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Cytokine and chemokine responses after exposure to ionizing radiation: Implications for the astronauts

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Abstract

For individuals traveling in space, exposure to space radiation is unavoidable. Since adequate shielding against radiation exposure is not practical, other strategies for protecting the astronauts must be developed. Radiation is also an important therapeutic and diagnostic tool, and evidence from the clinical and experimental settings now shows a firm connection between radiation exposure and changes in cytokine and chemokine levels. These small proteins can be pro- or anti-inflammatory in nature and the balance between those two effects can be altered easily because of exogenous stresses such as radiation. The challenge to identify a common perpetrator, however, lies in the fact that the cytokines that are produced vary based on radiation dose, type of radiation, and the cell types that are exposed. Based on current knowledge, special treatments have successfully been designed by implementing administration of proteins, antibodies, and drugs that counteract some of the harmful effects of radiation. Although these treatments show promising results in animal studies, it has been difficult to transfer those practices to the human situation. Further understanding of the mechanisms by which cytokines are triggered through radiation exposure and how those proteins interact with one another may permit the generation of novel strategies for radiation protection from the damaging effects of radiation. Here, we review evidence for the connection between cytokines and the radiation response and speculate on strategies by which modulating cytokine responses may protect astronauts against the detrimental effects of ionizing radiations.

Keywords: Radiation exposure; Non-targeted effects; Cytokines; Chemokines; Oxidative stress

1. Introduction

Ionizing radiation (IR) has been utilized clinically as a diagnostic tool and a cancer therapeutic agent for many years. While it is also used beneficially as an energy source, radiation has been wielded as a weapon too. As individuals, we are also constantly being exposed to natural background levels of radiation, either in the buildings that we live in or the air that is surrounding us. Astronauts on the other hand, are exposed to an additional variety of types and doses of radiation, with no protective measures readily available besides the minimal shielding practical in space. As a result it is important to identify the molecular cascades that are set in motion in response to radiation exposure. This information will not only aid in developing ways to sensitize tumors to radiation, but also protect and spare the normal tissue from radiation induced damage. While there is much that we do not know about the radiation response, we do know that an inflammatory response can be activated either directly from the IR and the damage it inflicts to the cells, or from the process of healing the damaged tissue. The major players in this inflammatory process are believed to be cytokines and chemokines.

Cytokines are small proteins with a molecular weight of less than 25 kDa (Janeway et al., 2001). They are released by various cells in response to a stimulus and can elicit a biological response through specific receptor binding

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(Janeway et al., 2001). The mechanisms of action for cytokines can be autocrine, affecting the same cells that release the cytokines, or paracrine, eliciting a response in cells in close proximity to the secretory cells (Dent et al., 2003; Dranoff, 2004; Janeway et al., 2001; Leonard, 2001). Additionally, certain cytokines can act in an endocrine manner and affect cells distant from the site of origin, mainly through cytokine release into the circulatory system (Janeway et al., 2001; Leonard, 2001).

Chemokines are a subclass of cytokines. Their size varies between 8 and 11 kDa (Balkwill, 2004; Homey et al., 2002). Some are homeostatic in nature, while others are chemotactic and induce the directed migration of leukocytes to the site of injury (Bachmann et al., 2006; Balkwill, 2004; Homey et al., 2002). Chemokines are classified into four highly conserved groups – CXC, CC, C, and CX3C – based on the location of the first two cysteine residues that are adjacent to the amino terminus (Balkwill, 2004; Fernandez and Lolis, 2002; Homey et al., 2002). At least fifty chemokines have been identified so far, all of which have specific or shared receptors, belonging to the G-protein coupled receptor family (Fernandez and Lolis, 2002).

2. Cytokine induction after radiation exposure

The atomic bombs at Hiroshima and Nagasaki in 1945 clearly illustrated the devastating powers of nuclear weapons and radiation. The survivors of the A-bombs, or *hibakusha*, serve as a constant reminder of the intensity of the destruction of the two cities and of the lingering effects of radiation on the exposed individuals. In a cohort study by Hayashi et al. (2003), conducted multiple decades after the bombings, measurement of C Reactive Protein (CRP) and Interleukin-6 (IL-6) levels in blood samples from 453 participants revealed significant upregulation of these two cytokines. This upregulation was accompanied by decreases in the percentage of $CD4^+$ helper T-cells in peripheral blood lymphocyte populations (Hayashi et al., 2003). Together these data indicate that the A-bomb exposure caused persistent, increased levels of cytokines and may prove to play a significant role in the risk to the survivors of developing non-cancer related problems including cardiovascular diseases (Hayashi et al., 2003).

Clastogenic factors have also been detected in the blood plasma of A-bomb survivors, children from the Chernobyl area, and salvage personnel of nuclear reactor accidents. Several studies have evaluated the ability of plasma from exposed individuals to induce chromosomal aberrations in normal lymphocytes (Emerit et al., 1994, 1997b; Faguet et al., 1984). The cytogenetic abnormalities observed included chromatid breaks and gaps, and hyperdiploidy (Emerit et al., 1997b; Faguet et al., 1984). Although the exact nature of the clastogenic factor(s) is/are not known, persistent free radicals and cytokines, in particular tumor necrosis factor alpha (TNF-α), have been implicated (Emerit et al., 1997a,b).

An interesting and unexpected effect of radiation has been sporadically reported after radiotherapy. It is termed the abscopal effect and refers to observing regression of tumors at areas distant from the site of irradiation. The mechanism underlying this phenomenon is not clearly understood. Evidence suggests, however, that cytokines may play an important role in this response. For example, a study by Van der Meeren et al. (2005) showed the induction of an inflammatory response in the lungs of mice after only the abdomen had been irradiated. The investigators found that after abdominal irradiation, levels of IL-6 in the lungs were up-regulated, together with changes in adhesion molecules, coagulation proteins, and an increase in vessels expressing Pecam1 (Van der Meeren et al., 2005). The authors concluded that the increase in inflammatory mediators in the plasma from these mice elicited the response observed in the lungs following abdominal irradiation.

A similar abscopal response was observed by Ohba et al. (1998). A 76-year-old male patient received radiotherapy for thoracic vertebral bone metastasis and unexpectedly exhibited regression of his hepatocellular carcinoma (Ohba et al., 1998). Serial measurements of multiple cytokines before and after irradiation revealed an increase of serum TNF-α at seven months post irradiation (Ohba et al., 1998). TNF-α is known for its ability to enhance cytolytic activity of natural killer cells and its increase may explain the effect observed in this patient (Hill et al., 1992; Ohba et al., 1998).

Another non-targeted phenomenon observed following irradiation has been termed the bystander effect. The bystander effect is defined by the observance of a characteristic radiation response in cells that were not directly irradiated, but instead were bystanders at the time of irradiation. Although this phenomenon has been well documented (Lorimore et al., 1998; Mothersill and Seymour, 1997; Seymour and Mothersill, 1997), the mechanism by which effects are induced in unirradiated cells is not yet known. Free radicals, nitric oxide, intercellular gap junction communication, and production of soluble factors appear to play major roles in these non-targeted effects of radiation exposure (Lorimore and Wright, 2003), both *in vitro* and *in vivo*. Using an *in vivo* model, Lorimore et al. (2001) demonstrated that following irradiation, genetically modified processes take place in lysosomal enzyme activities for the activation of macrophages and the clearing of apoptotic cells, which could in turn lead to the production of pro-inflammatory cytokines. The same investigators showed that with the use of a grid and α-particle irradiation, chromosomal instability is initiated in cells that are descendants of unirradiated cells, implicating interactions between the two cell populations (Lorimore et al., 1998). In an *in vitro* model, cells exposed to low fluences of α-particles exhibited increased transforming growth factor β1 (TGF-β1) in cell supernatants (Iyer et al., 2000). TGF-β1 is a cytokine that is capable of inducing increased intracellular reactive oxygen species (ROS). Furthermore, addition of cell supernatants from the exposed cells to