

How some mammals pause their pregnancies

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A seal hauling out of the water onto a California beach. Seals are among the mammals whose embryos can delay implantation and enter diapause, a temporary dormant state, to time the pregnancy for favorable conditions. Credit: Alice C. Gray

How do some mammals postpone the development of their embryos to await better conditions for having offspring? A recent study at the UW Medicine Institute for Stem Cell and Regenerative Medicine explored

this reproductive enigma, which can occur in more than 130 species of mammals as well as in some marsupials.

The study was study led by Abdiasis Hussein, a graduate student in the lab of Hannele Ruohola-Baker, UW professor of biochemistry and associate director of UW Medicine's Institute for Stem Cell and Regenerative Medicine. The findings were reported in *Developmental Cell*, a Cell Press scientific journal.

The results not only advance the understanding of delayed [embryo implantation](#), but also suggest how some otherwise rapidly dividing [cells](#), such as those in tumors, become quiescent.

In the suspended state of pregnancy called embryonic [diapause](#), an early-stage embryo refrains from implanting in the mother's uterus, where it could be nourished to grow into a baby. Instead, like a seed, the embryo remains dormant until certain molecular regulators prod it to germinate.

Diapause, or delayed implantation, is a biological strategy for waiting out conditions unfavorable to sustaining newborns, such as lack of food, insufficient maternal fat stores, or older siblings who haven't been weaned.

Bears, armadillos, seals, and some otters, badgers and other weasel-like animals undergo seasonal diapause, as a regular part of their reproductive cycles.



Diapause researcher Abdiasis Hussein in a lab at the UW Medicine Institute for Stem Cell and Regenerative Medicine in Seattle. Credit: Thatcher Heldring

Many types of bears, for example, breed in the late spring or early summer. The female then voraciously hunts for food. Only when the female bear has sufficient body fat and weight will one or more of her embryos implant months later, after she retreats to her den. Any cubs would be born in late winter.

To learn what puts a biochemical hold-and-release on [embryonic development](#), Hussein, Ruohola-Baker and their team induced diapause in a female mouse model by reducing estrogen levels. They then

compared diapause embryos to pre-implantation and post-implantation embryos. They also induced diapause in mouse [embryonic stem cells](#) by starving the cells, and compared those to actively growing mouse embryonic [stem cells](#).

In the wild, some animal embryos will delay implantation until their mother has enough energy and nutrients in her body to support them. Starvation or other stresses somehow provoke an embryonic stop-time. This response is an effort to protect their survival.

The researchers did extensive studies of how metabolic and signaling pathways control both the dormant and active states of mouse embryos and of mouse embryonic stems cells in lab dishes.

Metabolism concerns the life-sustaining chemical activities cells carry out to convert substances into energy, build materials, and remove waste. By analyzing these reactions' end products, called metabolites, the scientists could begin to pull together a picture of what happens to cause diapause, and how cells are released from its clutches.

The scientists also looked at [gene expression](#) in comparing cell states. They sought to determine what might be influencing how the DNA code was being interpreted, what critical proteins were being produced and in what amounts, in the suspended and active states.



A female elephant seal and her pup on a beach near Big Sur, California. Seals and other pinnepeds are among the mammals whose early-stage embryos can enter diapause -- a temporary dormant state -- and then implant and develop later. The timing of pregnancy and birth are thereby postponed to occur when conditions are more favorable for survival. Credit: Alice C. Gray

According to embryonic stem cell researcher Ruohola-Baker, epigenetic differences in interpreting the same DNA code, rather than any alterations in the DNA itself, may be key to understanding how embryos enter and exit diapause.

Further investigation pointed to a set of proteins vital in embryonic cell survival. The activity of the genes related to these proteins, as well as levels of certain amino acids, were ramped up in the diapausal [embryos](#).

For example, by using CRISPR gene-editing technology, Hussein and Julie Mathieu, UW assistant professor of comparative medicine, squelched the flow of glutamine, an amino acid that controls an important metabolic (energy-use) pathway.

The researchers collected additional data that indicated that this and other metabolic factors influenced a catalytic enzyme, mTOR, that regulates many cell processes, including cell proliferation, growth, and protein synthesis. mTOR is also involved in "sensing" cell nutrient and energy stores.

mTOR is already known to be a central regulator of metabolism and physiology in mammalian aging and cancer. It also manages aspects of embryonic growth and development. In this study, situations that inhibited mTOR led to the distinct metabolic profile that characterizes diapause. Researchers also found that this inhibition was reversible.

Understanding the mechanisms behind diapause could advance knowledge in medicine, as well as in wildlife biology. Carol Ware, a UW professor of comparative medicine, said that diapause is an essential means of survival for some species, and occurs under environmental stress in others.

Research on the mechanism of diapause in animals is an important step in seeing if this cellular response can be harnessed for clinical therapies, such as better in vitro fertilization procedures to help people have children.

Hussein believes this line of research might also have significance for future cancer studies. Figuring out why and when cancer cells enter quiescence might help explain their hunkering down to withstand chemotherapy, and reviving themselves later. Perhaps a therapy eventually could be devised, he said, that could wake up the cells to

coincide with the timing of anti-cancer drugs.

More information: Abdiasis M. Hussein et al, Metabolic Control over mTOR-Dependent Diapause-like State, *Developmental Cell* (2020). [DOI: 10.1016/j.devcel.2019.12.018](https://doi.org/10.1016/j.devcel.2019.12.018)

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