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Cardiac mitochondrial dynamics, autophagy and regeneration are stirred by doxorubicin in old CD-1 mice

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Abstract

Background: The chemotherapeutic agent doxorubicin (DOX) has been widely used in the treatment of solid tumors and hematological malignancies [1]. However, serious adverse side effects have emerged in patients treated with this drug, notably cardiotoxicity [2]. Moreover, aging is a risk factor for the development of cardiovascular diseases in cancer treated patients [3]. **Objective:** We herein aimed to evaluate the molecular effects of DOX on the cardiac muscle of old CD-1 mice. **Methods:** Old CD-1 male mice (19 months) were administered with a pharmacologically relevant cumulative dose of 9 mg/kg DOX (DOX group) or saline (CTRL group), distributed intraperitoneally for three weeks (biweekly). The experiments were performed with the approval of the national competent authorities (DGAV, reference nº 0421/000/000/2016). Animal welfare was monitored daily. Two months after the last drug or saline administration, mice were sacrificed for collection of blood and heart. **Results:** Serum glucose concentration was decreased after DOX administration, but no other differences were seen in serum markers evaluated. Regarding the heart, DOX increased the activity of citrate synthase (CS), suggesting increased mitochondrial density. Moreover, the content of peroxisome proliferator-activated receptor γ coactivator 1 α (PGC-1α) was decreased after DOX, pointing to decreased mitochondrial biogenesis. In parallel, the content of Beclin1 and microtubule-associated protein light chain 3 (LC3B) was decreased in DOX group, highlighting lower activation of autophagy. In addition, the content of mast/stem cell growth factor receptor Kit (SCFR) was increased after DOX, pointing to activation of cardiac regeneration. **Conclusions:** This work showed that even a low cumulative dose of DOX affects the cardiac muscle in multiple pathways requiring further studies to find new molecular mechanisms as to clinically address the cardiotoxicity induced by this anticancer agent.

Keywords: cardio-oncology; doxorubicin; mitochondrial biogenesis; autophagy; cardiac regeneration

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