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REGULATORY T CELLS PARTIALLY MEDIATE CARDIOPROTECTION OF LATE ISCHAEMIC PRECONDITIONING IN RATS

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Objectives Myocardial ischaemia-reperfusion (IR) injury (IRI) is associated with activation of the innate immune system and the resultant inflammatory response. Myocardial ischaemic preconditioning (IPC) is the most powerful endogenous protective mechanism against myocardial IRI, probably via the role of anti-inflammation. Regulatory T cells (Tregs) play an important role in the negative modulation of immune responses. This study was designed to test whether and how much Tregs contribute to mediation of myocardial IPC against IRI.

Methods IPC was induced by four episodes of 5 min ischaemia followed by 5 min reperfusion, and IR by 30 min ischaemia and then 48 h reperfusion in rats. (1) 96 rats were divided into two groups (n=48 per group): the control group, receiving sham operation without LAD occlusion; the ischaemic preconditioning group, giving a run of IPC. Each group was then divided into six sub-groups and rats from each sub-group were sacrificed respectively at successive time point (day 0, 1, 2, 3, 5 and 7) after myocardial IPC or sham operation. (2) Rats were divided into 4 groups (n=8 per group): Sham/Sham-IgG, underwent two sham operations at an interval of 48 h, and injected with placebo IgG at 24 h before the second sham operation; Sham/IR-IgG, underwent a sham operation and a run of 30 min IR (30 min myocardial ischaemia, then 48 h reperfusion) at an interval of 48 h, injected with placebo IgG at 24 h before 30 min ischaemia, and then kept reperfusion for 48 h; IPC/IR-IgG, underwent a run of IPC and a run of 30 min IR at an interval of 48 h, injected with placebo IgG at 24 h before 30 min ischaemia, and then kept reperfusion for 48 h; IPC/IR-NDS61, underwent a run of IPC and a run of 30 min IR at an interval of

48 h, injected with NDS61 at 24 h before 30 min ischaemia, and then kept reperfusion for 48 h. All rats were sacrificed after 48 h reperfusion.

Results IPC caused a significant increase in the number of Tregs at day 1, 2, 3 and 5, and in the expression of FoxP3 at day 1, 2 and 3 in the heart after IPC. As compared to the placebo IgG-treated non-preconditioned rats (Sham/IR-IgG), the IPC-induced cardio- protection (IPC/IR-IgG) reduced the infiltration of neutrophils, macrophages and CD4+T cells respectively by 45%, 53% and 50%, infarct size by 43%, and to improve LVEF by 36%. As compared to the placebo IgG-treated preconditioned rats (IPC/IR-IgG), the NDS61-treated preconditioned rats (IPC/IR-NDS61) had more accumulation of inflammatory cells (Neutrophils: $(2.62\pm0.61)\times103/mm^2$ vs $(1.77\pm0.41)\times103/mm^2$, $p<0.01$; Macrophages: $(1.51\pm0.56)\times103/mm^2$ vs $(0.96\pm0.41)\times103/mm^2$, $p<0.05$; CD4+T cells: $(2.36\pm0.46)\times103/mm^2$ vs $(1.49\pm0.44)\times103/mm^2$, $p<0.05$)), larger infarct size (IS/AAR: 37.50% ±4.75% vs 27.03%±3.27%, $p<0.001$) and poorer cardiac function (LVEF: 55.60%±6.34% vs 69.46%±8.39%, $p<0.001$).

Conclusions Our data suggest that the IPC-afforded cardioprotection against IRI is associated with Tregs, and Tregs' negative modulation of inflammation response following myocardial IR is partially contributable to the late IPC and affords cardioprotection against myocardial IRI.