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Fibrin glue as the cell-delivery vehicle for mesenchymal stromal cells in regenerative medicine

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Abstract

The use of tissue-engineering techniques such as stem-cell therapy to renew injured tissues is a promising strategy in regenerative medicine. As a cell-delivery vehicle, fibrin glues (FG) facilitate cell attachment, growth and differentiation and, ultimately, tissue formation and organization by its three-dimensional structure. Numerous studies have provided evidence that stromal cells derived from bone marrow (bone marrow stromal cells; BMSC) and adipose tissue (adipose-derived stromal cells; ADSC) contain a population of adult multipotent mesenchymal stromal cells (MSC) and endothelial progenitor cells that can differentiate into several lineages. By combining MSC with FG, the implantation could take advantage of the mutual benefits. Researchers and physicians have pinned their hopes on stem cells for developing novel approaches in regenerative medicine. This review focuses on the therapeutic potential of MSC with FG in bone defect reconstruction, cartilage and tendon injury repair, ligament, heart and nerve regeneration, and, furthermore, wound healing.

Key Words: *adipose-derived stromal cells, bone-marrow derived stromal cells, fibrin glues, mesenchymal stromal cells, regenerative medicine*

Introduction

Regenerative medicine is an alternative approach for replacing or regenerating tissue damage and organ loss. The strategies that promote tissue regeneration, instead of damaged tissue substitution, are usually based on the use of tissue-engineering techniques. The tissue-engineering approach in this review, which combines stem cells and fibrin glue (FG), provides a biocompatible scaffold material for the renewing cell sources.

Stem cells are characterized by the ability to differentiate into many lineage-specific cell types. With the development of two of the technologies that allow the isolation of stem cells, monoclonal antibodies and high-speed sorting of cells, stem cells are currently major cell sources in tissue engineering (1). Despite the pluripotency of embryonic fetal stem cells, research has been driven toward adult stem cells for use in tissue repair and regeneration, because of ethical, regulatory and availability concerns (2).

Several organs and tissues, such as skin (3), blood vessels (4), brain (5), skeletal muscle (6), liver (5), testis (7) and pancreas (5), have shown the existence of adult stem cells. Among the many available sources, mesenchymal stromal cells (MSC) derived from bone marrow or adipose tissue are commonly used as multipotent autologous cell sources and can be collected through relatively non-invasive methods (5).

Among MSC, bone marrow stromal cells (BMSC) have been considered the major source for many years in the field of tissue engineering (2). However, because of the ease of harvest and abundance, adipose-derived stromal cells (ADSC) are also regarded as attractive, readily available adult stem cells, and have become increasingly popular for use in many applications (2).

Characterization of MSC

MSC are identified through a combination of physical, phenotypic and functional properties (8):

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(a) adherence to plastic; (b) specific surface antigen expression; (c) multipotent differentiation potential to diverse lineages such as osteoblasts, adipocytes, chondroblasts, cartilage, muscle and neuronal-like cells. Surface antigen expression has been used extensively in immunology. Typical categories of surface marker proteins expressed in MSC include: adhesion molecules such as integrins (CD29, CD49e), receptor molecules such as hyaluronate (CD44), cadherins (CD144), surface enzymes (CD73), extracellular matrix proteins (CD90, CD105), intercellular adhesion molecules (CD54), vascular adhesion molecules (CD106), complement regulatory proteins, and histocompatibility antigens (9). MSC may be typically negative for CD45, CD34, CD31 and CD14, and positive for CD13, CD29, CD44, CD49e, CD54, CD55, CD63, CD73, CD90, CD105, CD106, CD144, CD146, CD166 and human leukocyte antigen (HLA). This phenotype is valid for both human and murine cells, with the exception of CD34, which may be positive in some murine MSC samples and may be positive very early in human cultures but very rapidly lost (10). The cluster of differentiation (CD) marker list of ADSC and BMSC is shown in Table I.

FG as the cell-delivery vehicle

Adult stem cells require an appropriate scaffold to facilitate cell attachment, growth and differentiation, and, ultimately, tissue formation and organization. The presence and properties of these scaffolds, which are primarily hydrogels such as FG (11–13) and platelet-rich gels (14), can greatly influence cell survival and differentiation.

Stacey *et al.* (15) observed a markedly decreased differentiation in two-dimensional (2-D) cultures compared with three-dimensional (3-D) scaffolds. Among 3-D scaffolds, including platelet-poor plasma, alginate, fibrin gel and collagen sponge, fibrin gel showed an optimal combination of mechanical characteristics and support of MSC differentiation and angiogenic factor secretion (16). The use of FG was advocated in tissue engineering for its 3-D characteristics, providing appropriate cells with contact with the culture environment through their surfaces.

Table I. Cell marker list of ADSC, BMSC and mouse ADSC or BMSC.

	Surface marker	ADSC (9,100–104) Human	BMSC (82,101,103,104) Human	ADSC or BMSC (82) Mouse
Positive markers	CD13	+	+	+/–
	CD29	+	+	+
	CD44	+	+/–	+/–
	CD49e	+	+	
	CD54	+	+	
	CD55	+	+	
	CD63	+	+	
	CD73	+	+	
	CD90	+	+/–	+/–
	CD105	+	+	+
	CD106	–	+/–	+
	CD144	+	+	
	CD146	+	+	
	CD166	+	+	
	HLA-ABC	+	+	
Negative markers	CD11b	–	–	+/–
	CD14	–		
	CD19	–		
	CD31	+/–	–	–
	CD34	+/–	+/–	+/–
	CD45	–	–	–
	Stro-1	+/–	+/–	
	CD3	–	–	
	CD117	–	–	–
	CD62L	–	–	
	CD95L	–	–	