IN THE NEWS

Eternal youth

Scientists from the UK and Japan have discovered an important new player in maintaining the immortality of embryonic stem (ES) cells. This breakthrough might one day allow scientists to turn any cell into an immortal, pluripotent cell that can be used for therapeutic purposes.

Shinya Yamanaka and his colleagues, from the Nara Institute of Science and Technology, and Austin Smith's group, at the Institute for Stem Cell Research in Edinburgh, independently identified a gene that was expressed specifically in pluripotent, undifferentiated cells. They named the gene *Nanog* — after the mythological Celtic land of the ever-young, Tir nan Og.

In two papers in *Cell*, the scientists showed that overexpression of Nanog prevented ES cells from differentiating. What is exciting is that Nanog seems to be a key factor in the transcription-factor network that is known to be required for the ES cell phenotype.

"As we know more and more about pluripotency, it probably will be possible to reprogram cells to make stem cells out of any cell in the body," said James Thomson, the University of Wisconsin scientist who first isolated human ES cells in 1998 (*Washington Post*, 30th May 2003).

Although most of their experiments involved using the mouse version of Nanog in mouse cells, some involved the human version, which was identified thanks to its structural similarity to mouse Nanog. "If Nanog has the same effect in humans as we have found in mice, this will be a key step in developing embryonic stem cells for medical treatments," said Austin Smith (*New Scientist*, 30th May 2003).

Arianne Heinrichs

GENE REGULATION

A stimulating experience

The transcription factor nuclear factor κB (NF-κB) controls cytokine-regulated processes and is regulated by the IκB kinase (IKK) complex comprising IKKα, IKKβ and IKKγ. Whereas IKKβ controls the degradation of inhibitors of NF-κB (IκBs), resulting in rapid nuclear accumulation of NF-κB, the role of the IKKα subunit has been more elusive. But now, reporting in *Nature*, the groups of Richard Gaynor and Albert Baldwin propose a new, nucleosomal function for IKKα.

Recent observations indicated that IKKα might have a role in cytokine-induced, NF-κB-dependent gene regulation, independent of that of IKKβ. Both groups showed that this role is likely to be nuclear, as cytokine induction resulted in the nuclear accumulation of IKKα but not IKKβ. To investigate the mechanism underlying IKKα's nuclear role, the groups carried out chromatin immunoprecipitation (ChIP) assays and showed that, in response to tumour-necrosis factor (TNF)-α stimulation, IKKα was recruited to NF-κB-responsive gene promoters.

As interactions between coactivator CREB-binding protein (CBP) and NF-κB subunit p65 have been shown to be important for NF-κB activation, Gaynor and colleagues tried to establish whether IKKα functions through complex formation with these coactivators. Indeed, IKKα interacts with CBP, but not with p65. Both groups showed that in *p65*$^{-/-}$ cells, IKKα is not recruited to NF-κB-regulated promoters, indicating that p65 is required for IKKα–promoter association.

So how does IKKα modulate transcriptional activation? Given that histone H3 modifications have been correlated with active gene expression, the Gaynor and Baldwin groups carried out ChIP assays using phosphorylated histone H3 antibodies and found that the kinetics of IKKα recruitment and histone H3 serine (Ser) 10 phosphorylation correlated, and that TNF-α-induced Ser10 phosphorylation was abolished in *IKKα*$^{-/-}$ cells. Cytokine-induced phosphorylation of histone H3 was suggested to be due to the direct kinase activity of IKKα, as IKKα (but not IKKβ) was shown to phosphorylate H3 on Ser10 using *in vitro* kinase assays.

CALCIUM

Channelling degeneration

The dystrophin–glycoprotein complex (DGC) provides structural support for the sarcolemma, the membrane that encloses myocytes, and genetic defects in the principal DGC components — dystrophin and sarcoglycan — lead to muscular dystrophy and/or cardiomyopathy in humans and animal models. Now, reporting in *The Journal of Cell Biology*, Shigekawa and colleagues begin to uncover the molecular events involved in myocyte degeneration.

Increased membrane fragility to mechanical stress and permeability to Ca^{2+} have been implicated in myocyte degeneration, and elevated Ca^{2+} concentrations ([Ca^{2+}]) have been reported in dystrophic myocytes. So, the authors decided to look for Ca^{2+}-entry mechanisms that could be responsible for pathogenic myocyte degeneration. They began by searching for mammalian homologues of the *Drosophila melanogaster* Ca^{2+}-permeable cation channels, which belong to the transient receptor potential channel family, because they are sensitive to physical stimuli.

Shigekawa and colleagues identified the growth-factor-regulated channel (GRC), which had previously been identified as a Ca^{2+}-permeable non-selective cation channel expressed in non-muscle cells. They found that, although the total GRC content was similar to normal, GRC expression was elevated in the peripheral sarcolemma of cardiac and skeletal muscle of BIO14.6 hamsters (deficient in δ-sarcoglycan), and the skeletal muscle of *mdx* mice (a model for Duchenne muscular dystrophy) and of myopathic patients.

Next, the authors looked at the properties of BIO14.6 and *mdx* myotubes. They found that GRC expression was increased in the sarcolemma (in normal myotubes GRC is located mostly in the interior), that it could be reduced by a Ca^{2+}-influx inhibitor (Gd^{3+}) and then re-established by Ca^{2+}. As phosphatidylinositol 3-kinase inhibitors didn't inhibit this translocation, it was concluded that Ca^{2+} was the primary regulator of GRC translocation. In normal myotubes, GRC translocated to the sarcolemma in response to insulin-like growth factor-1 or cyclic stretch in the presence of Ca^{2+} — responses that were abolished by Gd^{3+}.

In resting BIO14.6 myocytes, Shigekawa and colleagues found that there was a marked increase in Gd^{3+}-sensitive Ca^{2+} uptake, and acute elevation of external [Ca^{2+}] increased the intracellular [Ca^{2+}] — both responses were suppressed by another Ca^{2+}-influx inhibitor. Moreover, cyclic stretch in the presence of Ca^{2+} led to a high level of creatine kinase (CK) efflux, which is a marker of myocyte damage. Infection with δ-sarcoglycan cDNA corrected