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a dark kinase

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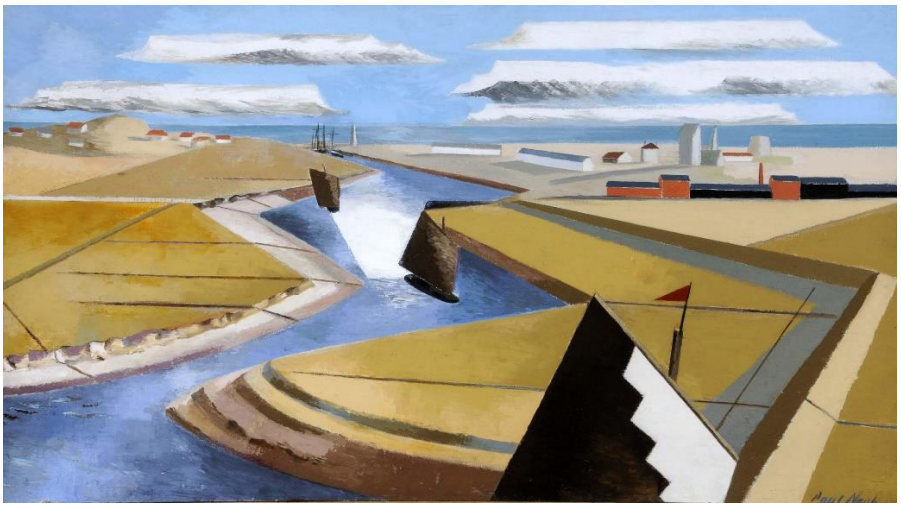
Spermatozoa. There are no other cells in humans – or indeed in any other animals – that have the capacity to wriggle and move forward the way spermatozoa do. Blood cells may dash around our bodies but they can only do so because they are swept up in the pulse and flow of blood. Spermatozoa make progress like little animals – which is why they were called 'animalcules' by the Dutch microbiologist van Leeuwenhoek who was the first to observe them under a microscope in the 17th century. Many organisms can move like spermatozoa, such as bacteria or protists for example, but these are unicellular from the start and really only have themselves to depend upon. Spermatozoa cannot survive on their own, as they don't have the genetic makeup for that, but they can move on their own. In fact, locomotion is really all they have evolved for. Their sole aim is to reach an ovum into which they will inject their DNA. So evolution has trimmed the architecture of spermatozoa down to the very essential: a head (in which resides the nucleus) attached to a powerful tail. The tail itself is a model of biological design and technology brought about by many proteins, among which a crucial kinase known as STK33.



The Rye Marshes

by Paul Nash (1889-1946)

A sperm's journey is an eventful and, more often than not, a tragic one. Tragic because, although its sole purpose in life is to fertilize an egg, there is little chance this will ever occur. Once a sperm has matured in the male testis and has been sent into a uterus with millions of fellow sperm, by the power of its tail it wiggles and writhes up the uterus making its blind way towards the Fallopian tube. There, moving in the opposite direction, one egg will hopefully be maturing as it slowly progresses from the ovary down to the uterus. Hundreds of thousands of sperm run out of stamina or miss the Fallopian tube altogether. Thousands manage to locate the tube, but miss the egg. Hundreds find the egg – but only one manages to worm its way through the egg's protective layers. Once it has, it ensures no other sperm will also succeed by initiating a chemical change in the egg's outer composition to harden it, thus creating a physical barrier. Understandably, such a journey requires endurance and vigour, which is what a sperm's tail is all about.

It has taken three hundred years to outline the amazing molecular workings of sperm – ever since the Dutch microbiologist van Leeuwenhoek first described them under his self-made microscope, the lenses of which were initially designed to check the quality of thread used in the fabric he sold in his draper shop. Today we know how sperm mature in the testes, how they move,

how they fertilize eggs. We know that they carry their DNA – half of the DNA needed to make a new individual – protected within the walls of a nucleus situated in what has been called the sperm's head. We know that there is a region on the very tip of the head that activates egg fertilization – the acrosome. We know that, without their tail, there would be no fertilization at all, nor journey for that matter, because their tail provides them with locomotion.

Besides being a wonderful example of biological architecture, a sperm's tail is metabolically intricate. It looks like a tail and, on the molecular scale, probably resembles your pet dog's tail in that it has a soft outer layer and a more rigid inner layer that does the wagging. All comparison ends here, however. The outer layer of a sperm's tail consists of a fibrous sheath that also surrounds the sperm's head. A firmer structure known as the axoneme runs from the beginning of the tail to the tip – exactly the same structure you will find in the cilia of protists. It is the axoneme that allows the tail to wriggle. Axonemes are highly-organised structures, consisting largely of proteins known as dynein and tubulin. In a nutshell, tubulin monomers assemble to form pairs of microtubules – 9 outer pairs and one central pair – which each span the length of the sperm's tail. Dynein monomers assemble to form 'dynein arms' that protrude from the outer partner of each microtubule pair. Interaction between the dynein arms and the outer pairs of microtubules create movement – the tail's wag if you like. To enable this, the tail requires energy. This is provided in the form of ATP by mitochondria that are located in the upper part of the tail just below the head – imagine them as the sperm's powerhouse.

This is when STK33, **s**erine/**t**hreonine **k**inase **33**, makes its appearance. Kinases have pivotal roles in human biology. They are like teachers who clap their hands to pull pupils out of their lethargy. It comes as no surprise, then, that an estimated 538 kinases are to be found in the human genome. How do they perform? Kinases phosphorylate substrates – usually other proteins – by using phosphorus extracted from ATP. Phosphorylation is a common post-translational modification of proteins, the finality of which is to kickstart downstream metabolisms. In the company of almost 200 other kinases, STK33 had been cooped in a corner called 'dark kinases' because very little was known about it. Until a team of researchers discovered that STK33 is involved in a sperm's overall design because when it is absent sperm are unable to move.

In particular, they found that without STK33 a sperm's fibrous sheath is misarranged. Now, the fibrous sheath acts as a scaffolding to support structures such as the axoneme, the nucleus and the mitochondrial 'powerhouse'. Without this scaffolding, like a human body that has lost its skeleton, these structures have nothing to hold onto, no template to follow. As a consequence, they are poorly assembled, or not assembled at all, and the sperm loses its means of locomotion. STK33 is like the architect who acts upstream of a project and, predictably, is evolutionarily conserved across the animal kingdom. Do we know which proteins STK33 phosphorylates? Yes. They are called **A-k**inase **a**nchoring **p**rotein **3** and **A-k**inase **a**nchoring **p**rotein **4** (AKAP3 and AKAP4) and are key components of the fibrous sheath. When STK33 is absent, AKAP3/4 are not activated. The fibrous sheath is consequently mal-arranged causing any subsequent structure formation to be mal-assembled – and there is little hope left for a sperm to reach an egg.

A greater understanding of kinases such as STK33 could help find therapeutic strategies for men suffering from infertility caused by mutated forms of STK33 for example. Conversely, STK33 could also prove to be a good candidate for male contraception. Today, scientists estimate that about 100 million unintended babies are born every year worldwide. If contraceptive options were not only more successful but also less limited for men, things would change for the better – as they did in the 1960s and 1970s when female contraceptive methods became available in our society. Inhibitors could be designed to block STK33 activity, thus rendering sperm immotile and unable to fertilise an egg. In the absence of inhibitors, STK33 would become functional again and the contraceptive effects reversed. This sounds wonderful. And it is. However, STK33 is not the first contraceptive candidate, many have had to be abandoned because of side effects. Fertility, indeed, cannot be pinned down to one entity. A sperm's environment is influential too – reminding us once again that an organism is never a simple sum of its parts.

Cross-references to UniProt

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