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The kink behind the wriggle

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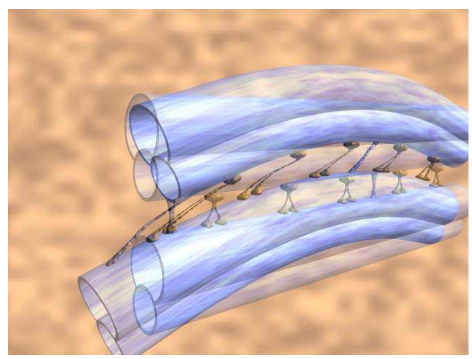
Were it not for dynein, none of us would be here. There is an intriguing thought. Indeed, dynein is at the heart of a sperm's wriggle. Without it, there would be no race to the egg. And, what is more, an egg depends on the movement of cilia in its long journey from the Fallopian tubes to the womb. And it is dynein which makes cilia quiver. Dynein is in fact central to numerous movements in and outside a cell, such as mitosis, vesicular mobility, debris removal in the lungs and chemical transport in our nervous system. It is a molecular motor; fed on biological fuel – ATP - it creates movement. Much research has been done on this extraordinary protein because of its key role in sperm mobility and hence fertility.

We know today, that the creation of a new human requires the fusion of both an egg and a sperm, followed by a share of their wares. Not so long ago however, it was thought that sperm alone was sufficient; discharged into the womb, it found there the cosy surroundings it needed to develop and grow. These were the days of the Spermists. Antony van Leeuwenhoek (1632-1723), a Dutch fabric merchant provided the inklings of clear sightedness when he offered detailed descriptions of human semen.

Leeuwenhoek invented – not the first microscope – but the first lens with greater definition. In his trade, magnifying lenses were used to count thread densities. It is thought that Leeuwenhoek must have come across Robert Hooke's Micrographia published in 1665, which is a record of Hooke's microscope observations of numerous organisms with outstanding illustrations. The book also includes pictures of textiles which must have been of interest to the fabric merchant, and Hooke's descriptions may well have inspired Leeuwenhoek to make observations with his own microscopes – which he shared with the Royal Society of London until his death.

The Dutch merchant was the first to discover and describe human spermatozoa. In fact, he spent the great majority of his life describing the spermatozoa of mollusks, fish, amphibians, birds and mammals. And following his observations, the theory of fertilisation was refined; Leeuwenhoek was the first to suggest that fertilisation only took place once the spermatozoa had actually penetrated the egg. How the spermatozoa made it all the way to the egg remained a mystery.



Microtubular movement produced by dynein complexes

And it has taken the best part of 300 years to find out. Scientists are now very near to understanding in great detail the wriggle of a sperm's tail at the molecular level. Much research has been done using the flagella of the alga *Chlamydomonas reinhardtii. Chlamydomonas'* flagella – like those of spermatozoa – are packed with microtubules, which are long tubular protein complexes, distributed in arrays. It has been known since the 1960s that the gliding of the microtubules along one another is what creates the flagellar twitch. We know today that dynein is lodged in between and along the length of the gliding microtubules, and that it is this protein which creates the movement in the first place.

Dynein is a multimolecular complex, made up of light chains, intermediate chains and heavy chains. The heavy chains are the molecular motors and provide the drive which will ultimately create the microtubular slide. The secondary structure of motor dynein is made up of a certain number of modules; the centre modules seem to be potential ATP binding sites while the end modules – the C- and N-termini of the protein sequence – behave like minute limbs which straighten and bend and give the microtubules the kick they need to move. The overall tertiary structure of the motor protein bears a vague resemblance to a two bladed propeller. The centre – or head – is globular, almost hexagonal with a hole in its middle, much like the nut for a bolt. Two 'limbs' sprout from the head at an angle of almost 180º: the stem and the stalk. The stalk is docked to the microtubule via a little globular region at its tip, while the stem is used for binding cargo. And this extraordinary 3D structure is the result of the folding of one long primary sequence.

How does this two-limbed nut make a sperm wriggle? There is an intriguing hypothesis. ATP binding, hydrolysis and release probably occur at the level of the dynein head region. Just before the power stroke – i.e. prior to the hydrolysis of ATP and the release of ADP – the stalk seems to be in a relaxed state and the stem sports a kink where it links to the head: the linker region. Once ADP-Pi is dispatched, three conformational modifications occur in the dynein molecule, the result of which is microtubule mobility. The sequence of events is still poorly understood but – in hydrolysing ATP and releasing ADP – the linker region disappears behind the head region, revealing the centre hole. Concomitantly, the stalk stiffens. The stalk is thought to be a superposition of two alpha helices; the power stroke would create a change of conformation in the helices making the stalk rigid and thereby transmitting the 'power information' to the microtubule. As the stem's linker region disappears and the stalk stiffens, the head region rotates. These three modifications sum up the dynein power stroke. Scientists argue that it is the change in the linker-head region which may be fundamental in the dynein power stroke.

Understanding dynein and the molecular process of its power stroke will not only be helpful in finding ways to fight infertility but could also be of particular assistance in understanding other disorders where cellular and intracellular movements are involved, such as gynaecological, bronchial and neurological disorders. We are light years away from the very first observations made by Leeuwenhoek. However, scientists today would not have the powerful instruments they do – or indeed their insight – were it not for the initial ingeniousness and curiosity of men like Leeuwenhoek in the first place.

Cross-references to Swiss-Prot

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