Commentary

SDF-1: CXCR4 Axis Is Fundamental for Tissue Preservation and Repair

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Adult stem cell therapy has demonstrated the potential for tissue preservation and repair in multiple organ systems including the heart,¹ liver,² brain,³ skin,⁴ and kidney.⁵ In some organ systems, such as the liver, there is evidence of real regeneration,⁶ whereas in other organ systems, such as the heart, there is little evidence for tissue regeneration.^{7,8} Regardless of whether tissue is regenerated in a given organ system, consistent evidence exists across all organ systems for modulation of cell death, leading to preservation of organ-specific tissue function. The similarity of tissue preservation across systems suggests that there may exist a common mechanism of use for adult stem cell therapy; furthermore, the findings that conditioned media from adult stem cells led to tissue preservation suggested that the effect was due, at least in part, to paracrine factor expression by the adult stem cells.^{8,9}

Early in the investigation of the mechanisms related to stem cell-based tissue repair, the stromal cell-derived factor-1 (SDF-1):CXCR4 axis was identified as a key factor in the recruitment of stem cells to areas of tissue injury in multiple organ systems.^{10–12} These findings led us to propose that the reestablishment of SDF-1 expression late after tissue injury could serve as a strategy to induce tissue repair;^{10,13} this hypothesis is now the focus of an on-going clinical trial in patients with chronic heart failure (NCT01082094, clinicaltrials.gov). More recently, studies by our group and others have demonstrated that the expression of SDF-1 at the time of acute injury induces the recruitment of endogenous tissue-specific stem cells¹⁴ as well as direct preservation of end-organ cells such as cardiac myocytes.⁸

Further demonstrating the importance of the SDF-1 in tissue repair, in this issue of the journal, Otsuka et al¹⁵ demonstrate the role of SDF-1 in inhibiting photoreceptor cell loss in retinal detachment. These investigators quantified the levels of vascular endothelial growth factor and

SDF-1 in the vitreous of patients with retinal detachment (RD) and proliferative diabetic retinopathy as well as other pathologies. Vascular endothelial growth factor and SDF-1 levels are increased in proliferative diabetic retinopathy;^{16,17} however, only SDF-1 levels were increased in RD. Interestingly, the up-regulation of SDF-1 in RD did not lead to proliferation of the vasculature of the retina. Consistent with the up-regulation of SDF-1 in response to RD is the correlation of vitreous SDF-1 levels with the extent and duration of RD.

The investigators took their observation of increased SDF-1 in the vitreous of patients with RD and nicely investigated the effects of SDF-1 in the R28 retinal precursor cell line and a rat model of RD. Their data demonstrate that there is minimal SDF-1 expression in the normal eye but that within 3 days of experimentally induced RD there is increased SDF-1 expression in the anti-glial fibrillary acidic protein-positive astrocytes. Based on the known biology of the SDF-1, the increased expression of SDF-1 in the vitreous could have multiple effects including recruitment of bone marrow-derived stem cells and local inhibition of cell death in CXCR4-expressing cells.

The lack of vascular changes associated with increased SDF-1 expression in patients with RD suggests that SDF-1 expression is not associated with significant recruitment of bone marrow-derived endothelial progenitor cells because it is associated with SDF-1-mediated myocardial healing.^{8,10} Rather, the mechanism of SDF-1-mediated healing or tissue preservation in the eye seems to be more related to that seen in the skin, the healing of which is also not associated with vascular growth.¹⁸

Otsuka et al¹⁵ demonstrate that SDF-1 expression in the eye in the setting of RD is associated with preservation of photoreceptors in the outer nuclear layer. Further demonstrating that the effects of SDF-1 are specific in response to injury, inhibition of SDF-1 signaling in the normal eye had no

Supported by the Skirball Foundation.

Accepted for publication August 13, 2010.

CME Disclosure: M.S.P. is listed on patent applications filed by the Cleveland Clinic Foundation for the use of SDF-1 and CXCR4 for tissue repair.

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Figure 1. Schematic representation of the effects of tissue injury on SDF-1:CXCR4 expression and the local and remote effects of modulating their local expression.

effects on cells in the outer nuclear layer. Of importance, the specificity of the SDF-1 response was mediated by the expression of CXCR4 by photoreceptors in the outer nuclear layer. CXCR4 expression in the normal retina was limited to the ganglion cell and the inner nuclear layers; however, in response to RD, there was significant CXCR4 expression in the outer nuclear layer and photoreceptor inner segments of the detached retina. The importance of the SDF-1:CXCR4 axis on cell survival was confirmed in studies using the R28 retinal precursor cell line in the setting of serum starvation, similar to what we have previously demonstrated in the setting of hypoxia and serum starvation using mesenchymal stem cells.⁸

Perhaps directly in the eye¹⁵ and skin¹⁸ and more circuitously in other organ systems including the heart¹⁰ and brain,¹⁹ up-regulation of the SDF-1:CXCR4 axis is a fundamental response to tissue injury and modulating SDF-1⁸ and CXCR4²⁰ expression can serve as a strategy to preserve and restore end-organ function. The se-

quence of events after tissue injury is generalized in Figure 1: i) After tissue injury there is a local up-regulation of SDF-1 expression. The increased SDF-1 expression leads to homing of endogenous and bone marrow-derived stem cells in some organ system. ii) The end-organ cells up-regulate CXCR4 expression. The local up-regulation of CXCR4 can lead to cellular dysfunction²¹ but renders the cell responsive to SDF-1-mediated survival.

As delineated in Figure 1, the up-regulation of SDF-1 can lead to stem cell homing and engraftment that seems to be associated with neovascularization. In the absence of stem cell homing as seen in this study by Otsuka et al¹⁵ and in recent studies on SDF-1-mediated surgical wound healing,¹⁸ SDF-1 expression does not seem to induce neovascularization.

One recurring question regarding the importance of the SDF-1:CXCR4 axis in tissue repair is if the axis is so critical, why does the up-regulation of CXCR4 on end-organ cells often occur at a time when SDF-1 expression

is declining²²? We have recently demonstrated that although SDF-1:CXCR4 coexpression is required for normal cardiac development,²³ once cardiac myocyte fate is determined, CXCR4 expression is no longer required.²⁴ Thus, one hypothesis is that because SDF-1:CXCR4 expression is intimately involved in tumor metastases,^{25,26} evolution has favored mammals that, in adulthood, have SDF-1 expression temporally misaligned with organ CXCR4 expression.

The study of Otsuka et al¹⁵ extends the end-organ systems involved in SDF-1:CXCR4 tissue preservation and repair. It also raises some important and interesting questions for future studies. In particular, the eye in response to RD, like the bone marrow, seems to have sustained SDF-1 expression. In most organ systems studied to date, SDF-1 is rapidly up- and then down-regulated.²² Previous studies have suggested that SDF-1 expression in stroke and myocardial infarction is due to modulation of intracellular hypoxia-inducible factor-1 α .²⁰ The lack of vascular endothelial growth factor expression in the vitreous of RD suggests that hypoxia-inducible factor-1 α is not responsible for SDF-1-mediated expression in RD. Thus, the mechanism of SDF-1 up-regulation in RD remains to be elucidated.

In summary, the study by Otsuka et al¹⁵ elucidates an important role for SDF-1 expression in preservation of photoreceptors and the outer nuclear layer of the eye after retinal detachment. These findings suggest that CXCR4 expression in the eye is modulated in injury and that exogenous SDF-1 delivery may serve as a strategy to further preserve tissue structure during healing. Future studies need to be focused not only on the therapeutic potential of SDF-1 in ocular disease states but also on the molecular mechanisms associated with SDF-1 up-regulation in the eye after retinal detachment as well as the mechanisms associated with specific CXCR4 expression in specific tissue layers of the eye.

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