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Dermatopathology effects of simulated solar particle event radiation exposure in the porcine model

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ABSTRACT

The space environment exposes astronauts to risks of acute and chronic exposure to ionizing radiation. Of particular concern is possible exposure to ionizing radiation from a solar particle event (SPE). During an SPE, magnetic disturbances in specific regions of the Sun result in the release of intense bursts of ionizing radiation, primarily consisting of protons that have a highly variable energy spectrum. Thus, SPE events can lead to significant total body radiation exposures to astronauts in space vehicles and especially while performing extravehicular activities. Simulated energy profiles suggest that SPE radiation exposures are likely to be highest in the skin. In the current report, we have used our established miniature pig model system to evaluate the skin toxicity of simulated SPE radiation exposures that closely resemble the energy and fluence profile of the September, 1989 SPE using either conventional radiation (electrons) or proton simulated SPE radiation. Exposure of animals to electron or proton radiation led to dose-dependent increases in epidermal pigmentation, the presence of necrotic keratinocytes at the dermal-epidermal boundary and pigment incontinence, manifested by the presence of melanophages in the derm is upon histological examination. We also observed epidermal hyperplasia and a reduction in vascular density at 30 days following exposure to electron or proton simulated SPE radiation. These results suggest that the doses of electron or proton simulated SPE radiation results in significant skin toxicity that is quantitatively and qualitatively similar. Radiation-induced skin damage is often one of the first clinical signs of both acute and non-acute radiation injury where infection may occur, if not treated. In this report, histopathology analyses of acute radiation-induced skin injury are discussed.

1. Introduction

NASA is planning exploration class missions that are expected to involve space travel over periods of months to years. The space radiation environment exposes astronauts to risks of acute and chronic exposure to ionizing radiation. Of particular concern is exposure to ionizing radiation in a solar particle event (SPE). In an SPE, magnetic disturbances in specific regions of the Sun result in the release of intense bursts of ionizing radiation, primarily consisting of protons that have a highly variable energy spectrum (Hellweg and Baumstark-Khan, 2007; Hu et al., 2009; Smart and Shea, 2003; Townsend, 2005; Wilson et al., 1999). Especially during space travel missions outside of the protection afforded by the Earth's magnetosphere, the risks of radiation dose absorbed from SPE exposure are a serious concern for astronauts spending extended time in the space environment. It is estimated that during an SPE event, astronauts conducting extravehicular activities (EVAs) could receive radiation doses to the skin which are 10-fold higher than doses to internal organs (Wu et al., 2009). Based on SPE events taking place in 1972 and 1989, skin doses to astronauts conducting EVAs were predicted to range from 7 to 32 Gy (Hu et al., 2009). Additionally, SPEs are difficult to forecast in advance. This makes the goal of accurately predicting the biological effects for SPE exposed astronauts even more critical so that potential adverse events can be anticipated and strategies for their mitigation can be developed.

Ionizing radiation has well documented effects on skin. Much of our current understanding of radiation-induced skin damage has been gleaned from animal experiments using beta radiation and X-rays and in humans, from patients receiving radiation therapy and fluoroscopically guided interventional procedures (Balter et al., 2010; Hopewell, 1990). In addition, a body of literature

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is limited, but available on normal tissue responses, specifically, radiation-induced skin injury after accidental radiation exposure. Adverse skin reactions can manifest a range of toxicities from inflammatory damage, as evidenced by erythema, hyperpigmentation, edema/hyper-proliferation, moist desquamation (skin thins and begins to weep), epilation (hair loss), dermal atrophy, and necrosis that may require surgical intervention. The time course and recovery from radiation damage to skin depends on the total dose and dose rate or fractionation schedule. Areas of skin that have apparently healed following acute damage can subsequently develop severe late effects including necrosis, dermal atrophy and other problems that largely relate to deterioration or collapse of the skin vasculature. In addition, sufficiently severe acute effects may never completely heal, with the potential consequence of leading to sub-acute damage and consequential late effects, including morbidity (Ricks and Fry, 1991; I.A.E. Agency, 1988).

Structurally, pig skin is very similar to human skin (Hopewell, 1990). The skin is organized into 3 primary layers: epidermis, dermis and hypodermis (Costin and Hearing, 2007; Yamaguchi et al., 2007). The epidermal layer is further subdivided into five layers or stratum: basale (basal, lowest), spinosum (spinous or prickle cell), granulosum (granular), lucidum (clear) and outermost corneum (horney). The relative thickness of the stratum corneum varies depending upon the anatomical location from which the skin was derived. The dermis, which sits below the epidermis, is comprised of two layers: a superficial papillary dermis and a thicker, reticular dermis. Directly below the dermis resides the hypodermis, which is primarily composed of subcutaneous fat. Pigs are frequently used as a model system in dermatological research as their skin responds to radiation exposure in a similar manner to that observed in humans. The pig model has been used previously to determine the response of skin to beta particles, neutrons, X-rays and heavy ions (Lippincott et al., 1975; van den Aardweg et al., 1988; Wilson et al., 2011; Zacharias et al., 1997; Ahmed et al., 2012). However, there is very limited information available regarding the acute effects resulting from total body exposure to simulated SPE radiation. Previously it has been demonstrated that electron simulated SPEs can be used as a form of standard reference radiation for these studies (Cengel et al., 2010) and evaluated the toxicity of a relatively superficial electron simulated SPE in a porcine model (Wilson et al., 2011). In the current report, an extension of the previous studies was conducted by evaluating the acute skin response of Yucatan miniature (mini-) pigs following total body exposure to either electron or proton radiation that specifically mimics the September 1989 SPE. Proton or electron radiation was utilized matching the fluence/energy profiles expected during historically recorded SPEs. Because the macroscopic depth dose distributions for eSPE and pSPE are matched closely, the acute effects from exposure to these two different types of radiation could be directly compared in these studies. Skin samples taken from animals before and after radiation exposure were analyzed over a 30 day time frame, as this is the approximate turnover time for skin (Lindwall et al., 2006; Hopewell et al., 2003).

One aim of this study was to determine the relative biological effectiveness (RBE) values for acute effects produced by proton simulated SPE radiation exposure compared to those effects produced by electron simulated SPE radiation (used as the standard, reference radiation). Here we describe histological findings in mini-pigs exposed to electron or proton simulated SPE total body irradiation, referred to as eSPE or pSPE, respectively, from this point forward.

Table 1
Animal irradiation conditions.

Total dose	Radiation[a]	Dose rate (Gy/hr)
Sham	None	0
5 Gy	eSPE	1.7
7.5 Gy	eSPE	2.5
10 Gy	eSPE	3.3
5 Gy	pSPE	5
7.7 Gy	pSPE	5
10 Gy	pSPE	5

[a] Animals received total body irradiation (TBI) and were irradiated with electron (e) or proton (p) simulated SPE radiation.

2. Materials and methods

2.1. Animals

Yucatan mini-pigs were obtained from Sinclair BioResources (Columbia, MO). The pigs ranged from 8 to 14 weeks old. Pigs were fed standard mini-pig chow two times daily and water *ad libitum*, and maintained on a standard 12 hr light/dark cycle. Animals were given daily enrichment activities and randomly placed in treatment groups of 3 animals per group (8 groups total). All animals and procedures carried out in this study were conducted under protocols approved by the University of Pennsylvania and Loma Linda University Medical Center (LLUMC) Institutional Animal Care and Use Committees.

2.2. Irradiation

All radiation exposures were given as total body irradiation (TBI). The types and doses of radiation used were designed to mimic SPE conditions and to represent the radiation environment which astronauts would realistically be exposed to in space (Hu et al., 2009; Wu et al., 2009; Cengel et al., 2010).

For the eSPE radiation exposures procedures, non-anesthetized animals (8–14 weeks of age) were placed in rectangular Plexiglas cages [75 cm (L) × 32.5 cm (H) × 30 cm (D); 0.5 cm thick wall]. The animals were irradiated with a mixture of energies (6 + 12 MeV) consisting of 80% 6 MeV electrons, relative to d_{max} = 11 mm and 20% 12 MeV electrons, relative to d_{max} = 26 mm, at total body doses of 5 Gy (1.7 Gy/hr), 7.5 Gy (2.5 Gy/hr), and 10 Gy (3.3 Gy/hr) (Cengel et al., 2010). The dose rate was not constant amongst the different dose exposures. ESPE irradiation was produced by a Clinac iX linear accelerator (LINAC; Varian Medical Systems) located in the Perelman Center for Advanced Medicine, University of Pennsylvania, at a source-to-skin distance of 5 m (see Table 1). The cages were rotated 180° every 25% dose and surface patient dosimetry verification devices (OneDose, Sicel Technologies, Morrisville, NC) were used to confirm the skin doses received. Animals were irradiated or sham-irradiated over a 3 hr exposure period.

A separate cohort of animals was exposed to pSPE radiation. For these experiments, a custom designed double scattering system was developed to allow delivery of a 50 cm diameter radiation field with a radiation flatness (dose uniformity) ≤3.5% or better. This system was installed on the research beamline at LLUMC and was tuned to deliver a dose of approximately 5 Gy/hr. A clinical modulator wheel was used to create a fully modulated 155 MeV/n proton beam, while radiation dose was prescribed at a depth of 1.1 cm in water along the central beam axis. A 2 stage bolus at the level of the animal chamber and beam weighting allowed for generation of a custom depth dose profile to match the combined 6 + 12 MeV electron beam, which itself was developed to mimic the dose profile of SPE protons (Fig. 1). This setup delivered a maximum proton range of 5.0 cm (approximately 80 MeV) at the entrance of the animal cage and a distribution of proton energies