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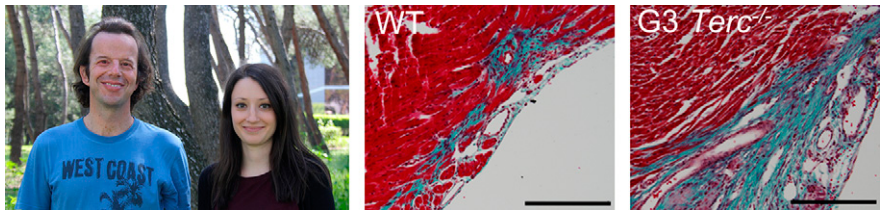
Telomeres come up short in heart regeneration

Cardiomyocyte telomeres erode after birth, inducing a cell-cycle arrest that limits the heart's capacity for regeneration.

FOCAL POINT



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Cardiomyocytes from neonatal mice are able to proliferate and replace damaged heart tissue, but they lose this regenerative capacity a week after birth. Ignacio Flores (left), Esther Aix (right), and colleagues reveal that this is partially due to a rapid shortening of cardiomyocyte telomeres that causes cell cycle arrest and binucleation. Telomerase-deficient mice undergo premature telomere shortening, and are therefore unable to regenerate damaged heart tissue even at one-day old, resulting in larger fibrotic regions (blue) 28 days after injury. The proliferative and regenerative capacity of these cardiomyocytes is restored by knocking out *p21*, a cell cycle inhibitor that is activated by telomere shortening.

During embryogenesis, and for about a week after birth, mouse cardiomyocytes can proliferate and replace damaged heart tissue, but this regenerative capacity is lost as the mice grow older (1, 2). Newborn humans, too, can repair injured myocardium (3), but, in adults, heart attacks cause permanent damage, often leading to heart failure and death. Aix et al. reveal that mouse cardiomyocytes lose their proliferative and regenerative capacity due to a dramatic shortening of their telomeres in the first week after birth (4).

Most mouse cardiomyocytes withdraw from the cell cycle and become binucleated in the first week after birth (5, 6). "We wanted to understand the mechanism behind this process," explains Ignacio Flores, from the Spanish National Center for Cardiovascular Research in Madrid. "Why do cardiomyocytes arrest their cell cycle, and what drives their binucleation?"

Flores and colleagues wondered whether the mechanism might involve telomeres, repetitive DNA sequences that protect the ends of chromosomes. If telomeres grow too short—due, for example, to a loss of the telomere-extending telomerase enzyme—cells can mistake chromosome ends for DNA double strand breaks, leading to checkpoint activation and cell cycle arrest. Moreover, chromosomes without telomeres can fuse to form anaphase bridges that may interfere with cytokinesis and cause binucleation.

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Flores and colleagues previously found that telomerase is essential for heart regeneration in zebrafish (7), but these animals, unlike mammals, retain their regenerative capacity into adulthood. Postdoc Esther Aix therefore examined the length of telomeres in newborn mouse cardiomyocytes (4). "And we found that the telomeres rapidly erode in the first week after birth," says Flores. This erosion coincided with a decrease in telomerase expression and was accompanied by the activation of the DNA damage response and an increase in anaphase bridge formation.

To investigate whether telomere erosion was the cause of cardiomyocyte binucleation and arrest, the researchers examined telomerase-deficient mice. These animals already had short telomeres on the first day after birth and, accordingly, many of their cardiomyocytes already showed DNA damage markers and anaphase bridges. Moreover, compared with one-day-old wild-type mice, the number of proliferative cardiomyocytes was reduced, whereas the number of binucleated cardiomyocytes was increased. "So telomere shortening contributes to binucleation," Flores says.

When Aix et al. injured the hearts of one-day-old mice, wild-type cardiomyocytes were able to proliferate and replace the damaged tissue. In contrast, telomerase-deficient cardiomyocytes failed to proliferate or regenerate the injured myocardium.

But how might shorter telomeres cause cardiomyocytes to withdraw from the cell cycle? Activation of the DNA damage response can induce expression of the cell cycle inhibitor p21, and Aix et al. found that *p21* expression was up-regulated in wild-type hearts in the week after birth, when most cardiomyocytes are losing their telomeres and exiting the cell cycle. Knocking out *p21* extended the regenerative capacity of these cells, allowing one-week-old *p21*-null mice to repair damaged cardiac tissue much more effectively than week-old wild-type animals.

Knocking out *p21* also restored the proliferation and regenerative capacity of telomerase-deficient cardiomyocytes, indicating that the postnatal erosion of telomeres induces cardiomyocyte arrest by activating p21. Maintaining the length of cardiomyocyte telomeres might therefore boost the regenerative capacity of adult cells, improving the recovery of cardiac tissue following a heart attack. "We are now developing telomerase-overexpression mouse models to see if we can extend the regenerative window," Flores says.

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