PAC 1 initiated proposal
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Proposed Topic - Effects of radiation on immune system and latent virus reactivation

The purpose of this NCRP commentary is to provide the current state of knowledge on the effects of ionizing radiation on the immune system and on latent herpes virus reactivation to the scientific community and government agencies. Its purpose is to better understand radiation-induced latent virus reactivation, which is possibly an underestimated consequence of ionizing radiation exposure. This activity should involve the radiation research community (academia, industry and regulatory agencies) and government agencies (NASA, DOD, CDC).

Background:
Ionizing radiation (IR) is known to have several effects on the immune system. While the immunosuppressive effects of high-dose ionizing radiation (HD-IR) is well known, the effects of low doses (LD-IR) on the immune system are controversial and poorly understood (Manda et al., 2012). One consequence of immunosuppression is the reactivation of latent viruses. Many of the viruses that cause latent infections are from the family of Herpesviridae: herpes simplex virus (HSV)-1, HSV-2, varicella zoster virus (VZV), Epstein–Barr virus (EBV), and others (Traylen et al., 2011). The genome of a virus that causes latent infection of cells must be transcribed and translated into viral proteins. This occurs when the virus is reactivated from a latent stage to a lytic stage. Certain viral genes that are specific to each virus initiate this reactivation process. Although some viral gene products have been identified, the exact mechanisms behind transcriptional activation that determine a virus' reactivation from latency are not known (Tal-Signer et al.,1997).

It is important to understand the effects of LD-IR and HD-IR on the immune system for the following reasons. First, its relevance for the medical radiation exposure. Over the last years, the rate of diagnostic imaging and associated radiation exposure has increased rapidly (Smith-Bindman et al., 2012). The numbers of positron emission tomography (PET) scans as well as nuclear diagnostic procedures are also increasing rapidly. Furthermore, these sometimes repeated and/or combined examinations might lead to radiation doses that are equivalent to or even higher than the yearly average of the internationally accepted dose limits for occupational exposure. Another reason to study the effects of LD-IR is to understand the influence of the combined effect of the

microgravity environment and LD-IR exposure in astronauts. Astronauts demonstrate a unique pattern of immune system dysregulation. Included are alterations in peripheral leukocyte distribution, reductions in T and NK cell function, apparently unaltered B cell function, and dysregulated cytokine profiles. Causal factors may include radiation exposure, radiation associated inflammation or alterations to gut microbiome, stress or circadian issues. Although latent virus shedding in astronauts is essentially asymptomatic (Mehta et al., 2013), astronauts do experience some level of clinical incidence during spaceflight (Crucian et al., 2016a). Some unique crewmembers experience a persistent atopic dermatitis which can be serious enough to require topical or oral steroid treatment (Crucian et al., 2016b). The precise relationship between radiation and these clinical manifestations is unknown. Regarding HD-IR, a recent study has shown that, compared with incidence rates of shingles reported in a general U.S. population, the age- and sex-standardized rates of shingles were 4.8 times higher (95% confidence interval (CI), 4.0–5.6) in patients with hematologic malignancies and 1.9 times higher (95% CI, 1.7–2.1) in those with solid tumors (Habel et al., 2013).

It is worth mentioning here that the consequences of latent viral reactivation can be very serious. For example, the reactivation of latent Varicella Zoster Virus (VZZ) may be complicated by post-herpetic neuralgia, zoster paresis, cranial nerve palsies, myelitis, meningoencephalitis, vasculopathy, or ocular disorders (Gilden et al, 2000). Similarly, reactivation of Epstein-Barr virus (EBV) may lead to lymphoproliferative disease and may play a role in Hodgkin's lymphoma, peripheral B and T cell lymphomas, and nasopharyngeal carcinoma (Pizzigalo et al., 2010).

Deep space missions beyond the Earth's protective Geomagnetic field are scheduled to begin in 2024, first with lunar orbital and landing missions, to be followed by Mars flyby and orbital missions in the 2030s. The astronauts participating in these missions will experience persistent elevated radiation, as well as increased magnitude of other spaceflight stressors, while (likely) a reduced capacity for exercise and nutritional countermeasures support. A central question is whether the detection of increased levels of viruses in humans during spaceflight is due to immunosuppression associated with travel in space or a direct effect of space environmental factors, such as radiation inducing reactivation of the virus from latency. Our recent study (Mehta et al., 2018) has shown that latent EBV can be reactivated by radiation exposure alone.

Proposal – seek funding to support the issuance of an updated NCRP report to address, but not limited to, the following topics:

- The effects of radiation on the immune system at low and high doses
- The role of radiation in the reactivation of latent virus
    - LET (radiation type and energy)
    - Dose
    - Dose-rate

Possible funding from Government Agencies (stakeholders and representatives)*

NASA Jason Weeks

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