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DNA damage response links short telomeres, heart disorder in Duchenne muscular dystrophy

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Progressively shortening telomeres—the protective caps on the end of chromosomes—may be responsible for the weakened, enlarged hearts that kill many sufferers of Duchenne muscular dystrophy, according to a study by researchers at the Stanford University School of Medicine.

The researchers found that the shortening occurred specifically in the heart muscle cells, or cardiomyocytes, of laboratory mice bred to model the disease. The shortening triggered a DNA damage response that compromised the function of the cells' energy generators, or mitochondria. As a result, the cardiomyocytes were unable to efficiently pump blood throughout the body.

The new study is an extension of a 2010 study published in *Cell* and a 2013 study published in *Nature Cell Biology* by the same researchers. It identifies possible new therapeutic approaches for Duchenne muscular dystrophy and is the first to connect the molecular dots between previously disparate observations in affected cells.

"This is the first time that telomere shortening has been directly linked to mitochondrial function via a DNA damage response in non-dividing cells," said Helen Blau, PhD, professor of microbiology and immunology. "We've outlined the molecular steps in this process that lead to death, giving novel insights into the condition and identifying alternative strategies for heading off heart failure in human patients with

Duchenne."

The researchers used a mouse model of the disease they developed for the 2013 study that is the first to accurately recapitulate Duchenne muscular dystrophy in humans.

The ongoing shortening of the telomeres in cardiomyocytes is particularly surprising because the cells rarely divide. Telomeres naturally decrease in length with each cell division, acting as a kind of molecular clock counting down a cell's life span. Their length is normally stable in healthy tissues that don't divide.

"In mice, cell division in the heart normally stops within one week of birth," said Blau, who is also the Donald E. and Delia B. Baxter Foundation Professor and director of the Baxter Foundation Laboratory for Stem Cell Biology. "But we saw a proliferation-independent reduction in telomere length."

Blau is the senior author of the study, which will be published online Oct. 31 in the *Proceedings of the National Academie of Sciences*. Postdoctoral scholar Alex Chang, PhD, is the lead author.

Difficult condition to study

Duchenne muscular dystrophy is the most prevalent form of the heritable muscular dystrophies. It is caused by mutations in the dystrophin gene that inhibit the production of the dystrophin protein, which connects the interior cytoskeleton of the muscle cell to the outside matrix. But until recently, it's been difficult to study because mice with the same dystrophin mutation didn't display the same symptoms as humans.

In the 2013 study, researchers in the Blau lab found that the reason

humans suffer more serious symptoms than do mice is because of differences in the average lengths of their telomeres: Mice have telomeres about 40 kilobases in length, while human telomeres range from around 5 to 15 kilobases. When the investigators introduced a second mutation in the mice that reduced telomere length to more closely match that of humans, the "humanized" animals began to display the typical symptoms of the disease, including progressive muscle weakness, enlarged hearts and significantly shortened life spans.

In particular, the researchers also observed that cardiomyocyte telomeres were significantly shorter than those in other muscle cells in the heart, such as the smooth muscle cells of the vasculature that do not require dystrophin for function. This was true not only in mice with mutated dystrophin, but also in four people with Duchenne muscular dystrophy who had recently died of cardiomyopathy. This was surprising because, although telomeres naturally shorten a bit with each round of cell division, their length is known to remain stable in non-dividing cells like cardiomyocytes.

"We knew from our previous study that telomeres play a role in the development of cardiomyopathy in Duchenne muscular dystrophy, but we didn't know the kinetics," said Chang. "Does this shortening occur suddenly, or gradually? Could it be possible to intervene? How exactly does it affect heart function?"

Telomere shortening in the absence of cell division

Chang investigated telomere length in the cardiomyocytes of mice lacking the dystrophin protein at one, four, eight and 32 weeks after birth. He found that, although the cells stopped dividing within one week, the telomeres continued to shorten, losing nearly 40 percent of their length by 32 weeks.

A closer investigation of the affected mouse cardiomyocytes indicated that telomere shortening correlated with increasing levels of a protein called p53 that is known to be elevated in the presence of DNA damage. P53 in turn inhibits the expression of two proteins necessary for mitochondrial replication and function.

"The decrease in the levels of these mitochondrial master regulators led to a reduction in the number of mitochondria in the cell and mitochondrial dysfunction," said Blau. "They make less of the energy molecule ATP and have higher levels of damaging reactive oxygen species. This is what leads to the cardiomyopathy that eventually kills the mice."

Treating 4-week-old mice with a mitochondrial-specific antioxidant limited subsequent mitochondrial damage, the researchers found.

Chang and Blau are interested in learning exactly how the absence of functional dystrophin contributes to telomere shortening in cardiomyocytes. They are also planning to investigate whether artificially lengthening the telomeres could head off heart damage in the mice.

"More research is clearly needed before we attempt to devise any new therapies for humans," said Blau. "But these findings highlight the important role telomeres play in this and possibly many other human diseases in nondividing tissues like neurons and heart muscle."

More information: Telomere shortening and metabolic compromise underlie dystrophic cardiomyopathy, *PNAS*, www.pnas.org/cgi/doi/10.1073/pnas.1615340113

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