Published in final edited form as:

Health Phys. 2016 March ; 110(3): 249–251. doi:10.1097/HP.0000000000000450.

Is Ionizing Radiation Harmful at any Exposure? An Echo that Continues to Vibrate

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Synopsis

In his “Failla Award” lecture, the late Professor Sheldon Wolff asked whether all radiation is harmful, or at least unremittingly harmful (Wolff 1992). Clearly, the absorption of ionizing radiation by living cells can disrupt atomic structures, producing chemical changes in macromolecules, including nucleic acids, proteins and lipids (Hall and Giaccia 2006). As a result, different signaling cascades responding to these stress conditions are triggered. For example, adaptive responses encompassing DNA repair and antioxidation reactions may be induced following exposures to low doses of sparsely ionizing radiations such as X- and γ -rays (Wolff 1998, Feinendegen et al. 2007, Auerbeck 2009). The protective mechanisms may over-compensate, resulting in stimulatory responses that enhance the well-being of the organism long after the exposure (Calabrese et al. 2011, Nomura et al. 2011). In fact, the stimulatory effects of ionizing radiation were noted shortly after the discovery of X-rays, in 1895, by Wilhelm Röntgen. In 1898, Atkinson reported that algae grew faster after exposure to X-rays (Atkinson 1898). In the intervening years, a wealth of data on the stimulatory effects of radiation were described in a variety of living systems (Luckey 1980), and in the absence of background radiation, single cell organisms were unable to proliferate (Planel et al. 1987). Notably, *in vitro* and *in vivo* exposures to low doses of sparsely ionizing radiations such as γ - or X-rays were protective to cellular DNA (Cai and Liu 1990, Mitchel et al. 1997, Feinendegen et al. 2007). Moreover, human cellular responses to low doses of radiation that are typical of certain occupational activities or diagnostic radiography were often shown to harbor lower levels of chromosomal damage than what occurred spontaneously at the basal level (de Toledo et al. 2006, Zhang et al. 2012), and were protected against subsequent challenge by radiation (Olivieri et al. 1984, Shadley and Wolff 1987, Shadley and Wiencke 1989, Azzam et al. 1994, Rigaud and Moustacchi 1994). These effects were clearly impacted by the rate of delivery of the radiation (Azzam et al. 1996, Redpath 2004). They were mediated by molecular and biochemical changes that differ from those induced by high doses (Coleman et al. 2005, Zhang et al. 2012). Whereas pro-apoptotic pathways may be induced at high doses, signaling pathways that promote healthy survival are induced at low doses (Simmons et al. 2009).

The above observations in mammalian systems mirror a vast literature on protective mechanisms that help both prokaryotes and non-mammalian eukaryotes to withstand external stimuli, including ultraviolet and ionizing radiations, heat, toxic chemicals, and infection (Calkins 1967, Samson and Cairns 1977, Demple and Halbrook 1983, Koval 1983,

Boreham et al. 1990, Wilder 1995). Together, the studies in prokaryotes, lower and higher eukaryotes show that several defenses act to restore DNA integrity following exposures to relatively low doses of harmful environmental agents, including ionizing radiation. In response to DNA damage, cells activate cell cycle checkpoints that provide time for DNA repair machinery to mend the damage. Further, antioxidant defenses (enzymes that scavenge reactive oxygen species, proteases to remove oxidized molecules) act to neutralize the induced oxidative stress, which may also result in minimizing the mutagenic potential of the byproducts of normal oxidative metabolism (Spitz et al. 2004). Emerging evidence suggests that intercellular communication also participates in promoting the protective effects (Klammer et al. 2010, Buonanno et al. 2015).

In contrast to adaptive protection observed at low doses (Feinendegen et al. 1987), there is extensive evidence that at high doses, ionizing radiation causes excessive DNA damage, often followed by cancer or degenerative diseases (Morgan et al. 1996, Little 2000, Buonanno et al. 2011). In addition, there is proof, including from our own laboratory, that even a single nuclear traversal by a densely ionizing particle such as an α -particle or a high atomic number and high energy (HZE) particle can trigger harmful effects that spread beyond the traversed cell and induce damaging effects in the nearby bystander cells (Nagasawa and Little 1992, Azzam et al. 2001, Zhou et al. 2001). However, should these observations with densely ionizing radiations be considered low dose effects when microdosimetric calculations reveal that a single traversal by such particles deposits extremely high dose in the directly hit area of the traversed cell? (Li et al. 2014)

Clearly, the expression of radiation-induced adaptive protection has significant social and economic implications, and there is great scientific interest in quantifying the extent of such a response at the population level, as well as in elucidating the underlying biochemical events. Human epidemiological studies would be indeed ideal to predict the health effects of exposure to low dose radiation, however these studies at low dose are limited due to the necessity of very large cohorts (several millions) to generate data with an acceptable level of confidence. Furthermore, epidemiological surveys examine the effects of exposures that happened several years earlier, and therefore may be biased by many variables during the intervening time until overt detrimental health effects are expressed. As a result, mechanistic laboratory studies remain essential to reduce the uncertainty in predicting the health risks of exposures to low doses and low fluences of radiation (Averbeck 2009). In this context, animal research on how exposure to low dose radiation at younger age modulates the latency of expression of age-related diseases such as cancer will further illuminate the magnitude of risk of exposure to low dose radiation. Animal models that consider the role of genetic susceptibility would be enlightening (Foray et al. 2012). In such studies however care should be exercised in extrapolating results across species; for example, the metabolic rate of the system being investigated may need to be integrated. Metabolic rates greatly vary, with that of humans being an order of magnitude lower than mice (Ames 1989), which may be a factor in determining species-specific long-term effects.

In sum, although there are great uncertainties about a causal relationship between low dose exposure and harmful health effects, it is nevertheless clear that there is little direct evidence of risk to the human population at low doses of ionizing radiations. An array of redundant

and inter-related mechanisms exist in mammalian cells to repair the damage when it occurs and to provide maximum protection not only for the irradiated cell but to the system as a whole.

Acknowledgement

Work in the authors' laboratory is supported by grants CA049062 from the National Institutes of Health (NIH) and NNX15AD62G from the National Aeronautics and Space Administration (NASA).

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