The merits of cellular stress during muscle development

Animals, including humans, and cells sometimes perform altruistic acts of suicide that benefit the group. Nowhere is this better illustrated than in apoptosis, or programmed cell death, when cells forsake themselves so that others may live. While the details to what happens inside apoptotic cells have been revealed by intensive studies over the last decade or so, the triggers of apoptosis in the body, especially under normal conditions, remain largely unknown. RIKEN's researchers are chipping away at those secrets. Along the way, they have discovered an upside to typically harmful stress, specifically to a type of a cellular trouble known as endoplasmic reticulum (ER) stress.

In cells, a delicate balance of activities regulates activation and inactivation, synthesis and decomposition, and death and differentiation. Various physical and chemical signals trigger changes that produce, fold, transfer, or break down proteins to sustain or destroy a cell. When proteins are not properly folded, and therefore either inactive or onerous, they need to be repaired. If repairs are not possible, they are usually broken down and recycled. Scientists believe that an important part of such quality control is done in the ER, where the state of newly synthesized proteins is monitored.

ER stress results when that quality control system cannot keep up with the rate of garbage accumulation. Extensive and unmanageable ER stress indicates a cell's weakness and causes it to be marked for death. This mark activates enzymes, caspase proteins, that participate in various signaling cascades that engineer the cell's death. This is apoptosis.

One of the primary reasons for the enthusiasm in apoptosis research is that a lack of or excessive cell death can be detrimental to an organism's health and either can lead to serious illness. However, apoptosis can also be triggered in healthy cells, especially during development. In studying these events, researchers have learned that caspase
activity is selective for various stages of development, including cell differentiation. Yet how these cascades are triggered or how selectivity is regulated remains largely unknown. Therefore apoptosis or caspase activation may seem to occur spontaneously.

Suspecting caspase-12 participation in muscle tissue cell death, Dr. Nobuhiro Morishima and his team of researchers at RIKEN Discovery Research Institute made two surprising findings. After confirming caspase-12's role in cell death during muscle differentiation, Dr. Keiko Nakanishi carefully examined the states of various proteins. She found caspase-12 activation in the differentiating muscle tissue of mouse embryos. More unexpectedly, caspase-12 activation in these tissues was nearly universal and it caused only 20% of the cells to die. They suspect that apoptosis can be cancelled if caspase-12 activation does not cross a threshold value.

Caspase-12 is the first actor in the ER stress-specific cascade, and its activation is almost synonymous with the onset of ER stress. In fact, the team detected ER stress by monitoring activity in the ER quality control system. But how did stress turn on caspase-12? Morishima's researchers searched for connection between the ER phenomenon and caspase-12 activation. They focused on three ER stress sensors that activate during ER stress and observed their responses to stress during muscle differentiation. Only transcription factor, ATF6, showed specific participation in the process. Furthermore, apoptosis and muscle differentiation were successfully suppressed in muscle progenitor cells treated with a specific inhibitor of the ATF6 activation enzyme. The researchers showed that ER stress and the associated signaling cascades are important for muscle differentiation and inducing apoptosis. The research team believes that the management of cellular stress could be important not only for maintaining health but also to improve it.

This positive role for ER stress complicates our known life story of cells. It will also tease out assumptions about dual roles for other cell processes with assigned functions and roles.

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