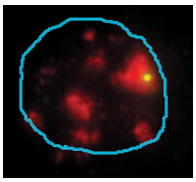
Chaperoning myosins

UCS proteins, such as *C. elegans* UNC-45, are essential for a variety of actin- and myosin-dependent processes in fungi, nematodes and *Drosophila* and have now been shown to exist in mammals. Originally thought to have a catalytic activity necessary for the formation of myofilament arrays, these proteins seem in fact to function as client-specific chaperones that facilitate folding of myosin motors. In a Commentary on p. 3983, Henry Epstein and co-workers discuss the experiments that led to this idea. Genetic analyses revealed that UNC-45 and its fungal relatives interact with conventional and unconventional myosins through a conserved UCS domain. Subsequently, experiments using recombinant UNC-45 showed that it forms a complex with muscle myosin and the chaperones Hsp90 and Hsp70 and that UNC-45 itself has general chaperone activity. Interestingly, vertebrates possess two distinct UNC-45 isoforms – a general cell isoform and a striated muscle isoform – which could have distinct roles in cytoskeletal maintenance and striated muscle differentiation, respectively (see p. 4013).

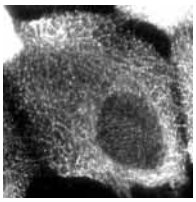
Tumour suppression by merlin and 4.1 proteins

Members of the protein 4.1 superfamily are FERM-domain proteins that connect cell-surface glycoproteins with the actin cytoskeleton. The superfamily includes protein tyrosine phosphatases, 4.1 proteins, and ERM proteins such as ezrin and merlin/schwannomin – the protein inactivated in neurofibromatosis 2. In a Commentary on p. 3991, David Gutmann and co-workers review work showing that certain 4.1 and ERM proteins are tumour suppressors, highlighting recent studies that have provided insight into how they function. Loss of merlin is associated with development of schwannoma and meningioma; similarly, loss of protein 4.1B has been linked with a variety of tumors. Merlin is known to associate with cell surface molecules such as CD44 and appears to engage in intramolecular interactions that regulate its ability to interact with actin and other proteins. Gutmann and co-workers propose that signalling through Rho GTPases activates kinases that block these intramolecular interactions and thereby inhibit tumour suppression by merlin. Given the sequence similarity shared by merlin and the rest of this superfamily, other 4.1 tumour suppressors might act in the same way.



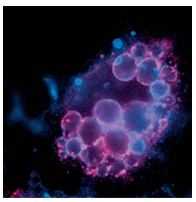
Nuclear organization in differentiating cells

Nuclear compartmentalization is believed to be essential for many processes. Splicing factors, for example, reside in discrete compartments (SFCs) with which active genes associate, and localization of genes to particular nuclear regions could constitute an important regulatory mechanism. But to what extent are changes in nuclear organization associated with tissue-specific gene expression in vivo rather than simply characteristic of transformed cell lines? Regina Armstrong and co-workers have examined nuclear organization during differentiation of primary oligodendrocyte cultures, which closely mimics in vivo oligodendrocyte differentiation (see p. 4071). Using genomic in situ hybridization, they show that *PLP*, a gene upregulated during oligodendrocyte differentiation, is associated with the nuclear periphery in both progenitor cells and differentiated oligodendrocytes and remains spatially separated from a coordinately regulated gene, *MBP*. The authors do, however, find that *PLP* transcription in differentiated cells induces local formation of SFCs and demonstrate that these are not associated with inactive genes. They therefore conclude that nuclear reorganization does occur during differentiation but is characterized by changes in the distribution of proteins such as splicing factors rather than gene localization/clustering.



Reversible cytokeratin remodelling

Cytokeratin (CK) intermediate filaments form a dynamic network in which CK subunits continually exchange over the entire surface. Remodelling of this network is essential for mitosis, cell migration and changes in cell morphology, but the underlying mechanisms remain uncharacterized – as do those that generate the granular CK aggregates characteristic of various diseases. Rudolf Leube and co-workers now reveal that tyrosine phosphorylation plays an important role (see p. 4133). They show that treatment of cells expressing a CK13-GFP fusion protein with the tyrosine phosphatase inhibitor orthovanadate leads to rapid disassembly of CK filaments and formation of granular CK aggregates containing the crosslinking protein plectin. They also show that CK from these aggregates is reincorporated into filaments within minutes of orthovanadate removal. Interestingly, treatment of cells with okadaic acid, a serine/threonine phosphatase inhibitor, also generates CK granules, but the process is not reversible and the aggregates produced do not contain plectin. It is thus tyrosine phosphorylation that drives reversible restructuring of the cellular CK network, and plectin might do more than just crosslink filaments.



LGP85 and endosome maintenance

Lysosomes and late endosomes are thought to exist in dynamic equilibrium, undergoing repeated cycles of fission and fusion. Their limiting membranes contain a common set of highly glycosylated transmembrane proteins, including LAMP-1, LAMP-2 and LGP85 (also known as LIMP-II). Whether these proteins are involved in endosome/lysosome dynamics or play some other role is unclear. To investigate the possibility, Yoshitaka Tanaka and co-workers have overexpressed them in COS cells. They observe that overexpression of LGP85 (but not LAMP-1 or LAMP-2) induces formation of abnormally large endosome-like structures (see p. 4117). Transport of cargo out of these structures is blocked, and they accumulate free cholesterol. Interestingly, the authors show that coexpression of a dominant-negative form of Rab5b (a GTPase that functions in endosomal/lysosomal membrane trafficking) inhibits the effect of LGP85, implicating the GTPase in formation of the large endosomes. Tanaka and co-workers thus propose that LGP85 is important for the biogenesis and maintenance of endosomes/lysosomes and drives their reorganization by interacting with components of the vesicle fission/fusion machinery.

Sticky Wicket – scooped!

Finding out that someone has scooped you is not pleasant. Same idea, same method, same reagents – and they get all the glory! Caveman's been there before, but claims all is not lost. After all, close inspection of the data might not only make a salvage operation possible but actually improve your next paper (see p. 3975).

In the next issue of JCS

Commentaries

Spectraplakins. K. Röper et al.
Roles for non-collagenous domains of collagens. N. Ortega and Z. Werb

Research Articles

Regulation of osteoclastogenesis by JNK1 and c-Jun. J.-P. David et al.
EMT induction by TGF-β1 and EGF in thyrocytes. M. Grände et al.
PTP-PEST regulates Rac1. S. K. Sastry et al.
Integrin β tails activate Rac1. A. L. Berrier et al.
Myogenic progenitor regeneration capacity. R. J. Jankowski et al.
In vivo activities of myosin II tail chimeras. S. Shu et al.
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Caveolae, microtubules and actin. D. I. Mundy et al.
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Differential signalling by thrombospondin-1. J. S. Lymn et al.
The role of keratins in response to osmotic shock. M. D'Alessandro et al.
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Keratinocyte defects in synd1ko mice. M. A. Stepp et al.