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Mobilization of mesenchymal stem cells by stromal cell-derived factor-1 released from chitosan/tripolyphosphate/fucoidan nanoparticles

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ABSTRACT

Stromal cell-derived factor 1 (SDF-1) is an important chemokine in stem cell mobilization, and plays a critical role in the biological and physiological functions of mesenchymal stem cells (MSC). However, the use of SDF-1 in tissue regeneration is limited by two drawbacks, which are its short half-life and ready degradation by enzymes. This study investigates the release of SDF-1 from chitosan-based nanoparticles (NP) and evaluates the effect of released SDF-1 on the migration of MSC. Among the prepared chitosan-based NP a chitosan/tripolyphosphate/fucoidan (CS/TPP/F) NP is the most effective carrier for SDF-1 release. CS/TPP/F NP are spherical and effectively encapsulate SDF-1. The CS/TPP/F NP protected SDF-1 against proteolysis and heat treatment and controlled its release for up to 7 days. The concentration of released SDF-1 reached 23 ng ml^{-1}. According to in vitro experiments on cells the released SDF-1 retained its mitogenic activity, promoted the migration of MSC and enhanced PI3K expression. Biocompatible CS/TPP/F NP may be effective as carriers for the delivery and controlled release of SDF-1 to mobilize stem cells in tissue engineering applications.

1. Introduction

Tissue regeneration is a complex biological process that involves chemotaxis and the division of cells, neovascularization and the synthesis of extracellular matrix (ECM) proteins. Recently, stem cells have been extensively studied as powerful therapeutic tools for a wide range of tissue repair applications owing to their unique pluripotency and regenerative properties [1–3]. In most relevant research transplanted exogenous stem cells are applied directly to the injured tissue, in what is called cellular therapy [4,5]. Frequently, however, most cells die within a few weeks following transplantation [6,7]. A sudden change in the extracellular microenvironment is hostile to transplanted cells. Additionally, such cellular therapy has various limitations, including a limited range of cell sources, the expense of obtaining sufficient cells to achieve a response, the need for xenogenic components to expand the cells. An alternative strategy for cellular therapy is the chemotactic mobilization of stem cells from bone marrow [8,9]. Controlled mobilization may reduce the exposure of stem cells to a harsh environment and allow them to slowly remodel a new environment. A key step in this mobilization strategy is to choose an effective chemokine and a corresponding suitable delivery system.

Among the chemokines investigated herein stromal cell-derived factor 1 (SDF-1) is of particular interest. SDF-1 is a well-characterized chemokine attracting stem cells and so is a strong candidate for promoting regeneration. Circulating CXCR4-positive tissue-committed stem cells are chemo-attracted from peripheral blood to damaged organs by SDF-1, which is highly expressed in injured tissues [10]. CXCR4 is the receptor of SDF-1. The SDF-1/CXCR4 system plays a pivotal role in the retention of hematopoietic stem cells in bone marrow [11,12] and is involved in cardiogenesis [13], the migration of primordial germ cells [14], and the recruitment of endothelial progenitor cells to ischemic tissues [15]. However, exopeptidases [16] and matrix metalloproteinase-2 [17,18] that are activated in injured tissue [19,20] cleave SDF-1. This proteolytic activity probably limits the effectiveness of SDF-1 in an inflammatory environment. Based on these facts, controlling and prolonging the release of SDF-1 should optimize the advantageous effects of recruiting stem cells to the injured sites. Sustained injection of SDF-1 using an Alzet osmotic pump can recruit endothelial precursor cells from the circulation into an in vivo tissue engineering chamber. This process is termed homing of endothelial precursor cells [21]. Bone marrow stromal cells can be induced to migrate in response to the controlled release of SDF-1 from poly(lactide ethylene oxide fumarate) (PLEOF) hydrogels [22]. The controlled release of SDF-1 from poly(ethylene glycol) fibrin patches can increase the rate of c-kit^+ cell homing to infarcted heart [23]. Gelatin hydrogels release SDF-1 in a sustained fashion, accelerating angiogenesis at the implantation site [24]. The use of an alginate hydrogel patch to deliver SDF-1 is a novel means of accelerating healing and reducing scarring associated with clinical wounds [25].

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