

In Vitro Evaluation of Anthracycline-induced Cardiotoxicity and Mitigation by Perturbation of Angiotensin Signalling

Cardiotoxicity is a major complication of many anticancer therapies which impacts quality of life and survival of patients. The anthracycline class of anticancer therapies can induce cardiotoxicity acutely, however more frequently it arises as a debilitating chronic toxicity that occurs months or years after completion of treatment. There is an urgent need for improved in vitro models to accurately predict and model these cardiac liabilities, and to drive our understanding of the molecular mechanisms responsible for these toxicities. Recently, clinical studies have demonstrated that drugs which perturb angiotensin signalling may reduce the cardiotoxicity of anthracyclines. However, despite showing promise, the mechanism of toxicity and the molecular relationship to angiotensin signalling in the heart is unresolved. Furthermore, the majority of in vitro cardiotoxicity studies to date have either used inappropriate cell models or utilised end-point assays; strategies that fail to account for the physiological parameters of cardiac cells and the progressive nature of human toxicity development. This study has qualified the use of hiPSC-derived cardiomyocytes and the human AC10 cardiomyocyte cell line paired with impedance-based systems (xCELLigence technology) for detection of both structural and functional cardiotoxicity. A range of pharmacological and biological mediators were used to qualify these technologies, with both structural hypertrophy and physiological contractility monitorable. Using these models and technologies, this study demonstrates induction of cardiomyocyte hypertrophy by anthracyclines which is reduced by blockade of angiotensin signalling, thus implying a relationship at the cardiomyocyte level between anthracycline-induced cardiotoxicity and angiotensin signalling. Beat characteristics of hiPSC-derived cardiomyocytes have also been assessed during exposure to anthracyclines alone and during angiotensin blockade to elucidate the effects of cardiomyocyte hypertrophy on contractility. A major advantage of these systems is that longer-term real-time non-invasive experiments can be conducted, thus allowing recapitulation of the progressive nature of human toxicity development and subsequently a robust clinically relevant method for assessing drug-induced cardiotoxicity. Further studies uncovered anthracycline-induced elevated expression of the angiotensin type I receptor and several genes implicated in angiotensin II signalling. This provides further evidence for a direct molecular relationship between anthracycline-induced cardiotoxicity and angiotensin signalling, with clear translational potential for clinical mitigation of this dose-limiting toxicity in the treatment of cancer.