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COMMENTARY

Bone marrow mesenchymal stem cells and liver regeneration: believe the hypoxia!

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Abstract

There are limited data on the efficacy of mesenchymal stem cells (MSCs) in models of extensive hepatic resection. In the previous issue of *Stem Cell Research & Therapy*, Yu and colleagues demonstrate that transient hypoxic preconditioning of MSCs improves their efficacy in a rat model of massive hepatectomy. This effect appears to be mediated, in part, by increased vascular endothelial growth factor (VEGF) production by the preconditioned MSCs as well as the injured liver. Neutralizing VEGF antibodies ameliorated the benefit of hypoxia-preconditioned MSCs, establishing VEGF as a key mediator of their benefit. This novel approach merits further exploration both mechanistically and to establish the functional advantages of MSCs in other injury settings.

The study by Yu and colleagues [1] in the previous issue of *Stem Cell Research & Therapy* investigated the biological effects of hypoxia-preconditioned bone marrow-derived mesenchymal stem cells (HP-MSCs) and their utility in a rat model of massive hepatectomy. The authors demonstrate that administration of conventionally cultured bone marrow-derived MSCs into the hepatectomy model resulted in increased percentages of proliferating cell nuclear antigen (PCNA)-positive cells and cyclin D1 levels in the liver but did not affect serum albumin levels, liver-to-body weight ratio (LBWR), or survival rates of the rats. However, use of HP-MSCs resulted in a far more potent therapeutic effect as evidenced by significantly increased cyclin D1 and PCNA-positive cell levels, serum albumin levels, LBWR, and survival rates.

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The use of rodent MSCs in liver damage has previously been studied, and reported mechanisms include reductions in oxidative stress [2] and cellular infiltrates [3]. Of note, studies with murine MSCs also report a reduction in fibrosis [4] when infused in models of chronic liver damage with carbon tetrachloride.

In contrast to drug- or toxin-induced models of liver damage, this study [1] tests MSCs in a setting where there has been surgical resection of liver tissue. The mechanisms contributing to this enhanced action were explored with vascular endothelial growth factor (VEGF) proposed as the major mediator of their action. However, although HP-MSCs produced higher levels of VEGF at both the protein and mRNA level, there was a similar rise in production by the injured liver. The infusion of neutralizing antibodies to VEGF (six separate doses) ameliorated any beneficial effects of HP-MSCs, although it was not clear whether this was achieved by an action on the HP-MSCs or on the liver. Nevertheless, these data suggest that hypoxic preconditioning of cells for a short period (24 hours) may markedly improve their biological action, which may possibly be mediated by VEGF.

This study is the first to suggest that HP-MSCs have improved properties in the setting of hepatocyte proliferation. This functional enhancement of MSCs by hypoxia is not surprising, as their native environment in the bone marrow is hypoxic, and plays an essential role in regulating their function [5]. Hypoxic culture of MSCs is commonly used as a way of ensuring timely expansion *in vivo* without recourse to the use of cytokines such as fibroblast growth factor but usually requires continuous exposure to hypoxia. In that regard, it is notable that the improvements in function which are seen here occur after only a brief exposure to hypoxia. It would be informative to understand the effect of this period of hypoxia on other MSC functions such as immunomodulatory and tri-lineage differentiation, as there are data indicating that prolonged hypoxia can help maintain the

multi-potent [6] and immunomodulatory differentiation [7] abilities of MSCs. Furthermore, it would be helpful to assess whether hypoxic preconditioning of MSCs alters their adhesion molecule profile as that may alter their ability to migrate to the injured liver [8] and in turn may impact on their efficacy.

MSCs have been shown to upregulate a variety of growth factors in hypoxic conditions, including hypoxia-inducible factor-alpha and VEGF [9], which are well-known pro-regenerative, pro-angiogenic, and anti-apoptotic factors. This is relevant considering the role of VEGF as an important regulator in liver regeneration, stimulating liver sinusoidal endothelial cell proliferation and thus aiding maintenance of their architecture [10]. Although increased VEGF production by HP-MSCs is found in association with the enhanced liver regeneration, the liver parenchyma also produced increased amounts of VEGF. Parenchymal VEGF production may be mediated by cytokines such as interleukin 6, hepatocyte growth factor, and insulin-like growth factor-1 released from infused HP-MSCs [10], although this needs further study. Moreover, to identify whether HP-MSC -secreted VEGF was required for the action of MSCs, knockdown or silencing experiments in HP-MSCs would be necessary.

In summary, the study by Yu and colleagues offers a novel approach by which the therapeutic effects of MSCs can be enhanced to improve liver regeneration. Testing the action of these MSCs in other models of liver damage will be informative and establish whether they can be used to treat diseases such as liver cirrhosis.

Abbreviations

HP-MSC: Hypoxia-preconditioned mesenchymal stem cell; LBWR: Liver-to-body weight ratio; MSC: Mesenchymal stem cell; PCNA: Proliferating cell nuclear antigen; VEGF: Vascular endothelial growth factor.

Competing interests

The authors declare that they have no competing interests.

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