Migration of Stromal Cells in Response to Sustained Release of Stromal Derived Factor-1α

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Statement of Purpose: SDF-1α is a member of the CXC chemokines, constitutively secreted from the marrow stromal cells, and binds to cell surface CXCR4 receptors for its biological function. It has been demonstrated that marrow-derived osteo-progenitor cells are mobilized in the circulation after bone fracture and migrate to the damaged tissue by chemoattraction of SDF-1α to form bone in transplanted animals. Therefore, addition of SDF-1α to the implanted scaffold can potentially enhance mobilization, migration, and homing of osteo-progenitor cells to the regenerating region and accelerate bone formation. However, native SDF-1α has a relatively short half-life. The objective was to determine the release characteristics of SDF-1α from degradable poly(lactide-co-ethylene oxide fumarate) hydrogels and its effect on migration of bone marrow stromal cells.

Methods: Poly(lactide-ethylene oxide fumarate) (PLEOF) macromer, N,N'-methylene-bis-acrylamide crosslinker, and SDF-1α (250 ng/ml) were mixed in PBS and crosslinked by redox initiation [1]. Disk-shaped hydrogels were incubated in PBS at 37°C under mild agitation. At each time point, the supernatant was poured into siliconized microvials, fresh PBS was added and allowed to incubate until the next time point. The active concentration of released SDF-1α was measured by ELISA. For cell migration experiments, BMS cells were isolated from the bone marrow of young adult male Wistar rats as described [1]. A transwell cell migration assay was used to measure cell migration in response to different SDF-1α concentrations. BMS cells (labeled with calcein AM) were seeded at a density of 0.4x105-4x105 cells/ml in the upper transwell. At each time point, the SDF-1α released from the hydrogel was to the lower chamber of the cell migration assay. The seeded cells were allowed to migrate from the upper chamber to the lower side of the membrane for 12 h in response to the gradient in SDF-1α concentration between the lower and upper chambers. Next, the cells in the upper chamber were removed using a sterile coated swab and migrated cells were enzymatically lifted from the lower side of the membrane with 0.05% trypsin/0.53 mM EDTA. The number of migrated cells was quantified by measuring the fluorescence a plate reader.

Results: Labeling BMS cells with calcein AM did not cell viability as the cells had similar proliferation rate before and after labeling. Swelling ratio of PLEOF hydrogel was 4.5±0.3 corresponding to 82% water content. Encapsulation efficiency of SDF-1α in PLEOF hydrogel was 74±3%. Figure 1 shows the release kinetics of SDF-1α from PLEOF hydrogel. The burst release was approximately 20%. The SDF-1α release profile was relatively linear with 90% of the encapsulated SDF-1α released after 2 weeks.

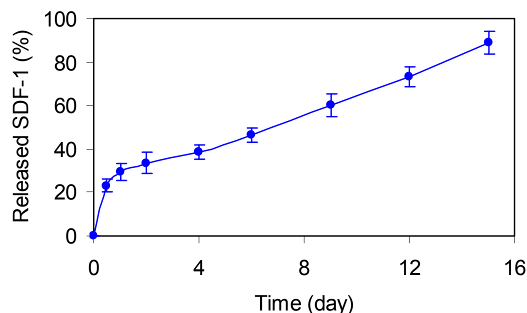

Figure 1. Release characteristics of SDF-1α from the PLEOF hydrogel.

The effect of hydrogel incubation time on migration of BMS cells is shown in Figure 2. In the absence of SDF-1α, only 4.5±0.4% of the seeded cell migrated to the lower side of the membrane after 12 h. On the other hand, after 15 days incubation, 170 ng (90% with 75% encapsulation efficiency) SDF-1α was released from the hydrogel which increased the fraction of migrated cells to 22±1%. Therefore, 15 days release of SDF-1α resulted in 4.8 fold in migration rate.

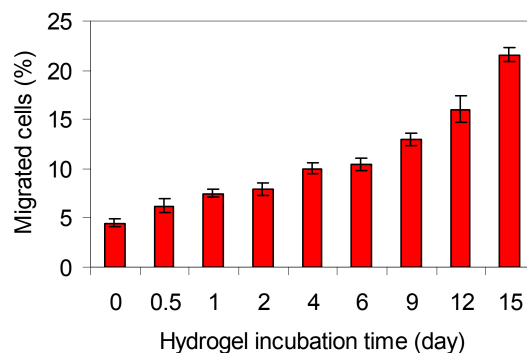

Figure 2. Effect of sustained release of SDF-1α from PLEOF hydrogel on migration of BMS cells.

Conclusion: Migration BMS cells in response to SDF-1α released from PLEOF hydrogel increased by 4.8 fold, compared to hydrogel without encapsulated SDF-1α. Sustained delivery of SDF-1α in biodegradable implants can potentially enhance mobilization, migration, and homing of progenitor cells to the regenerating.

References

2. He, X.; Jabbari, E. Biomacromolecules 2007, 8: 780-792.

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