Role of Mitochondrial Connexin 43 In Doxorubicin-Induced Cardiotoxicity

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Doxorubicin (DOXO), is widely used in cancer treatment, but its clinical utility has been hampered by a feared effect, the cardiotoxicity that is dose and time-dependent. The mechanisms for its cardiotoxicity may be multifactorial, including the generation of reactive oxygen species (ROS), disruption of calcium homeostasis within the mitochondrion, mitochondrial dysfunction and induction of cardiomyocyte apoptosis. Connexin 43 (Cx43) is a predominant junctional protein in the intercellular communication channel that critically regulates ions and small molecules translocation and it is responsible for electrical communication between cardiomyocytes. Cx43 plays a pivotal role in cardioprotection and studies have demonstrated the role of mitochondrial Cx43 (mCx43) in controlling apoptosis initiation. Accordingly, mCx43 prevents the cytochrome c release into the cytosol, reducing cytosolic and mitochondrial ROS production and mitochondrial calcium overload induced by DOXO administration.

In this study we evaluated how the DOXO-induced cardiotoxicity is associated with variation in the expression and/or localization of Cx43. DOXO (0.25, 0.5 or 1 µM) has been administrated on rat heart cell line, H9c2, and observed after 3h and 6h. Our results show that DOXO induces an increase in mitochondrial Cx43 content, encouraging the translocation of the protein to the mitochondria, with a mechanism that involves Hsp90 and TOM20.

We demonstrate that mCx43 hinders the accumulation of calcium into the mitochondria and delayed the time taken for depolarization. In conclusion, our data indicate that mCx43 could provide cytoprotection against DOXO-induced cardiotoxicity as observed in ischemia-reperfusion induced injury.