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ASSOCIATION OF STAT3 WITH HSF1 PLAYS A CRITICAL ROLE IN G-CSF-INDUCED CARDIO-PROTECTION AGAINST ISCHAEMIA/REPERFUSION INJURY

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Objectives Granulocyte Colony-stimulating Factor (G-CSF) has been shown to be cardio-protective against ischaemia through activating Jak2/Stat3 pathway, however, the mechanism is unclear. Heat shock transcription factor 1 (HSF1), a definite endogenous protective protein in cardiomyocytes, may interact with Stat family under stress conditions. We hypothesised that G-CSF could induce cardio-protection against ischaemia/reperfusion (I/R) through association of HSF1 with Stat3.

Methods To test the hypothesis, we built cardiac I/R injury model with HSF1 knockout (KO) mice and wild type (WT) mice by occlusion of the left anterior descending (LAD) coronary artery for 30 min and subsequent release of the occlusion for 24 h. These mice were administered with G-CSF (100 µg/kg/day) or vehicle subcutaneously for three days before surgery.

Results As expected, G-CSF induced significant cardio-protections against I/R injury, characterised by higher ejection fraction (EF%), lower left ventricular end diastolic pressure (LVEDP), increased dP/dt value and decreased infarct area as compared with the vehicle treatment in WT mice. In HSF1-KO mice, however, these cardio-protections induced by G-CSF were greatly attenuated. Inhibition of oxidative stress-induced cardiomyocyte apoptosis by G-CSF also disappeared due to the deficiency of HSF1 in vitro and in vivo. Furthermore, G-CSF increased the phosphorylation and the association of Stat3 with HSF1, which enhanced transcriptional activity of HSF1. Inhibition of either Stat3 or HSF1 by pharmacological agents suppressed G-CSF-induced association of the two proteins and anti-apoptotic effect on cardiomyocytes.

Conclusions Our data suggest that G-CSF stimulates phosphorylation and association of Stat3 with HSF1 and therefore enhances transcriptional activity of HSF1, leading to the cardio-protection against I/R injury.