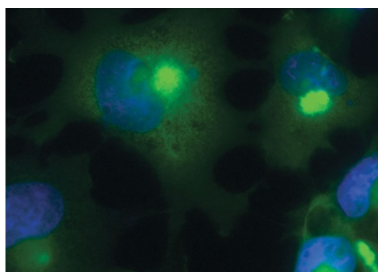
Ufm sighting

Covalent attachment of ubiquitin and ubiquitin-like (UBL) modifier proteins is a major post-translational regulatory mechanism. Ubiquitin and UBLs are linked to target proteins through an enzymatic cascade consisting of activating (E1), conjugating (E2) and ligating (E3) enzymes. At least 10 ubiquitin-like modifier proteins exist in mammals, with attachment of different UBLs resulting in different consequences for the cell. Now another human UBL has been identified. Ufm1 (ubiquitin-fold-modifier 1) contains a 'ubiquitin-like fold' despite lack of overall sequence identity to ubiquitin or other modifier proteins. Like ubiquitin, Ufm1 is synthesized as a precursor protein. Its C terminus is cleaved to expose a conserved glycine residue that is necessary for subsequent enzymatic steps. The study has also identified E1-like (Uba5) and E2-like (Ufc1) enzymes for Ufm1. Ufm1 is covalently attached to several cellular proteins, and characterizing Ufm1 target molecules will be the next step toward elucidating the biological significance of this protein-modifying system. (*EMBO J.* advance online publication, 8 April 2004; doi:10.1038/sj.emboj.7600205). *RC*

HDACs and aggregates

At the heart of most neurodegenerative diseases are protein inclusions of misfolded proteins. In amyotrophic lateral sclerosis (ALS), mutant Cu/Zn superoxide dismutase-1 (SOD1) protein is found in inclusions reminiscent of 'aggresomes', large bodies containing aggregated proteins outside a cell's nucleus. Inhibiting proteasome activity can allow misfolded proteins to accumulate, thereby leading to the formation of aggresomes. While an individual cell typically has only one aggresome particle, it can also contain aggresome precursors, the micro-aggregates. Micro-aggregates are delivered to the microtubule-organizing center by the dynein/dynactin motor complex. Being able to disrupt aggresome formation would lead to new insights into the mechanism of aggregation and would provide a means to study the role of aggregation in diseased neurons. To this end, Corcoran *et al.* recently developed a high-throughput screen to search for chemical inhibitors of aggresome formation. Using fluorescence microscopy of COS1 cells expressing GFP-tagged SOD1 mutants, they found that inhibitors of histone deacetyleases (HDACs) could inhibit aggresome formation. One HDAC inhibitor, Scriptaid, blocked aggresome formation by inhibiting the recruitment of the dynactin subunits, p150^{Glued} and P50 dynamitin to the micro-aggregates. Left without the ability to transport along microtubules, the micro-aggregates remained dispersed throughout the cytoplasm. It is unclear exactly how the deacetylation of histones makes recruitment of the motor complex possible, but perhaps it modulates the transcription of another key player in the recognition or binding of the misfolded proteins. (*Curr. Biol.* **14**, 488–492, 2004) *MB*



Research Notes written by Mirella Bucci, Rosemary Clyne, Evelyn Jabri and Deirdre Lockwood

SR proteins and translation

Serine arginine–Rich (SR) proteins are RNA-binding proteins well known for their role in alternative splicing in the nucleus. However, some of these proteins shuttle between the nucleus and cytoplasm, suggesting that a subset of SR proteins function in mRNA transport, cytoplasmic RNA localization, stability and/or translation. Indeed, recent work from Joan Steitz's laboratory has implicated shuttling SR proteins as adaptors for mRNA export. Now, the Cáceres laboratory shows that the shuttling SR protein, SF2/ASF, and to a lesser extent 9G8 and SRp20, associate with the ribosome and enhance translation. SR proteins have an N-terminal RNA-binding domain, as well as a C-terminal arginine and serine rich (RS) domain implicated in protein-protein interactions and essential for shuttling. Using a tethered function assay in *Xenopus* oocytes, Sanford *et al.* show that the RS domain of SF2/ASF is sufficient to interact with the ribosome and to stimulate translation, whereas the N-terminal RNA-binding domain was dispensable for these functions. Furthermore, the ability of SF2/ASF to move from the nucleus to the cytoplasm plays an important role in enhancing translation *in vivo*. Interestingly, the ability of shuttling SR proteins to activate translation could be recapitulated *in vitro* using a HeLa cell-free translation system. The details of how shuttling SR proteins affect ribosomal activity remains to be investigated. Nevertheless, the data demonstrate that the family of SR proteins are important in the early nuclear as well as late cytoplasmic RNA processing events and hence may function to couple cellular RNA metabolic processes. (*Genes & Dev.* 18, 755–768, 2004). *EJ*

Never go back

Transport vesicles carry proteins between compartments to ensure their proper placement in the cell. It has been known for some time that newly formed vesicles budding from one compartment and heading toward another do not fuse back with the membrane from which they came. How does the cell prevent such a back fusion from happening? Kamena and Spang have identified in yeast a protein called Tip20p that could play a role in such a process. Tip20p resides at the ER membrane and has been shown to be required for Golgi-derived vesicles fusion with the ER. The authors observed that one temperature-sensitive Tip20p mutant allowed more efficient Golgi-to-ER vesicle fusion to occur at a high temperature compared with a membrane containing the wild-type protein. However, the mutant also affected the ER-to-Golgi transport, as ER-derived vesicles from the mutant *tip20* cells fused poorly with the Golgi membrane at this temperature. These observations suggested that the vesicles did not reach their target and might have fused back to the donor membrane. Further experimentation confirmed this scenario and showed that this mutant allowed purified, ER-derived vesicles to fuse back with the ER membrane, whereas the wild-type Tip20p did not. These results suggest that Tip20p participates in an active mechanism that maintains a directed transport of vesicles. Further studies will be necessary to clarify how Tip20p distinguishes the vesicles derived from various compartments. (*Science*, **304**, 286–289, 2004) *DL*

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