Wolf Reik: Inheritance beyond DNA

Reik takes on the dual nature of epigenetic regulation and finds that it can satisfy his dual tastes for basic research and medicine.

For all it has given to science, Mendelian genetics is now a simplistic view of inheritance. On top of the DNA code lies another genetic "language," the epigenetic code. Wolf Reik has built a career of decoding this language.

Reik jumped on the now crowded epigenetic bandwagon when it was in its infancy, during both his PhD with Rudolf Jaenisch in Germany and his postdoc with Azim Surani in the UK. At the Babraham Institute, where he's been for 15 years now, Reik has delved into the molecular aspects of epigenetics and its role in imprinting (1)—the developmental control of gene expression based on a gene's maternal vs. paternal origin. His group has discovered that imprinting is controlled both by noncoding RNAs (2) and by the three-dimensional arrangement of chromatin (3). Along the way, Reik and colleagues have uncovered functions for imprinted genes in fetal growth (4).

The Reik laboratory is now examining developmental changes in epigenetic marks as cell fates are established (5). They are also interested in how the widespread erasure of epigenetic information may help reset pluripotency in germ cells or in the zygote, for example (6).

In a recent conversation, Reik confessed to daydreams of a clinical practice while he focuses on the basic mechanisms behind epigenetic reprogramming. That reverie, he explains, is sated by collaborative projects that bring together his molecular studies and epigenetics-related human disorders.

SCIENTIFIC IMPRINTS

How did you end up in a scientific career?

I guess partly because both of my parents are scientists. [laughs] We were exposed to a scientific kind of thinking throughout our lives. As a teenager I was interested in many different things, including literature and music. Studying medicine at that time kept a number of my options open.

At university in Germany, I did several clinical stints, which I really enjoyed. I also worked in a country hospital in Brazil, which was both interesting and rewarding. It showed me that you can really help people even with quite limited technology.

How, then, did you come to pursue research rather than a clinical practice?

It was always lurking in the back of my mind that I might enjoy research. Then I went to a seminar by Rudolf Jaenisch; he's a very good speaker, and he can enthuse people. I thought, "Wow, there's a world there that I don't know about."

The next day I went to his laboratory and said, "Can I please do a PhD here?"

What did you work on in his laboratory?

I was already getting excited about epigenetic mechanisms of development. The word "epigenetics" wasn't out there yet, I don't think, but it must have been in my intuitive thinking that that's what I was looking for. There was work going on at that time on DNA methylation and how it controlled the expression of retroviruses that were integrated into the genome. I constructed a new kind of retroviral vector, which could be easily cloned out again, to look at developmental and epigenetic regulation of gene expression in mammals.

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Why did you leave Germany after finishing your PhD?

I wanted to learn more about mammalian embryogenesis, and the UK at that time was probably the key country where many laboratories were active in understanding embryo development in mammals. So I traveled to the UK and visited several laboratories and came across Azim Surani, who had just discovered the phenomenon of imprinting a couple of years earlier.

Wolf Reik

I thought it was really exciting that there was another type of inheritance that was not DNA based and was inspired by the depths of Azim's thinking on the new principles of epigenetics. When I joined his laboratory, he told me that I had to figure out the molecular mechanism of this imprinting. That was an easy challenge. [laughs]

How'd you meet that challenge?

We put transgenes into the mouse genome, in different locations, and we discovered that under certain circumstances, the expression, the DNA methylation, and the epigenetic behavior of the transgene depended on whether it was passed down from mother or father. That observation put imprinting into the molecular world for the first time.

Upon receiving a five-year fellowship to start a tenure track position, you chose to stay in the UK. What's appealing about the UK, and the Babraham specifically, for your research?

The UK has a relatively flat science structure, with less of a hierarchical system than I was used to in Germany. Hierarchy to some extent can inhibit the free flow of ideas, which is so important for science. And the Babraham has an excellent tradition

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in mammalian molecular embryology and really good people to collaborate with.

THE PARADOX OF EPIGENETICS

What's interesting to you about the field of epigenetics and imprinting?

Imprinting is both heritable and reversible, even though that might sound slightly contradictory. It's shorter term than DNA inheritance, and it can be switched from being more stable to being more flexible. How this is achieved is really what fascinates me now.

The reversibility aspect struck us when we came across epigenetic reprogramming, when the information is erased from the genome on a large scale during periods of development. This is linked to many different biological purposes, one of which includes the return of developmental pluripotency to embryonic cells. You probably need to erase epigenetic information on quite a large scale to make that possible.

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It is also important for inheritance, because the large-scale erasure limits the amount of epigenetic information that can be inherited across generations.

Then how do you save epigenetic information that should be inherited?

There are two important scenarios, one of which is the idea that the machinery that erases the information is targeted very specifically to particular locations in the genome, for example through sequence-specific DNA-binding proteins. The other is that some genes might specifically protect themselves. They might use DNA-binding proteins that put them into a chromatin conformation that is not accessible to the erasure machinery.

Since you're looking at the geography of chromatin, how do you deal with the three-dimensional aspect of the work?

The technologies we're using are based on chromatin conformation–capture technique. The DNA in the nucleus is arranged kind of like a bowl of spaghetti, the strands intersect and touch each other. If you apply a cross-linking agent to the nucleus, it links together all the DNA ends that are close to each other at that point in time. Then we use high-throughput sequencing to unravel which bits of the genome were in close contact with each other.

What do scientists believe is the evolutionary force behind imprinting?

Imprinting has evolved, independently, in only placental mammals and seed plants, where the endosperm is the equivalent of the placenta—a tissue for the nutrition of the embryo. In both cases, there is an important asymmetry: most of the resources that the embryo receives come from the mother, and very little come from the father.

The thinking is that this asymmetry has driven the appearance of imprinted genes. Many paternally expressed imprinted genes help an embryo grow bigger and therefore extract resources from the mother to the benefit of the child, or the paternal genome, in essence.

But the mother has to spread out her resources over her reproductive lifespan. If she gives all of her resources to one child, her other children might lose out. Imprinted genes that are maternally expressed have evolved often to suppress fetal growth. It's a tug-of-war.

THE MEDICAL SLANT

How do you keep a link to your enjoyment of clinical work?

The mechanisms behind the erasing of epigenetic information are important for several practical applications, because if you understand how the genome is epigenetically reprogrammed, you are better able to devise stem cell and regenerative medicine applications.

You can also help IVF technology, which is still quite inefficient; factors that determine its efficiency are very likely to be epigenetic in nature. We have found a slightly increased risk of epigenetic defects in children born to couples who have used IVF or really any form of assisted reproductive technology.

We have also collaborated on studies on a human imprinting disorder called Beckwith-Wiedemann syndrome. In this disorder, a particular cluster of imprinted genes is deregulated, resulting in much larger babies who have an increased risk of childhood tumors. We have found that paternally expressed imprinted genes are overactive in these babies, making them grow abnormally.

These types of projects keep my few medical brain cells ticking. It also plays out in the other direction, since recently we found that a particular class of Beckwith-Wiedemann patients have a mutation in a gene we think is important for imprints to be established in the germ line. Now we're going back to recreate the mutations in mice. We hope to create an animal model of the disease and at the same time gain insights into mechanistic aspects of imprinting.

Does your own family share your interest in science?

My wife's a molecular immunologist and runs a laboratory in Cambridge. My son is 13, so at the moment he's only interested in football and other sports. My 16-year-old daughter is quite science oriented, but she also studies English literature, so she's keeping her options open, just as I did.

Sounds like that might also be imprinted.

That could well be, actually.

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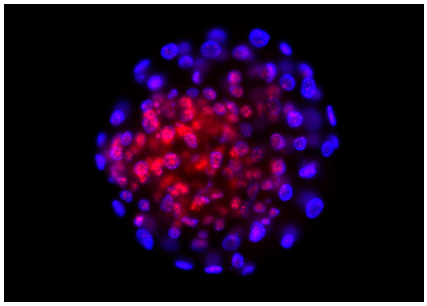

Reik and his laboratory are interested in epigenetic changes that occur as embryos develop.