Contribution of *in vitro* 1H-NMR metabonomics for studying doxorubicin-induced cardiotoxicity and protective effects of dexrazoxane

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Currently, doxorubicin (DOX) treatment in oncology is limited by its irreversible cardiotoxicity. The main known toxicological mechanism is the induced oxidative stress, leading to cardiomyocytes death. Nowadays, the main strategy to deal with this cardiotoxicity is the co-administration of dexrazoxane (DEX), an antioxidant. However, this strategy shows limited efficacy and there is a need for new cardioprotective tools. The goal of this research is to study DOX-induced metabolic alterations and the protective role of DEX in order to highlight possible new targets to counteract DOX cardiotoxicity.

Rat cardiomyoblasts H9C2 were cultured in DMEM according to ECACC guidelines. For metabonomic investigations, cells were randomly assigned into 4 groups for 24h of exposure : a control group, a 0,3 µM DOX-exposed group, a 3 µM DEX-exposed group and a group pre-incubated with 3 µM of DEX during 30 min before 0,3 µM DOX exposure. Acquired ^{1}H-NMR spectra were baseline and phase-corrected, TSP-calibred and subdivised into normalized integrated sub-regions of 0,04 ppm wide. Multivariate data analysis were performed on data and discriminant metabolites were identified using several databasis.

The metabonomic study highlighted some metabolic alterations due to DOX exposure : a switch from mitochondrial aerobic energy metabolism to cytosolic anaerobic metabolism, a cell response to oxidative stress by an increased intracellular taurine level, modification of amino acids metabolism. The metabonomic study also highlighted metabolic effects of DEX pre-incubation : recovery of mitochondrial aerobic metabolism, activation of choline metabolism for biological membranes synthesis, activation of creatine phosphorylation and an increased secretion of succinate. Interestingly, choline metabolism activation may be linked to cell survival and growth pathways and could be a potential target for improving cardioprotection during DOX exposure and is therefore attractive for further investigations.