

**Aims** We hypothesized that SDF-1 $\alpha$  is a potential mediator of RIPC-induced protection.

**Methods and Results** Rats were anaesthetized and subjected to RIPC, consisting of 3 cycles of 5 minutes ischaemia by application of a tourniquet around the hind limb followed by 5 minutes of reperfusion. SDF-1 $\alpha$  levels in rat plasma were measured using an ELISA kit. There was a 50% increase ( $p<0.01$ ) in SDF-1 $\alpha$  levels in plasma obtained from rats subjected to RIPC ( $890\pm 70$  pg/ml,  $n=8$ ) compared to the control group ( $590\pm 50$  pg/ml,  $n=8$ ). Pharmacological inhibition using AMD3100, a highly specific antagonist of CXCR4 signalling, was used to investigate the involvement of SDF-1 $\alpha$  in RIPC. Rats were treated intraperitoneally with AMD3100 ( $10\ \mu\text{g/kg}$ ), prior to the RIPC protocol. The hearts were then excised and subjected to IR injury using the in vitro isolated Langendorff perfusion model. RIPC decreased the infarct size from  $53\pm 3\%$  to  $27\pm 3\%$  ( $n=6$ ,  $p<0.05$ ). Cardioprotection was abolished by AMD3100 ( $40\pm 4\%$  vs  $53\pm 3\%$ ,  $n=6$ ,  $p<0.05$ ). In separate experiments using myocytes isolated from rat hearts, SDF-1 $\alpha$  was shown to reduce cell death, as measured by propidium iodide, following 3 h hypoxia and 1 h re-oxygenation ( $20\pm 5\%$  vs.  $34\pm 5\%$ ). RIPC also improved functional recovery of cardiac papillary muscle from  $53\pm 13\%$  ( $n=4$ ) to  $84\pm 5\%$  ( $n=6$ ,  $p<0.05$ ) and was similarly blocked by AMD3100 ( $46\pm 7\%$ ,  $n=6$ ). Further, the direct application of SDF-1 $\alpha$  was shown to be protective in this model ( $89\pm 9\%$  vs.  $55\pm 9\%$  control,  $n=4$ ,  $p<0.05$ ) and was blocked by AMD3100 ( $60\pm 11\%$ ). We also measured the serum levels of dipeptidase (DPPIV) which is known to cleave and inactivate SDF-1 $\alpha$ . We observed no change in DPPIV activity after RIPC. This suggests that increased synthesis and release of SDF-1 $\alpha$  caused the increase in plasma levels.

**Conclusion** RIPC increases circulating levels of SDF-1 $\alpha$ , which acts via the CXCR4 receptors in the heart to attenuate IR injury. These results suggest that this chemokine might be an essential mediator of RIPC.

253

#### REMOTE ISCHAEMIC PRECONDITIONING IS MEDIATED VIA THE SDF 1 $\alpha$ /CXCR4 SIGNALLING AXIS

P Selvaraj, D He, C Boi-Doku, J Kearney, R Yellon, S Davidson, D Yellon *The Hatter Cardiovascular Institute, UCL*

doi:10.1136/heartjnl-2013-304019.253

**Background** Ischaemic preconditioning is one of the most potent experimental modalities known to decrease infarct size following ischaemia-reperfusion (IR) injury. Much interest has been stimulated by the phenomenon of Remote Ischaemic Preconditioning (RIPC) which occurs when a preconditioning stimulus is applied to a limb remote from the heart to stimulate cardioprotection. The protection is believed to be mediated by an unidentified humoral factor between 3.5 and 30 kDa. Stromal cell-derived factor-1 $\alpha$  (SDF-1 $\alpha$  or CXCL12) is a chemokine of 10 kDa that is induced by hypoxia and recruits stem cells. However it also exerts a direct and acute cardioprotection via its receptor, CXCR4.