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## Phenotypic profiling of structural cardiotoxins in vitro reveals dependency on multiple mechanisms of toxicity.

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Morphological damage to cardiomyocytes or loss of viability (structural cardiotoxicity) is a common cause of attrition in preclinical and clinical drug development. Currently, no predictive in vitro approaches are available to detect this liability early in drug discovery, and knowledge of the mechanisms involved is limited. Human embryonic stem cell-derived cardiomyocytes (hESC-CMs) and the rat myoblastic H9c2 cell lines were used to phenotypically profile a panel of structural cardiotoxins by live-cell fluorescent imaging of mitochondrial membrane potential, endoplasmic reticulum integrity, Ca(2+) mobilization, and membrane permeability combined with an assessment of cell viability (ATP depletion). Assay results were normalized to known therapeutically relevant concentrations. By comparing the outcome of each assay to the known in vivo effects, hESC-CMs offered an improved model over H9c2 cells for the detection of structural cardiotoxicity at therapeutically relevant concentrations. Inhibition of the spontaneously beating phenotype, a feature of stem cell-derived cardiomyocytes, revealed some degree of cardioprotection following 10 out of 13 structural cardiotoxins, illustrating the intricate relationship between the function and structure of cardiomyocytes. Classification of structural cardiotoxins into mechanistic themes revealed mitochondria and calcium mobilization to be major distal targets, with only 4 out of 15 compounds affecting contractile function in freshly isolated canine cardiomyocytes at therapeutically relevant concentrations. Our data demonstrate the utility of hESC-CMs during drug development to support structural cardiotoxicity hazard identification and to gain insight into the intricate mechanisms implicated in structural cardiotoxicity.

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