% of children in the US, and is widely accepted to have a profound defect in the stratum corneum function and increased transepidermal water loss (Choi and Maibach, 2005; Imokawa, 2001; Jungersted *et al.*, 2008; Laughter *et al.*, 2000; Murata *et al.*, 1996; Pilgram *et al.*, 2001). AD patients are far more susceptible to skin infections by organisms such as *Staphlococcus aureus* and *Herpes simplex* (Kedzierska *et al.*, 2008; Lebre *et al.*, 2008; Niebuhr *et al.*, 2008; Scott *et al.*, 2007). It has been speculated that AD individuals would be more susceptible to severe radiation skin injury, however the definitive answer has yet to be elucidated.

Skin Immune Response Following Radiation

In addition to the physical barrier, the skin is provides a system of immune surveillance that maintains homeostasis and is poised to respond to environmental insults. Key cells within the epidermal layer involved in this surveillance are the Langerhans cells (LC) (Valladeau and Saeland, 2005). Keratinocytes also play an important role because they are capable of producing large amounts of cytokines, in particular interleukin 1-α (IL-1α) and tumor necrosis factor (TNFα) (Takashima and Bergstresser, 1996). The LC, along with dermal dendritic cells (DC) are essential antigen presenting cells and are responsible for the uptake of antigens that may breach the skin barrier (Kupper and Fuhlbrigge, 2004). The dermis also contains mast cells and T cells, which are also important players in radiation-induced immune response (Kalesnikoff and Galli, 2008; Muller and Meineke, 2011; Stelekati *et al.*, 2009). Furthermore, the dermis is richly supplied with blood vessels and lymphatic vessels, which serve as the conduits by which migrating DC can traffic to the draining lymph nodes and present antigen to T cells (Kupper and Fuhlbrigge, 2004).

Ionizing radiation incites signaling between the epidermis and dermis (Figure 1). Keratinocytes, fibroblasts, and endothelial cells in the skin stimulate resident (i.e., LC, DC, mast cells, T cells) and circulating immune cells (Muller and Meineke, 2007, 2011). Numerous cytokines and chemokines are produced in response to these activation signals, which act on the endothelial cells of local vessels causing the upregulation of adhesion molecules (Muller and Meineke, 2007). Adhesion molecules that have been implicated include intercellular adhesion molecule 1 (ICAM1), vascular cell adhesion molecule 1 (VCAM1), and E-selectin (Holler *et al.*, 2009; Yuan *et al.*, 2005). Transendothelial migration of immune cells, such as neutrophils, macrophages, and leukocytes, from circulation to irradiated skin is considered a “hallmark” of radiation-induced skin injury (Holler *et al.*, 2009; Muller and Meineke, 2007). Acute radiation skin toxicity has been correlated with increased formation of various cytokines and chemokines, most notably IL-1α, IL-1β, TNFα, IL-6, IL-8, CCL4, CXCL10, and CCL2 (Holler *et al.*, 2009; Okunieff *et al.*, 2006; Xiao *et al.*, 2006). Research demonstrated that both the epidermal LCs and the dermal DCs are depleted from the skin following local irradiation (Cummings *et al.*, 2009). This is time and radiation dose dependent for both subsets of cells (Cummings *et al.*, 2009). An important question, which has not yet been addressed, is whether this depletion is due to death of the cells or migration to the draining lymph node. The effects of ionizing radiation on DC are largely unknown and in humans are limited to studies on populations of DC generated *in vitro* from peripheral blood mononuclear cells (PBMC). A recent study on DC populations has revealed that they do not undergo apoptosis after as much as 30 Gy and maintain their ability to ingest particles and to migrate. However, their antigen presenting capabilities as measured by their ability to induce T cell responses were found to be slightly impaired (Merrick *et al.*, 2005). Merad *et al* demonstrated that DC were replaced by donor cells within 2 months in lethally irradiated C57BL/6-CD45.2^{+} mice that received a bone

marrow transplant from C57BL/6-CD45.1^{+} donor mice (Merad *et al.*, 2002). In contrast, the host LC persisted in the recipient mice for up to 18 months following irradiation (Merad *et al.*, 2002). Interestingly, in this same study it was demonstrated that an additional injury (UV radiation) resulted in rapid disappearance of LC and replacement by circulating LC precursors. These studies suggest that LC are quite radio-resistant.

Recently, Muller and Meineke demonstrated that ionizing radiation results in degranulation of mast cells in the dermis (Muller and Meineke, 2011). Mast cell-derived histamine, serotonin, TNFα, and tryptase significantly alter the release of CCL8, CCL13, CXCL4, and CXCL6 by dermal fibroblasts (Muller and Meineke, 2011). Research to date suggests that fibroblasts are responsible for fibrosis and other the late radiation (Brown and Rzucidlo, 2011; Muller and Meineke, 2007, 2011). Transforming growth factor-β (TGFβ), Smad3, vascular endothelial growth factor (VEGF, and CCL11 (eotaxin) have been identified as key mediators of radiation-induced late injury (Anscher, 2010; Muller and Meineke, 2007; Okunieff *et al.*, 2006; Xiao *et al.*, 2006). TGFβ is a potent chemoattractant for various inflammatory cells and a stimulant for extracellular matrix production by fibroblasts (Anscher, 2010; Lee *et al.*, 2010). TGFβ initiates a fibrotic response through its receptor Smad3 on fibroblasts (Anscher, 2010; Lee *et al.*, 2010). Reduction in radiation-induced fibrosis in Smad3 knockout mice has demonstrated its link to late radiation skin injury (Ashcroft *et al.*, 1999; Flanders *et al.*, 2003; Flanders *et al.*, 2002; Lee *et al.*, 2010).

Oxidative stress is generated at the time of radiation exposure, as well as days after irradiation due to propagation of free radicals (Benderitter *et al.*, 2007). Radiation skin injury also involves imbalances in antioxidant status and redox control of wound healing (Benderitter *et al.*, 2007; Holler *et al.*, 2009; Muller and Meineke, 2007, 2011; Williams and McBride, 2011). The immediate damage of ionizing radiation is a result of robust, but transient, production of reactive oxygen species (ROS) (Williams and McBride, 2011). However, inflammatory cell recruitment and cytokine generation also lead to chronic generation of ROS. Specific genes that have been implicated in oxidative stress following radiation exposures include superoxide dismutases (SOD), glutathione peroxidases (GPX), thioredoxins (TDX), heme-oxygenases (HOX), and heat shock protein-27 (HSP27) (Benderitter *et al.*, 2007; Williams and McBride, 2011). SOD1, GPX1, TDX1, TDX2, and HSP27 were up-regulated in healing skin after irradiation. However, these genes were down-regulated, while HOX1 and HOX2 were up-regulated in non-healing skin after irradiation (Benderitter *et al.*, 2007). Benderitter *et al.* further implicated a Th2-mediated immune response for non-resolution of inflammatory response and delayed wound healing following irradiation (Benderitter *et al.*, 2007). Catalase has also been identified as a potential mitigator for radiation skin injury due to its ability to reduce TNFα-induced production of cytokines and reactive oxygen species (Doctrow *et al.*, 1997; Rosenthal *et al.*, 2011; Young *et al.*, 2008).

Areas Needing Investigation: Weaknesses in Measurement and Treatment

Measuring Severity of Radiation Skin Injury

A gold standard for clinically rating the severity of radiation skin injury does not exist (Table 2). The most commonly used scoring systems are the National Institutes of Health Common Toxicity Criteria-Adverse Event (CTCAE) and the Radiation Therapy Oncology Group (RTOG) toxicity scoring system (Salvo *et al.*, 2010). However, other scoring scales, such as the Oncology Nursing Society (ONS), Douglas & Fowler (D&F), and Radiation Dermatitis Severity (RDS) scales, have been developed to more accurately represent the varying levels of the actual skin reaction. In contrast to the CTCAE and RTOG scoring systems, the newer scales have smaller defined increments to represent subtle, yet critical, changes in the skin. The CTCAE and RTOG scales range from 0 to 4 with increments of 1,

whereas the ONS, D&F, and RDS scales are 0 to 4 or 1 to 5 with increments of 0.5. Table 2 shows the various scoring systems employed to measure acute radiation-induced skin reactions. Radiation-induced late effects in the skin (Table 3) are primarily rated by the RTOG/European Organization for Research and Treatment of Cancer (EORTC) or Late Effects Normal Tissue Task Force/Subjective, Objective, Management, and Analytic (LENT/SOMA) classifications, which range from Grade 1 to 4 (Hoeller *et al.*, 2003). Both scales measure late skin and subcutaneous tissue changes, but the LENT/SOMA scale also incorporates pain intensity.

Over the past few years, patient-reported outcomes have become common instruments to aid in accurate assessment of various symptoms (Neben-Wittich *et al.*, 2010). Recently, Neben-Wittich *et al* reported that the Skindex-16 and Skin Toxicity Assessment Tool, two patient-report outcomes (PRO) instruments, did not correlate with CTCAE scoring system. Both PRO instruments provided a more complete measure of toxicity compared to the CTCAE scores. The importance of PRO instruments in radiation skin toxicity is further supported by a comparative study performed in 2007 (Ryan *et al.*, 2007). Ryan *et al* demonstrated a disconnect between clinically-reported and patient-reported radiation-induced skin reaction (Ryan *et al.*, 2007). The study showed that African-Americans reported more severe post-treatment skin reactions compared to Caucasians after receiving radiation therapy. Both of these studies (Neben-Wittich *et al.*, 2010; Ryan *et al.*, 2007) demonstrate that patient-reported information is critical for effective symptom management. Overall, further research is required for development of a standard and accurate scoring system for radiation skin injury.

Evidenced-based Management of Radiation Skin Injury

Over the years, “washing with mild soap” has been the only intervention recommended for radiation-induced skin reactions (Bolderston *et al.*, 2006; McQuestion, 2006). In 2010, a systematic review revealed a lack of evidence to support “washing with mild soap” as an intervention for radiation-induced skin reactions (Salvo *et al.*, 2010). This study (Salvo *et al.*, 2010). Although, topical corticosteroid and non-steroidal creams appeared to reduce the severity of skin reactions; there was no clear indication of a preferred topical agent. Amifostine and oral enzymes emerged as somewhat effective preventative agents; whereas pentoxifylline reduced late, but not acute, effects of radiation on the skin (Benderitter *et al.*, 2010; Salvo *et al.*, 2010). Long treatment (≥3 years) of pentoxifylline and tocopherol (i.e., Vitamin E) significantly reduced radiation-induced fibrosis. Unfortunately, cessation of pentoxifylline-tocopherol treatment prior to three years resulted in a “rebound effect” and more severe radiation-induced fibrosis (Delanian *et al.*, 2005). Additionally, IMRT was acknowledged as a technological intervention that has significantly reduced skin reactions from radiation (Pignol *et al.*, 2008; Salvo *et al.*, 2010). In 2011, McQuestion published evidence-based guidelines for skin care management in radiation therapy (McQuestion, 2011) which recommended: 1) washing with lukewarm water and mild soap, 2) using un-scented, lanolin-free, water-based moisturizing cream, and 3) IMRT. Overall, an effective intervention for radiation-induced skin reactions remains to be elucidated (McQuestion, 2011; Salvo *et al.*, 2010).

National Cancer Institute (NCI) and the National Institute of Allergy and Infectious Disease (NIAID) both have interest in development of effective radiation mitigators and protectors (Ryan *et al.*, 2011a). Due to the unpredictability and barriers to medical treatment following a radiological or nuclear event, an effective remediation strategy must be a radiation mitigator (Ryan *et al.*, 2011a; Williams and McBride, 2011). However, for cancer radiotherapy, elucidation of the differences in the mechanisms involved in the response of skin and other normal tissues to radiation in comparison to tumors is a critical component in this development (Ryan *et al.*, 2011a). Most importantly, interventions that ameliorate

radiation-induced toxicities in one scenario of radiation exposure may also work in other scenarios of exposure (i.e., “dirty bomb” versus radiotherapy).

Targeted gene therapy has emerged as a promising radiation mitigators and protectors. Preclinical studies have identified the following potential targets: TGFβ1 pathway inhibitor (Anscher, 2010; Lee *et al.*, 2010), synthetic SOD/catalase mimetics (Greenberger, 2008; Rosenthal *et al.*, 2011), recombinant Interleukin-12 (Cummings *et al.*, 2009), toll-like receptor-5 agonist (Burdelya *et al.*, 2008; Gudkov and Komarova, 2010), and inhibitors of cyclin-dependent kinases (Gudkov and Komarova, 2010) have. Furthermore, pravastatin reduced radiation skin injury by maintaining endothelial cell function after radiation exposure by increasing endothelial nitric oxide synthase (Holler *et al.*, 2009). Curcumin, a component of turmeric, has also demonstrated ability to reduce radiation skin toxicity through its potent antioxidant and anti-inflammatory activities (Okunieff *et al.*, 2006; Ryan *et al.*, 2011b). Recently, Atiba *et al* observed acceleration of radiation delayed wound healing in mice upon stimulation of TGFβ-1 and basic fibroblast growth factor (bFGF), suggesting the growth factor treatment may mitigate radiation skin injury (Atiba *et al.*, 2011). Although these agents still require formal and extensive clinical testing, the targeted approach appears specific and propitious.

Recently, stem cell therapy combined with surgical excision has demonstrated success in improving wound repair of severe radiation burns. As previously discussed, surgical excision and grafting of radiation burns is complicated due to the ill-defined margins of radiation damage. Lataillade *et al* used dosimetry-guided excision and mesenchymal stem cell injections to promote healing of a severe radiation burn on a man's buttocks from Iridium-192 (Lataillade *et al.*, 2007). After failure of the initial surgical excision and skin graft, a secondary excision was performed followed by mesenchymal stem cell injections around the lesion at the cutaneous and muscular levels, as well as in the bed of the lesion under the skin graft. No recurrence of radiation burn was observed 5.5 months post-radiation (Lataillade *et al.*, 2007). Similarly, Bey *et al* used five local mesenchymal stem cell administrations combined with surgical excision and autograft on the arm of a man exposed to Iridium-192 (Bey *et al.*, 2010). Although the arm had functional and cosmetic limitations, there was no recurrence of the radiation burn. Ebrahimian *et al* demonstrated that adipose tissue-derived stem cells (ADSCs) also promote wound healing in irradiated skin of mice (Ebrahimian *et al.*, 2009). Control of inflammatory waves, improved wound healing, and stabilization of skin barrier are imperative to minimizing radiation-induced skin injury from localized or total body radiation exposure.

Future Challenges: Cutaneous Radiation Syndrome and Combined Injury

Recent events in Japan, the United Kingdom involving radioactive Polonium-210, as well as the nuclear weapons testing in North Korea, suggest increased potential for and reality of a nuclear and/or radiological event. It is recognized that any skin injury in the setting of radiation poisoning greatly increases the risk of death. Skin injury due to radiation exposure is a major component of the multi-organ toxicity, which could occur due to an industrial or terrorist-related incident (Jungersted *et al.*, 2008). A second injury, such as a burn, or wound after non-lethal or sublethal radiation exposure significantly increases mortality from ~12% to 75% (Jiao, 2009; Security, 2009). The combined injury effect of trauma or burns with total body radiation injury at Hiroshima lowered the LD_{95} and LD_{50} by approximately 2 Gy (Flynn and Goans, 2006). These data confirms that a lower dose of radiation is required when combined with skin trauma or burns to cause death in 95% (LD_{95}) or 50% (LD_{50}) of individuals. Prolonged contact with fallout on the skin can result in serious skin damage plus increased total body dose (Bridges and al., 2007; Flynn and Goans, 2006). A 10 kiloton nuclear device has the potential to inflict second degree burns on exposed skin up to 1.4

miles from ground zero, whereas a 1 megaton device could inflict second degree burns within 15 miles from ground zero (Hatchett, 2009). In the Chernobyl Nuclear Power Plant accident, skin involvement ranged from 4% to 50% of the total body surface from gamma-ray (Cs-137) and beta particle (Sr-90) emissions (Gottlober *et al.*, 2001), permitting detailed observation of cutaneous radiation syndrome. Early radiation changes in skin, such as erythema and blistering, were observed within a year after the accident. Late radiation changes in the skin were observed 14 years after the accident and included epidermal atrophy, telangiectasias, keratoses, pigment changes, fibrosis, and ulcers (Gottlober *et al.*, 2001). More generally, acute radiation effects in skin occur between 12 hours to 5 weeks and include erythema, pigmentation changes, dry desquamation, and moist desquamation. Chronic radiation effects in the skin can take weeks to years to appear and include fibrosis, necrosis, ulceration, and vascular damage (Williams, 1988) Vascular damage influences levels of nutrients, oxygen available to skin tissue, as well as epithelial cell viability. The resultant fibrosis is a chronic, slowly cumulative effect and represents a hyponutritional state of the dermis (Hall and Giaccia, 2006). Although the skin reactions appear similar between cutaneous radiation syndrome and localized irradiation, cutaneous radiation syndrome also involves multi-organ exposure from total body radiation (Williams and McBride, 2011). Therefore, the complications from combined or secondary injury to the skin following sublethal total body radiation exposure are a direct result of radiation-induced multi-organ dysfunction.

Research of cutaneous radiation syndrome from total body irradiation is limited because prospective human studies are unethical and radiological/nuclear events are unpredictable. Much of our understanding of cutaneous radiation syndrome comes from our comprehension of localized skin irradiation. However, the National Institutes of Allergy and Infectious Disease has established a network of Centers for Medical Countermeasures against Radiation (CMCR), a collaborative network of academic institutions, whose primary goal is to identify, develop and deploy medical countermeasures for radiation toxicity after an unfortunate event (Williams and McBride, 2011). To plan effective remediation strategies, knowledge about mechanisms responsible for acute and chronic radiation effects in skin, from localized and total body irradiation, is needed.

Summary

Over last ten years, the field of radiation skin injury has made substantial progress. This review summarized the strengths and weaknesses in published research. An expansion in the knowledge on the mechanistic effects of radiation in skin, as well as other normal tissues, has enabled innovative growth. Unfortunately, no gold standard exists for the measurement or management of radiation skin injury. Development of agents to prevent or mitigate radiation skin injury will benefit the general population, as well as patients receiving cancer treatment.

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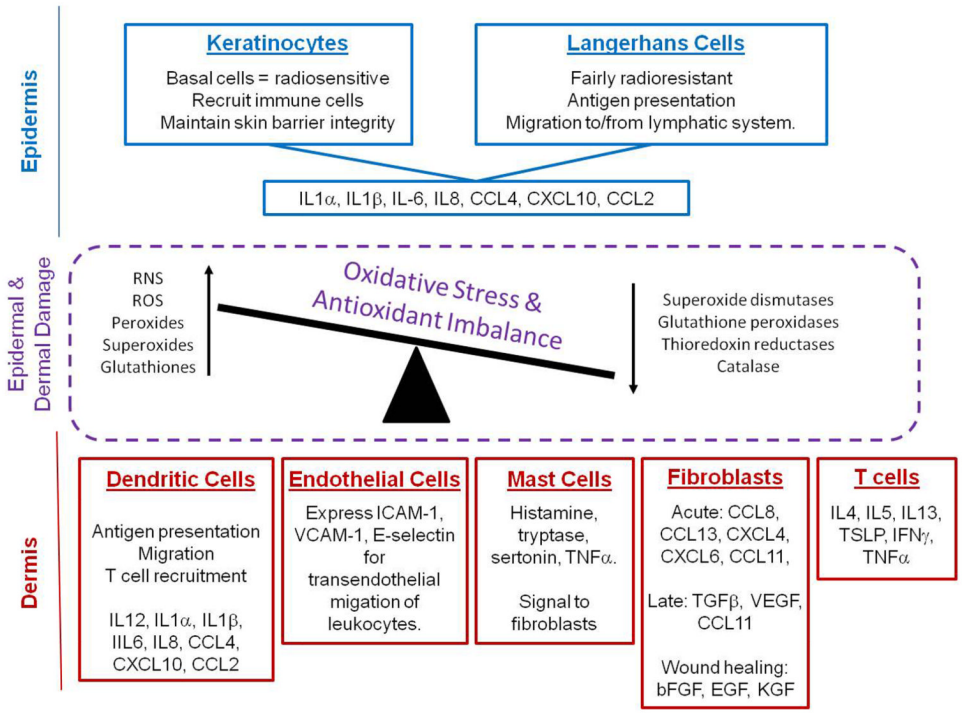

Figure 1. Schematic identifying the key cells and mediators involved in radiation skin injury

Ionizing radiation incites signaling between the epidermis and dermis through resident skin cells. In the epidermis, immediate damage to the basal keratinocytes and burst of free radicals, result in the increased formation of various cytokines and chemokines, most notably IL-1α, IL-1β, TNFα, IL-6, IL-8, CCL4, CXCL10, and CCL2. Keratinocytes, along with fibroblasts and endothelial cells in the dermis, stimulate resident skin cells and recruit circulating immune cells, such as neutrophils and macrophages. Additionally, langerhans cells in the epidermis and dendritic cells in the dermis migrate to lymph nodes for antigen presentation and immune cell stimulation. Degranulation of mast cells release derived histamine, serotonin, TNFα, and tryptase. Fibroblast stimulation is involved in acute, late, and healing of radiation skin injury Oxidative stress is generated at the time of radiation exposure, as well as days after irradiation due to propagation of free radicals and inflammatory cell recruitment, creates and antioxidant imbalance. RNS = reactive nitrogen species; ROS = reactive oxygen species; bFGF = basic fibroblast growth factor; EGF = epidermal growth factor; KGF = keratinocyte growth factor.

Table 1
Acute Skin Changes with Localized Radiation Dose

Acute Skin Effect	Dose (Gy)	Onset
Early transient erythema	2	hours
Faint erythema; epilation	6-10	7-10 days
Definite Erythema; hyperpigmenation	12-20	2-3 weeks
Dry desquamation	20-25	3-4 weeks
Moist desquamation	30-40	≥4 weeks
Ulceration	>40	≥6 weeks
Late Skin Effect		
Delayed Ulceration	>45	Weeks after radiation
Dermal Necrosis/Atrophy	>45	Months after radiation
Fibrosis	>45	6 months to ≥ 1 year after radiation
Telangiectasia	>45	6 months to ≥ 1 year after radiation

* Information compiled from (Bey *et al.*, 2010; Brown and Rzucidlo, 2011; Hymes *et al.*, 2006; Mendelsohn *et al.*, 2002; Wolbarst *et al.*, 2010)

Table 2
Comparison of Acute Radiation Skin Injury Scoring Systems

RTOG		NIH CTCAE	
Score	**Observation**	**Score**	**Observation**
0	No change over baseline	**0**	None
1	Erythema; dry desquamation; epilation	**1**	Faint erythema or dry desquamation
2	Bright erythema; moist desquamation; edema	**2**	Moderate to brisk erythema
3	Confluent moist desquamation; pitting edema	**3**	Confluent moist desquamation
4	Ulceration, hemorrhage, necrosis	**4**	Skin necrosis or ulceration
Oncology Nursing Society (ONS)			
Score	**Observation**		
0	No change		
1.0	Faint or dull erythema		
1.5	Bright erythema		
2.0	Dry desquamation with or without erythema		
2.5	Small to moderate amount of moist desquamation		
3.0	Confluent moist desquamation		
3.5	Ulceration, hemorrhage, or necrosis		
Douglas & Fowler			
0	Normal		
0.25	50/50 doubtful if any difference from normal		
0.5	Very slight reddening		
0.75	Definite but slight reddening		
1	Severe reddening		
1.25	Severe reddening with white scale; “papery” appearance of skin		
1.5	Moist breakdown in one very small area with scaly or crusty appearance		
1.75	Moist desquamation in more than one small area		
2	Moist desquamation in 25% of irradiated area		
2.25	Moist desquamtion in 335 of irradiated area		
2.5	Moist desquamation in 50% of irradiated area		
2.75	Noist desquamation in 66% of irradiated area		
3	Moist desquamation in most of irradiated area		
3.25	Moist desquamation in most of irradiated area with slight moist exudate		
3.5	Moist desquamation in most of irradiated area with moist exudates; necrosis		
Radiation Dermatitis Severity Scale			
0.0	Normal or None		
0.5	Patchy faint/slight follicular eyrthema; faint hyperpigmentation		
1.0	Faint and diffuse erythema; diffuse hyperpigmentation; mild epilation		
1.5	Definite erythema; extreme darkening/hyperpigmentation		
2.0	Definite erythema/hyperpigmentation with fine dry desquamation; mild edema		

RTOG		NIH CTCAE	
Score	**Observation**	**Score**	**Observation**
2.5	Definite erythema/hyperpigmentation with branny/scaly desquamation		
3.0	Deep red erythema with diffuse dry desquamation; peeling in sheets		
3.5	Violaceous erythema with early moist desquamation; peeling in sheets; patchy crusting		
4.0	Violaceous erythema with diffuse moist desquamation; patchy crusting; ulceration; necrosis		

* Data compiled from (Elliott *et al.*, 2006; Holler *et al.*, 2009; Jensen *et al.*, 2011; Okunieff *et al.*, 2006; Pommier *et al.*, 2004; Ryan *et al.*, 2011; Xiao *et al.*, 2006)