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ALTERATIONS OF THE CALRETICULIN-STAT3 PATHWAY ASSOCIATES WITH MITOCHONDRIA DAMAGE IN A RAT MODEL OF DILATED CARDIOMYOPATHY

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Objectives To study the calreticulin-signal transducer and activator of transcription 3 (STAT3) signalling pathway and its effect on mitochondria damage in the progress of dilated cardiomyopathy (DCM).

Methods Thirty-five male Sprague-Dawley rats were divided into three groups including the untreated group, a control group treated orally with 0.15% carboxy methylcellulose-Na solution and a model group treated with suspension of furazolidone (700 ppm) dissolved in 0.15% carboxy methylcellulose-Na for 30 weeks. The cardiac function and structure were measured using the echocardiographic and hemodynamic studies and paraffin-embedded sections staining respectively. The signal molecules involved in the calreticulin-STAT3 pathway were investigated by real-time quantitative polymerase chain reaction and western-blot. At last the cardiac mitochondria structure and function were detected.

Results Compared with the control and untreated groups, the rats in the model group had enlarged left ventricular dimensions, and reduced systolic and diastolic function. Focal and diffuse areas of myocardial degeneration and interstitium fibrosis were present in the rat hearts of model group. Calreticulin mRNA expression was 3-fold higher in the model group than that in control group, and the protein level of calreticulin was also significantly higher than that in the control and untreated groups ($p<0.05$). The protein expression of STAT3 and p-STAT3 in the whole myocardium and cardiac mitochondria were both significantly down-regulated in the model group ($p<0.05$). The gene and protein levels of manganese superoxide dismutase (MnSOD), downstream to STAT3, were also significantly decreased in the model group ($p<0.05$). Under electron microscopic observation, the cardiac mitochondria in the model group were swelling with fractured or dissolved cristae. The mitochondrial membrane potential level of the isolated fresh cardiac mitochondria, and the enzyme activities of cytochrome c oxidase and succinate dehydrogenase in the model group were both significantly decreased as compared with control and untreated groups ($p<0.05$).

Conclusions A rat model of DCM induced by furazolidone was successfully established. It might be that furazolidone-induced DCM is due to the alterations of calreticulin-STAT3 pathway. Down-regulated expression and activity of STAT3 can not only promote mitochondrial membrane permeability pore to open directly, but also induce mitochondrial damage indirectly through inhibiting the expression of MnSOD.