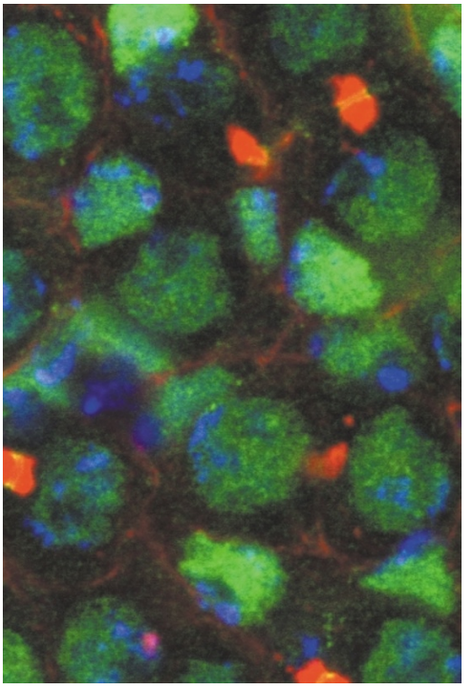

further defined, it offers an intriguing insight into how stem-cell renewal can be achieved and regulated.

Simon Frantz

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physiological role for CARM1 by showing that CARM1 induces apoptosis in neuronal cells. Nerve growth factor promotes the survival of neurons by inducing CREB-dependent expression of Bcl-2 — an anti-apoptotic factor — in neuronal cells. This CARM1-induced apoptosis was dependent on CARM1-HMT activity and was linked to the inhibition of Bcl-2 induction.

Methylation by CARM1 serves as a unique transcriptional switch, as it can activate the expression of NR-dependent genes, whilst inhibiting the expression of CREB-dependent genes. This study is the first report of direct methylation of a transcriptional cofactor, and, as CREB-dependent signalling pathways are developmentally and physiologically important, methylation by CARM1 could have very broad biological implications.

Rachel Smallridge

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CYTOSKELETON

Comet tales

The GTPase dynamin is crucial for vesicle fission during endocytosis and secretion. But can dynamin also influence actin dynamics? Initial evidence came from reports that dynamin interacts with actin-regulatory proteins and localizes at actin-rich sites. Two papers in the *Proceedings of the National Academy of Sciences* now show that dynamin can control actin nucleation from membranes, thereby regulating comet formation and movement.

To explore a functional link between dynamin and actin, the groups studied the regulation of actin nucleation in actin comets. Comets are induced by infection with *Listeria monocytogenes* or by the accumulation of phosphatidylinositol 4,5-bisphosphate, which induces the activity of actin-regulatory proteins. The groups tagged dynamin 2 with green fluorescent protein (GFP) and stained for filamentous (F-)actin using phalloidin or the actin-binding protein cortactin. The pattern of GFP fluorescence strongly resembled that of F-actin in the comets. Dynamin was further enriched at the tips of vesicles near the membrane.

Live imaging confirmed that dynamin is incorporated into the forming comets. But does it have an active function in these structures? To test this, both groups made use of dynamin mutants to assess any changes in actin tail formation or dynamics. GTPase-deficient dynamin–GFP mutants — which exert a dominant-negative effect on endocytosis — reduced the number and the speed of comets, and caused them to appear short and curled.

The region of dynamin that directly binds to actin-regulatory proteins is its proline-rich domain (PRD). Its involvement in targeting dynamin to actin comets was studied using a PRD-deletion mutant (dynaminΔPRD–GFP), which led to fewer comets. Unlike the GTPase-deficient mutant, however, the comets were longer. Significantly, dynaminΔPRD–GFP couldn't be detected in the comets, indicating that the PRD is required to target dynamin to these — and possibly other — actin structures.

So, what is the functional role of dynamin in actin comets? Given its ability to bind to components of the actin-nucleating machinery, dynamin might regulate actin-nucleation. On the basis that it can also associate with the lipid bilayer, it could direct this nucleation to specific sites, such as the coated pits involved in endocytosis. It is also likely, however, that the interaction between dynamin and actin occurs at non-endocytic sites.

Katrin Bussell

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Image courtesy of John Laborde, San Diego, California, USA.

APOPTOSIS

Death TRAIL

The road to cell death involves two distinct routes — the 'extrinsic' and 'intrinsic' pathways, which proceed through death receptors or through mitochondrial events, respectively. Although these pathways converge at the level of effector caspases, they are thought to be completely separate before that. However, a report by Xiangwei Wu and colleagues in *Genes and Development* now adds to the growing evidence for crosstalk between these two pathways. They have discovered that death by an extrinsic pathway involving TRAIL relies on intrinsic, mitochondrial events to kill human cancer cells.

Wu and co-workers used cells lacking Bax — a component of the intrinsic pathway — to show that this protein is needed for TRAIL-induced apoptosis. Moreover, whereas Bax was found in the cytosol before treatment with TRAIL, Bax translocated to the mitochondria after treatment. An inhibitor of the TRAIL-mediated extrinsic pathway prevented this translocation, suggesting that this movement depends on the extrinsic pathway.

What's the effect of Bax's translocation to the mitochondria, and how does this link to the intrinsic signalling pathway? Wu and colleagues showed that the loss of Bax blocks the release of intrinsic signalling factors (namely cytochrome *c* and Smac/DIABLO) from the mitochondria. But whereas TRAIL-induced apoptosis could still occur without cytochrome *c*-mediated caspase activation, the liberation of Smac/DIABLO was crucial.

Smac/DIABLO binds to (and removes the inhibitory effect of) a protein called XIAP, which normally inhibits caspase activity and blocks cell death. So Wu and colleagues propose that the TRAIL-mediated translocation of Bax allows the release of Smac/DIABLO from the mitochondria. This lifts the anti-apoptotic effects of XIAP, allowing cell death to proceed.

Alison Mitchell

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