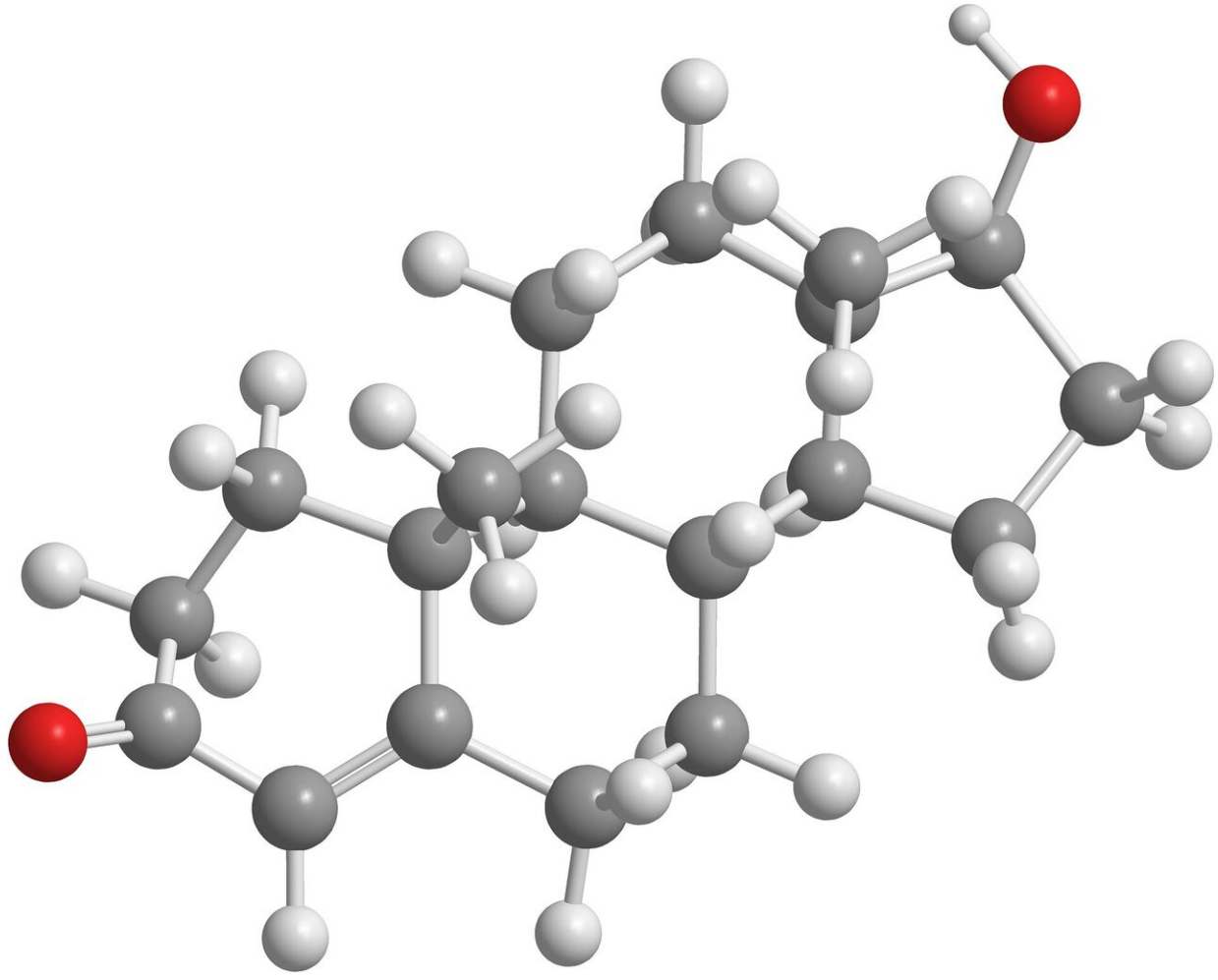
New understanding of ovarian follicle development may lead to novel reproductive therapies

May 3 2021



Credit: Pixabay/CC0 Public Domain

For the first time, researchers have shown how Mullerian inhibiting substance (MIS), also known as anti-Mullerian hormone, a key reproductive hormone, suppresses follicle development and prevents ovulation in females. "Understanding the mechanism of follicle development by MIS opens the door to creating novel approaches to contraception, preserving the eggs of young girls undergoing chemotherapy, enhancing the success of fertility treatment, and potentially delaying menopause," says David Pépin, Ph.D., an associate molecular biologist in the Department of Surgery at Massachusetts General Hospital (MGH) and senior author of new research published in the *Proceedings of the National Academy of Sciences (PNAS)*.

Follicles are like small cocoons within the ovary that house eggs, which, when activated, nurture the growth of an egg and secrete hormones that influence stages of the menstrual cycle. Women are born with all the ovarian follicles and immature eggs they will ever have—about a million—which are continuously used until they are depleted at menopause. Nearly all these follicles will never reach maturity, instead mostly degenerating during growth, leaving only the best to ovulate. As a result, only a few hundred will ever reach ovulation starting at puberty. "Even in utero, primordial—or immature—follicles start to activate and most are lost even before puberty is reached," says Pépin. Still, some primordial follicles can stay dormant for decades until they are roused and grow large enough to release an egg, a process that can take as long as a year. "One role of MIS is to slow the development of primordial follicles so that they last throughout the entire reproductive lifespan," says Pépin. "But until now, we didn't know how primordial follicles responded to MIS to stay dormant."

In a series of experiments using mice, the researchers conclusively showed that there is an MIS receptor on the primordial follicles' granulosa cells, which guide egg development—an area of previous debate—and that the hormone inhibits their growth, keeping them

dormant. Surprisingly, MIS treatment also inhibited almost every cell type within the ovary and interfered with the communication between germ cells and granulosa cells, which is necessary to coordinate follicle growth. The researchers injected mice with a gene-therapy virus, which caused them to produce elevated levels of MIS.

"We discovered that high amounts of the hormone will shut down the ovaries, putting them in a kind of hibernation and preventing follicles from growing normally," says Marie-Charlotte Meinsohn, Ph.D., a research fellow in the Department of Surgery at MGH and lead author of the study. The researchers then identified the genes that were regulated by MIS in dormant follicles.

The research has multiple applications that are currently being investigated. Targeting the MIS receptor with a drug, for example, may help preserve the primordial follicles in girls undergoing chemotherapy for cancer, thus avoiding infertility. Learning how primordial follicles remain dormant could teach us how to slow the aging process in the ovaries by maintaining a greater reserve of follicles, thereby maintaining production of hormones such as estrogen. Delaying menopause may not only expand a woman's reproductive life, but it might also delay some of the health problems women encounter with the loss of estrogen after menopause, leading to healthier aging.

Therapeutic treatment with MIS may also enhance the success of in vitro fertilization. "One of the challenges of IVF is to synchronize the development of multiple follicles so one can retrieve more eggs," says Pépin. "If we can temporarily suppress follicle advancement with MIS, more synchronized follicles will be available to be stimulated with fertility treatment, resulting in the retrieval of many more eggs," as the team recently showed in a publication in the *Journal of the Endocrine Society*.

The researchers are also studying MIS as a novel hormonal contraceptive . "Other hormone contraceptives interfere with ovulation, which occurs at a late stage of follicle development," says Pépin. "We are interested in developing a contraceptive that blocks primordial follicles from maturing at an earlier stage so ovulation can't occur."

A contraceptive targeted at early follicle development could also prevent cycling and menstruation, which would be beneficial in disorders such as endometriosis and the heavy bleeding that can occur with uterine fibroids. The researchers are also investigating whether an injection of a gene-therapy virus that elevates levels of MIS can provide permanent contraception for feral cats and dogs.

The next step for the researchers is determining which of the identified genes regulated by MIS play the most important role in preventing primordial follicle activation. "Some of the pathways identified in this study could represent new drug targets which would allow us to translate MIS for the benefit of women's health," says co-author Patricia K. Donahoe, MD, director of the Pediatric Surgical Research Laboratories.

More information: Marie-Charlotte Meinsohn el al., "Single-cell sequencing reveals suppressive transcriptional programs regulated by MIS/AMH in neonatal ovaries," *PNAS* (2021). www.pnas.org/cgi/doi/10.1073/pnas.2100920118

Provided by Massachusetts General Hospital