AGEING

Old at heart

Telomere shortening occurs with age and could contribute to some of the pathologies of ageing. The groups of Maria Blasco and Piero Anversa have joined efforts to study the consequences of telomere dysfunction on the cardiac phenotype, as heart failure is a frequent cause of death in the elderly, and their findings are described in *The EMBO Journal*.

Blasco and co-workers studied telomerase RNA knockout (*Terc*$^{-/-}$) mice that lack telomerase activity at the second (G2) and fifth (G5) generation. Quantitative fluorescence *in situ* hybridization (Q-FISH) analysis confirmed that cardiac myocytes in G5 *Terc*$^{-/-}$ mice had significantly shorter telomeres than those from G2 *Terc*$^{-/-}$ mice, which, in turn, were shorter than in wild-type mice.

The tumour suppressor p53 — which modulates apoptosis and growth arrest — has been correlated with telomere dysfunction. Indeed, increased p53 expression was seen most clearly in myocyte nuclei from G5 *Terc*$^{-/-}$ mice, which had the shortest telomeres.

On examining heart function, Blasco and colleagues found that G5 *Terc*$^{-/-}$ mice had severe left ventricular (LV) failure, whereas LV function in G2 *Terc*$^{-/-}$ mice was normal. This led the authors to conclude that the cardiac phenotype in G5 *Terc*$^{-/-}$ mice is due to a critical shortening of telomeres rather than telomerase deficiency.

Next, the authors examined cardiac anatomy. Heart and LV weights were significantly decreased in G5 *Terc*$^{-/-}$ mice compared with wild-type and G2 *Terc*$^{-/-}$ mice. These findings corresponded to a significant increase in the volume (hypertrophy), and a significant decrease in the number, of myocytes in G5 *Terc*$^{-/-}$ mice versus wild-type and G2 *Terc*$^{-/-}$ mice. G2 *Terc*$^{-/-}$ hearts were also abnormal, but the changes were less pronounced than in G5 *Terc*$^{-/-}$ hearts.

But which mechanisms are responsible for hypertrophy and cell loss — increased cell death and/or impaired proliferation? Blasco and colleagues found that cell growth was impaired in G2 and G5 *Terc*$^{-/-}$ myocytes, and that the reduction was twofold higher in G5 than in G2 *Terc*$^{-/-}$ mice. In addition, cardiomyocyte death by apoptosis was 63% and 39% greater in G5 than in wild-type and G2 *Terc*$^{-/-}$ hearts, respectively.

So, the authors concluded that telomere shortening might be an important causal factor of heart failure in the elderly, and that telomerase-based therapies should be considered.

Arianne Heinrichs

References and links

ORIGINAL RESEARCH PAPER Leri, A. *et al.* Ablation of telomerase and telomere loss leads to cardiac dilation and heart failure associated with p53 upregulation. *EMBO J.* **22**, 131–139 (2003)

FURTHER READING Blasco, M. Telomerase beyond telomeres. *Nature Rev. Cancer* **2**, 627–632 (2002)

TRANSCRIPTION

Hitch a ride

The transcriptional activator CREM is essential for spermatogenesis, as it regulates the activity of several post-meiotic genes. ACT binds to CREM and functions as its transcriptional coactivator. While investigating the CREM–ACT activation mechanism, Paolo Sassone-Corsi and colleagues found an unexpected player — KIF17b, a testis-specific member of the kinesin family of microtubular motor proteins — as they now report in *Science*.

Using full-length ACT as bait, Sassone-Corsi and co-workers identified KIF17b — an isoform of the brain-specific kinesin KIF17 — in a yeast two-hybrid assay. They showed that KIF17b is highly, and exclusively, expressed in testis, and that KIF17b and ACT are co-expressed during testis development. The KIF17b–ACT interaction was strong *in vitro*, and also *in vivo*, as the proteins present in mouse testis extract co-immunoprecipitated.

Knowing that ACT and most kinesins are localized in the nucleus and cytoplasm, respectively, Sassone-Corsi and co-workers examined the intracellular localization of both proteins at different stages of spermatid development. Although ACT is indeed nuclear, it becomes more cytoplasmic at a specific point during spermatid maturation, which coincides with ACT depletion from the nucleus. The same dual localization pattern was observed for KIF17b at this stage. In COS and NIH3T3 cells transfected with KIF17b and ACT constructs, there was total colocalization of the co-expressed proteins. In most cells, the proteins were cytoplasmic, and in others, they were nuclear and cytoplasmic. These data implied that KIF17b might have a nuclear export activity that regulates the intracellular localization of ACT.

So, does KIF17b have a role in nuclear shuttling? To address this question, KIF17- and ACT-transfected cells were treated with leptomycin B (LMB), which disables the nuclear export receptor Crm1. In treated cells, KIF17b was sequestered in the nucleus, indicating that KIF17b can be actively transported from the nucleus to the cytoplasm through the Crm1 receptor.

Next, Sassone-Corsi and colleagues assayed two CREM-dependent promoter–reporter constructs for transcriptional activity in the presence of ACT and different doses of KIF17b. As KIF17b is responsible for ACT depletion from the nucleus, it did not come as a surprise that transcriptional activation was inhibited in the presence of excess KIF17b. ACT-dependent transcriptional activation could subsequently be recovered by sequestering ACT–KIF17b in the nucleus using LMB treatment.

Together, these data provide the first evidence for a direct functional connection between a microtubular transporter protein and transcriptional regulation.

Arianne Heinrichs

References and links

ORIGINAL RESEARCH PAPER Macho, B. *et al.* CREM-dependent transcription in male germ cells controlled by a kinesin. *Science* **298**, 2388–2390 (2002)