Currently, doxorubicin anti-cancer treatment is limited by its irreversible cardiotoxicity which depends on cumulated dose and can range from subclinical myopathy to patient’s death (1,2). The main toxicological mechanism is the production of reactive oxygen species (ROS), leading to an oxidative stress causing apoptosis or necrosis in cardiomyocytes, clinically expressed by a progressive heart failure (3). Nowadays, the main strategy to deal with this cardiotoxicity is the co-administration of dexrazoxane, a cardioprotective agent reducing ROS production through iron chelation. However, this strategy shows limited efficacy and there is a need for new cardioprotective strategies (2). The goal of this research is to studying doxorubicin-induced metabolic alterations and the protective role of dexrazoxane. This strategy should help in highlighting possible new targets to counteract doxorubicin cardiotoxicity.

1. Cellular viability assessment

H9C2 cells viability was measured 24, 48 and 72 hours after a single exposure to doxorubicin (0.3 μM), dexrazoxane (3 μM) and dexrazoxane + doxorubicin, by crystal violet assay. Results highlighted that dexrazoxane is able to protect partially against doxorubicin-induced cell death.

2. Metabolic study design

3. Metabolic effects of doxorubicin

Results of the metabonomic study suggest an oxidative stress-induced impairment of the Krebs cycle, resulting in a metabolic switch to anaerobic conditions with glycolysis as main ATP production pathway. Pyruvate is metabolized mainly into lactate and amino acids. A decrease of proteins synthesis and an increase of antioxidant defenses are suggested too.

Multivariate data analysis

Identification of corresponding metabolites

3. H9C2 cells were seeded in 175 cm² flasks and kept growing during 48 hours. Cells were randomly separated into 4 groups : control cells, cells exposed to 0.3 μM doxorubicin, cells exposed to 3 μM dexrazoxane and cells exposed to dexrazoxane 30 min before doxorubicin exposure. A 1H-NMR based metabonomic study was carried out on both intracellular and extracellular compartments.

4. Metabolic effects of pre-incubation with dexrazoxane

Dexrazoxane reduces the doxorubicin-induced oxidative stress, leading to a recovery of mitochondrial metabolism with a decrease of lactate production and an increase of proteins synthesis. Choline metabolism is highly stimulated for membranes synthesis and an important secretion of succinate is noticed.

References