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OMA-Gosh, Where's that TAF?

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How transcription is silenced in early embryos has long been a mystery. In this issue, Guven-Ozkan et al. (2008) report that transcriptional repression during worm embryogenesis is mediated through sequestration of the general transcription factor TAF-4 and is regulated by mechanisms that orchestrate the transition between maternal and zygotic gene expression.

For most multicellular organisms, mRNA transcription is essentially shut down in both late-stage oocytes and the early embryo. During oogenesis, transcription generally ceases before fertilization, and oocytes may be maintained in a state of transcriptional inhibition for extended periods of time (Walker et al., 2007). Transcription is also silenced during the earliest embryonic stages, in which the embryo is dependent upon proteins and mRNAs of maternal origin (Schier, 2007). Embryonic transcription is generally delayed until the degradation of these maternal mRNAs during the complex transition from maternal to zygotic gene expression. Previous indirect evidence has suggested that this transcriptional silencing in the early embryo might be enforced by a repressor that is titrated during embryonic cell divisions or by limiting general transcription factors. In an exciting new study, Guven-Ozkan et al. (2008) link transcriptional silencing in early embryos of the worm *Caenorhabditis elegans* to mechanisms that mediate other aspects of the maternal-to-zygotic transition.

Oocyte maturation in *C. elegans*, the process by which oocytes prepare for fertilization, requires the proteins OMA-1 and OMA-2, which are zinc finger proteins of the CCCH class that bind to RNA (Detwiler et al., 2001). OMA-1 and OMA-2 appear during late oogenesis and are important not only for maturation but also for early embryonic development. In their new study, Guven-Ozkan et al. identified a surprising aspect of these embryonic functions for OMA-1 and OMA-2: in early embryos, these OMA proteins bind and inhibit TAF-4, a component of the general transcription factor TFIID. TFIID—composed of the TATA-binding protein (TBP) and multiple TBP-associated factors (TAFs)—establishes the transcription start site and is required for most RNA polymerase II (pol II) transcription (Wright et al., 2006). TAF-4 is critical for TFIID stability (Wright et al., 2006) and seems to be required for essentially all pol II transcription in the early *C. elegans* embryo (Walker, et al., 2007).

In the *C. elegans* embryo, transcription begins in somatic cells at the four-cell stage (Figure 1). Guven-Ozkan et al. found that in one- and two-cell embryos, OMA proteins inhibit TAF-4 function by binding to this nuclear protein and sequestering it in the cytoplasm. Interestingly, OMA proteins inhibit the nuclear accumulation of TAF-4 through clever molecular mimicry. TAF-4 maintains its localization in the nucleus by binding to TAF-12 via histone fold-like domains. To titrate TAF-4 away from its usual binding partner, the OMA proteins bind to TAF-4 through a domain that resembles the TAF-12 histone fold. Indeed, Guven-Ozkan and colleagues observed that if OMA protein levels were reduced, TAF-4 accumulated in the nuclei of one- and two-cell stage worm embryos, leading to activation of general transcription and perturbation of embryonic development. Mutagenesis experiments performed by the authors further revealed that the TAF-4-binding region of OMA proteins is both distinct from their RNA-binding region and dispensable for oocyte maturation, thus elegantly discriminating between OMA protein functions in oocyte maturation and embryonic development.

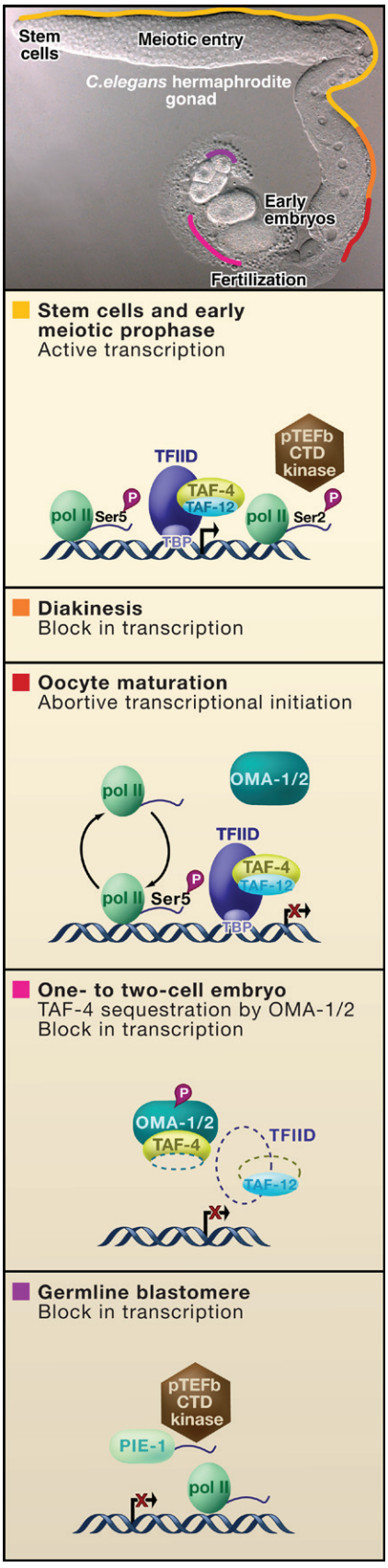

Figure 1. Global Transcriptional Repression in *C. elegans*

In the *C. elegans* hermaphrodite gonad and early embryo (top), oocytes arise from a stem cell population and enter meiosis. Meiotic oocytes are transcriptionally active. Transcription is mediated by the general transcription factor TFIID—composed of the TATA-binding protein (TBP) and multiple TBP-associated factors (TAFs)—which establishes the transcription start site. TAF-4, an essential TFIID component, is maintained in the nucleus by its interaction with TAF-12, another TFIID component. At diakinesis, the last stage of meiotic prophase, an unknown mechanism shuts down mRNA transcription. During oocyte maturation, a process that requires the proteins OMA-1 and OMA-2, abortive transcription initiation events that depend on TAF-4 take place. These events involve phosphorylation of serine 5 (Ser5) in the C-terminal domain (CTD) of RNA polymerase II (pol II), a marker of transcription initiation. In the early embryo at the one- to two-cell stage, OMA proteins phosphorylated by MBK-2 block transcription by directly sequestering TAF-4 in the cytoplasm. Transcription begins in somatic blastomeres at the four-cell stage, but in the germline blastomere, transcription is further delayed by the OMA-related protein PIE-1, which inhibits transcriptional elongation by preventing the kinase p-TEFb from phosphorylating the RNA polymerase II C-terminal domain at serine 2 (Ser2).

Interestingly, the interaction of OMA proteins with TAF-4 is regulated by a mechanism that sets in motion other aspects of the maternal-to-zygotic gene expression transition. During the meiotic cell divisions that occur after fertilization, OMA proteins are phosphorylated at a key residue by the kinase MBK-2, which targets many maternally expressed proteins for degradation during the maternal-to-zygotic transition (Stitzel et al., 2006). Remarkably, the researchers found that this phosphorylation event is also required for OMA proteins to bind to TAF-4. Thus, the signal that dooms OMA proteins for destruction also seems to direct them to do one final job, that is, to snatch up TAF-4 and prevent transcription from starting prematurely. If the degradation of phosphorylated OMA proteins is blocked, they persist in the cell and continue to inhibit transcription, further supporting the notion that OMA proteins act as transcriptional repressors.

Although the OMA protein-TAF-4 interaction seems to be a robust mechanism for inhibiting transcription, it is not involved in preventing inappropriate transcription during late oogenesis (Figure 1). *C. elegans* oocytes exhibit high transcriptional activity until diakinesis, the last stage of prophase in the meiotic cell cycle. At diakinesis, transcription is shut down by an unknown mechanism that is independent of OMA proteins (Walker, et al., 2007). OMA proteins are present at high levels in late-stage oocytes, but TAF-4 remains concentrated in the nucleus (Guven-Ozkan, et al., 2008). How can this discrepancy be explained? Because MBK-2 does not phosphorylate OMA proteins until after fertilization, it is likely that OMA proteins would not be able to bind to TAF-4 at these earlier stages. Furthermore, the interaction between TAF-4 and OMA proteins may require breakdown of the nuclear envelope, which occurs during oocyte maturation. Why would a different transcription repression mechanism be needed in diakinetic oocytes? Guven-Ozkan and colleagues suggest that binding to TAF-4 may be incompatible with OMA protein function during oocyte maturation. Alternatively, it is possible that TAF-4 is needed at this stage to prepare embryonic genes for future expression, perhaps analogous to other systems where pol II is poised at genes that need to undergo rapid induction (Margaritis and Holstege, 2008). Indeed, oocyte maturation signals induce apparent abortive transcriptional events that require TAF-4 (Walker, et al., 2007).

The findings of Guven-Ozkan et al. have broader implications for other members of the CCCH class of zinc finger proteins. After TAF-4 is freed from the OMA proteins, transcription repression continues in the embryonic germline through the actions of PIE-1, a related CCCH zinc finger protein (Figure 1). PIE-1 inhibits transcription elongation by interfering with p-TEFb, a kinase that phosphorylates serine 2 of the pol II C-terminal domain during elongation (Zhang et al., 2003) (Figure 1). PIE-1 also inhibits other transcription steps through an unknown mechanism (Ghosh and Seydoux, 2008). Together with the Guven-Ozkan et al. study, these findings reveal a fascinating functional complexity in CCCH zinc finger proteins. Although CCCH class proteins are generally involved in mRNA destabilization or translational regulation, OMA-1, OMA-2, and PIE-1 also target different protein complexes to inhibit transcription (Guven-Ozkan et al., 2008; Zhang et al., 2003).

Thus, transcription during *C. elegans* oogenesis and embryogenesis is inhibited at different stages by at least three distinct mechanisms (Figure 1).

Why has so much variation arisen in mechanisms of transcriptional repression? Perhaps customized transcription silencing mechanisms coevolved with specific developmental strategies and needs. For example, it may be important that repression by PIE-1 is rapidly reversible because germ cell precursors in the early embryo divide to generate somatic daughter cells that must become transcriptionally active quickly. Sequestration or replacement of general transcription factors may simply be an effective method for blocking or redirecting transcription, as has been observed in some organisms where specialized TAFs redirect transcription programs toward germline genes (Wright et al., 2006). There are many ways to alter transcription globally in order to influence differentiation. Although OMA proteins and PIE-1 are not widely conserved across species, it seems likely, as Guven-Ozkan et al. point out, that similar mechanisms may be used in higher organisms to broadly regulate transcription and to forestall differentiation.

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Stressing the Brain, Fattening the Body

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Obesity is characterized by chronic activation of inflammatory pathways in peripheral tissues. In this issue, Zhang et al. (2008) demonstrate that inflammation also occurs in the central nervous system where it disrupts activity of the hypothalamus leading to resistance to leptin that is mediated by activation of IKK and the endoplasmic reticulum stress response.

The development of obesity and type 2 diabetes is influenced by a complex interaction of environmental and genetic factors. It is becoming clear that obesity is characterized by chronic activation of inflammatory pathways and that this chronic inflammation is causally linked to insulin resistance and type 2 diabetes (Hotamisligil, 2006). Although this inflammatory etiology is principally studied in peripheral organs, such as liver and adipose tissue, obesity-induced inflammatory changes and their impact on leptin and insulin action have also been reported in the central nervous system (CNS), including the hypothalamus (De Souza et al., 2005). Insulin action in the CNS has systemic consequences, and normal functioning of the hypothalamus is paramount not just for regulation of food intake but also for broader metabolic homeostasis. Conversely, central signals can control peripheral glucose metabolism and insulin sensitivity, particularly in the liver. In the brain, the hypothalamus is a primary site of convergence and integration of multiple nutrient-related signals including central and peripheral neural signals as well as hormonal and nutritional cues. The arcuate nucleus, situated in the mediobasal hypothalamus (MBH), integrates hormonal signals (such as insulin, leptin, and ghrelin) and metabolic fuels (such as glucose and lipids) to regulate food intake and energy balance (Cone, 2005) (Figure 1). Impaired regulation of arcuate nucleus neurons leads not only to obesity but also to aberrant glucose homeostasis, although the mechanisms underlying this neuronal dysfunction are not yet clearly resolved.

Activation of inflammatory signaling pathways by immune signals or nutrients inhibits insulin action. This inhibitory input involves activation of inflammatory kinases such as c-Jun N-terminal kinase (JNK) and inhibitor of kappa B kinase (IKKβ). Activation of both pathways in the liver leads to systemic insulin resistance, whereas inhibition of JNK or IKK pathways protects animals against obesity-induced insulin resistance and obesity-induced expression of inflammatory cytokines (Hotamisligil, 2006). Although inflammatory changes have been detected in the CNS of obese mice (De Souza et al., 2005), the biological consequences and underlying mechanisms remain unclear. In this issue of *Cell*, Zhang et al. (2008) now offer important insights into the link between nutritional signals and activation of inflammatory and stress pathways in the hypothalamus.

In their study, Zhang and colleagues found that IKKβ is expressed principally in neurons of the MBH but is normally