Xanthine oxidase inhibition attenuates doxorubicin-induced cardiotoxicity in mice

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Background: Accumulating evidence suggests that high serum uric acid (UA) is associated with left ventricular (LV) dysfunction. Although xanthine oxidase (XO) activation is a critical regulatory mechanism of the terminal step in ATP and purine degradation, the pathophysiological role of cardiac tissue XO in LV dysfunction remains unclear.

Objectives: We hypothesized that cardiac XO is activated in doxorubicin-induced LV dysfunction, and XO inhibitors ameliorate LV function by inhibiting cell death signals as well as by modifying cardiac purine metabolism.

Methods: Either doxorubicin (10 mg/kg) or vehicle was intraperitonially administered in a single injection to ICR mice. Mice were treated with or without oral XO inhibitors (febuxostat 3 mg/kg/day or topiroxostat 5 mg/kg/day) for 8 days starting 24 hours before doxorubicin-injection. The LV function was assessed by echocardiography at day 6 and by ex vivo heart perfusion at day 7.

Results: Cardiac tissue XO activity measured by a highly sensitive assay with liquid chromatography/mass spectrometry (n=8 each) and cardiac UA content (n=3–6) were significantly increased in doxorubicin-treated mice at day 7 and dramatically reduced by XO inhibitors. Accordingly, XO inhibitors substantially improved LV ejection fraction (n=8 each) and LV developed pressure (n=9 each) that had been impaired by doxorubicin administration. Intriguingly, the expression of GPX4, a negative regulator of ferroptosis, was decreased in doxorubicin-treated hearts but improved by XO inhibitors (n=6 each). Furthermore, metabolome analyses revealed an enhanced purine metabolism in doxorubicin-treated hearts, and XO inhibitors suppressed the serial metabolic reaction of hypoxanthine–xanthine–UA.

Conclusions: Doxorubicin administration induces cardiac tissue XO activation associated with an impaired LV function. XO inhibition attenuates the doxorubicin-induced cardiotoxicity partly through an anti-ferroptotic effect and the conservation of tissue ATP levels by modulating purine metabolism. The present study suggests that pharmacological XO inhibition represents a potential therapeutic strategy for the treatment of doxorubicin-induced cardiotoxicity.