Radioresistance: Implications for Astrobiological and Medical Research

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SUMMARY

Ionizing radiation is commonly thought to be dangerous to, and even incompatible with, terrestrial life, due to its damaging effects on vital biomolecules like DNA. However, there exist organisms such as tardigrades, as well as several bacterial species, such as *Deinococcus radiodurans*, which have been observed to survive exposure to radiation levels in excess of 5000 Gy. This resistance is accomplished through differing mechanisms that, in general, involve processes to protect or rapidly repair molecules such as DNA that are damaged by high-energy ionizing radiation. In this Letter to *The iScientist*, the current understanding of the biology of radioresistant organisms is explored through a discussion of tardigrades and *D. radiodurans* as examples. Subsequently, it is argued that furthering our understanding of these organisms and the mechanisms by which they withstand ionizing radiation have important applications for a variety of fields. These include applications to the astrobiological search for life beyond Earth, as understanding the potential limits of radioresistance may allow for the expansion or constraint of possible environments in which extraterrestrial life may survive, guiding future life detection efforts. At the same time, mechanisms of DNA repair in radioresistant organisms may provide avenues of exploration in the search for interventions that may be applied to addressing DNA damage in humans, a problem associated both with cancer and aging.

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INTRODUCTION

Ionizing radiation refers to radiation that contains enough energy to ionize atoms and molecules by raising the energy level of electrons such that they become unbound (Bacal and Romano, 2016). This includes electromagnetic radiation in the high ultraviolet, X-ray, and gamma range, but can also include subatomic particles, such as those that comprise cosmic rays (Nordheim, et al., 2015). In a biological context, ionizing radiation is dangerous to life due to its ability to penetrate living organisms and break chemical bonds in deoxyribonucleic acid (DNA) and other biomolecules (Melott and Thomas, 2011).

This damage can result in alterations of the nucleobases in the DNA molecule, or single-strand and double-strand breaks (Figure 1). While many organisms have mechanisms by which they repair damage to DNA (e.g., MacRae, et al. 2015), large amounts of ionizing radiation can cause significant irreparable damage that ultimately leads to mutation or cell death (Sutherland, 2014).

While it has generally been thought that high radiation environments are thus extremely dangerous to, and even incompatible with, terrestrial life, there in fact exist some organisms that have been observed to have the capability to survive in high radiation environments. These radioresistant organisms have been the subject of

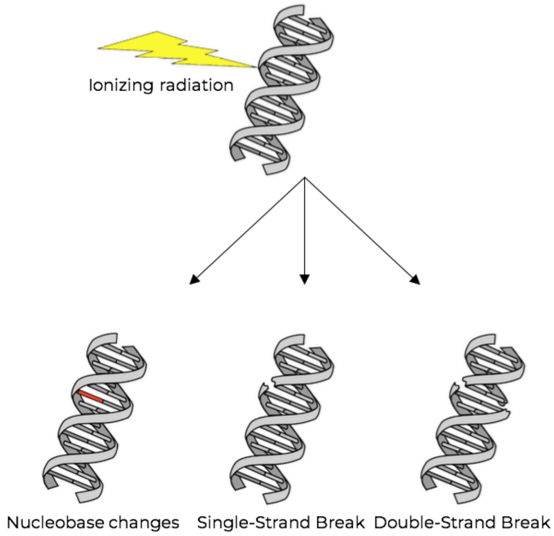

Figure 1: When DNA is exposed to ionizing radiation, it may be damaged in several ways, including changes to the nucleobases within the DNA molecule, or breaks in one or both strands of the DNA double helix.

study into the mechanisms by which they are able to survive such hostile environments. Examples include the tardigrades, a phylum of animals commonly referred to as "water bears" that are ubiquitous on Earth, as well as several bacterial species such as *Deinococcus radiodurans*. Here, current knowledge of the radioresistance mechanisms of these organisms is reviewed; subsequently, it is argued that furthering this understanding may prove valuable for a variety of fields, including astrobiological and medical research.

TARDIGRADES

Tardigrades are a phylum of animals comprising various species of "water bears", microscopic organisms that are ubiquitous on Earth, which have been found in diverse environments ranging from the oceans to alpine habitats (Weronika and Łukasz, 2017).

Tardigrades are notable for being resistant to a variety of extreme conditions, having survived desiccation, extreme temperatures, and extremely high radiation experimental environments (Weronika and Łukasz, 2017). While the exact level of radioresistance varies between species within the phylum, experimentally observed median lethal dosages of radiation survived by one species, *Milnesium tardigradum*, have been measured to be 5000 Gy of X-rays or 6200 Gy of heavy ions (Horikawa, et al., 2006). In comparison, a 4 Gy dose is considered lethal to a human (Hashimoto and Kunieda, 2017).

In tardigrades, radioresistance, along with resistance to other extreme conditions, is achieved through cryptobiotic states such as anhydrobiosis, in which the organism's metabolism rate is significantly decreased and water content is reduced. Tardigrades possess various unique biochemical characteristics that impart increased resistance to these extreme conditions, such as the use of trehalose to stabilize biomolecules in the anhydrobiotic state (Weronika and Łukasz, 2017); these are also of great interest to various scientific disciplines, but fall outside the intended scope of this work's argument as their relationship to radioresistance are either unclear or minimal.

Among the various biochemical adaptations of tardigrades, it has been found that they produce a unique protein, Dsup, which suppresses DNA damage by radiation (Hashimoto, et al., 2016). At this time, however, the exact mechanism by which this protection is conferred is not yet clear. Thus far, it has been demonstrated that Dsup-expressing cells observed immediately following exposure to radiation, before significant repair would have time to occur, suffered less extensive DNA fragmentation, suggesting that Dsup functions to protect DNA from damage rather than being a component of a DNA-repair mechanism. Dsup is known to be a DNA-binding protein, and it has been found that it is necessary for the protein to bind to DNA in order to exert its protective effect (Hashimoto and Kunieda, 2017). Given the many unknowns in this process, research is ongoing to further elucidate the mechanism underlying Dsup-conferred DNA protection, as well as the evolutionary origins of this protein.

BACTERIA

While tardigrades are considered extremotolerant in that they possess mechanisms by which they may survive extreme environments for a duration of time, several species of extremophilic bacteria are able to not only tolerate high radiation environments, but are able to thrive and reproduce normally in such situations (Rampelotto, 2013).

One of the most well-studied species of such bacteria is *Deinococcus radiodurans*. Experimentally, *D. radiodurans* has been observed to survive a variety of extreme conditions, including acute exposure to 7 kGy of radiation with a lethality rate of only 10% (Slade, et al. 2009); other studies have shown resistance to radiation from 5 to 15 kGy, depending on growth conditions (Minton, 1996).

Deinococcus radiodurans possesses a variety of radioresistive mechanisms. First, the bacterium contains four copies of its genome when in the stationary phase, and this can increase further when the bacterium is undergoing active reproduction to eight to ten copies (Makarova, et al., 2001). Furthermore, the bacterium possesses a DNA-repair mechanism that allows it to repair double-stranded breaks, even when they are numerous, as is the case after exposure to high doses of ionizing radiation. This is facilitated by the protein DdrB, which is hypothesized to function as part of an early stage of repair through a process of single-stranded annealing. It has been shown that DdrB-deficient strains of *D. radiodurans* do not suffer reduced viability when exposed to lower-doses of radiation, suggesting that the single-stranded annealing process only becomes important at high ionizing radiation levels (De la Tour, et al., 2011). This serves as a unique back-up process to the homologous recombination process facilitated by the protein RecA (Figure 2), which is a common protein to a variety of bacterial species; homologous proteins exist in other domains as well, such as Rad51 in yeast (Rajpurohit, et al., 2016).

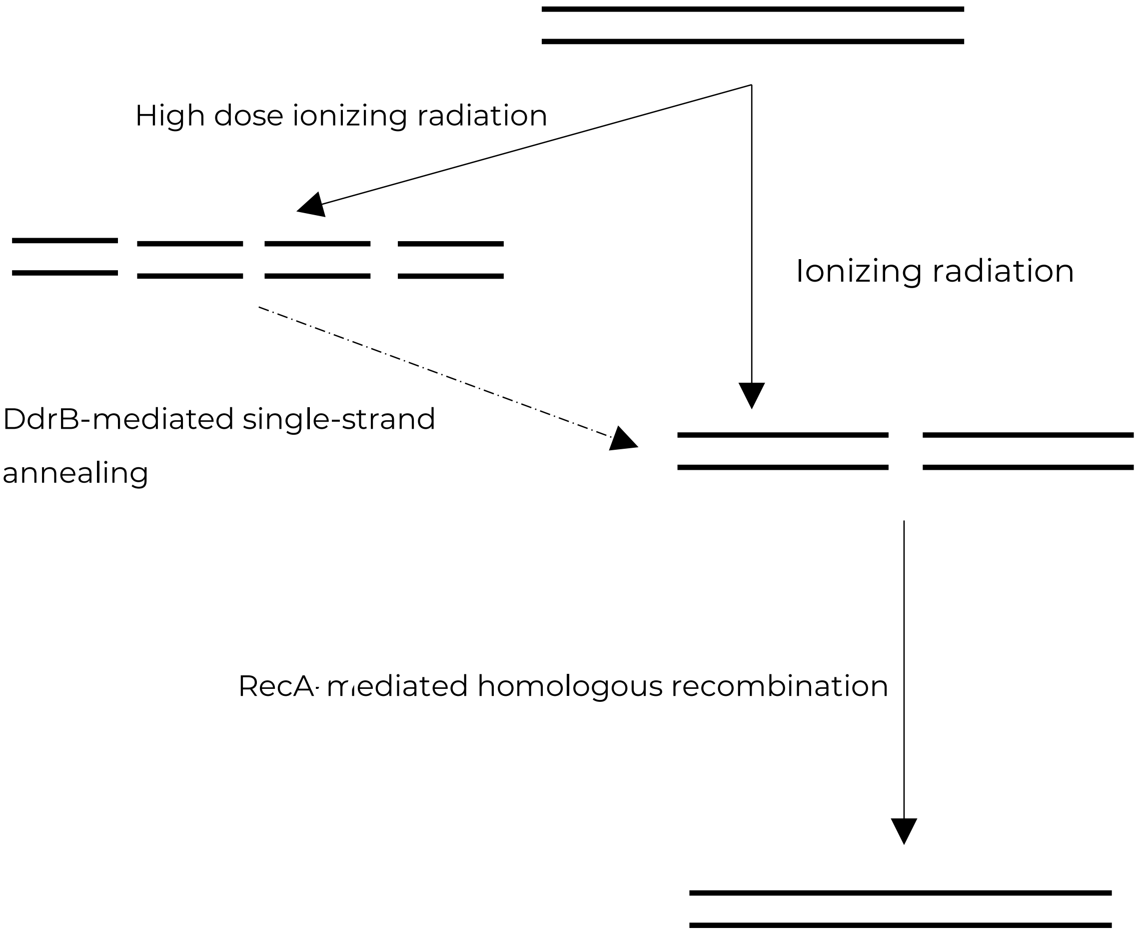

Figure 2: A simplified representation of the hypothesized role played by DdrB single-strand annealing in the repair of radiation-induced double-strand breaks in *D. radiodurans*. The particular pathway mediated by DdrB, and thus unique to *D. radiodurans*, is highlighted with a dot-dashed line. DdrB begins the repair process in situations in which DNA is fragmented severely by high doses of ionizing radiation, before the products of single-strand annealing enter the RecA mediated pathways.

DISCUSSION

Radioresistant organisms and their unique biological processes represent an interesting subject of study for a variety of scientific disciplines. Better characterization of the mechanisms and limits of radioresistance can allow astrobiologists to better understand the range of potential environments in which life may survive on extraterrestrial bodies. While the Earth possesses a protective magnetosphere that shields the surface from ionizing cosmic rays (Chancellor, Scott and Sutton, 2014), and an atmosphere that attenuates much of the high energy ionizing electromagnetic radiation (Thomas, 2009), many other bodies in the Solar System of astrobiological interest do not have these characteristics. Mars, one of the subjects of most intense astrobiological study, no longer possesses a magnetosphere due to the cooling of its core (Lammer, Stumptner and Molina-Cuberos, 2002). As such, its surface is exposed to a high radiation level, estimated to be approximately 0.213 mSv/day, or 77.8mSv/yr (Simonsen and Zeitlin, 2017), compared to the annual dose on Earth of 2.4mSv/yr (Atri and Mellott, 2014). An exact conversion of this value into Gy is difficult to produce because a significant portion of the radiation on Mars is from cosmic radiation, and the Relative Biological Effectiveness (RBE) of cosmic radiation, required to calculate the conversion, is poorly defined. However, the RBE has been previously estimated at around 4 (Aceto, Leith and Baker, 1974), suggesting that considering radiation alone, organisms like tardigrades and *D. radiodurans* would be capable of withstanding the Martian radiation environment. Examples such as this suggest that a better understanding of mechanisms by which life may resist radiation damage can provide guidance on constraining the environmental parameters in the search for life in the Universe.

Besides aiding the search for life in the Universe, research into radioresistant organisms may produce benefits in medicine as well. Fundamentally, radioresistance is based on protecting DNA from damage, and repairing the damage that does occur when exposed to insults like radiation. DNA damage is also an important component of such processes as malignant transformation in the etiology of cancer, as well as in aging (Hoeijmakers, 2009). As such, a better understanding of the mechanisms by which these extraordinary organisms are able to protect and repair their genetic material may yield benefits in the search for interventions to protect human DNA, and mitigate the development of malignancy and the effects of cellular aging. For example, research on the tardigrade Dsup has shown that human cells transfected to express this protein were much more resistant to radiation-induced damage than wildtype cells (Hashimoto, et al., 2017). Whether such a cell-line is more resistant to DNA damage in general, or only in the case of high radiation exposure, has not yet been investigated, however. Further investigation may reveal whether interventions such as gene therapy involving this pathway or those from other radioresistant organisms like *D. radiodurans* may prove beneficial to human cells and may thus be of interest to medical research.

In conclusion, research into the biochemical processes by which radioresistant organisms like tardigrades and *D. radiodurans* survive high doses of DNA-damaging ionizing radiation may prove beneficial for a variety fields, including clarifying the range of conditions in which the astrobiological search for life may be conducted, as well as elucidating potential avenues of investigation for medical research on cancer and aging.

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