A Conversation with Wolf Reik

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Wolf Reik is Associate Director of Research at the Babraham Institute, a Professor of Epigenetics at the University of Cambridge, and a founder of the Wellcome Trust Sanger Institute–European Bioinformatics Institute Single-Cell Genomics Centre.

Rhiannon Macrae: I thought we could start very generally with the idea of epigenetic mechanisms. What are these and why do they matter?

Dr. Reik: Generally speaking, epigenetic mechanisms can do a number of different things. Epigenetic memory is often associated with DNA methylation, but there are other mechanisms, like chromatin inheritance. In differentiated somatic cells, you have quite a strong epigenetic memory that helps them maintain cell identity. There's also epigenetic reprogramming, which occurs in germ cells and early embryos on a global scale. This probably has to do with the erasure of epigenetic memory, but also with bringing cells back to a pluripotent state. They forget what they've done before, so they can start anew and develop in many different directions. Quite recently, we've seen a third epigenetic mechanism that results in epigenetic heterogeneity in cells during early development.

Rhiannon Macrae: You mentioned that there's a global effect, a sort of erasure during reprogramming. When does this happen and what's going on?

Dr. Reik: In terms of DNA methylation, which is probably the best-studied mechanism in terms of reprogramming, this happens very quickly after fertilization in early embryos and also in primordial germ cells (PGCs). There's global active demethylation, particularly in the paternal genome. The maternal genome can partly be actively demethylated but there's also passive demethylation during preimplantation development such that in the blastocyst you reach a low level of global methylation that is somehow associated with a naïve state of pluripotency in the inner cell mass. This also occurs in embryonic stem cells derived from the inner cell mass. Similarly, global methylation erasure occurs in PGCs which limits the potential in mammals of transgenerational epigenetic inheritance. What's exciting is that these global erasure processes are conserved in mammals including humans. You can think of DNA methylation as “locking down” a gene expression program in somatic

cells. Reprogramming erases that and the early pluripotency factors set things up again for pluripotency. DNA methylation comes back on a little bit later, when the cells exit pluripotency and begin priming for differentiation. At that stage, something quite paradoxical happens: Methylation and demethylation systems come on at the same time.

Rhiannon Macrae: Is it a stochastic effect where the bulk is moving toward a more methylated state? What are the dynamics of that?

Dr. Reik: There could well be stochastic components, but also it's probably a programming system that many cells experience simultaneously. What probably happens is that the cells are driven by methylation and demethylation at the same time. The methylome becomes very dynamic and that dynamic state brings about very rapid changes in methylation, particularly in sequences like enhancers that control gene expression states. We think that the system is creating epigenetic heterogeneity in the cells as they prime for differentiation.

We've developed methods to sequence the methylome in single cells. We've also developed a method that can sequence the methylome and the transcriptome from the same single cell, giving us for the first time a direct readout of the links in single cells and also of the heterogeneity of the system. We can now look at the transcriptional heterogeneity at the same time as the methylation heterogeneity and find couplings between the two. For example, enhancer methylation variability is in some instances coupled, or at least associated, with transcriptional heterogeneity in the system.

Rhiannon Macrae: Are there cells in the embryo in which methylation returns earlier than lead the rest of the population toward the exit from pluripotency? Is there any communication between cells about their relative methylation states?

Dr. Reik: We don't have any direct insights into that because we have to dissociate the cells to do our single-

cell analyses. There could be communication between cells and they could be instructing each other in terms of what the heterogeneity should look like on the population level. Alternatively, it could also be a stochastic system where you're trying to create transcriptional noise in the system. This could help, because every cell would be slightly different than its neighbor. That could make the cell fate decision switches more fluid at a particular time and drive the cells in slightly different directions. Because there's a massive cell fate decision program leading up to gastrulation, these decisions have to be made very quickly at that time point. Linking epigenetic noise with transcriptional noise could help.

Rhiannon Macrae: It suggests that if you looked at this in 10 different embryos, it would be a random decision as to which population of cells take which routes, because the transcriptional noise randomly creates opportunities to differentiate down different cell paths.

Dr. Reik: We don't know that yet. It would be interesting to look at. We'd have to remove all the cells from a number of different embryos and sequence each of them to see what sort of variability there might be from embryo to embryo. What's interesting here is potentially to be able to relate intra- with interindividual variability.

Rhiannon Macrae: Being able to combine methylome and transcriptome data in one is a new development. What kinds of problems can you now try to address?

Dr. Reik: One important area to look at is any kind of system where the cells go through a rapid process of decision-making, like cell fate changes or differentiation. The exit from pluripotency into gastrulation is an absolutely fascinating one. Another one to think about is whether transcriptional heterogeneity increases as a result of the aging process or at least accompanies the aging process, leading to greater diversity in cell and organ function, and mistakes of course. This could bring new insights into whether or not transcriptional heterogeneity during aging is accompanied by an epigenetic program. You can think about aging in different ways. You could think about it as a more or less random process of damage, or you could think about it as a process that is epigenetically regulated in some ways; perhaps a system is in place to create epigenetic heterogeneity.

Rhiannon Macrae: We're celebrating the 150th anniversary of Gregor Mendel's laws. Do you remember learning about the laws of inheritance or doing a Punnett square for the first time?

Dr. Reik: I can't remember the details. I didn't pay that much attention at school, as a general rule. I think though that I always had in the back of my mind, how particulate inheritance was, how digital. I think when we first started to think about epigenetics, there was a movement from a digital view of inheritance to a more analog model. This is exciting as it provides a more fluid counterpoint to thinking about inheritance.

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