Cell biology

An unexpected social servant

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Cells communicate through signals that must be propagated from cell surface to nucleus. Tracking the signals generated by the transforming growth factor-β protein reveals a surprising partner in this process.

During the development and maintenance of multicellular organisms, cells spend a lot of time communicating with each other to ensure that they are behaving in an appropriate and harmonious manner. This 'social' behaviour is mediated by the production of various signals outside the cell. These are interpreted in responding cells by networks of signal-transduction proteins that regulate the appropriate cellular response. One major class of signals emitted by cells in all animals is the transforming growth factor-β (TGF-β) superfamily of growth and differentiation factors, which control normal development and biological processes, as well as cancer progression[1]. On page 205 of this issue, Lin and colleagues[2] report an unexpected participant in the network that interprets TGF-β family signalling — cytoplasmic promyelocytic leukaemia protein (cPML).

PML is involved in a range of biological functions that include cell ageing, cell proliferation and programmed cell death[3]. As its name suggests, when these functions are disrupted, the result is acute promyelocytic leukaemia (APL) — so PML is classed as a tumour-suppressor protein. Most tumour-suppressing activities of PML are ascribed to its nuclear functions, but the function of the cytoplasmic form (cPML) was a mystery. Now it seems that it is a key accessory protein in the transduction of TGF-β signals.

At the cell surface, TGF-β interacts with two receptor complexes that function together to activate a downstream pathway of signalling proteins called Smads (Fig. 1). Smads move to the nucleus, where they can modulate cellular responses by regulating the expression of specific target genes[4]. One major feature of cell signalling is that receptors at the cell surface are transported into the cell, where they can either be recycled back to the cell surface, or be degraded. In the case of TGF-β receptors, this internalization transfers some of the receptors into an organelle called the early endosome — a process that is crucial for TGF-β signal transduction in some cells[5]. The importance of early endosomes in TGF-β signalling is probably manifested by the presence of a protein called SARA (for 'Smad anchor of receptor activation') that can bind to both Smads and TGF-β receptors[6].

Lin *et al.*[2] report that cPML is crucial in orchestrating the dance that goes on during a signalling event, coordinating the receptors,

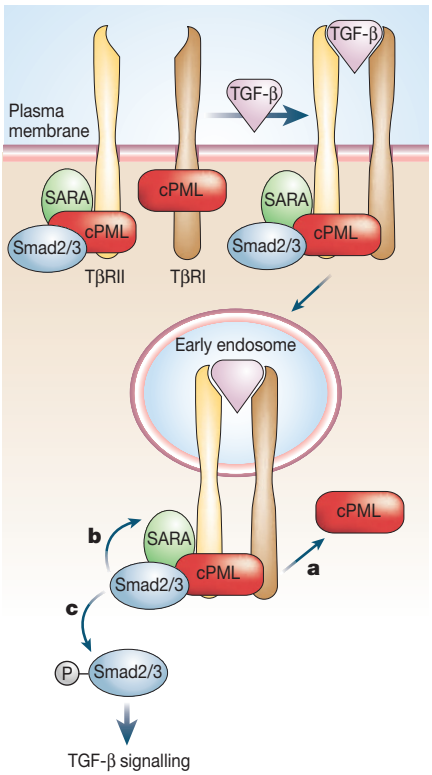

Figure 1 **Transforming growth factor-β (TGF-β) signalling. Lin *et al.*'s work[2] suggests a role for the cytoplasmic form of promyelocytic leukaemia protein (cPML). At the cell surface, cPML might interact with the two TGF-β receptors (TβRI and TβRII) and act as a bridging factor between SARA and Smad2/3. Upon stimulation with TGF-β, cPML promotes the transfer of the complex containing TβRI, TβRII, SARA and Smad2 into early endosomes. There, cPML might dissociate from the complex** (a)**, allowing Smad2/3 to interact with SARA** (b) **and to be phosphorylated** (c) **by TβRI. Phosphorylated Smad2/3 moves into the nucleus to propagate TGF-β signalling.**

SARA, Smads and the internalization process. They found that loss of cPML destroys TGF-β signalling, and began to dissect the molecular pathways that underpin the process. One surprise to come out of the work is that cPML is required for the interaction of Smads with SARA. This is puzzling because SARA can bind directly to Smads[7], so why is cPML necessary for the interaction *in vivo*? Another remarkable result from the paper provides a clue: cPML also binds to TGF-β receptors and is required for the movement of both the TGF-β–receptor complex and SARA into the early endosome. One possible implication is that SARA can only bind to Smads inside the endosome, and that one role of cPML is to bring the two together. These findings suggest that interference with receptor localization and SARA–Smad interactions is the main mechanism by which loss of cPML abrogates cellular responses to TGF-β.

The results raise lots of interesting questions, an obvious one being: how does cPML regulate the localization of receptors and SARA to the early endosome? Does it promote the transfer of the TGF-β receptor into the endosome; does it regulate the time that the receptor complex stays in the endosome; or does it control the targeting of SARA to early endosomes? One hint at an answer comes from the observation that cPML has a RING-finger domain. In other cell-surface-located receptors, this domain mediates their trafficking by helping to attach a protein tag called ubiquitin to them[8]. So, one function of cPML might be to promote the internalization of the receptors.

The finding that cPML is required for TGF-β signalling also converges nicely with observations that APL cell lines do not respond to TGF-β[2]. APL is almost always linked with a rearrangement of the genes encoding PML and the retinoic-acid receptor-α (RARα). The outcome is a fusion involving one copy of the *PML* gene, which produces a PML–RARα fusion protein; this has aberrant activity[2] and inhibits the activity of the normal PML in these tumours.

To wrap up their story, Lin *et al.* investigated TGF-β resistance in APL cell lines that contain the PML–RARα rearrangement. They confirmed that, in these cells, cPML–Smad complexes could not be detected and TGF-β treatment does not promote Smad activation. By treating the cells with retinoic acid, which causes degradation of PML–RARα, the authors reversed this effect, confirming that PML–RARα does indeed confer TGF-β resistance by interfering with normal cPML still present in the cell. Thus, the work also touches on how the loss of functional cPML might contribute to the 'antisocial' behaviour of cancers that display resistance to TGF-β. Moreover, it reveals a link between anomalies in trafficking events in the TGF-β system and alterations in the signalling properties of cancer cells. ■

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