IN THE NEWS

The ultimate stem cell?

A study, published in *Science*, has shown that parthenogenesis of unfertilized ovaries could provide a viable and ethical alternative to cloning and destroying human embryos.

A team from Advanced Cell Technology (ACT) and the Wake Forest University School of Medicine have shown that macaque oocytes can be tricked into dividing into blastocytes without the presence of sperm. Embryonic stem cells from these blastocytes could differentiate into muscle, fat and heart cells, and even neurons.

Developing the same procedure in humans is producing encouraging results. "The bottom line is that we are very confident of repeating the result in humans," José Cibelli at ACT told *The New York Times* (1 February 2002).

The advantage of this method is that "because parthenotes are incapable of developing into a fetus, their use may bypass some of the ethical objections that have dogged current experiments on normal embryos", (*BBC News*, 31 January 2002).

But several issues remain. "The majority of diseases that stem cells would treat are age related. [But] older women no longer produce egg cells from which to make parthenote stem cells," Harry Griffin at the Roslin Institute told *Nature Science Update* (1 February 2002). "[They] also lack the influence of male chromosomes, which have subtle effects on cell growth and development," Azim Surani, at the University of Cambridge told *Nature Science Update*. "We cannot assume that they [parthenote cells] will behave normally when implanted in an organism."

Simon Frantz

P53 FAMILY

From damage to death

As family ties go, the links between p53 and p73 are strong. Both are induced by DNA damage (as well as other cellular stresses), and both in turn modulate the expression of specific target genes. The two proteins are also modified post-translationally, although relatively little is known about this process for p73.

A report by Massimo Levrero and colleagues in *Molecular Cell* now describes the events that surround one form of post-translational modification — acetylation — of p73. They find that, like p53, the p73α isoform is acetylated in cells treated with the DNA-damaging agent doxorubicin. However, whereas p53 can be modified *in vivo* by the acetyltransferases CBP or PCAF, p73α is not affected by these enzymes — instead, it is acetylated by p300.

Non-acetylatable p53 mutants do not show impaired activation of transcription in response to DNA damage. So Levrero and colleagues looked at the transcriptional activities of wild-type p73α and a non-acetylatable mutant (p73αRRR). Both p73α and p73αRRR could activate transcription; however, p73αRRR was impaired in inducing apoptosis in response to doxorubicin, suggesting that acetylation of p73 regulates its ability to mediate apoptosis in response to DNA damage.

The authors confirmed this by showing that, in cells microinjected with p73α, apoptosis is potentiated by treatment with doxorubicin; an effect that was not seen with p73αRRR or in the presence of a p300 inhibitor. They then found that endogenous p73 is recruited *in vivo* to the promoter of *p53AIP1* — a gene that, when overexpressed, induces apoptosis. Unlike p73α, p73αRRR was not efficiently recruited to the *p53AIP1* promoter after DNA damage. So, DNA-damage-induced acetylation potentiates the pro-apoptotic function of p73 by enhancing p73's ability to activate the transcription of pro-apoptotic target genes. Finally, the authors showed that c-ABL — which activates p73's pro-apoptotic functions — is required for the p300-dependent acetylation of p73α in response to DNA damage.

These results highlight some of the subtle differences that are emerging between p73 and p53; differences that might ultimately contribute to the transcription of distinct target genes in response to DNA damage.

Alison Mitchell

References and links

ORIGINAL RESEARCH PAPER Costanzo, A. *et al.* DNA damage-dependent acetylation of p73 dictates the selective activation of apoptotic target genes. *Mol. Cell* **9**, 175–186 (2002)

FURTHER READING Yang, A. & McKeon, F. p63 and p73: p53 mimics, menaces and more. *Nature Rev. Mol. Cell Biol.* **1**, 199–207 (2000)

CELLULAR MICROBIOLOGY

Protein injection

Legionella pneumophila is an aquatic bacterium that infects protozoan hosts in freshwater ecosystems. However, if it is inhaled by humans it causes a severe form of pneumonia known as Legionnaires' disease. It is an intracellular pathogen that hijacks host vesicle transport to make a vacuole that supports its replication, and this replication occurs in phagocytes in humans.

Vacuole biogenesis requires the bacterial Dot/Icm transporter — a type IV protein secretion apparatus. Bacterial proteins are thought to translocate, through Dot/Icm, across the membrane of the phagosome — the membrane-bound vesicle that surrounds the bacteria after phagocytosis — into the host cell. These bacterial proteins can then act to alter vesicle transport.

The injected proteins have remained elusive, but now, reporting in *Science*, Roy and colleagues describe the identification of RalF, a bacterial protein that is injected into the host cell through Dot/Icm.

The authors showed that RalF is required for the recruitment of the host protein ADP ribosylation factor 1 (ARF1) to *Legionella* phagosomes. ARF1 is an important regulator of vesicle transport from the endoplasmic reticulum to the Golgi. It is a GTP-binding protein, and the authors showed that, using its Sec7-homology domain, RalF functions as an ARF guanine nucleotide exchange factor.

As the Sec7-homology domain in RalF is only the second to be identified in prokaryotes, and the authors could not identify the *ralF* gene in any other *Legionella* species, they speculated that its presence in *L. pneumophila* is likely to have resulted from horizontal gene transfer. They hypothesized that genes acquired recently, encoding proteins secreted by Dot/Icm, might enhance bacterial replication in new environments and might also increase bacterial virulence. In the future, identification of additional Dot/Icm substrates will enable us to further understand how an environmental organism has become a human pathogen.

Rachel Smallridge

References and links

ORIGINAL RESEARCH PAPER Nagai, H. *et al.* A bacterial guanine nucleotide exchange factor activates ARF on *Legionella* phagosomes. *Science* **295**, 679–682 (2002)

WEB SITE

Craig Roy's laboratory: http://www.med.yale.edu/micropath/fac_roy.html