BY NATALIE VON DER LEHR

Early pre-programming of genes

Did you ever wonder how the newly fertilized egg knows exactly what to do and how to develop? Part of the answer is in the epigenetic marking of genes.

DNA, which carries all genetic information, is organized and wrapped around proteins called histones. These histones can be modified in different ways in order to determine which genes should be active and which should be silent. This concept has been known for a while and is referred to as the histone code – the different combinations of epigenetic markings that result in different outcomes. A research group at the University of Oslo in Norway has now been able to show that the early embryo, at least in Zebrafish, contains genes that are epigenetically marked, or encoded, by modified histones, before any activation of these genes takes place. "This strongly suggests that shortly after fertilization, the early embryo has already set up some sort of gene activation program before any gene is actually turned on – a pre-patterning of developmental gene activation, if you will," says Philippe Collas, professor at the University of Oslo and leader of the study.

ZEBRAFISH AS A MODEL SYSTEM

Collas and colleagues have based their studies on the embryos of Zebrafish. After fertilization, there is a three-hour period with multiple cell divisions before embryonic genes are turned on. By comparison this period lasts for two to three days in humans. "This ten cell-cycle window before gene

activation gives us a fantastic opportunity to examine how the embryo prepares for further development," says Collas, adding that studies on human embryos would be difficult from a practical and ethical point of view.

PUTTING TWO AND TWO TOGETHER

Collas and his colleagues already had a hunch that specific processes might in some way determine how embryonic transcription is initiated and the genes involved, when two scientific papers strengthened their hypothesis. One was from the laboratory of Alexander Schier (Harvard University), published in 2010. "They proposed that in Zebrafish, embryonic gene activation coincides with the appearance of histone modifications in the genome; but to us it was hardly imaginable that the embryonic gene expression program would be setup so late after fertilization, at the same time as genes are activated. Something had to happen before that, some developmental programming had to take place," recounts Collas. The other study, from the Brad Cairns Laboratory (HHMI, University of Utah), showed that Zebrafish sperm contain histones that are modified by different epigenetic marks; interestingly, these modified histones mark genes essential for early development. The authors postulated that these marks may be transmitted from sperm to the new embryo after fertilization, where they may play a role in the developmental program. "After the publication of that paper, we just put two and two together and felt that we were on the right track," says Collas.

THE GOLDEN ASSAY TO STUDY HISTONE MODIFICATIONS

In collaboration with research groups from Norwegian School of Veterinary Science, the University of Birmingham and the Genome Institute of Singapore, Collas and his team set out to identify the modifications of histone H3 and the positions these might occupy in the genome to pre-pattern and later regulate embryonic gene activation. For that they used a method called ChIP (chromatin immunoprecipitation) which gives information about the specific modifications of the histones that are bound to DNA. "This is really the golden assay for the study of histone modifications," comments Collas. They combined the ChIP approach with hybridization to custom-designed high-density promoter microarrays to determine the promoters marked by modified histones. The recently published data shows the occupancy of specific gene sets by modifications of histone H3, in particular tri-methylation of particular lysines, known to mark active, repressed or potentially active genes.

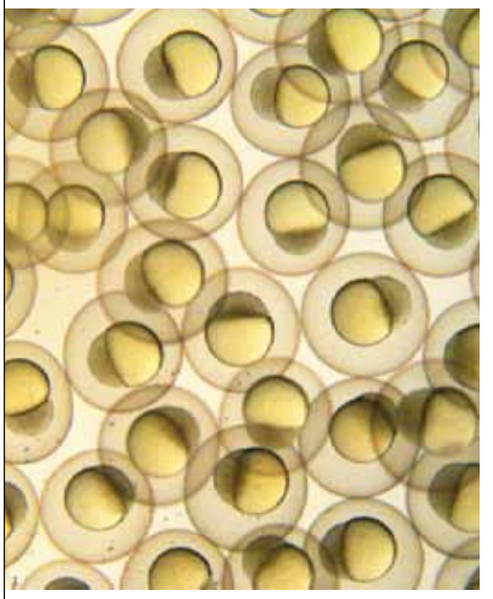
THE ONSET OF LIFE IN DETAIL

The next big question is what happens to these regulatory marks after fertilization. "As we see it, our findings are consistent with two models. The first model is that the marks detected in sperm by our colleagues remain associated with the sperm genome through fertilization; the other is that they are first taken off and then repositioned," explains Collas. He seems to favor the first idea, because not only would it be "a waste of energy to first remove the marks and then put them back", but that mechanism "would also require some other kind of information" to be carried over from sperm into the fertilized egg to be able to reposition the marks correctly. In order to investigate this further, Collas and colleagues will now look at the whole process in more detail. The first question they want to answer is at how early a stage the marks are present. Then they want to know their function. By knocking down or mutating genes that have a role in the modification process they hope to get an answer. "Zebrafish has the advantage that we can easily obtain many synchronous embryos and we are looking at a rather short timeframe with many cell divisions. So these kinds of studies are quite doable," explains Collas.

TAKING IT FURTHER

Zebrafish is a common model for the study of development and many mechanisms identified in fish also apply to humans. In the long run Collas and colleagues plan to investigate whether the same mechanism of early pre-programming of a gene expression program also applies to stem cells. "This knowledge may in the future affect the way we look at stem cell differentiation, fetal development, the ageing process and disease development," says Collas.

Article:
Lindeman et al., Prepatterning of Developmental Gene Expression by Modified Histones before Zygotic Genome Activation, Developmental Cell (2011), 21: 993-1004 (doi:10.1016/j.devcel.2011.10.008)



Fertilized zebrafish-eggs.

Zebrafish.

Philippe Collas.