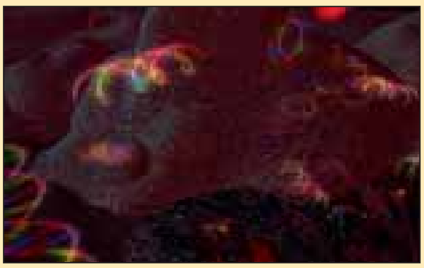
Recent Papers from European Labs

Origin of Life in Budapest/Barcelona

A Start, Perhaps

The origin of life on earth debate has always prompted the "What came first?" questions; the chicken or the egg? Or, in more recent times, genetics or metabolism? Many theories exist about chemical evolution, which finally led to the creation of the first primitive cell. Vera Vasas and Eörs Szathmáry from the Institute for Advanced Study in Budapest, together with the evolutionary biologist Mauro Santos from the Universitat Autònoma de Barcelona have now been able to demonstrate that one of them might not be very likely, after all (*Proc. Natl. Acad. Sci. USA*, publ. online before print, Jan. 4, 2010). But let's start from the beginning.

The first simple, organic molecules are formed from inorganic substances, as shown with the famous experiment by Stanley Miller and Harold Urey (*Science* 117: 528-9). However, in order to form the very first precursor of a cell, three things are required: genetics, metabolism and cellular compartments. It's still unclear, though, which of them came first. The most popular theory is the genetics or RNA-first hypothesis, in which RNA is a self-catalytic molecule that stores



genetic information. How the first RNA molecule originated is still unexplained to-date and, thus, alternative hypotheses, like the metabolism-first approach, have gained interest in recent years.

In the metabolism-first model, amphiphilic molecules, which spontaneously generate micelles and vesicles, come into play. In their lipid-world hypothesis, Daniel Segré *et al.* proposed, using theoretical and computational approaches, that micelle-like molecular assemblies, which split when they have reached a critical size, are capable of "compositional inheritance", propagating compositional information by a template-independent mechanism of replication to their descendents (*Proc. Natl. Acad. Sci. USA* 97: 4112-17 and *Orig. Life Evol. Biosph.* 31:119-45). Whether this form of inheritance is fit enough to qualify these so-called "compositional genomes" for Darwinian evolution and thereby back-up the metabolism-first theory, was now mathematically put to the test by Vasas *et al.*

And the answer is, non-covalent molecular assemblies, like the ones proposed by Segré, are most likely unable to undergo Darwinian evolution, thus giving the metabolism-first hypothesis a proper stab in the back! The authors' reason, "Computed population dynamics […a] clearly illustrates that compositional assemblies do not evolve. […] the number of possible types is smaller than the number of individuals and, hence, evolution does not discover novelties in an open-end manner," pointing to the already earlier suggested limited hereditary potential of these assemblies, which "could only have had the limited role of accumulating prebiotic material and increasing environmental patchiness".

Given this fundamental limitation, the RNA-first hypothesis is once again front-runner in the stakes to be the most likely scenario for the origin of life, despite the fact that there are still many remaining uncertainties. Thus Vasas *et al.* conclude, "We do not know how the transition to digitally encoded information has happened in the originally inanimate world; that is, we do not know where the RNA world might have come from, but there are strong reasons to believe that it had existed."

-KatGra-

Cellular senescence in Milan

Better than Death

We are all familiar with the foreboding tales of the Brothers Grimm. For example, *Schneewittchen* ("Snow White" in English) who, after several attempts on her life by her stepmother, fell into a state of deep sleep – as if dead – sufficient to appease her stepmother and fool her friends.

Death-like sleep and death are not limited to the pages of fairy tales but are also used by living organisms as fail safe mechanisms to prevent transformation of pre-malignant cells into tumour cells. Senescence, a cellular state akin to death-like sleep, is the focus of an elegant study in this month's edition of *Nature Cell Biology* (vol. 12: 54-9). A team of scientists from Italy, Sweden and Spain lead by Stefano Campaner and Bruno Amati from the European Institute of Oncology (IEO) in Milan have uncovered an unanticipated role for cyclin dependent kinase 2 (Cdk2) in suppressing c-Myc-induced senescence. c-Myc is an oncogene, genes we normally associate with tumorigenesis, proliferation and cell renewal. Interestingly, c-Myc can also induce tumour-suppressive responses such as senescence. With such conflicting roles, elucidating the signalling pathways leading to the varying cellular responses has been challenging.

How to prevent falling asleep

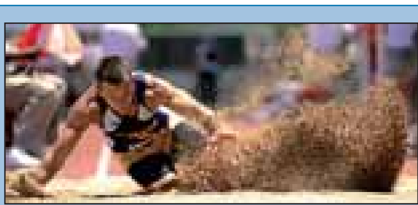
Overexpression of c-Myc was previously shown to promote cell cycle progression via Cdk2 activation but the signalling mechanism remained unknown. The original goal of this study was to understand Cdk2's role in c-Myc-induced proliferation using mouse embryonic fibroblasts (MEFs) from $Cdk2^{+/+}$ and $Cdk2^{-/-}$ mice. Initial experiments went without surprises – transient expression of c-Myc induced proliferation. Then came the unexpected – prolonged activation of c-Myc led to senescence of the MEFs from $Cdk2^{-/-}$ mice. Re-expressing Cdk2, as opposed to other Cdks, prevented senescence, suggesting that Cdk2 was specific in inhibiting c-

Myc-induced senescence. Further analysis of the pathways involved in c-Myc-induced senescence revealed that both the ARF-p53-p21 and p16-pRB pathways were important, as senescence was absent in Cdk2$^{-/-}$ cells lacking any of these proteins. Signals leading to senescence in the Cdk2$^{-/-}$ cells were also investigated and oxidative stress, as opposed to other forms of genotoxic stress, appears to be a major cause. In support of this observation, antioxidants inhibited c-Myc-induced senescence in the Cdk2$^{-/-}$ cells.

Therefore, would Cdk2 loss slow down tumour formation? When Cdk2 was decreased in mice overexpressing c-Myc in their B-cell lineage (normally resulting in lymphoma), elevated ß-gal staining, a senescence marker, was observed with a delay in the onset of lymphoma. Thus the therapeutic potential of Cdk2 inhibition was studied and confirmed because pharmacological inhibition of Cdk2, while concurrently increasing c-Myc levels, resulted in senescence in mouse fibroblasts and human cancer cell lines. Altogether, it appears that Cdk2 not only prevents c-Myc induction of senescence but its inhibition of c-Myc in overexpressing tumours may be worth pursuing as an anti-cancer therapeutic. -RosMar-

Transcriptional control in Uppsala

Just Jumped In



About 100 years ago, farmers began selecting less fatty pigs in order to provide consumers with leaner, healthier meat. At the Department of Medical Biochemistry and Microbiology of Uppsala University, Leif Andersson and colleagues began studying the underlying genetic changes responsible for transforming the wild boar to the leaner domesticated pig, as a means to better understand complex traits and disorders.

In 2003, Andersson's group identified a single nucleotide substitution (G to A) in intron 3 of the insulin-like growth factor 2 (IGF2) of the domesticated pig, resulting in increased expression of *IGF2* in skeletal muscle and elevated skeletal muscle mass (*Nature* 425, 832-36). The data suggested that the mutation prevented binding of a nuclear protein, which represses *IGF2* transcription but the identity of the repressor was unknown – until now.

ZBED6, a previously unknown protein, has been identified as the repressor of IGF2 in a collaborative study, which involves research groups from Sweden, including Andersson's, together with scientists at the Broad Institute in Massachusetts, USA (Markljung *et al.*, *PLoS Biol.* 7(12): e1000256). *ZBED6*, a conserved gene detectable in all placental animals, is an example of a domesticated transposon, i.e. a so-called "jumping gene", which has lost its ability to jump since it inserted itself into the genome of placental animals over 150 million years ago.

In mouse, *Zbed6* RNA was detected in several tissues, with highest levels in muscle and brain. Further analysis using C2C12 cells – a progenitor cell line isolated from mouse, which develops into skeletal muscle cells – localised ZBED6 to the nucleolus, suggesting a role in cellular proliferation and growth.

Six days after decreasing ZBED6 through RNA interference, a significant increase in *Igf2* mRNA levels were observed, consistent with elevated *Igf2* levels in pig skeletal muscle carrying a mutation in the ZBED6 target site. Further observations in the knockdown cells were increased cell proliferation, myotube formation and wound healing after scratching the surface of cells.

Interestingly, these events occurred three days after knockdown, suggesting that they were mediated by other genes targeted by ZBED6. A search for these "other" genes using ChIP-sequencing experiments revealed something amazing – ZBED6 function is not limited to regulating IGF2 but actually appears to regulate thousands of other genes involved in various functions such as development, transcription, differentiation, cell signalling and muscle development. Many of these identified target genes are involved in basal cellular function but several are also associated with a number of diseases, in particular developmental disorders.

Therefore, a story that began with understanding muscle development in the pig, has led to the discovery of a master puppeteer with the potential ability to regulate countless important cellular pathways. -RosMar-