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RESEARCH HIGHLIGHT

Depending on maternal Yap

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In a recent paper in *Cell Research*, Yu *et al*. show that maternally inherited Yes-associated protein (Yap), a co-activator of TEAD family transcription factors, plays a key role in activating embryonic transcription following fertilization in the mouse.

After fusion of the two gametes at fertilization, the newly formed zygote utilizes maternally inherited proteins and RNAs to begin its progression through development, while initially transcription from the zygotic genome is largely absent. During the first two cell cycles, a minor and a major wave of zygotic transcription, also referred to as zygotic genome activation (ZGA), take place. Genes activated in these waves are enriched for housekeeping functions (basic cellular functions, including protein and nucleic acid metabolism), which take over the role of declining maternal housekeeping proteins, while developmental genes involved in lineage formation and differentiation are typically activated slightly later, during subsequent waves of transcription [1-3]. Clearly there must be maternally inherited factors involved in activating zygotic transcription, but little is still understood about this process. Yu *et al*. [4] noted that high levels of *Yap* mRNA and protein are maternally supplied and persist in the early mouse embryo. Moreover, they showed that Yap protein is inactive (cytoplasmic) in oocytes and is only gradually translocated to the nucleus after fertilization, suggesting that it might be involved in early activation of transcription. To test this, they generated mice with oocyte-specific conditional mutation of *Yap*. This maternal deletion of *Yap* did not result in any obvious oocyte phenotype; instead embryos lacking maternal *Yap* were delayed in development and mostly blocked at the morula stage. By expression profiling the authors showed that a large number of genes normally transcribed during the first waves of ZGA are not activated in maternal *Yap* mutant 4-cell embryos. Thus they identified *Yap* as a *bona fide* maternal effect gene, adding it to the slowly growing list of factors that are maternally expressed, yet have essential functions only in the next generation.

By comparing down-regulated genes in maternal *Yap*-deficient embryos with available Yap ChIP data from mouse embryonic stem cells [5], the authors identified a number of potential direct Yap/Tead targets in the embryo. The promoters of two of these genes, *Rpl13* (ribosomal protein L13) and *Rrm2* (ribonucleotide reductase M2), showed Yap-Tead-dependent activity in a luciferase assay. Moreover, when Yap-Tead1 was overexpressed in oocytes, *Rpl13* and *Rrm2* transcription was up-regulated, although the translocation of Yap protein to the oocyte nucleus was not demonstrated. Thus there is a strong indication that at least two genes are direct targets of Yap-mediated activation during ZGA.

These two examples, along with the finding that down-regulated genes in maternal *Yap* mutants were significantly associated with GO terms such as translation and metabolic processes, identify Yap as an activator of early housekeeping genes in ZGA. However, numerous genes were still properly activated during maternal *Yap*-deficient ZGA, and some embryos made it through to the blastocyst stage, suggesting that maternal Yap is not the only factor involved. Further work is needed to identify embryo-specific Yap targets and reveal how broadly this factor is used in ZGA. It has been previously demonstrated that preimplantation development in zygotic *Yap* mutants was normal [6]. However, zygotic *Yap*/*Taz* double mutants died before the 16- to 32-cell morula stage [7]. This strongly suggests that, although expressed at low levels, the homologue Taz may act redundantly and dampen the effects of Yap loss. Whether Taz serves redundant functions during ZGA has not been addressed.

In a number of cellular situations, including the preimplantation embryo, Yap nuclear localization, and hence its transcriptional activity, is regulated by upstream components of the Hippo signaling pathway. Different cell-contact mediated signals can activate the serine-threonine kinases, Lats1/2, which will phosphorylate Yap and lead to its retention in the cytoplasm. When the Hippo pathway is inactive, Yap is not phosphorylated, allowing shuttling to the nucleus, association with Tead proteins and induction of transcription of target genes. In the preimplantation mouse embryo where the Hippo pathway dictates the specification the inner cell mass (ICM) and trophectoderm (TE) lineages, inactive Hippo signaling and nuclear Yap are hallmarks of polar TE progenitors. In this context nuclear Yap together with Tead4 are responsible for the activation of the key TE-specific transcription factor Cdx2. Several upstream components of the Hippo signaling pathway, including Lats1/2, Merlin/Nf2 and Amot, have been shown to be

involved in the regulation of Yap localization leading up to blastocyst lineage specification [7-9].

It is not yet clear whether the regulation of maternal Yap activity leading up to ZGA is controlled by upstream Hippo signaling or by other cellular pathways that can also regulate Yap/Tead activity. Merlin/Nf2 is certainly not involved, as maternal/zygotic loss-of-function mutants show no defects until the blastocyst stage, when all cells become Cdx2 positive [9]. Intriguingly, the authors demonstrated that Yap translocation into the nucleus following fertilization is decreased in wild-type embryos when cultured in sub-optimal media, potentially accounting for their decreased developmental potential. They further showed that treating the embryos with lysophosphatidic acid (LPA) during culture restored nuclear Yap levels and developmental competence. LPA can act through G-protein coupled receptors (GPCRs) to inhibit Lats1/2. While GPCR-mediated Hippo regulation has been shown to function in certain cells and tissues [10, 11], it has not been demonstrated to function in the embryo. It will be interesting to further investigate the mechanisms of how Yap is kept cytoplasmic in oocytes and whether inactivation of the Hippo pathway after fertilization is involved in ZGA.

Based on previous expression profiling studies, *Yap* mRNA was shown to be abundant in human oocytes and early embryos as well [12]. It remains to be seen whether its role in ZGA is conserved and whether LPA would also have a beneficial effect on human pre-implantation culture.

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