Intracellular recycling: The key to surviving potent anti-cancer drugs

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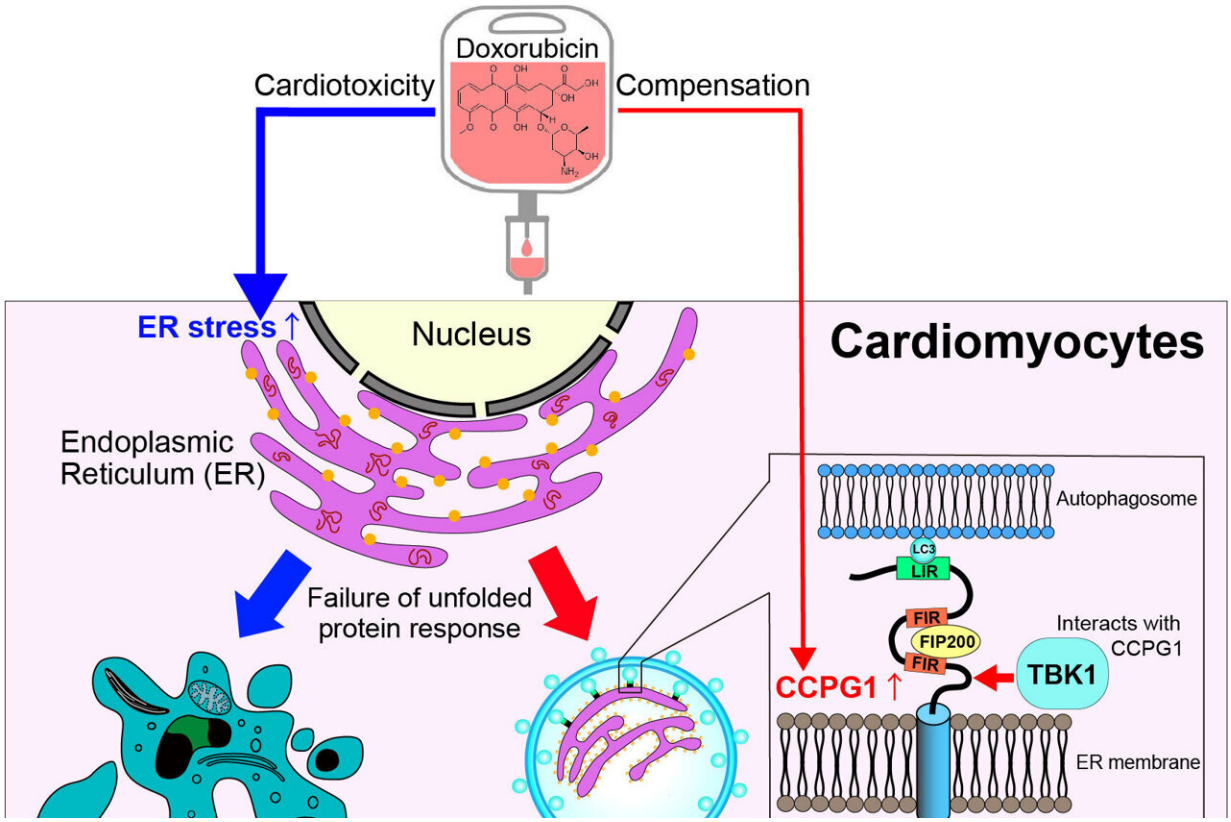

ER-phagy alleviates anthracycline cardiotoxicity. Credit: Department of Cardiovascular Medicine, TMDU

A cell contains many specialized subunits, called organelles, that carry out important tasks such as energy generation, protein synthesis, and

calcium outflux. But what happens when something goes wrong with one of the organelles?

In a study recently published in the *JACC: CardioOncology*, researchers from Tokyo Medical and Dental University have discovered how an organelle 'eats itself' for the good of the entire cell when damaged by chemotherapy drugs.

This act of targeted degradation is called autophagy and serves to remove defective cellular components. Autophagy is triggered by cellular stress and damage from harmful molecules; emergency signals then trigger the regeneration of structural units, maintaining balance and function in the human body.

One potential source of such damage is anti-cancer drugs, such as anthracyclines. These drugs are prescribed for various types of cancer but are associated with an increased risk of serious cardiotoxicity. Doxorubicin (Dox), an anthracycline drug, can induce oxidative stress in a cells' endoplasmic reticulum (ER), an essential organelle that, among other things, controls protein synthesis and calcium outflux in cardiomyocytes.

Severe ER impairment in cardiomyocytes can eventually lead to cardiac dysfunction. The ER is the organelle that the researchers observed carrying out autophagy during drug-induced stress.

"Endoplasmic reticulum-selective autophagy (ER-phagy) could be a useful protective mechanism against drug-induced cardiotoxicity," explains first author Shun Nakagama. "However, there is a lack of research showing the presence of ER-phagy in cardiomyocytes. We therefore aimed to determine whether ER-phagy is helping to protect the heart from drug-induced ER stress."

The researchers developed a novel ER-phagy monitoring system in cardiomyocytes to visualize the activation of ER-phagy and identify protein regulators that control selective autophagy in the presence of Dox-induced ER stress. Additionally, a mouse model was used to determine an accurate representation of the cardioprotective role of ER-phagy in mammals.

"Our results showed that ER-phagy indeed alleviates Dox-induced cardiomyopathy," says corresponding author Yasuhiro Maejima. "We determined that Dox-induced ER-phagy was activated by the interplay between two protein regulators: cell-cycle progression gene 1 and TANK binding kinase 1. ER stress, caused by Dox, was exacerbated without this protein interaction, which then decreased cell survival."

As anthracycline-induced cardiotoxicity is common and serious in cancer patients, further research can elucidate the potential therapeutic efficacy of autophagy-promoting drugs to alleviate Dox-associated heart disease.

More information: Shun Nakagama et al, Endoplasmic Reticulum Selective Autophagy Alleviates Anthracycline-Induced Cardiotoxicity, *JACC: CardioOncology* (2023). DOI: 10.1016/j.jaccao.2023.05.009

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