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> ONE MONTH, ONE PROTEIN <

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becoming one

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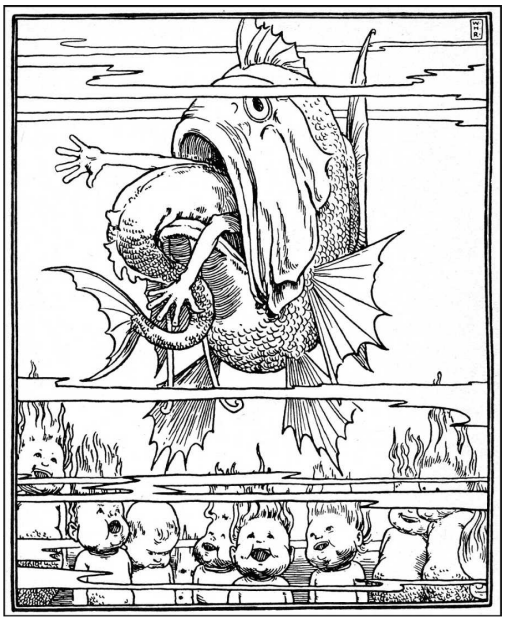
There are different ways of producing progeny. In eukaryotes, the most widespread method is for two reproductive cells of the opposite sex to meet and fuse. This may sound straightforward but mating is never an easy affair. Not only must the two cells belong to the same species but they must also make sure that they belong to different mating-types. They then have to know how to recognise each other, adhere to one another, fuse and create a space in which their nuclei will meet, mingle and ultimately give birth to a new individual – a series of events that demonstrates how accidental any form of life is in the first place. Though to date very little is known about reproductive cell fusion on the molecular level, each of these steps probably involves a complex interplay of many different proteins. In the green alga *Chlamydomonas reinhardtii* scientists have unveiled part of the molecular mechanics of a protein that has a direct role in fusing such cells. It has been called Hapless 2.



The adventures of Uncle Lubin (1902)

by William Heath Robinson (1872-1944)

The act, or indeed the art, of mating is used by Mother Nature to ensure the continuation of a species – besides offering life a means to perfect and diversify itself through the forces of evolution. Change, and ways of sustaining change, keeps life healthy and prosperous. Such a notion only began to seep into general scientific thought in the mid-19th century following the publication of Charles Darwin's book "On the Origin of Species" and his theory of evolution. Meanwhile, out in the wild, evolution had been going on for millions of years regardless of what scholars were thinking. The most widespread way of keeping life alive is by mixing the genes of two opposing mating-types. Humans do it this way, as do most other eukaryotes.

For centuries, naturalists theorized on how humans were made. The link between semen and something inside the womb had been acknowledged, but what exactly was going on inside? Following studies on hen's eggs, the English physician William Harvey (1578-1657) stated that all life comes from the egg thus shaking the foundations of 'spontaneous generation'. In 1677, the Dutch businessman and scientist Antonie van Leeuwenhoek was able to observe human sperm cells under the microscope. At the time, the prevailing theory of human development was preformationism, in which organisms grow from miniature versions of themselves. The spermists believed that a 'mini-me', so to speak, exists in every sperm cell, while the ovists maintained that everything begins in the egg. It took another century before the Italian priest and biologist Lazzaro Spallanzani (1729-1799) described mammalian reproduction for the first time, and demonstrated that both semen and an ovum are required to create an animal.

Chlamydomonas is a choice organism for studying reproduction as it is unicellular and moves by using flagella much in the way mammalian sperm cells do. Male and female *Chlamydomonas* gametes – otherwise known as minus (male) and plus (female)

gametes respectively – are attracted to one another via proteins that gather at specific parts of the male gamete plasma membrane. Hapless 2, or Hap2, is among these proteins. When mating occurs, a minus and plus gamete move towards each other and are anchored to one another by way of their flagella. Following this stage, mating structures that resemble protruding tubes grow from each of the gametes and end up touching each other in a sort of cellular kiss. The lipid bilayers of each gamete then fuse to form a larger cell with a sole cytoplasm between them, thus allowing their nuclei to unite.

What is Hap2's role in this *Chlamydomonas* embrace? Hap2 gathers in the region of the male plasma membrane that becomes the tip of the mating tube. The protein has no apparent role in recognizing the opposite sex or in gamete adhesion, but it does seem to be essential and directly involved in gamete fusion. From a structural point of view, Hap2 is very similar to what are known as Class II fusogens, which are sex-restricted transmembrane proteins scattered across many eukaryotic taxa – from green algae to cnidarians, arthropods, hemichordates and higher plants. It isn't, however, found in vertebrates. Such a broad distribution across eukaryotes suggests a mechanism for gamete fusion that probably goes all the way back to the last eukaryotic common ancestor (LECA).

As all other 'ancient' Class II fusogens, Hap2 is a transmembrane protein, composed of three ß sheet-rich domains, with an ectodomain reaching into the extracellular space and a tail that extends into the cell's cytoplasm. The cytoplasmic tail seems to be required for targeting Hap2 to the mating structure. When the male gamete is about to fuse with its female counterpart, Hap2 spontaneously adopts a functional homotrimeric hairpin conformation within the lipid bilayer – a characteristic of this class of fusogens. Concomitantly, two 'fusion' loops located in the fusogen's ectodomain are thought to insert themselves into the female gamete plasma membrane thus initiating plasma membrane fusion *per se*. The lipid bilayers of both gametes then begin to merge to form one continuous plasma membrane which harbours a continuous cytoplasm and the two nuclei. Once fusion is complete, Hap2 is degraded thus demonstrating a role specific to gamete fusion.

Though vertebrates do not have Hap2, there is a chance that gamete fusion follows similar paths, and *Chlamydomonas* is a model organism for studying the process closer. A greater knowledge of how it all works should be of help in the field of reproductive biology and provide novel ways of countering human sterility. Even more intriguing perhaps: Hap2 is encoded by various human pathogens, including *Trypanosoma*, *Toxoplasma* and the parasite *Plasmodium* that transmits malaria. This could inspire biologists to engineer molecules that hinder Hap2 function – by targeting its ectodomain for instance – thus preventing cell fusion, and providing an elegant and effective way of fighting malaria, for example, a disease that currently affects hundreds of millions of people around the world. As usual, a great deal more work is required. There is little chance, too, that Hap2 prompts cell fusion on its own. But it is a step towards the understanding of that fascinating process where two organisms unite to create new life.

Cross-references to UniProt

Hapless 2, *Chlamydomonas reinhardtii* : A4GRC6

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