Letter to Editor

# Therapeutic potential of Stem Cell Preconditioning for Ischemic Heart Diseases / Letter to the Editor

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## Abstract

Preconditioning (PC), is an approach to improve therapeutic potential of stem cells against ischemic environment. PC has several advantages over other therapeutic techniques as this results in increase of transplanted stem cells recruitment, retention, survival and subsequently the induction of a more supportive environment within the damaged tissue via secretion of angiogenic factors. Special attention is needed to recognize new materials, compounds, and conditions to assess the feasibility of PC for being applied in clinics to treat the ischemic diseases.

***Keywords*:** stem cell preconditioning, cardiovascular diseases, ischemic heart diseases, progenitor cells

## Introduction

Cardiovascular diseases especially ischemic heart disease are the most common cause of death and hospital admissions in most developing countries including Iran. From the perspectives of regenerative medicine, inducing neoangiogenesis and neovascularization in ischemic areas can be very helpful to restore organ perfusion and reduce the impacts of this problem. Various other therapies for cardiovascular diseases are clinically investigated and performed.

Recently, cell-based regenerative medicine using several cell sources and novel strategies e.g. preconditioning etc. have appeared as an alternative therapy for curing cardiovascular diseases (Wilschut et al., 2012). Preconditioning (PC), which is a well-known protective phenomenon activated by ischemic stress, where cells can sense and adapt to the environment by changing their cellular phenotypes and functions, has recently been applied in clinics to treat ischemic diseases (Yu et al., 2013). Different chemokine factors in preconditioned stem cells and ischemic heart and their role in angiogenesis, neovascularization, and regeneration of damaged tissues have been investigated. SDF-1/CXCR4 has been described as a vital chemokine axis in ischemic heart to orchestrate the rapid revascularization of injured and ischemic tissues. SDF-1 released by ischemic tissues, promotes the sprouting of small endothelial tubes from pre-existing capillaries, the egress of stem cells from bone marrow (BM), and their homing and differentiation into the injured tissue (Yu et al., 2013). PC strategies can affect the SDF-1/CXCR4 functions using different kinds of cells as shown in Table 1.

**Table 1:** Effects of some PC strategies on SDF-1/CXCR4 axis

| Cell Type | PC | Protocol | Effect | Ref. |
|---|---|---|---|---|
| MSC | HP | 1% $O_2$ for 24 h | CXCR4 expression, SDF-1-dependent migration | (Hung et al., 2007) |
| MSC | HP | 3% $O_2$ for 24 h | CXCR4 and CXCR7 expression, SDF-1-dependent migration, adhesion and survival | (Liu et al., 2010) |
| PBMNC | HP | 2% $O_2$ for 24 h | CXCR4 expression, adhesion retention | (Kubo et al., 2009) |
| CLK | HP | 0.1% $O_2$ for 24 h | CXCR4 expression | (Tang et al., 2009) |
| BM-ckit+ cells | AP | pH 7.0 for 24 h | CXCR4 expression SDF-1-dependent migration | (Cencioni et al., 2013) |

MSC: Mesenchymal stem cell PBMNC: Peripheral blood mononuclear cell CLK: cardiosphere-derived, Lin(-)c-kit(+) progenitor, HP: Hypoxic preconditioning AP: Acidosis preconditioning.

Preconditioning of cells via exposure to hypoxia, anoxia, acidosis, low level lasers or other treatments prior to cell injection into the damaged

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tissue, render stem cells more resistant to ischemia (Herrmann et al., 2010).

PC is a promising strategy as it results in the increase of transplanted stem cells recruitment, retention, survival and the induction of a more supportive environment, within the damaged tissue, via secretion of angiogenic factors (Wei et al., 2012). The clinical based outcomes using preconditioning are urgently required. The preconditioning methodologies should be tested carefully in clinical studies, so we could define a better future for stem cell therapy. As PC is a promising approach in the treatment of ischemic heart diseases, the problem which is a major cause of death in our country, optimizing the conditions for PC could greatly reduce the huge life loss.

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## References

1- Cencioni C., Melchionna R., Straino S., Romani M., Cappuzzello C., Annese V., Wu J. C., Pompilio G., Santoni A., Gaetano C., Napolitano M. and Capogrossi M. C. (2013) *Ex vivo* acidic preconditioning enhances bone marrow ckit+ cell therapeutic potential via increased CXCR4 expression. Eur Heart J 34:2007-2016.

2- Herrmann J. L., Wang Y., Abarbanell A. M., Weil B. R., Tan J. and Meldrum D. R. (2010) Preconditioning mesenchymal stem cells with transforming growth factor-alpha improves mesenchymal stem cell-mediated cardioprotection. Shock 33:24-30.

3- Hung S. C., Pochampally R. R., Hsu S. C., Sanchez C., Chen S. C., Spees J. and Prockop D. J. (2007) Short-term exposure of multipotent stromal cells to low oxygen increases their expression of CX3CR1 and CXCR4 and their engraftment in vivo. PLoS One 2:e416.

4- Kubo M., Li T. S., Kamota T., Ohshima M., Qin S. L. and Hamano K. (2009) Increased expression of CXCR4 and integrin alphaM in hypoxia-preconditioned cells contributes to improved cell retention and angiogenic potency. J Cell Physiol 220:508-514.

5- Tang Y. L., Zhu W., Cheng M., Chen L., Zhang J., Sun T., Kishore R., Phillips M. I., Losordo D. W. and Qin G. (2009) Hypoxic preconditioning enhances the benefit of cardiac progenitor cell therapy for treatment of myocardial infarction by inducing CXCR4 expression. Circ Res 104:1209-1216.

6- Wilschut K. J., Ling V. B. and Bernstein H. S. (2012) Concise review: stem cell therapy for muscular dystrophies. Stem Cells Transl Med 1:833-842.

7- Yu S. P., Wei Z. and Wei L. (2013) Preconditioning strategy in stem cell transplantation therapy. Transl Stroke Res 4:76-88.