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Cardiotoxicity of drugs - New concepts

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Circulating histones are major mediators of cardiac complications in sepsis

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Introduction: The most common pathological change in critical illness is multiple organ failure, including cardiac complications, which often leads to early death. However, the underlying molecular mechanisms are not fully understood. Recently, the secondary hit by circulating histones causes great attention.

Method: Both septic animal models and patients with sepsis were investigated. Circulating histones were detected and their association with organ injury markers was analyzed. Intervention with anti-histone antibodies was carried out to confirm the cause-effect relationship.

Results: Circulating histones were dramatically elevated in both animal models and septic patients. Their levels were strongly associated with the severity of organ injury, particularly cardiac injury marker, cardiac troponins. Using anti-histone scFv in mouse models could significantly reduce the release of cardiac troponins as well as the incidence of the cardiac arrhythmia, and cardiac failure induced by histone infusion or sepsis. In addition, histones binding prothrombin initialized coagulation and significantly contribute to dysregulated coagulation leading to disseminated intravascular coagulation (DIC) and microcirculation impairment.

Conclusion: Circulating histones play critical roles in sepsis, including inflammation, coagulation activation, and multiple organ injury, particularly cardiac complications. This lays a foundation for future anti-histone intervention to reduce the unacceptably high mortality rates of sepsis.

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Induction of interferon-related genes limits the cardiotoxicity of liposomal doxorubicin in pigs

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Background: The clinical application of the anthracycline anticancer drug doxorubicin (DOX) is severely compromised by its cardiotoxic effects. Liposomal formulation of doxorubicin (LDOX) reduces adverse effects by altering the biodistribution profile. The molecular mechanisms of anthracycline-induced toxicity are incompletely understood.

Purpose: We investigated the molecular effects of encapsulated and free DOX in a translational large animal model by transcriptomic profiling in order to identify strategies for cardioprotection.

Methods: We treated domestic pigs with drug doses equivalent to human therapies, of either DOX (n=6), epirubicin (n=9), or LDOX (n=9) and compared the cardiac, laboratory and hemodynamic effect with saline-treated animals (n=5, controls). Cardiac magnetic resonance imaging with gadolinium late enhancement and transthoracic echocardiography quantified heart function and myocardial fibrosis. Gene expression profiles of the left and right ventricles were analyzed after the completion of three treatment cycles by next generation sequencing and validated by quantitative PCR. The extent of cardiac fibrosis and the presence of protein biomarkers were examined by histochemistry and immunofluorescence analyses.

Results: High morbidity of epirubicin-treated animals (7 of 9) resulted, and impeded further evaluation of this group. We found different degrees of cardiotoxicity in all groups, reflected by increase of plasma markers NT-proBNP (569±144 and 458±113 vs. 44±5 pg/mL) and Troponin I (1.30±0.85 and 1.33±0.22 vs. 0.01±0.01 ng/mL) and an impact on body weight (46±11 and 69±13 vs. 75±3 kg, DOX and LDOX vs. Co, respectively). We identified stronger reduction of the left ventricular systolic function (LV enddiastolic volume 1.96±0.24 and 1.62±0.41 vs. 1.20±0.13 mL/kg, DOX and LDOX vs. controls) and myocardial fibrosis in animals treated with DOX compared to LDOX. DOX downregulated interferon-stimulated genes, induced upon DNA damage repair and promote cell survival, but LDOX upregulated these genes in both the left and right ventricle. The cardioprotective translocator protein (TSPO) acts as a central node in the network of differentially regulated genes. Compared to controls, the expression of TSPO was inhibited 2.7-fold by DOX, but was unchanged by LDOX. Immunohistochemistry showed a predominant mitochondrial pattern with slightly increased cytosolic localization of TSPO after LDOX application. Severe cardiac fibrosis with activation of collagen was found in all treatment groups, with a higher extent in the DOX group.

Conclusions: These results indicate that the reduction of myocardial drug accumulation through LDOX activates a DNA damage response pathway reflected by stimulation of interferon-inducible genes, which might be responsible for the limitation of cardiotoxicity. The study identified potential targets, such as TSPO, for developing strategies for targeted mitigation of anthracycline induced cardiotoxicity.