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CARDIO-ONCOLOGY
SESSION TITLE: MOLECULAR CARDIO-ONCOLOGY: THE NEW FRONTIER

Abstract 15199: Pyridoxamine Limits Mitochondria-Dependent Ferroptosis in a Rat Model of Doxorubicin-Induced Cardiotoxicity

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Abstract

Background: The use of doxorubicin (DOX) chemotherapy is limited by cardiotoxicity characterized by mitochondrial iron accumulation and ferroptosis, both interesting targets for cardioprotection. We found that pyridoxamine (PM) protects against DOX cardiotoxicity in rats. In this study, we hypothesized that PM is cardioprotective by restoring iron regulation and limiting mitochondria-dependent ferroptosis.

Methods: Female Sprague Dawley rats of six weeks old were divided into a DOX group (2 mg/kg/week, 8 weeks, IV, N=7) or control group (CTRL, saline, N=7). Others were treated with PM via drinking water (1 g/L) while receiving DOX or saline (DOX+PM, N=9 and CTRL+PM, N=8). Iron regulation, lipid peroxidation and mitochondrial damage in cardiac tissue were evaluated by qPCR, 4-hydroxynonenal (4-HNE) staining and transmission electron microscopy. Data were compared by 1-way ANOVA or Kruskal-Wallis test with posthoc tests. P values are presented with a mean difference (MD) and [95% CI] or mean rank difference (MRD).

Results: DOX significantly increased ZIP14 (P=0.049 vs CTRL, 11.20 MRD) and mitoferrin-1 expression (P=0.0002 vs CTRL, 1.49 MD [0.71, 2.28]), indicating increased cytosolic and mitochondrial iron import. The DOX group showed features of ferroptosis including swollen mitochondria with disrupted cristae (Fig. 1), decreased mitochondrial density (P=0.085 vs CTRL, –0.12 MD [–0.24, 0.01]) and increased 4-HNE levels (P=0.029 vs CTRL, 6.90 MD [0.56, 13.24]). PM treatment significantly decreased ZIP14 (P=0.0055 vs DOX, –12.90 MRD) and mitoferrin-1 expression (P=0.0008 vs DOX, –1.17 MD, [–1.88, –0.46]), indicating restored iron regulation. PM also significantly increased mitochondrial density (P=0.0028 vs DOX, 0.22 MD [0.06, 0.37]) and limited mitochondrial damage (Fig. 1).

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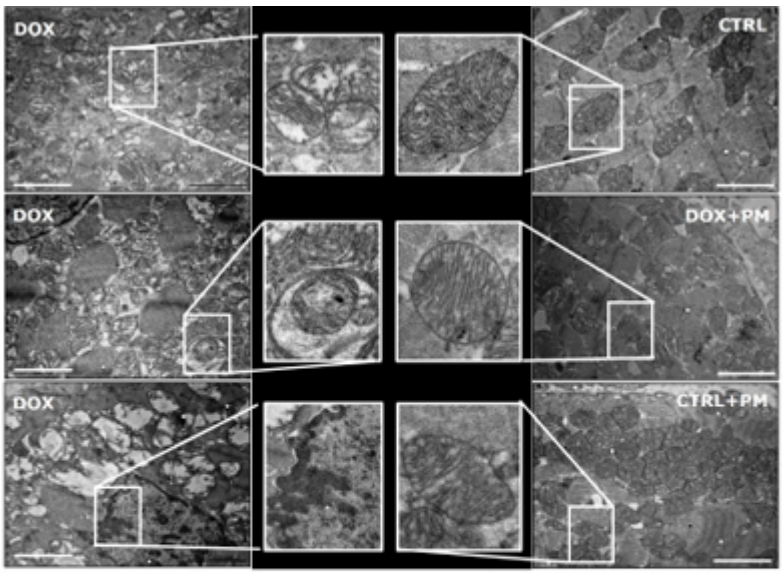

Figure 1. PM limits DOX-induced mitochondrial damage. Representative TEM pictures of LV cardiomyocytes. In the DOX group, cardiomyocytes showed swollen mitochondria with disrupted cristae, autophagic vacuoles containing damaged mitochondria, and condensed chromatin, which was less pronounced in the DOX+PM group. Cardiomyocytes of CTRL, DOX+PM and CTRL+PM groups showed typical intracellular organization of myofilaments (light grey), mitochondria (dark grey), and cytoplasm (white). Magnification: 6000×. Scale bars: 2 µm. PM, pyridoxamine. DOX, doxorubicin. TEM, transmission electron microscopy. LV, left ventricular.

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Footnotes

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