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Stathmin/Op18: catastrophe again?

Scientists have long searched for a 'catastrophe factor' that could explain how microtubules (MTs) become dynamic during mitosis. A bona fide catastrophe factor is a protein that is activated specifically at the onset of mitosis and induces MT catastrophes; at least four candidates are known: Kar3, stathmin/Op18, XKCM1 and XKIF2. However, although these four proteins destabilize MTs and can induce MT catastrophes *in vitro*, they are not activated at the onset of mitosis and therefore are 'MT-destabilizing factors' rather than 'catastrophe factors'. However, in combination with MT stabilizers (microtubule-associated proteins), these MT destabilizers are crucial for the regulation of MT dynamics during the cell cycle.

Among the four MT destabilizers, the 150-amino-acid Stathmin/Op18 stands out because of its ability to sequester tubulin dimers, the building block of MTs. Thus, the previously reported MT catastrophe-promoting activity could be explained by the sequestering activity, as the latter would result in a decrease in the amount of free tubulin and therefore an apparent increase in the catastrophe frequency. Howell *et al.*[1] now show that the tubulin-sequestering and catastrophe-inducing activities of stathmin/Op18 are pH dependent; at the standard pH 6.8 used by people working on MT dynamics, stathmin/Op18 strongly sequesters tubulin without increasing the catastrophe frequency. By contrast, at a pH of 7.5, the tubulin-sequestering activity is strongly reduced, whereas Stathmin/Op18 now causes a 4–7-fold increase in the catastrophe frequency. This is the first MT dynamics regulator for which a clear pH-dependent change in activity has been shown; it bears resemblance to actin-binding proteins such as ADF/cofilin. The ability to induce catastrophes requires the first 25 amino acids of stathmin/Op18, whereas the binding to tubulin requires amino acids 100–147. Considering the slightly alkaline pH of the cytoplasm, it is possible that stathmin/Op18 can both sequester tubulin and induce catastrophes *in vivo*. How stathmin/Op18 functions *in vivo*, and exactly how stathmin/Op18 induces catastrophes remain unknown; the authors hypothesize that stathmin/Op18 might increase the tubulin GTPase activity.

1 Howell, B., Larsson, N., Gullberg, M. and Cassimeris, L. (1999) Dissociation of the tubulin-sequestering and microtubule catastrophe-promoting activities of oncoprotein 18/stathmin *Mol. Biol. Cell* 10, 105–118

DIY at the bench: plentiful PI 3-kinases complicate chemotaxis

At its heart, science is rather like DIY – an attempt to complete practical tasks without access to appropriate tools. For both, however, the appearance of new tools can be a mixed blessing. In the newly launched *Nature Cell Biology*, Vanhaesebroeck *et al.*[1] have added to the 'chemotaxis signalling' toolkit by investigating the involvement of phosphoinositide (PI) 3-kinase in the macrophage response to colony-stimulating factor 1 (CSF-1). Their results both add to our knowledge of signalling pathways and raise substantial questions about established principles.

PI 3-kinase is a heterodimer comprising an adaptor molecule and a catalytic (p110) subunit. The latter exists in two ubiquitous isoforms (p110α and p110β) and an additional leukocyte-specific isoform (p110δ). Most previous PI 3-kinase studies have employed inhibitors such as wortmannin and LY294002, despite the fact that these inhibit all PI 3-kinase isoforms equally. However, Vanhaesebroeck *et al.* have inhibited single isoforms with isoform-specific antibodies and show that they have very different roles during CSF-1 signalling.

All three isoforms are expressed by macrophages and are recruited to the CSF-1 receptor upon ligand binding. Antibody against p110α blocked CSF-1-induced DNA synthesis, but did not affect CSF-1-induced actin rearrangements. However, antibodies against p110δ and p110β had the converse effect. Similarly, although antibody against p110α had no effect on macrophage migration along a CSF-1 gradient, the other two antibodies inhibited chemotaxis.

This work is a significant step forwards in our understanding of a complex phenomenon but also highlights

This month's *headlines* were contributed by Søren Andersen, Roy Golsteyn, Volker Haucke, Tom Misteli, Robin May and Kirsten Sadler.