Developmental biology

Waking up the genome in mouse embryos

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Activation of gene transcription is precisely regulated in early embryos. The identification of key transcription factors now shows how the transcription machinery is guided to the right place at the right time in mice. **See p.1047**

At fertilization, the animal genome is inactive, and the earliest stages of development are driven by pre-existing proteins and RNA transcripts that have been stored in the egg. As the fertilized egg divides into two cells, developmental control is gradually handed over to the embryo. The pre-existing RNA (known as maternally loaded RNA) is degraded, and the embryonic genome (called the zygotic genome) is activated[1]. On page 1047, Ji *et al.*[2] describe the identification of a family of transcription factors involved in kick-starting the zygotic transcription program in mice, and provide evidence that these factors have a role in targeting the transcriptional machinery to the correct genes.

It is crucial for normal development that specific genes are activated at specific times. However, the enzyme responsible for transcription, RNA polymerase II (RNA pol II), typically lacks the intrinsic capacity to identify the genes that need to be transcribed. Instead, transcription factors bind to DNA elements in sequences called promoters and enhancers (which regulate the expression of specific genes), and recruit RNA pol II to those sites, thus guiding gene expression.

Key transcription factors involved in zygotic-genome activation (ZGA) have been identified in flies and fish[3–7]. In mammals, however, they have long remained elusive. The transcription factor DUX has been reported to be involved in ZGA in mice[8,9], but because DUX is not required for embryonic development[10], its relevance has been debated.

One way to identify transcription factors that could have a role in ZGA is to ask which proteins are abundantly produced in the fertilized egg. This method is rooted in the assumption that any factors involved in ZGA should be maternally loaded, readily available to act. Another approach is to look for specific DNA sequences in the promoters and enhancers of genes that are activated in the early embryo, and to ask which transcription factors could bind to these sequences. Ji *et al.* used a combination of these approaches to identify the OBOX family of transcription factors as promising candidates for involvement in mouse ZGA. The OBOX family consists of eight genes (*Obox1–8*).

In mouse embryos, ZGA begins at the one-cell stage, with a minor wave of transcription in which a handful of genes are activated[11]. This is followed by a major wave at the late two-cell stage, in which about 1,000 genes are activated[12–14]. The minor wave of transcription is crucial for the major wave and for development. Ji *et al.* showed that deleting six of the eight *Obox* genes (*Obox1, 2, 3, 4, 5* and *7*) affected both the minor and the major waves. Embryos stopped developing at the two- or four-cell stage.

The six relevant *Obox* genes are expressed at different times in the early embryo: some are maternally loaded, some are zygotically expressed. Remarkably, restoring expression of either class could restore developmental progress and transcription. This shows that the different *Obox* genes can compensate for one another (at least in part), and argues against the assumption that factors involved in genome activation should be maternally loaded.

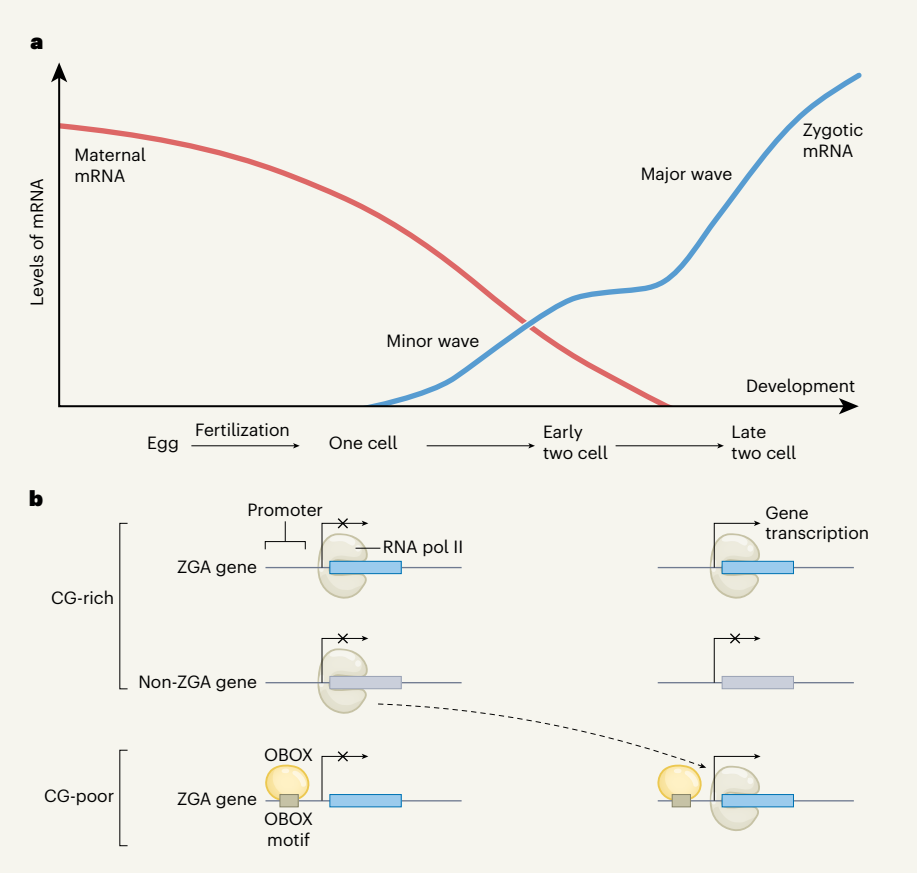

Figure 1 | OBOX transcription factors guide RNA pol II enzyme to target genes. a, The genome of mouse fertilized eggs is inactive, with messenger RNA from the mother used for protein production. During early development, levels of this maternal mRNA decline, and transcription of the embryonic genome (zygotic genome activation; ZGA) is activated in two waves, the minor and major wave. **b**, Ji *et al.*[2] outline a mechanism by which OBOX proteins kick-start the major wave. RNA pol II by itself finds promoter DNA sequences that are rich in the bases cytosine and guanine (CG-rich) at around the one-cell stage. These can be promoters either for genes involved in ZGA or for other embryonic genes not involved in ZGA. By contrast, OBOX proteins are needed to recruit RNA pol II to CG-poor promoters for ZGA genes at the two-cell stage, perhaps owing to relocation of the enzyme from CG-rich non-ZGA genes (dashed arrow). Transcription of major-wave ZGA genes, mediated by RNA pol II and OBOX, begins at the two-cell stage.

Obox4 stands out in this context, because Ji and colleagues found that restoring its expression could not compensate for loss of the other genes. This suggests that the OBOX4 protein might have functions that differ from those of the other family members, which would be in line with its distinct protein sequence. A preprint[15] posted last year also found that *Obox4* is required for mouse ZGA — but only in the absence of *Dux*. DUX and OBOX4 activate minor-wave genes, and their simultaneous depletion causes developmental arrest. Thus, DUX and OBOX4 compensate for one another during ZGA in mice, explaining why DUX was previously found to regulate the transcription of minor-wave genes but not to be required for viability.

Perhaps the most sophisticated part of Ji and colleagues' work is their analysis of the mechanism by which OBOX factors power up the major wave. RNA pol II must be loaded onto the promoter of a gene to activate transcription. If a promoter is rich in the bases cytosine and guanine (and so known as CG-rich), RNA pol II seems to be able to bind without the need for gene-specific transcription factors — and, indeed, at the one-cell stage, RNA pol II is already loaded onto such promoters[16]. On promoters that are CG-poor, however, sequence-specific transcription factors are needed to recruit RNA pol II. Ji *et al.* found that OBOX proteins specifically recognize and bind to the regulatory sequences of CG-poor ZGA genes to recruit RNA pol II and activate transcription of major-wave genes (Fig. 1).

Interestingly, some of the genes with CG-rich promoters to which RNA pol II is bound in embryos at the one-cell stage are not activated during ZGA (ref. 11). In line with this, RNA pol II is normally no longer bound to these promoters at the two-cell stage. Ji and co-workers showed that, in the absence of OBOX proteins, RNA pol II is aberrantly retained on these promoters. This suggests that the recruitment of RNA pol II to OBOX target genes results in the relocation of RNA pol II from (CG-rich) non-ZGA genes to (CG-poor) ZGA genes. Thus, OBOX proteins are required not only to activate transcription during genome activation, but also to prevent aberrant transcription.

> **"Transcription of the embryonic genome (zygotic genome activation) is activated in two waves."**

The inactivated genome of early embryos is tightly packaged, and so largely inaccessible to binding by transcription factors or other proteins. To activate the genome, the DNA needs to be made accessible. In fish and fly embryos, the transcription factors involved in ZGA are pioneer factors — that is, they bind to inaccessible DNA, increase accessibility and facilitate the recruitment of other factors. Whether OBOX proteins themselves have all the features of pioneer factors remains to be investigated, although there are hints that they might, because DNA in *Obox* mutant embryos is less accessible than in controls. Last year[17], the protein Nr5a2 was found to be a genuine pioneer factor that affects the transcription of many genes during mouse ZGA. It will be interesting to see how OBOX, Nr5a2 and DUX proteins, potentially in combination with other as-yet-unidentified factors, together increase DNA accessibility and recruit RNA pol II to specific genes.

A hurdle in human *in vitro* fertilization is that about 40% of embryos arrest during ZGA (ref. 18). Although the *Obox* genes are rodent-specific, the human genome has evolved a set of genes belonging to the same class of transcription factor[19]. The current study paves the way for understanding whether, and how, these transcription factors — divergent but perhaps with conserved functions — kick-start the human developmental program.

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The authors declare no competing interests.
This article was published online on 17 July 2023.

From the archive

Pondering different perceptions of colour, and a romance novel set against a backdrop of atomic espionage.

50 years ago

Surface Color Perception. By Jacob Beck — This book is concerned with the enormous gap that exists between the approach to colour by the physicist and by the artist. The physicist ... starts with ... the nature of the light coming to the eye from various objects, and the way that nerve signals are generated and modified ... The artist ... starts from ... perceptions of the colour and the lightness of the objects themselves. The author ... ignores the known way that nerve signals are generated and processed ... Instead, his treatment is to speculate upon the way that one aspect of perception may interact with others to account for what subjects say they see ... The central problem is ... how we manage to name the colour and lightness of objects around us "correctly" even when the colour and brightness of the illumination are changed.

From *Nature* 31 August 1973

100 years ago

Atoms. By T. C. Wignall and G. D. Knox — "Atoms," a highly imaginative romance, reflects strongly some of the most cherished popular conceptions or misconceptions about the growth of science. Super-financiers contend with ... the regular international anarchist associations ... to corner the world's supplies of energy. A colossal plant for producing power from coal ... springs up at the word of command, and is converted ... into an atomic energy plant by the discovery of *sublimium*. Sublimium disintegrates everything it comes into contact with except *refracton*, and it is conveyed in capillary tubes of the latter ... in minute quantities from the laboratory to the furnaces. The authors ... succeed, not only in showing us the effects of Paris being converted into an inferno through anarchists blowing up the refracton tubes, but also ... a brilliantly successful conclusion with the hero and heroine happily off for the honeymoon.

From *Nature* 1 September 1923