tone H3 methyltransferase activity of CARM1, resulting in enhanced NR-dependent gene activation. Furthermore, and most important, Xu *et al.* also show that CARM1 methylates the KIX domain of CBP/p300 (see the figure). Methylation of the KIX domain interferes with the ability of CBP/p300 to interact with CREB's KID motif (*11*), causing the loss of CREB-dependent gene activation (see the figure). Upon methylation, then, the limiting pool of CBP/p300 becomes available for interaction with other transcription factors that regulate, for example, NR-dependent gene transcription.

This transcriptional "switch" from CREB-regulated to NR-regulated gene expression is especially intriguing because the CREB family of transcription factors is crucial for many cellular events, such as glucose homeostasis, growth factor–dependent cell survival, and generation of an immune response. Moreover, the CREB family has been implicated in learning and memory (*11*). Although phosphorylation of CREB is sufficient for it to induce expression of its target genes, additional cofactors, such as CBP, are required for further gene activation in response to mitogens or stress. It remains unclear how phosphorylated CREB discriminates between various cellular signals, although there are several hypothetical ways that CREB's interaction with CBP could be blocked (*11*).

Methylation of CBP/p300 by CARM1 appears to destabilize the structure of the KIX domain, implying that interactions between CBP/p300 and other proteins may also be disrupted. Indeed, Xu *et al.* show that interaction between the transcription factor c-myb and CBP/p300 is lost upon methylation of the KIX domain. Thus, CARM1-mediated methylation of the KIX domain could be one way to modulate the specificity of CBP/p300 binding to gene-specific transcription factors. However, it is necessary to consider the implications of these findings in the context of natural promoters—such as the promoter for the retinoic acid receptor–β (RAR-β) gene—on which CREB, RAR, and another nuclear hormone receptor, RXR, form a complex that regulates transcription of this gene.

The existence of the CREB-NR molecular switch raises some additional questions. Does methylation of the KIX domain of CBP/p300 impose an irreversible signal that dictates which genes are to be transcribed? Does the activation of such genes require stepwise signaling at the promoter? If so, then how is the promoter to be silenced when new environmental conditions present themselves? Is arginine methylation of CBP and surrounding nucleosomes a reversible reaction, or does methylation of the KIX domain mark CBP/p300 for destruction? If so, is there any link between arginine methylation and ubiquitination? Several points also remain to be addressed regarding the regulation of CARM1 itself: What signal activates CARM1, and how does CARM1 activate NR-dependent but not CREB-dependent transcription? How are these signals integrated at composite promoters where transcription depends on both CREB and NR? Clearly, with so many potential points of regulation, gene expression will continue to unveil new steps in its elaborate dance.

The observation that CARM1 is an essential part of a molecular switch that determines whether CBP/p300 is to be used for NR-dependent or CREB-dependent gene activation allows us to speculate on ways this molecular switch can be exploited for medical purposes. For example, drugs that can demethylate proteins and so specifically antagonize CARM1 activity could potentiate CREB-dependent gene activation. Such antagonists might enhance long-term potentiation in neurons and hence improve learning and memory, or may boost the immune response in immunosuppressed individuals. In contrast, induction of CARM1 may increase sensitivity to nuclear hormones or raise an organism's threshold to stress signals. In any case, this new molecular switch will provide fascinating insights into the sophisticated mechanisms of gene regulation.

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NOTA BENE: DEVELOPMENT

A SAC of Crumbs and Stardust

Epithelial cells like to know which way is up. They exist in neat rows, one on top of another, each cell bound tightly to its neighbor through protein complexes (junctions) that unite the cells and allow them to communicate. It is the segregation of these protein complexes to specific regions of the plasma membrane that enables epithelial cells to distinguish top from bottom. This cellular polarity ensures that epithelial tissues retain their highly organized architecture.

But what events in the embryo trigger epithelial cells to acquire this polarity? Work in fly embryos established that a transmembrane protein called Crumbs becomes localized at the apex of epithelial cells early in development. Two groups reporting in *Nature* (*1*, *2*) now reveal that Crumbs is not the lone director of apical polarity in fly epithelia. Clinging to the cytoplasmic tail of Crumbs is an accomplice called Stardust. Each protein depends for its localization and stability on the other, and loss of either protein dooms epithelial tissues to a disorganized existence.

The lateral surfaces of a fly epithelial cell contain three junctions: the subapical complex (SAC), closest to the top of the cell; the zonula adherens, in the middle; and beneath it, the septate junction. Both groups show that during gastrulation, Stardust, like Crumbs, becomes localized to the apicolateral region of the epithelial cell plasma membrane where the SAC forms. If Stardust is absent, the SAC does not form and is unable to direct assembly of the zonula adherens. The result is loss of epithelial cell polarity and the progressive disorganization of epithelia as embryogenesis progresses.

Discovering Stardust in fly sensory neurons, as well as in epithelial tissues, suggested to the investigators that Stardust could be involved in the polarity of embryonic neuroblasts, cells derived from epithelia that eventually form the fly's central nervous system. Intriguingly, it turned out that neither Stardust nor Crumbs seemed to be involved in neuroblast polarity, a task left to the Bazooka–Dm-Par-6–aPKC triumvirate of proteins. Stardust, however, accumulates in the dendritic tips of sensory neurons such as those of fly stretch mechanoreceptors (*1*). The researchers propose that Stardust may lead a duplicitous existence, directing epithelial cell polarity in the fly during early embryogenesis, but contributing to mechanosensory transduction later in development. –ORLA SMITH

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