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LETTER TO THE EDITOR

Reveal more mechanisms of precondition mesenchymal stem cells inhibiting inflammation

Yi Li, Qian-Qian Chen, En-Qiang Linghu

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Yi Li, Qian-Qian Chen, Department of Gastroenterology, First Medical Center of Chinese PLA General Hospital, Beijing 100853, China

En-Qiang Linghu, Department of Gastroenterology and Hepatology, First Medical Center of Chinese PLA General Hospital, Beijing 100853, China

Corresponding author: Qian-Qian Chen, MD, Associate Chief Physician, Associate Professor, Department of Gastroenterology, First Medical Center of Chinese PLA General Hospital, No. 28 Fuxing Road, Haidian District, Beijing 100853, China. qian_qian_chen@163.com

Abstract

Hypoxia can get more ability to inhibit inflammation. But how it impact on survival time of mesenchymal stem cells (MSCs) is confusing and how preconditioned MSCs inhibiting inflammation are partially known. Those issues decided the value of preconditioned MSCs by hypoxia.

Key Words: Mesenchymal stem cell; Hypoxia-inducible factor 1α; Hypoxia; Inflammation; Macrophage

Core Tip: Precondition of mesenchymal stem cells (MSCs) can change the characteristic of MSCs and enhance its biological activity in specific aspects. Both hypoxia and the over-expression of hypoxia-inducible factor 1α can inhibit inflammation. But more mechanisms on precondition MSCs inhibiting inflammation should be revealed to promote curative effect.

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TO THE EDITOR

Mesenchymal stem cells (MSCs) have immunomodulatory effects, which can effectively inhibit inflammation and promote tissue regeneration[1]. Its homing effect makes MSCs more targeted in regulating local inflammation. In order to enhance the immune regulatory ability of MSCs, researchers explored different methods to pretreated MSCs to improve the immune characteristics of MSCs[2,3]. The *World J Stem Cells* published a research paper titled "Hypoxia and inflammatory factor preconditioning enhances the immunosuppressive properties of human umbilical cord mesenchymal stem cells"[4], indicating that hypoxia culture and inflammatory factor pretreatment can enhance the ability of MSCs to inhibit inflammation. This paper confirmed through cell experiments that preconditioning MSCs have stronger anti-inflammatory abilities, but also observed the aging characteristics of MSCs, which means that the time for MSCs to exert active effects *in vivo* may be shortened.

THE VALUE AND THE LIMITATION OF THE ARTICLE

In fact, this study did not confirm at the animal level that preconditioning MSCs with hypoxia and inflammatory factors have a better inhibitory effect on inflammation. On the other hand, the aging characteristics of MSC need more evidence. The study from Haneef *et al*[5] indicated the proliferation, survival, and migration of MSCs are induced by hypoxic preconditioning. Anyhow, we have reason to assume that, just like the *in vitro* environment, the inflammatory and hypoxic environments in the body can also enhance the anti-inflammatory effect of MSCs.

REVEALING MECHANISMS OF PRECONDITIONED MSCS IS BENEFIT TO THE SELECTION OF TREATMENT STRATEGIES

However, does the survival time of MSCs *in vivo* affect their anti-inflammatory effects? The study by Yang *et al*[6] demonstrated at the animal level that preconditioned MSCs with hypoxia indeed have stronger anti-inflammatory regulatory effects than untreated MSCs. However, it is worth noting that this study only observed the effects of preconditioned MSCs at a single time point, lacking an evaluation based on the cumulative effects over a longer period of time. Therefore, currently we can only demonstrate that preconditioning MSCs is more effective in controlling acute inflammation, but it is difficult to say that the MSCs survive longer, the benefits are more obvious. Some studies have begun to challenge the view that "only live MSCs exert anti-inflammatory effects". Schrodt *et al*[7] found heat-inactivated MSC induced human monocytes to distinct immunosuppressive phenotypes. Montalbán-Hernández *et al*[8] found fused cells between human-adipose-derived MSCs and monocytes keep stemness properties and acquire high mobility. Therefore, the next step should focus more on different ways to preconditioned MSCs and the anti-inflammatory mechanism of preconditioned MSCs. In addition, the hypoxia-inducible factor 1 alpha (HIF1α) signaling pathway can be activated by hypoxia and produce immune regulatory effects. Our team improved the immunosuppressive properties of MSCs by over-expressing HIF1α with genetic modification perspective[9]. This is another way to simulate preconditioned of hypoxia through genetic modification. Further evaluation can be conducted on the anti-inflammatory effects of MSCs with two different intervention methods: Hypoxia preconditioned and HIF1α overexpression.

FOOTNOTES

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ORCID number: Qian-Qian Chen 0009-0006-9078-5711; En-Qiang Linghu 0000-0003-4506-7877.

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