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Commentary

Outer Space and Oocyte Developmental Competence

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Mammalian oocytes are quite special cells for many reasons, but one of their most amazing characteristics is that while in the ovary they remain blocked at diplotene of prophase one of the first meiotic division [1]. Because the oocyte can remain in this resting state in the ovary until menopause in women, the oocyte can retain this meiotic cell cycle block for more than 50 years [2]. A lot can happen in 50 years, and for that entire time in the ovary, the primordial follicle containing its primary oocyte is exposed to a wide variety of environmental conditions that have an impact on the health of the oocyte and affect its potential for fostering normal development and health of the offspring derived from it [1–4]. Our genome is constantly subject to modification by the environment [3, 4]. The environmental affect on the genome begins with gametogenesis and extends through preimplantation development, pregnancy, and postpartum development and throughout life [3, 4].

The study by Kujjo et al. entitled “RAD51 Plays a Crucial Role in Halting Cell Death Program Induced by Ionizing Radiation in Bovine Oocytes,” published in this issue of *Biology of Reproduction*, reveals to us an additional environmental factor that can influence oocyte health over time [5]. Uniquely, we have to look to outer space for the source of this environmental factor [6]. Kujjo et al. inform us that high-energy cosmic rays originating from supernovas, traveling at the speed of light, strike the earth at the rate of one cosmic ray per square centimeter per minute and can penetrate more than a mile into the earth's crust [5]. To put this into clear terms, Kujjo et al. state that during every night's sleep a human can expect to be bombarded with up to 1 million cosmic rays [5]. This occurrence poses a series of very interesting questions, such as: How do we prevent accumulating genomic damage from these cosmic rays? Does this type of environmental insult accumulate over time? Most importantly, are oocytes susceptible to this type of insult, and could it contribute to the decline in fertility women experience beyond the age of 35, normally well before menopause and before the absolute cessation of their reproductive function occurs?

Although our exposure to cosmic rays may be increasing because of global warming and ozone depletion, all species on this planet, including humans, have nevertheless been exposed

to cosmic rays for their entire history [6–8]. Therefore, what mechanisms have we evolved to minimize the damage caused by cosmic ray exposure on our reproductive cells? This is the unique and important question that Kujjo et al. explore [5]. Successful completion of this study required an international collaboration between investigators from Michigan State University; the United States National Superconducting Cyclotron Laboratory; Waseda University in Tokyo; the RIKEN Systems and Structural Biology Center, Yokohama, Japan; and the LARCel Programa Andaluz de Terapia Celular y Medicina Regenerativa, Sevilla, Spain [5].

The investigators contrasted the effects of radiation exposure between murine and bovine oocytes. They observed important species differences in their responses to radiation, with murine oocytes activating high levels of caspases as a prelude to necrotic death, whereas bovine oocytes activate annexin-V, cytochrome C release, and an incomplete cell death program [5]. Subsequent experiments focused on the mechanisms affecting these outcomes. It was discovered that inhibition of RAD51 or increasing caspase 3 levels before irradiation induced high levels of cytoplasmic fragmentation [5]. In contrast, microinjection of RAD51 before irradiation significantly decreased cytoplasmic fragmentation and DNA damage in oocytes [5].

The decision of the researchers to focus their studies on RAD51 was quite intuitive. Although DNA double-strand breaks (DDSBs) are detrimental to genome stability, they are events that commonly occur during both meiotic and mitotic cell division [9–11]. All cells have a capacity to repair DDSBs employing homologous recombination-based mechanisms that require the coordinated involvement of a number of protein families [9–11]. Among these protein families are the RAD proteins [9–11]. RAD51 displays DNA-stimulated ATPase activity, preferentially binds to single-stranded DNA, and mediates ATP-dependent strand exchange events with homologous duplex DNA [11]. A role for RAD51 in repairing DDSBs during early development was reported by Perez et al. [9], who microinjected RAD51 into fertilized oocytes and observed reduced DNA damage, reduced apoptosis, and improved embryo development in AKR/J mice, a mouse strain displaying a very poor DDSB repair mechanism. The same group of researchers also demonstrated that mouse embryos overexpressing RAD51 display reduced DNA damage and cytoplasmic fragmentation [10]. Deletion of RAD51 results in early embryonic lethality [12] and the RAD51C hypomorph displays meiotic failure in both males and females [13]. Therefore, Kujjo et al. [5] focused their studies on investigating the effects of radiation damage on oocyte health on an ideal candidate, i.e., RAD51. They have convincingly demonstrated

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that RAD51 is an important component of the adaptive mechanism that reduces DNA damage in oocytes.

This innovative study has also generated several important new concepts. These include the premise that mammalian germ cells are equipped to at least respond in an adaptive way to the deleterious effects of exposure to radiation, but not all species have an identical capacity to adapt to these types of environmental influences. It is intriguing to speculate that differences in lifespan, particularly reproductive lifespan, may underlie the species differences observed in this study. For example, mice, with their short lifespan, may not be subject to the same lifetime exposure that longer-lived species such as cattle would see; thus, the necessity of evolving a highly responsive protective mechanism is not as great in the mouse as it is for the cow. Overall, we also have to consider what this study means to humans, with our longer lifespan and longer reproductive period. Are we more susceptible to gamete radiation damage? Or do we have robust RAD51-based DNA repair and apoptotic protective mechanisms? Is it possible that the effects of cosmic radiation comprise an underlying mechanism that contributes to the sharp decline in female fertility beyond age 35? It is certainly on the minds of pilots and airline service employees [7, 14].

This novel study reveals an important role of RAD51 as a potent protector of our DNA and a suppressor of gamete cell death pathways. Perhaps this pathway acts to reduce oocyte loss and extend female fertility as long as it can be preserved. Finally, this study has importantly revealed another key aspect of our environment and how it impacts our overall reproductive health. However, don't let thinking about cosmic rays keep you from a good night's sleep; RAD51 is there to help you out.

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