

# Ischaemic preconditioning and stem cell mobilisation

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Ischaemic preconditioning (IPC) (1) refers to repeated brief episodes of ischaemia, which itself does not result in cells death, protects the myocardium from a subsequent ischaemic insult. A better understanding of the mechanism of this cardio-protective effect could potentially lead to the development of novel therapeutics that can be used in the clinical setting. Previous studies (2) have been mainly focused on the role of different signalling pathways, such as phosphatidylinositol 3-kinase (PI3-kinase), Akt, nitric oxide synthase, guanylyl cyclase, and mitochondrial K (ATP) channels, in mediating the cardio-protection during IPC. More recent studies (3, 4) have demonstrated that IPC-mediated cardioprotection is also related to stem cell mobilisation and production of cardioprotective cytokines which enhanced the recovery after ischaemia-reperfusion and chronic ischaemic injury.

In this Theme Issue of *Thrombosis and Haemostasis*, Gyöngyösi et al. (5) describe that IPC enhances mobilisation and recruitment of haematopoietic stem cells (HSC) and mesenchymal stem cells (MSC) in a porcine myocardial ischaemia-reperfusion model. The use of a clinically relevant chest model of infarction in large animals is

a strength of this study. During the early phase of IPC, both HSC and MSC were quickly recruited from the circulating pool to the infarction areas and border zones, suggesting that IPC might enhance stem cell mobilisation and retention into the ischaemic areas as exogenous administration of cytokines (6). Nevertheless, the functional status as well as the fate of recruited stem cells must be addressed before the IPC can be fully evaluated in the clinical setting. It has been reported that the recruited c-kit+/lin- progenitor cells accumulated in heart tissues were dysfunctional and undergoing senescence in response to ischaemia (7). Furthermore, the depletion and impairment of endogenous stem cells in patients with cardiovascular disease might also limit the mobilisation of stem cells during IPC (8).

Prior studies (9–11) have demonstrated that the paracrine effects of bone marrow-derived stem cells may play a more important role than stem cell trans-differentiation in enhancing the neovascularisation of the ischaemic myocardium. Indeed, Gyöngyösi et al. showed that brief episodes of ischaemia raised the cytokines levels, including stromal-derived factor 1 $\alpha$  (SDF-1 $\alpha$ ) and vascular endothelial growth factor (VEGF) during the early phase of

IPC, which might contribute to the MSC and HSC mobilisation and enhancement of neovascularisation. In contrast to the measurement of the circulating levels of cytokines, it would be even more valuable to determine if local concentrations of VEGF or SDF-1 $\alpha$  were also increased in response to IPC. Furthermore, whether the recruited MSC and HSC are functional and could further contribute to the cardioprotective effects of IPC remains unclear.

In addition to providing further insight into the mechanisms of cardioprotection by IPC, this study by Gyöngyösi et al. (5) may have potential clinical implication for stem cell therapy in cardiac repair. Although different types of stem cells have been investigated as novel therapy for cardiac repair and showed initial promising results (12, 13), one of the major challenges that remains is the poor cell retention and survival in a hostile ischaemic environment. In rodent experiments, treatment of IPC not only promoted the survival of the transplanted skeletal myoblast via the release of paracrine factors (14), but also enhanced kit+/Lin- stem cell survival and homing to ischemic myocardium by activation of SDF-1 $\alpha$ /CXCR4 axis (15).

Taken together, IPC treatment not only protects myocardium from subsequent is-

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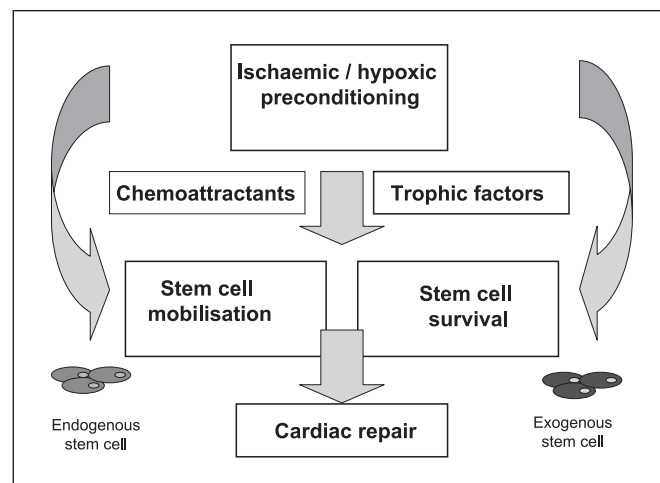
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**Figure 1: Potential effects of ischaemic preconditioning to enhance stem cell therapy for cardiac repair.**

chaemic insult, but also promotes endogenous stem cell mobilisation. Therefore, IPC treatment may provide a novel strategy to enhance the therapeutic efficacy of stem cell therapy for cardiac repair by mobilisation of endogenous stem cells, and improving the retention and survival exogenous transplanted stem cells (Fig. 1). The future holds much promise.

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