IN THE NEWS

Uncoupling radical attacks

"Scientists have uncovered a possible way of interfering with the process which could be responsible for a host of age-related illnesses," reported BBC News (5 January, 2001).

A study by Martin Brand and colleagues published in the 3 January issue of *Nature* describes how superoxide activates uncoupling proteins. They found that superoxide increases mitochondrial proton conductance by affecting the uncoupling proteins, UCP1, 2 and 3, and concluded that the interaction between superoxide and UCPs might reduce the concentrations of reactive oxygen species inside mitochondria.

"These free radicals… can cause damage to the genetic information held in cells. This damage… has been linked to the development of age-related conditions such as Alzheimer's disease, diabetes and certain cancers. The… uncoupling proteins, help shift the free radicals away from sensitive areas of the cell to other areas where they can be safely dealt with," said BBC News.

Brand said he believes that a lack of these uncoupling proteins might make it difficult for cells to dispose of free radicals and that strategies aimed at upregulating these proteins could be of therapeutic value. "The role of uncoupling proteins could be fundamental to protecting against degenerative disease and ageing," he told BBC News. "We hope that by understanding their role, we could find potential new ways to prevent or treat free-radical linked diseases. For example, we might be able to decrease cellular ageing by using chemicals which switch these proteins on."

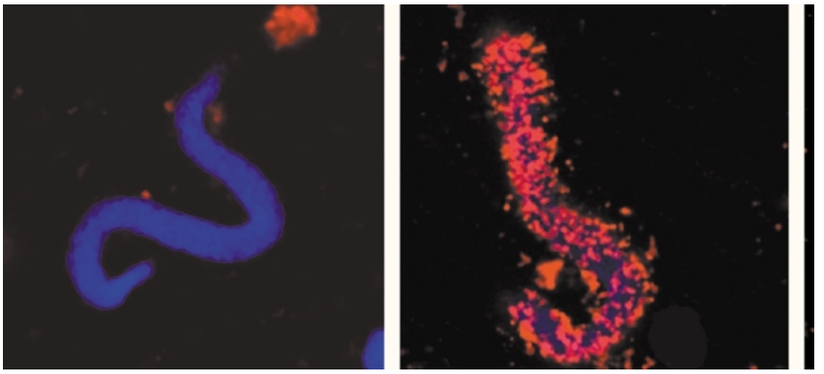
Simon Frantz

NUCLEAR ENVELOPE

Step by step

During each round of cell division, the nuclear membrane breaks down and then reforms. It was long suspected that nuclear envelope assembly involves membrane fusion, and Hetzer and colleagues now report in *Nature Cell Biology* that this is indeed the case. The surprise is that not one, but two distinct fusion mechanisms seem to operate during this process.

The authors used an *in vitro* assay in which (in the presence of cytosol) demembranated sperm nuclei assemble nuclear envelopes from $DiIC_{18}$-labelled vesicles that are derived from *Xenopus laevis* eggs. Different stages can be distinguished by confocal microscopy (see figure). Precursor vesicles first bind to the chromatin and then fuse into a tubular network on the surface of chromatin. Next, this network becomes a closed nuclear envelope, which later expands during nuclear growth.



Hetzer and colleagues used this assay to test the involvement of p97 — an AAA ATPase that had previously been implicated in homotypic fusion of post-mitotic Golgi and of transitional endoplasmic reticulum (ER). Antibodies against p97 and depletion of p97 from the cytosol both efficiently blocked nuclear envelope formation.

The authors next wondered whether p97 acts through its known acolytes, p47 or the Ufd1–Npl4 complex. Affinity depletion of all putative p97 adaptors, but not p97, from the cytosol inhibited nuclear envelope assembly, indicating that p97 cannot function alone. Adding recombinant p47 to the depleted cytosol did not rescue the process, but adding recombinant Ufd1–Npl4 complex resulted in the formation of sealed nuclear envelopes that were competent for nuclear transport. However, the nuclei that formed under these conditions were markedly smaller and reached their normal size only if the authors also added recombinant p47 to the assay. From a series of sequential add-back experiments, Hetzer

DEVELOPMENT

Surfing for Sef

During the development of any organism, individual signalling pathways are activated to induce differentiation. The control of these pathways is tightly regulated, and usually involves negative feedback and the use of pathway-specific antagonists. In the 1990s, the gene *Sprouty* was identified as a novel inhibitor of the fibroblast growth factor (FGF) signalling pathway. Work published in this month's issue of *Nature Cell Biology* now identifies the molecule Sef (for 'similar expression to *fgf* genes') as a specific inhibitor of FGF signalling in zebrafish (see figure, in which dark staining represents *sef* expression).

FGFs are growth factors that control proliferation, differentiation, migration and embryonic patterning. FGF8 has a particular role during the early development of zebrafish embryos — it controls dorsal–ventral patterning. It achieves this through the activation of the Ras/Raf/MEK/mitogen-activated protein kinase (MAPK) pathway, which represses expression of bone morphogenetic protein (BMP).

Both Igor Dawid and colleagues, and Christine Thisse and co-workers used a zebrafish embryo DNA library combined with an *in situ* hybridization screen to identify Sef as a novel modulator of FGF signal transduction. Sef encodes a transmembrane protein with homologues in other species, and it seems to have a conserved tyrosine phosphorylation domain. This conserved tyrosine could be a functional residue that is necessary for transducing signals downstream of activated Sef, although the precise role of this conserved sequence is unknown.

The expression of Sef is positively regulated by FGF8 — overexpression of FGF8 in injected embryos leads to an expansion of the *sef* expression domain, whereas *acerebellar* mutants (which lack FGF8 function) or embryos overexpressing a dominant-negative form of the FGF receptor have reduced *sef* expression.

When both groups ectopically expressed *sef*, the zebrafish embryos lacked dorsal polarity (similar to the phenotype induced by expression of a dominant-negative FGF receptor), indicating that Sef can inhibit FGF signalling. Morpholino antisense-oligonucleotides to Sef generated embryos that looked similar to the dorsalized phenotypes induced by ectopic FGF8 expression, again suggesting that Sef acts as an antagonist to FGF signalling.

Thisse and colleagues then showed that Sef expression does disrupt the MAPK signalling pathway. In addition, Dawid and colleagues co-immunoprecipitated the FGF receptor with Sef — an interaction that required the