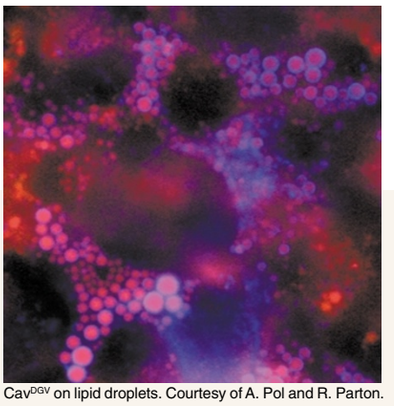
LIPIDS

Shifting the fat?



Cav^{DGV} on lipid droplets. Courtesy of A. Pol and R. Parton.

Three groups report in *The Journal of Cell Biology* that, under some conditions, caveolins — cholesterol-binding proteins characteristic of caveolae — localize to intracellular lipid droplets. This localization raises more questions than it answers, but the new findings will certainly open avenues for investigation.

Pol and colleagues were following up their previous studies, in which they discovered that a truncation mutant of caveolin-3 (Cav^{DGV}) inhibits signalling through H-Ras but not through K-Ras. They now find that Cav^{DGV} localizes to lipid droplets, and that it redistributes cholesterol from the plasma membrane (where it is important for maintaining functional lipid raft signalling domains) to late endosomes.

Ostermeyer and colleagues investigated how caveolin-1 travels from the endoplasmic reticulum (ER) to the plasma membrane. They added an ER-retention signal to the carboxyl terminus of the molecule (Cav–KKSL), and obtained a clear-cut result: Cav–KKSL did not reach the plasma membrane, so its transport is through the biosynthetic pathway. But to their surprise, Cav–KKSL was not retained in the ER; it accumulated on lipid droplets.

Last, Fujimoto and colleagues studied the intracellular route of overexpressed caveolin-2β, and found that it too localized to lipid droplets, whereas its close relative caveolin-2α did not.

Many of the results obtained in the three studies coincide, even if the authors interpret their results in different ways. Ostermeyer and colleagues propose that caveolins accumulate in lipid droplets only if they are slow to exit the ER. This is the case for mutant proteins (which might not fold fast enough), for overexpressed proteins (which might saturate the export machinery), and for cells treated with brefeldin A, a fungal metabolite that collapses the Golgi into the ER. Pol and colleagues, on the other hand, argue that, as a small proportion of endogeneous caveolins can reach lipid droplets, and Cav^{DGV} acts as a dominant-negative mutant, these structures might represent an intermediate station on the normal intracellular route of caveolins.

The new findings are intriguing and bring lipid droplets under the spotlight. But many questions remain. Are caveolins targeted to lipid droplets under physiological conditions? How are they targeted to this compartment? And above all, what is the function of this localization?

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APOPTOSIS

Competing for XIAP

Caspases are powerful destructive agents which, once activated, lead to certain death. Or do they? According to a report in *Nature* by Emad Alnemri and colleagues, a cell can be snatched from the jaws of death through the recruitment, by activated caspase-9, of its own inhibitor.

Death is, as Tennyson famously said, the end of life. It's no surprise, then, that caspase pathways must be tightly regulated. The so-called intrinsic death pathway, which responds to most death stimuli, is switched on through recruitment of the weakly active procaspase-9 by an adaptor molecule called Apaf-1. Procaspase-9 is then processed by autoproteolytic cleavage to yield active caspase-9.

Alnemri and colleagues knew that caspase-9 can be inhibited by the X-linked inhibitor of apoptosis protein (XIAP). To find out how this inhibition works, they reconstituted, *in vitro*, caspase-9–Apaf-1 complexes containing either fully processed caspase-9 or the procaspase form, and then studied their interactions with XIAP. Although both complexes were catalytically active, only the fully processed caspase-9 could be inhibited by XIAP. This, it turns out, is because XIAP cannot associate with the unprocessed procaspase-9.

Does this mean that processing is required for inhibition by XIAP? To test this idea, the authors identified a conserved motif of four amino acids, which becomes exposed at the amino terminus of the caspase-9 small subunit after proteolytic processing. This motif also has considerable homology to a sequence that binds IAPs in the *Drosophila* death proteins Grim, Reaper and Hid. Systematic mutation of the residues in this motif confirmed that they are needed for binding of XIAP to caspase-9.

Inhibition of caspase-9 can be overcome by a protein called Smac/DIABLO, which also interacts with XIAP and also contains the conserved four residues at its amino terminus. Alnemri and colleagues wondered whether the binding of Smac/DIABLO and caspase-9 to XIAP is mutually exclusive, and found that, indeed, the caspase-9 IAP-binding motif abolishes the binding of Smac/DIABLO to XIAP (and vice versa).

The inference, say the authors, is that "Smac competes with caspase-9 for binding the same pocket on the surface of XIAP, which could explain the ability of Smac to promote the catalytic activity of caspase-9 in the presence of XIAP". They also point out that, unlike for other caspases, proteolytic processing of caspase-9 is required for its inhibition rather than its activation. And, as Donald Nicholson discusses in the accompanying News and Views article, these results could have exciting implications for cancer therapy, as synthetic mimics of XIAP-binding peptides might sensitize cancer cells to apoptotic stimuli.

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