Hyaluronic acid-laminin hydrogels increase neural stem cell transplant retention and migratory response to SDF-1α

C.P. Addington[a], **S. Dharmawaj**[b], **J.M. Heffernan**[a,c], **R.W. Sirianni**[a,c] **and S.E. Stabenfeldt**[a]

a - School of Biological and Health Systems Engineering, *Arizona State University, Tempe, AZ, United States*
b - Department of Biomedical Engineering, *New Jersey Institute of Technology, Newark, NJ, United States*
c - Barrow Brain Tumor Research Center, *Barrow Neurological Institute, Phoenix, AZ, United States*

Correspondence to S.E. Stabenfeldt: *Arizona State University, PO Box 879709, Tempe, AZ 85287, United States.*
sarah.stabenfeldt@asu.edu
http://dx.doi.org/10.1016/j.matbio.2016.09.007

Abstract

The chemokine SDF-1α plays a critical role in mediating stem cell response to injury and disease and has specifically been shown to mobilize neural progenitor/stem cells (NPSCs) towards sites of neural injury. Current neural transplant paradigms within the brain suffer from low rates of retention and engraftment after injury. Therefore, increasing transplant sensitivity to injury-induced SDF-1α represents a method for increasing neural transplant efficacy. Previously, we have reported on a hyaluronic acid-laminin based hydrogel (HA-Lm gel) that increases NPSC expression of SDF-1α receptor, CXCR4, and subsequently, NPSC chemotactic migration towards a source of SDF-1α in vitro. The study presented here investigates the capacity of the HA-Lm gel to promote NPSC response to exogenous SDF-1α in vivo. We observed the HA-Lm gel to significantly increase NPSC transplant retention and migration in response to SDF-1α in a manner critically dependent on signaling via the SDF-1α-CXCR4 axis. This work lays the foundation for development of a more effective cell therapy for neural injury, but also has broader implications in the fields of tissue engineering and regenerative medicine given the essential roles of SDF-1α across injury and disease states.

Introduction

The chemokine stromal cell-derived factor-1α (SDF-1α also known as CXCL12) has been implicated as a potent mediator of cellular mobilization in several physiological systems during developmental stages, as well as in maintenance of pluripotent stem cell niches and response to injury or disease. Through interaction with its primary receptor, CXCR4, SDF-1α directs primordial germ cell migration and influences the development of immune cells [1–3]. The SDF-1α-CXCR4 signaling axis is also essential in maintaining adult bone marrow and neural stem cell niches after development [4–7]. Beyond providing normal physiological cues, SDF-1α orchestrates inflammatory and thus endogenous reparative responses to injury or disease. Specifically, SDF-1α has been implicated in mobilizing beneficial stem cells in response to injury, such as the egress of marrow-derived stem cells to regions of injury or stress [8–11]; recruitment of mesenchymal stem cells to sites of myocardial infarction [12,13]; and recruitment of neural progenitor/stem cells (NPSCs) to sites of neural injury [14–17].

Viewing the SDF-1α-CXCR4 signaling axis through a therapeutic/intervention lens evokes the potential to exploit this endogenous cell recruitment mechanism for cell transplantation paradigms. Cell survival and retention in neural transplantation is particularly dismal with pre-clinical studies reporting survival and retention rates of 2–3% [18,19]. Past research has explored the utility of overexpressing CXCR4 in mesenchymal stem cell transplants after stroke and traumatic brain injury resulting in improved transplant survival and retention, presumably through interaction with local, injury-induced

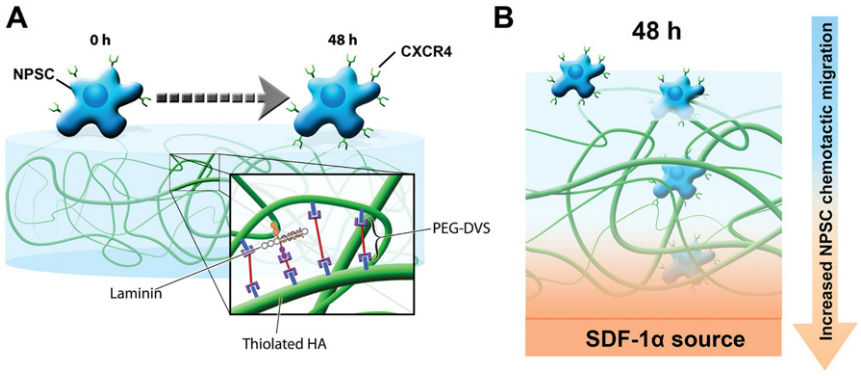

Fig. 1. Schematic illustrating the effect of the HA-Lm gel on NPSCs. After 48 h of culture on the HA-Lm gel, NPSCs (shown as blue cells) upregulate CXCR4 (shown as green cell surface receptor) (A). This correlates with increased NPSC chemotactic migration towards an SDF-1α source (shown in orange and labeled) that is dependent on both HA and laminin components of the gel (B) [30].

increases in SDF-1α [14,15,20,21]. While effective, genetic engineering methods for increasing cell transplant sensitivity to SDF-1α are limited in their clinical relevance. As such, there is significant motivation for developing clinically translatable neural transplantation platforms to address transplant retention and survival. Observations of the endogenous NPSC response to SDF-1α and the roles of extracellular matrix components in mediating this response provides inspiration for alternative methods of increasing SDF-1α sensitivity in neural applications.

Endogenous NPSCs home to sites of neural injury in an SDF-1α-dependent manner, using the vasculature as a migratory pathway [16,22,23]. By doing so, NPSCs take advantage of the unique matrix composition of the vasculature, where crosstalk between the basement membrane protein laminin and SDF-1α has been shown to synergistically increase NPSC migration [24]. Moreover, the matrix composition of the neural stem cell niche itself may serve to prime endogenous NPSCs to respond to SDF-1α. Specifically, the niche is, in part, comprised of the glycosaminoglycan hyaluronic acid (HA) [25,26], which has been shown to increase CXCR4 expression in several stem cell types including NPSCs [27–30]. Therefore, we previously developed a hybrid tissue engineering hydrogel composed of HA and laminin-111 (HA-Lm) that serves to both increase CXCR4 expression in NPSCs (via HA interactions) and provide critical vascular basement membrane signaling to enhance NPSC migratory response to SDF-1α (via laminin interactions; Fig. 1) [30]. This HA-Lm gel platform was shown to increase NPSC CXCR4 expression via CD44

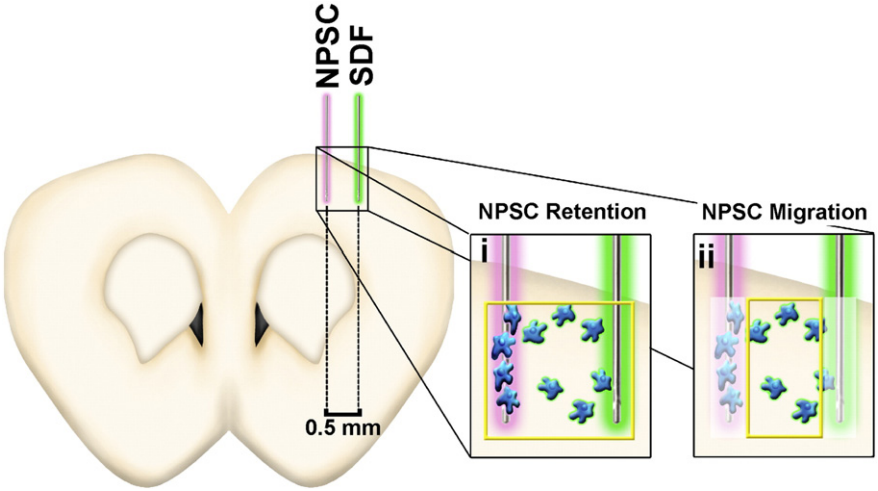

Fig. 2. Experimental overview and schematic illustrating NPSC retention and migration. SDF-1α was injected 0.5 mm lateral of the NPSC injection site and NPSC retention was calculated based on image sections including both needle tracks (i), where NPSC migration was calculated based on image sections excluding NPSCs that remained within the needle track (ii).