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Stem cell membrane engineering for cell rolling using peptide conjugation and tuning of cell–selectin interaction kinetics

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ABSTRACT

Dynamic cell–microenvironment interactions regulate many biological events and play a critical role in tissue regeneration. Cell homing to targeted tissues requires well balanced interactions between cells and adhesion molecules on blood vessel walls. However, many stem cells lack affinity with adhesion molecules. It is challenging and clinically important to engineer these stem cells to modulate their dynamic interactions with blood vessels. In this study, a new chemical strategy was developed to engineer cell–microenvironment interactions. This method allowed the conjugation of peptides onto stem cell membranes without affecting cell viability, proliferation or multipotency. Mesenchymal stem cells (MSCs) engineered in this manner showed controlled firm adhesion and rolling on E-selectin under physiological shear stresses. For the first time, these biomechanical responses were achieved by tuning the binding kinetics of the peptide-selectin interaction. Rolling of engineered MSCs on E-selectin is mediated by a Ca^{2+} independent interaction, a mechanism that differs from the Ca^{2+} dependent physiological process. This further illustrates the ability of this approach to manipulate cell–microenvironment interactions, in particular for the application of delivering cells to targeted tissues. It also provides a new platform to engineer cells with multiple functionalities.

1. Introduction

Cell membrane engineering (CME) is an emerging research area [1–12]. It refers to the modification of cell membranes with biological, chemical or physical methods to alter cell functions [1–3,6–17]. Engineering cells to present natural or synthetic ligands on their membranes has become a promising modality to control cell–microenvironment interactions that are crucial in tissue regeneration. One potential application of CME is to navigate cells, such as stem cells, to targeted tissues [2,10]. Stem cells hold great promise for regenerative medicine. However, one of the major obstacles of stem cell-based therapy is the homing and retention of cells in tissues requiring regeneration [18,19]. One goal of CME is to modify human bone marrow-derived mesenchymal stem cells (hMSCs) to target receptors expressed on inflamed vessels of injured tissues. A natural response to injury is inflammation, during which certain circulating cells are recruited. Inflammatory cytokine-activated endothelial cells express adhesion molecules, E- and P- selectins to induce the rolling of leukocytes in postcapillary venules in the presence of Ca^{2+}, as well as vascular cell adhesion molecule 1 to mediate the firm adhesion of leukocytes [20].

For leukocytes and other cells to tether and roll on inflamed vessels, specific receptors on their membranes must be glycosylated with sialyl Lewis X (sLex), a tetrasaccharide [21–23]. hMSCs

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