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Cells and secretome – towards endogenous cell re-activation for cartilage repair☆

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ABSTRACT

Regenerative medicine approaches to cartilage tissue repair have mainly been concerned with the implantation of a scaffold material containing monolayer expanded cells into the defect, with the aim to differentiate the cells into chondrocytes. While this may be a valid approach, the secretome of the implanted cells and its effects on the endogenous resident cells, is gaining in interest. This review aims to summarize the knowledge on the secretome of mesenchymal stem cells, including knowledge from other tissues, in order to indicate how these mechanisms may be of value in repairing articular cartilage defects. Potential therapies and their effects on the repair of articular cartilage defects will be discussed, with a focus on the transition from classical cell therapy to the implantation of cell free matrices releasing specific cytokines.

Contents

Abbreviations: ACI, Autologous chondrocyte implantation; ACPCs, Articular cartilage progenitor cells; ASCs, Adipose stem cells; BMP, Bone morphogenetic protein; Bcl-2, B-cell lymphoma 2; Bcl-xL, B-cell lymphoma-extra large; BCA-1, B cell–attracting chemokine 1; CCR6, Chemokine receptor-6; CCL5/RANTES, Chemokine (C-C motif) ligand 5; CD, Cluster of differentiation; CFU, Colony forming unit; CXCR, Chemokine receptor type; DKK1, Dickkopf WNT Signaling Pathway Inhibitor 1; DNA, Deoxyribonucleic acid; EGF, Epidermal growth factor; FasL, Fas ligand; FGF, Fibroblast growth factor; Flk-1, Fetal liver kinase-1; FRZB, Frizzled-Related Protein; GDF-5, Growth differentiation factor-5; GREM1, Gremlin-1; HA, Hyaluronan; HGF, Hepatocyte growth factor; ICAM-1, Intercellular adhesion molecule-1; IFP, Infrapatellar fat pad; IGF-1, Insulin growth factor binding protein-1; IL-1β, Interleukin-1-beta; IL-1Ra, Interleukin-1 receptor antagonist; IL-10, Interleukin-10; LIF1, Leukemia inhibitory factor 1; MIP-3 α, Macrophage inflammatory protein 3α; Mig, Monokine induced by interferon-γ; MMP, Matrix metalloproteinase; MSCs, Mesenchymal stem cells; PLGA, Poly(lactide-co-glycolide); PEG, Poly(ethylene glycol); PGE2, Prostaglandin E2; rAAV, Recombinant adeno-associated virus; SH3, SRC homology 3; SDF-1α, Stromal cell derived factor-1; SERPIN, Serine protease inhibitor; TGF-β, Transforming growth factor-beta; TIMP, Tissue inhibitor of metalloproteinase; TNF, Tumor necrosis factor; TRAIL, TNF-related apoptosis-inducing ligand; TSG6, Tumor necrosis factor α-induced protein 6; VEGF, Vascular endothelial growth factor.

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1. Introduction

The repair of hyaline articular cartilage is still a major issue in orthopedics [1]. Mesenchymal stem cells (MSCs) have been heralded as the next major development in the repair and regeneration of diseased or injured tissues. However, their use in cartilage repair is still limited, with only 16% of reported cell therapy procedures for cartilage repair using MSCs, with the remainder chondrocytes [2]. The potential of MSCs for cartilage repair has to date focused mainly on their multipotential capabilities [3–5], with protocols and materials developed towards the aim of inducing a phenotypic change of the MSCs into chondrocytes [6–8]. While it is clear MSCs have the potential to become a range of cell types, such as chondrocytes [7], osteoblasts [9–11], adipocytes [3,12], neurons and myoblasts, MSCs are increasingly being investigated for their other functional abilities. The potential for endogenous cell homing, anti-inflammatory effects, and their ability to modify cell function by way of cytokine secretion are all gaining in importance. In order to perform these more recently identified abilities, MSCs have been shown to secrete a wide array of various soluble signaling molecules. These molecules are now seen as a major functional capability of MSCs and offer the potential for novel therapies which aim to increase secretory activity. Autocrine signaling of MSCs has also been shown to be at least in part responsible for their classical differentiation into chondrocytes [13]. This has led them to be likened to a growth factor factory, or drugstore [14]. Although donor variation has been observed in the levels of cytokine secretion, it has been shown that general expression levels are higher than control fibroblasts [15]. While this review is concerned with cartilage repair, papers reporting relevant data obtained from other tissues will also be included. This is also in part due to the fact that secretome manipulation in cartilage is in relative infancy compared to other tissues.

Various strategies are available when considering how to modify the local concentration of growth factors and cytokines within an articular cartilage defect (Fig. 1). Naïve or monolayer expanded MSCs can be locally implanted and held in place by way of a scaffold material. The cells could also be injected within the joint cavity and home to the defect. In addition, the cells could be modified, either by preconditioning or by genetic modification. Finally, the desired cytokine stimulus could be implanted directly as a protein, thus attracting the resident endogenous cells and avoiding the need for cellular manipulation *ex vivo*. Each of these options will be discussed in more detail below.

There has been a recent change in the paradigm when considering the mechanism of action of mesenchymal stem cells. The classical use of MSCs has been directed differentiation into mature, tissue specific cells in order to provide cellular material to effect a repair. However, it is becoming increasingly apparent that at the *in vitro* level, MSC differentiation is not as robust as initially believed, with stable and efficient differentiation being difficult to achieve. Particularly in the case of chondrogenesis, where progression to terminal hypertrophy is a significant issue [16]. Tracing studies *in vivo* support this, in that few if any cells survive longer than a few weeks after implantation [17,18]. MSC implantation has been demonstrated to enhance tissue repair. This, combined with the question over long term cell survival suggests that it is initial short term paracrine effects which may play the greatest role in repair. Thus, there is a real need to investigate and characterize MSC secretome.

An appealing mechanism by which MSCs enhance repair is the secretion of soluble signaling molecules, which then modify the response of the surrounding endogenous cells. This review will highlight the role of implanted cells and their influence on suchresident, endogenous cells. Screening methods to identify molecules of interest and their mechanism of action will also be discussed. In addition to the classical chondrogenic differentiation typically associated with progenitor cells,

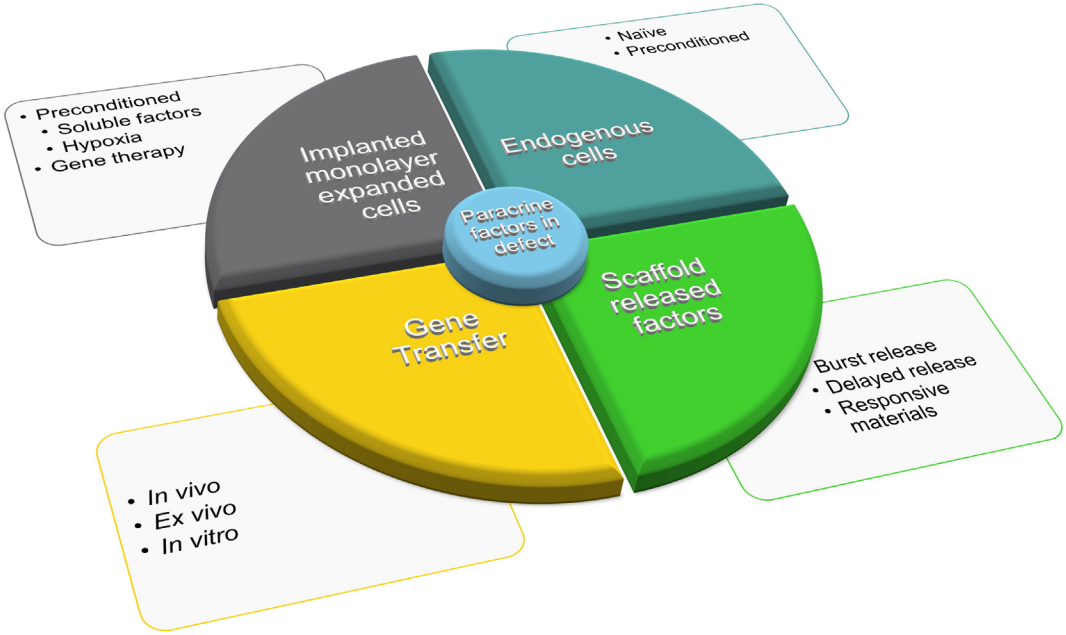

Fig. 1. Various methods which can be applied to modify the paracrine factors found within the articular cartilage defect.

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