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> ONE MONTH, ONE PROTEIN <

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# it's a thin line

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**One cell. One organism. One fate: male, or female. The way Nature designs things, you would expect traits as fundamental as those that make a boy a boy or a girl a girl, for instance, to be inscribed in their respective DNA from the very start. In a way they are, of course, but there is a subtlety: if what defines gender is for some reason missing, then the other sex may emerge almost by default. So the process is far more than a simple case of gender that is genetically predetermined. The same goes for *Musca domestica*, or the common housefly, as it does for many other animals. There seems to be a sort of switch which, when on or off, will produce one sex or the other. This particular part of the sex decision system is preserved in many organisms, and scientists are beginning to realise that the upstream mechanisms leading to the definitive sex switch are surprisingly diverse and, in the case of *Musca domestica*, can even change from fly to fly. But one thing is preserved: to become male or female, you need a factor that will ultimately push the on/off sex switch. In the housefly, that factor is Mdmd, or *Musca domestica* male determiner.**

Illustration by Arthur Rackham (1867-1939)

In 'Aesop's Fables', illustrations by Arthur Rackham (1912)

It is unnecessary to introduce *Musca domestica*, the only animal – with mosquitoes – we all kill with premeditation on a regular basis, and barely without a second thought. Houseflies are a nuisance. And there's a fair chance they will continue to be so, since they have been on the planet for hundreds of millions of years and they love our company – our food in particular. Their lives are spent dashing between dirty places where they breed and lay their eggs, and our plates where they eat our food, and leave behind their saliva and faeces – making them a potential health hazard in the process. Flies can be the carriers of all sorts of diseases, either externally or internally. In fact, they are known to carry over 100 pathogens and are a problem in hospitals and during disease outbreaks.

Their role as pathogen vectors became somewhat over-exaggerated in the early 20th century, when countries like Canada and the United States put the blame on houseflies for spreading tuberculosis and polio for example, while China – and well into the 1960s – exhorted its population to kill off the country's main pests: i.e. mosquitoes, sparrows, rats… and flies. In the same vein, perhaps, flies were used by the Japanese during WWII to kill hundreds of thousands of Chinese in Baoshan and Shandong by releasing over each city a "bomb" of flies previously coated with *Vibrio cholerae*, the bacteria that causes cholera. In contrast to this rather dark side to *Musca domestica*, the Egyptians wore fly amulets, possibly to bestow fecundity on their owner, and flies frequently appeared in European vanitas paintings in the 16th and 17th centuries as an incarnation of the transient nature of life.

Besides their continuous presence in our lives and plates, houseflies are also extensively used by scientists in their research. Very little is known about sex-determining factors in mammals or insects – though, in the 1990s, a sex-determining factor known as Sry was identified on the Y chromosome in humans*. Like humans, male houseflies carry a copy of each sex chromosome, i.e. XY, while females

are XX. But there is little more we can compare between these two organisms. Male houseflies sometimes actually lack a Y chromosome, thus suggesting that what makes them male – the M factor – is not necessarily located on the Y chromosome, or is also present elsewhere. It turns out that the housefly M factor is usually found on Y, but it can also be observed on one of the non-sex chromosomes, and sometimes more than once within the same fly!

What has come as a surprise to life scientists in the past years is that the upstream processes leading to sex determination seem to be hugely variable in insects. Even between two contemporary houseflies! You would expect something as crucial as what is going to produce a male or a female to have been engraved deep in an organism's DNA eons ago and not prone to constant change. But that is not the case, and this is why it has been so difficult for researchers to study. However, though the upstream pathways of sex determination are subject to change, there is a threshold beyond which things have not budged: the sex switch gene, which has been given various names according to the animal it belongs to, and is known as *transformer (Md-tra)* in the housefly.

As mentioned, the housefly M factor – baptised *Mdmd*, for *Musca domestica male determiner* – is found on Y, though not necessarily. How does *Mdmd* promote male sex? How does it act on the downstream sex switch gene? Though its presence is needed for the making of a male housefly, very little is known yet on the way it does so. There are two possibilities. *Mdmd* could be a spliceosome-associated protein able to splice the precursor mRNA of the sex switch (*transformer*) and then to reassemble the exon junctions. In this light, it could either selectively promote the male splicing mode or prevent the female splicing mode – either way, you get a male fly. Or perhaps *Mdmd* prevents an F factor (female factor) from promoting the female splicing of the sex switch thus promoting its male splicing. Whichever mechanism is used, insect sex determination is based on alternative splicing.

Even if they are 'only' houseflies, it is always a little unnerving to realise that something as fundamental as gender decisions is a case of switching genes on, or off. It really is a thin line between being male or female. Getting to know M factors such as *Mdmd* better will help scientists understand how Nature 'picks' one sex or the other, and perhaps help to fine-tune the definition of gender – whose contours seem to be more and more blurred. A greater molecular knowledge of *Mdmd* could also help to find ways of controlling houseflies, especially in parts of the world where epidemics spread fast. Acting directly upon *Mdmd*, for instance, could help reduce female populations, and hence reproduction, thus diminishing housefly population in the long run. This said, houseflies could also be put to good use by getting them to deal with waste products, and by using the protein-rich maggots they produce as fodder for animals. A way of turning a nuisance into a convenience and perhaps an answer to the American poet Ogden Nash's cheeky verses "God in his wisdom made the fly; And then forgot to tell us why."

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** Read "The tenuous nature of sex", PS issue 80*

## Cross-references to UniProt

Male determiner protein Mdmd (III), *Musca domestica* (House fly) : P0DP78

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