Newly identified enzyme could play key role in childbirth and muscle diseases

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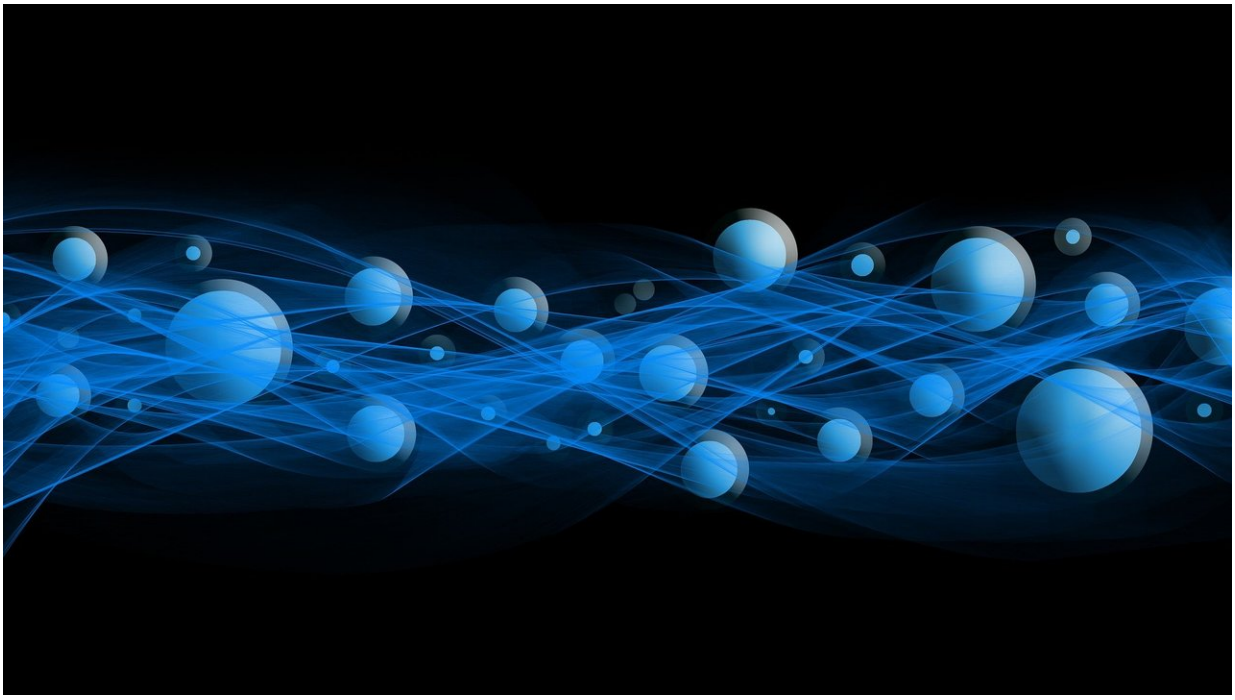

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Since the 1960s, scientists have known of a modification that occurs to a particular molecule in muscles, especially after exercise. What scientists haven't known is how that modification happens, or even why.

Now, in a serendipitous finding that started with seemingly unrelated work in viral infections, a team of Stanford scientists discovered not

only how the modification takes place – it's through an enzyme called SETD3 – but found that the enzyme likely helps coordinate muscle contractions by the uterus during childbirth. More broadly, SETD3 could also be a hitherto unrealized factor in a range of human muscle tissue diseases.

The modification to muscle cells involves the protein actin, which in part makes up the filaments that contract within muscles. The actin gets adorned with a molecule, called a methyl group, at a certain location where a molecule dubbed histidine is found. Because of this activity – transferring a methyl to a histidine – the newly identified SETD3 is what's known as a histidine methyltransferase.

Until now, nobody had identified a histidine methyltransferase in humans or other animals. The study revealed that the methylation accelerates the formation of new actin filaments in cells, priming them for greater strength when next flexed.

"The histidine methylation we uncovered in this study appears to be a far more common way of regulating proteins than previously appreciated," said co-lead author Alex Wilkinson, a postdoctoral scholar in the lab of Or Gozani, the Dr. Morris Herzstein Professor of Biology. The study was published Dec. 10 in the journal *Nature*.

"Overall, there are a lot of 'firsts' in the study," said Gozani, a study co-author. "We discovered a first-in-class enzyme, the first function for histidine methylation in animals or plants, solved a 50-year-old mystery by determining the function of actin histidine methylation and raised the curtain on a new field that may impact human health."

Study co-lead author Jonathan Diep, a graduate student in the lab of Stanford associate professor of microbiology and immunology Jan Carette, pointed out there could be other histidine methyltransferases

hiding right under our noses. "The discovery of an entirely new class of methyltransferases could have major implications in expanding our repertoire of cellular targets for drug development," Diep said.

A fortunate find

The truth about SETD3's function might have remained a secret for another half-century had Carette's lab not stumbled upon the enzyme while investigating viral infections. To understand the enzyme's activity in normal animal physiology, Carette reached out to Gozani, an international expert in methyltransferases, who happened to be working just a few buildings away. Despite their expertise, Gozani's group initially could not make heads or tails out of the obscure biomolecule. "All of us were struck by how little was known about this enzyme," Carette said.

To characterize SETD3 and figure out its function, Wilkinson, Diep and their colleagues at Stanford and in Xiaodong Cheng's lab at the University of Texas MD Anderson Cancer Center conducted a series of experiments and measurements. These included gauging its mass, testing its biological activity on actin, as well as other molecules, and crystallizing the enzyme to observe its structure.

Wilkinson ultimately put the puzzle pieces together, deducing that SETD3 was not just any methyltransferase, but the first histidine methyltransferase to be found in animals; the only kind previously documented occurs in yeasts. "It was one of those times when everything came together and it's why we do science," said Gozani.

Aiding uterine contractions

Claude Nagamine, an associate professor of comparative medicine, led

the genetic experiments that revealed SETD3's impact on childbirth. The researchers bred mice that lacked SETD3. In the absence of that enzyme, the precise smooth muscle coordination necessary for uterine contractions during labor could not take place, a condition known as dystocia.

The Stanford scientists found that SETD3 might have a similar part to play in humans. Working with cultures of human uterine smooth muscle cells, the team showed that low levels of SETD3 impaired contraction under conditions that model labor.

In mice at least, dystocia is not terribly problematic. Unborn fetuses are eventually reabsorbed by the mother without ill effect to her. For dystocia in humans, in some cases a doctor can administer a hormone (or its synthetic equivalent) called oxytocin to stimulate contractions. In women with SETD3 dysfunction, that oxytocin wouldn't work and those women would require caesarean sections. This surgery carries far more risks than a normal vaginal delivery and requires longer hospital stays. Studies have also found better health outcomes in children born naturally.

If SETD3 mutations do turn out to impair childbirth in people, women and their physicians could plan ahead for the possibility of a caesarean section. "Clinicians could possibly screen women to help identify those who might be at higher risk for C-sections," said Gozani. "Overall, given that actin is an essential protein for a diverse set of cellular functions, we think we may be only scratching the surface when it comes to this enzyme's methylation effects across the animal kingdom."

More information: Alex W. Wilkinson et al. SETD3 is an actin histidine methyltransferase that prevents primary dystocia, *Nature* (2018). DOI: 10.1038/s41586-018-0821-8

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