Doxorubicin-associated mitochondrial iron accumulation promotes cardiotoxicity

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Doxorubicin is a widely used as a component of chemotherapy regimes; however, the use of doxorubicin is associated with severe cardiotoxicity. It is unclear exactly how doxorubicin promotes cardiotoxicity, but it has been proposed that doxorubicin-associated cardiomyopathy develops as the result of reactive oxygen species (ROS) production and iron accumulation.

In this issue of the *Journal of Clinical Investigation*, Hossein Ardehali and colleagues at Northwestern University determined that doxorubicin accumulates within the mitochondria of cardiomyocytes and this accumulation promotes mitochondrial ROS production and iron accumulation.

In a mouse model of doxorubicin-associated cardiotoxicity, overexpression of a protein that enhances mitochondrial iron transport reduced mitochondrial iron, ROS, and protected animals from doxorubicin-induced cardiomyopathy. Treatment of animals with dexrazoxane, which attenuates doxorubicin-induced cardiotoxicity, decreased mitochondrial iron levels and reversed doxorubicin-induced cardiac damage. Furthermore, heart samples from patients undergoing doxorubicin therapy revealed higher levels of mitochondrial iron in patients with cardiomyopathies compared to patients without cardiac complications.

These data suggest that therapies that limit mitochondrial iron accumulation have potential to limit doxorubicin-associated

cardiotoxicity.

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