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A dynamic opportunity for drug discovery

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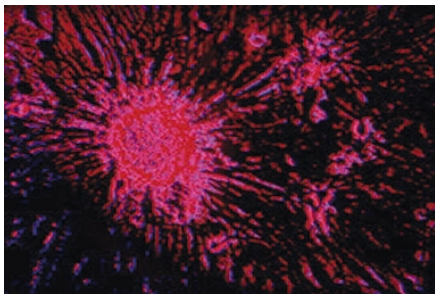
Of all the tens of thousands of proteins that our bodies produce, the functions of only a tiny fraction are known. But occasionally proteins that we thought we understood surprise us with something new. One such protein is Dynamin-2.

Dynamin-2 has previously been well characterized. It's a polymeric GTPase, formed by self-assembling monomers. Within cells, Dynamin-2 is usually found associated with cell membranes and, consistent with other similar proteins, it has been mooted as being involved in cell signalling. For example, Dynamin 2 has been shown to be necessary for phagocytosis in macrophages, it regulates hormone secretion in neuroendocrine cells and is quite likely to have a membrane-trafficking or secretion role.

A potential new role

A group at the Mayo Institute in Minnesota (http://www.gmit.ie/) have discovered a potential new role for Dynamin-2. Mark McNiven, whose group conducted this research, was surprised to find Dynamin-2 lurking in the cytoplasm [1]. 'We found Dynamin-2 in the perinuclear region' said McNiven. 'This was unexpected, so we used a number of techniques to confirm our findings.' Digging deeper, the Mayo group found that Dynamin-2 associates with γ-tubulin at the centrosome. γ-tubulin forms microtubules - the structures that form the mitotic spindles during the chromosome separation stage of cell division. The Mayo finding then, suggests that Dynamin-2 has a role in cell division. Dynamin-2 consists of three main regions: the C-terminal GTPase domain; an N-terminal PH



('pleckstrin homology') domain, which is involved in Dynamin-2's membrane interaction; and a third domain, the function of which is not known, Intriguingly, McNiven's group showed that it is in this region that Dynamin-2 interacts with γ-tubulin.

Microtubules as a drug target

What is Dynamin-2 doing at the centrosome? That question still needs to be fully answered, but Dynamin-2's association with the machinery of cell division is an area that could be exploited for drug discovery. 'We've seen that by reducing the levels of Dynamin-2, the centrosome structure falls apart,' said McNiven. Conversely, in some cancers Dynamin-2 undergoes enhanced expression. 'In work we've not published yet, we've seen that in certain human pancreatic tumours, levels of Dynamin-2 are increased three- or fourfold,' continued McNiven. Microtubules, and the formation of the mitotic spindle, are already targets for drug discovery. Linking with the potential of McNiven's work, drugs currently used to fight cancer, for example, colchicine and paclitaxel are drugs currently in use that interfere with microtubule formation. Ryoko Kuriyama, of the University of Minnesota (http://www.umn.edu), agrees that Dynamin-2 is a good candidate for drug discovery. She continued, 'there are currently no drugs that act on the centrosome – for example, they target myosin motor proteins or disturb mitotic spindle organisation.'

Selectively killing cancer cells

Disturbing the cell division cycle effectively prevents cells from reproducing properly, ultimately killing the cells. This is the basis for the use of microtubule-disrupting drugs as cancer therapies. Naturally, the drug has the same effect on non-cancerous cells too. Cancer cells spend far more of their time dividing. Non-cancerous cells, on the other hand, spend most of their time quiescent – not dividing. This allows the therapy to have a more marked effect on cancer cells. McNiven believes that, although drugs active against Dynamin-2 and the centrosome might still be non-specific, they could still prove to be better practically.

The future for the Mayo team that made this discovery will not involve designing drugs against Dynamin-2. 'We don't design drugs, but we may be involved in screening drugs developed by others,' says McNiven. The future lies in deciphering exactly what it is that Dynamin-2 does to maintain the centrosome's structure, how it links this newly-discovered function with its membrane-trafficking role, and in looking at the effect of disrupting these roles. Accepting there's a lot still to do, Kuriyama admitted, 'The centrosome is more dynamic than was previously known.'

Reference

1 Thompson, H.M. *et al.* (2004) Dynamin 2 binds γ-tubulin and participates in centrosome cohesion. *Nat. Cell Biol.* 6, 335–342

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