Characterisation of novel molecular mechanisms involved in anthracycline-induced cardiotoxicity

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Cardiotoxicity is a major complication of many anticancer therapies, often impacting the quality of life and overall survival of patients. Consequently, greater understanding of the molecular mechanisms responsible for these adverse effects and identification of therapeutic strategies to mitigate the underpinning toxicities are of the utmost importance. Recent clinical studies have demonstrated that medicines acting upon the angiotensin signalling pathway may reduce anthracycline-induced cardiotoxicity and improve clinical outcomes. However, despite showing promise, the molecular mechanisms and pathways responsible for angiotensin-mediated mitigation of anthracycline toxicity are currently unclear.

STUDY AIMS

- The aim of this study was to investigate the molecular mechanisms of anthracycline-induced cardiotoxicity and identify the role of angiotensin II.
- Using in vitro real-time impedance-based cell analyses (xCELLigence system) changes in cell survival, morphology and drug response were evaluated against a human adult ventricular cardiomyocyte cell line (AC10).
- Human iPSC-derived cardiomyocytes (Cor.4U - axiogenesis) were also evaluated for changes in contractility, morphology and drug response using the CARDIO xCELLigence system.
- The response of these cardiomyocytes to angiotensin II, doxorubicin (anthracycline), and blockade of the angiotensin II receptor were investigated.

RESULTS

- Angiotensin II induces hypertrophy of AC10 cardiomyocytes
- Telmisartan reduces doxorubicin-induced IPSC-derived cardiomyocyte hypertrophy and does not affect contractility
- Telmisartan reduces cardiotoxicity of doxorubicin in AC10 cardiomyocytes at both low and high concentrations relative to doxorubicin alone (n=3xSE) *p<0.05

CONCLUSION

- Angiotensin II and doxorubicin induce cardiomyocyte hypertrophy in AC10 and iPSC-derived cardiomyocytes.
- Blockade of the angiotensin receptor by telmisartan mitigates the hypertrophic and cardiotoxic effects of doxorubicin, but does not affect anti-cancer efficacy.
- Reduction of doxorubicin-induced cardiomyocyte hypertrophy by blockade of the angiotensin pathway strongly implies a relationship between doxorubicin-mediated toxicity and angiotensin II activity.
- These data support blockade of angiotensin signalling as a therapeutic strategy for managing anthracycline-induced cardiotoxicity.

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