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# Off to a Rough Start: Environmental Exposures May Alter Germ Cell Development

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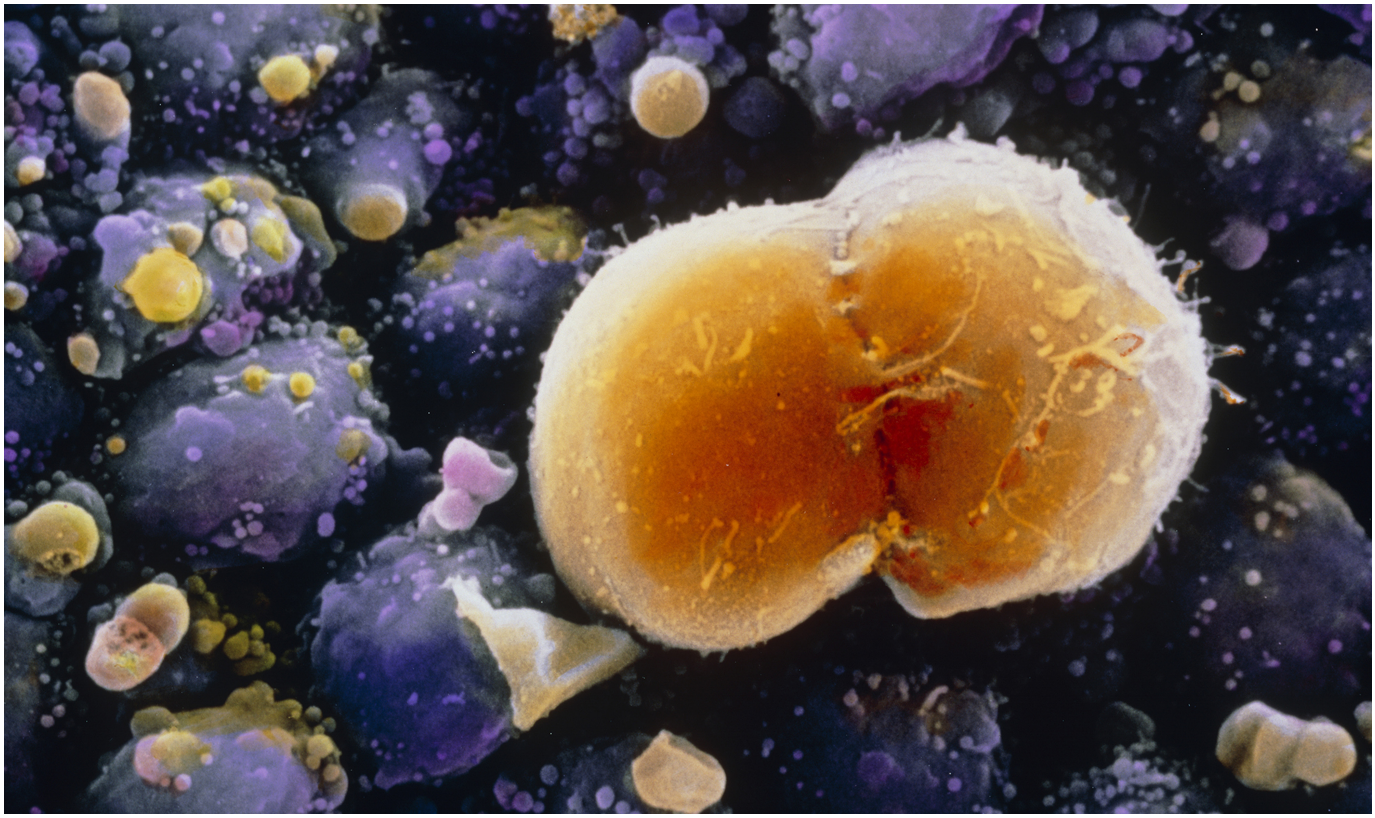
Normal development of germ cells—precursors of egg and sperm cells—is integral for the survival of a species. Prenatal exposure to toxic environmental agents can have profound effects on reproductive health decades after birth,[1] yet our understanding of germ cell development has long been hampered by technical challenges.[2] In an *in vitro* study recently published in *Environmental Health Perspectives*, researchers show for the first time how toxicant exposures at environmentally relevant concentrations can influence the earliest stages of germ cell specification.[3] The results add to mounting evidence that the timing of exposure is critical when assessing chemical toxicities.

Multicellular life is made possible by interactions between two cell types: somatic cells that carry out the essential tasks required for life, and germ cells that transfer genetic information to future generations.[2] In mammals, germ cell development starts in the epiblast (also known as the primitive ectoderm), a layer of cells that gives rise to the embryo and also contributes to extraembryonic tissues, such as the future amniotic sac. The newly formed primordial germ cells (PGCs) move into extraembryonic tissues, where, guided by cues from neighboring somatic cells, they proliferate and are folded into the embryo.[4] Finally, they migrate to their final destination: the developing gonads.[5,6]

During proliferation and relocation, PGCs undergo a complex reprogramming process known as epigenetic erasure, which involves removal of biochemical modifications to DNA and some of its associated proteins.[7,8] Errors that are introduced during this sensitive window can bridge generations and lead to both early-life[9,10] and adult-onset outcomes such as infertility,[11] cancer,[12] and other diseases.

Examining the impact of early environmental exposures on germ cell development has been hampered by its intrinsic complexity: PGCs exist in very limited numbers during embryogenesis and move from one site to another, whereas toxic exposures can span multiple developmental stages from conception through childhood.[2] Past studies have therefore been limited to evaluating exposure effects long after PGCs have moved to the developing ovary or testis and differentiated into oocytes or spermatocytes.[2] Patricia Hunt, Edward Meyer Distinguished Professor at Washington State University, who was not involved in the new study, notes that the work provides insight into a period of germ cell development that has remained virtually inaccessible until now.

To capture these key developmental events, the investigators used an established mouse embryonic stem cell model of *in vitro* differentiation into epiblast-like cells (EpiLCs), followed by PGC-like cells.[13,14] "We're standing on the shoulders of [germ cell biology] giants," says Patrick Allard, senior author of the study. "They have shown that this technology is highly representative of the mammalian *in vivo* context, so it can now be applied to the question of environmental health."



Scanning electron micrograph of a primordial germ cell undergoing division in the ovary of a 7-week-old embryo. Eventually these cells will become oocytes (eggs). Magnification: ×1920 at 6 × 7 cm size. Image: © Professors Pietro M. Motta and Sayoko Makabe/Science Source.

The researchers studied the effects of exposure to bisphenol A (BPA), a pervasive environmental contaminant and known endocrine disruptor used primarily in the production of plastics.[15] Exposure of EpiLCs to environmentally relevant concentrations of BPA led to greater proliferation, compared with unexposed EpiLCs. However, this effect was also associated with increased DNA damage in BPA-treated cells. Although PGC differentiation was not affected, gene expression analyses revealed BPA-specific alterations to the cells' gene expression landscape—changes that the authors suggested may affect gamete function later in life. "While one might expect [BPA exposure] to have global effects on the different types of cell lineages, the more subtle perturbations observed are more relevant to the biology of humans or infertility overall," says Renee Reijo Pera, director of the McLaughlin Research Institute for Biomedical Sciences, who was not involved in the study.

These effects were not observed in a cell line that is genetically male, suggesting that responsiveness to BPA at this stage of germ cell development may be sex specific. "Even though developmental biologists have long thought of PGCs as [an] asexual stage, the differences in gene expression profiles observed highlights the need to pay attention to X-linked gene dosage effects on environmental toxicant sensitivity," says Steen Ooi, first author of the new paper.

Hunt believes this system can also open the door for more in-depth mechanistic studies. Ooi thinks it would be particularly useful to dissect the epigenetic phenomena underlying how the "memory" of exposure is transmitted to later stages in development. Allard adds that a long-term goal would be to replicate some of these findings in human cells, saying, "We hope to one day develop *in vitro* systems to recapitulate the entire reproductive cycle in a dish, characterizing every single stage of germ cell development and reproduction."

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