OF MICE AND WOMEN

Edith Heard – I've been fascinated by how two chromosomes in the same cell can be so different in their behavior and their expression. So I decided to work on a process called X-chromosome inactivation, that only happens in females, it doesn't happen in males normally, and where one of the two X-chromosomes is silenced, early on in development. And that leads to an equal dosage of gene expression between males and females, males have only one X, females have two, to make sure that the dosage is equivalent you have to shut down one of the two Xs and that's X-inactivation, and you find it in different mammals, so humans, mice, rabbits, elephants, all females, do X-inactivation. The mechanism of X-inactivation must be conserved between mammals, because it's essential, if you don't have X-inactivation, you're dead! If you're female…

And for many, many years, we were wondering how this process happens where two chromosomes in the same soup of proteins and RNAs, are so differently treated, one of them is on, and the other one's off! So, how do you do that, how does the cell know that it has two and has to shut down one, and how does it shut down one and yet keep the other one on? And so that's been my Holy Grail for the last twenty-six or twenty-seven years. We started working on mice to understand this process, because mice are a nice model to do embryology and genetics in and we realized that this process happens in a very dynamic way during early development. So then we thought, well, let's take a look at another mammal, to see whether it happens in the same way or differently. So we looked in, in rabbits, and now rabbits and mice are supposed to be quite similar at the evolutionary level, or quite close, and we realized that in rabbits things happen quite differently. In rabbits, the two X-chromosomes both start to become silenced initially, and then one of them seems to come back on, whereas in mice you just choose one of the two Xs to shut down. So then we thought, oh, well, we better go and look in another mammal, so then we went to humans! And now humans are supposed to be further away from mice and rabbits, I mean, that seems kind of obvious, they don't, you know, we don't have fur and so on… Hi, hi! And so, we looked in human embryos, with, you know, all of the ethical agreements and everything and licenses and we looked to see just when and how does X-inactivation happen, and then we were even more surprised, because there we realized that in humans, just as in rabbits, the two X-chromosomes start to become inactivated but actually much later, and on top of that, the single X in male embryos also seems to show the first signs of X-inactivation, but then, but then actually the X stays active.

So basically we looked in three different mammals and we saw three very different situations, even though at those stages of development the embryos

look just the same. And so I think this really opened up our eyes to the fact that for the same ultimate purpose, which is to achieve equal dosage between males and females, so you have to shut down one of the two X-chromosomes, there are many different ways you can actually end up doing that, so evolution is very much about tinkering, as François Jacob famously once said, you have the same sets of tools but you just put them together in different way, to end up with something that works!

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