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How a protein modification navigates sperm to the egg

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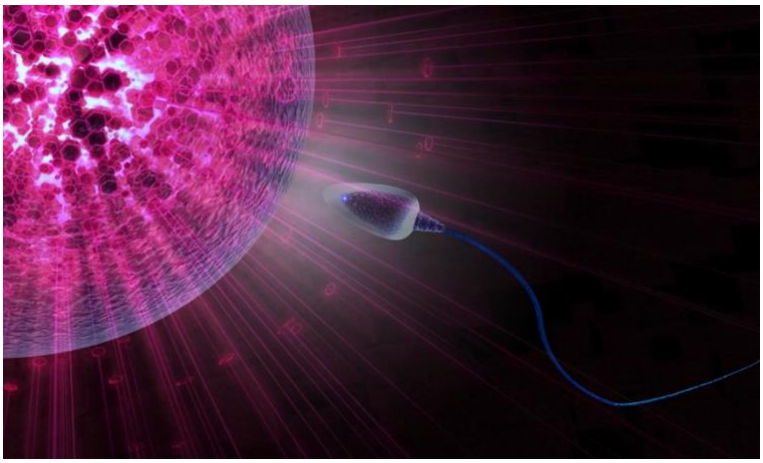
For fertilisation, millions of sperm cells race toward the egg by rhythmically wagging their tail. How they head to the goal straight is unknown. A new study reveals that a chemical modification on proteins controls the sperm tail's behaviour, and in its absence, amazingly, sperm turns to swim circularly, rather than to swim straight toward the egg, causing defects in male fertility.



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Mammalian fertilisation is a dynamic, spectacular event. Millions of sperm race toward the egg, and only one winner can eventually fuse with it and lead to a new life. A sperm is a special type of cell with a tail-like appendage (named flagellum) allowing it to swim straight (imagine how a tadpole swims!). In a new study, we asked how a sperm heads to the goal straight.

Rhythmic movements of the sperm tail are driven by elongated stretches of protein filaments called cytoskeleton. Like the human skeleton forms the basic shape of our body, the cytoskeleton defines the shape of the cell. Beyond being an architectural framework, microtubules – key components of the cytoskeleton – help the sperm wag its tail and move forward by using in-house 'motor' proteins called dyneins. Dyneins can convert chemical energy into mechanical force, and they can do this locally by 'walking' along elongated microtubule fibres. Thousands of dyneins walk back and forth on adjacent microtubule fibres in coordination, and in turn, rhythmically bend and straighten the sperm tail. This resembles how paddles are moved in synchrony to move a galley forward. On the galley the rowers are coordinated by a supervisor, but what about the dyneins?

A chemical decoration on proteins called glycylation is likely the trick. We know this type of protein modification happens on microtubules. Interestingly, glycylated microtubules have been only found in sperm tails and similar structures. This suggests that the glycylation may give a unique

function to microtubules in sperm tails, which is potentially associated with the tails' dynamic movements. However, this chemical modification has been poorly investigated and its biological meaning remains unclear.

To explore the role of microtubule glycylation in sperm tail dynamics, we used genetically engineered mice. Using mice as a model animal is beneficial because they share a very similar genetic background and physiology with humans. In other words, what happens in mice most probably occurs in humans too. We edited the DNA of mice to remove the genes that are essential for glycylation. Comparing these mice lacking glycylation with normal mice, we can understand the biological function of this chemical modification.

To our surprise, the lack of glycylation did not lead to any distinct defects in mouse behaviour and general health. However, when it comes to fertilisation, the male mice showed a reduced fertilisation capacity and an abnormal sperm swim style. Notably, the lack of glycylation altered the beat of sperm tails, which was less frequent and less symmetrical. Moreover, the sperm tails were more curved towards the sperm head. As a result, the glycylation-deficient sperm could no longer swim along a straight line and tended to swim in circles. This finding reveals that glycylation is essential for keeping the rhythmic beats of sperm tails, and important for the sperm not to get lost during the travel.

To take a deeper look, we next explored how internal architectures of a sperm tail look at the molecular scale in amazing detail using a cutting-edge microscopy named cryo electron microscopy. While the overall molecular architectures of the sperm tail were unaffected in the absence of glycylation, we found that dyneins were particularly disorganised. This suggests that glycylation on microtubules serves as the 'galley supervisor' that assures the coordinated movement of the dyneins. It also explains why the sperm turned to circularly swim when glycylation was absent.

In summary, we demonstrated that glycylation – a tiny chemical decoration on proteins – arranges dyneins along microtubules, which leads to the rhythmic movement of sperm tails and efficient fertilisation in mice. As we expect this happens in humans as well, our results shed light on a new molecular mechanism possibly causing male infertility. It's noteworthy that various cells have appendages called cilia that are structurally related to sperm tails. Dysfunctional cilia with the lack of motility cause diseases called ciliopathies, which widely affect different organs. Since microtubule glycylation is also present in cilia, future studies will extend our understanding of the potential roles of glycylation in health and disease.