Advanced Drug Delivery Reviews xxx (2014) xxx–xxx

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

Tissue engineering strategies to study cartilage development, degeneration and regeneration☆

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ARTICLE INFO

Available online xxxx

Keywords:
Cartilage tissue
Developmental biology
Scaffolds
Signals
Drug targets
In vitro models

ABSTRACT

Cartilage tissue engineering has primarily focused on the generation of grafts to repair cartilage defects due to traumatic injury and disease. However engineered cartilage tissues have also a strong scientific value as advanced 3D culture models. Here we first describe key aspects of embryonic chondrogenesis and possible cell sources/culture systems for in vitro cartilage generation. We then review how a tissue engineering approach has been and could be further exploited to investigate different aspects of cartilage development and degeneration. The generated knowledge is expected to inform new cartilage regeneration strategies, beyond a classical tissue engineering paradigm.

Contents

☆ This review is part of the *Advanced Drug Delivery Reviews* theme issue on "Scaffolds, Cells, Biologics: At the Crossroads of Musculoskeletal Repair".

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http://dx.doi.org/10.1016/j.addr.2014.08.010
0169-409X/

Please cite this article as: M. Bhattacharjee, et al., Tissue engineering strategies to study cartilage development, degeneration and regeneration, Adv. Drug Deliv. Rev. (2014), http://dx.doi.org/10.1016/j.addr.2014.08.010

1. Introduction

Over the past decades the first generation of tissue engineering research focused on generating cartilage tissue constructs in order to restore or replace structure–function properties in injured or degenerated cartilage. As an avascular tissue with only one cell type, cartilage engineering appeared to be a simple target. However despite these efforts, the development of clinically relevant, functionally equivalent engineered cartilage tissue constructs for load bearing applications remains elusive [1], with the few exceptions related to nonloading cartilage needs in restricted patient cohorts [2,3]. The major challenges to reproducibly enhance clinical outcomes in articular cartilage treatment using engineered tissues are largely unsolved, as addressed and discussed in recent reviews [4–8]. In particular, a consensus has not yet been reached on several critical components of cartilage tissue engineering strategies, such as the cell source, the biomaterial design criteria, the dose and delivery mode of signaling factors, as well as the required stage of maturation and associated release criteria predictive of clinical potency.

Despite the open translational challenges, engineered cartilage tissues have been increasingly recognized as biological systems offering the opportunity to investigate mechanisms and processes of chondrogenesis and its regulation by physico-chemical signals or pharmacological compounds [9]. Ultimately, the generated knowledge is expected to develop innovative and effective strategies for the future of cartilage repair in patients.

Therefore, this article will first provide an overview on the biology of cartilage development, as it represents the basis of cartilage engineering, and on available sources of cells to recapitulate chondrogenesis in vitro. We will then describe how engineered cartilage models could be further exploited as a tool to mimic and understand aspects of cartilage development, degeneration and regeneration.

2. Articular cartilage development

Cartilage developmental stages mainly include mesenchymal/precartilaginous condensation, interzone formation, cavitation and stabilization of articular cartilage. During mesenchymal condensation, undifferentiated mesenchymal cells (Fig. 1A) migrate from the lateral plate mesoderm. These prechondrocytic mesenchymal cells first move away from the center and initiate cellular packing by increasing the unit area/volume of the cells without cellular proliferation [10,11], thereby resulting in cellular aggregation (Fig. 1B) towards the center [12]. In humans, the formation of nodules by the prechondrocytes can be visualized at the 5th–6th weeks of embryogenesis. At this stage morphologically dense and minimal cartilaginous matrix containing architecture is observed until the 11th–12th weeks (evidenced by the absence of the mesenchymal marker CD146) [13]. The cellular

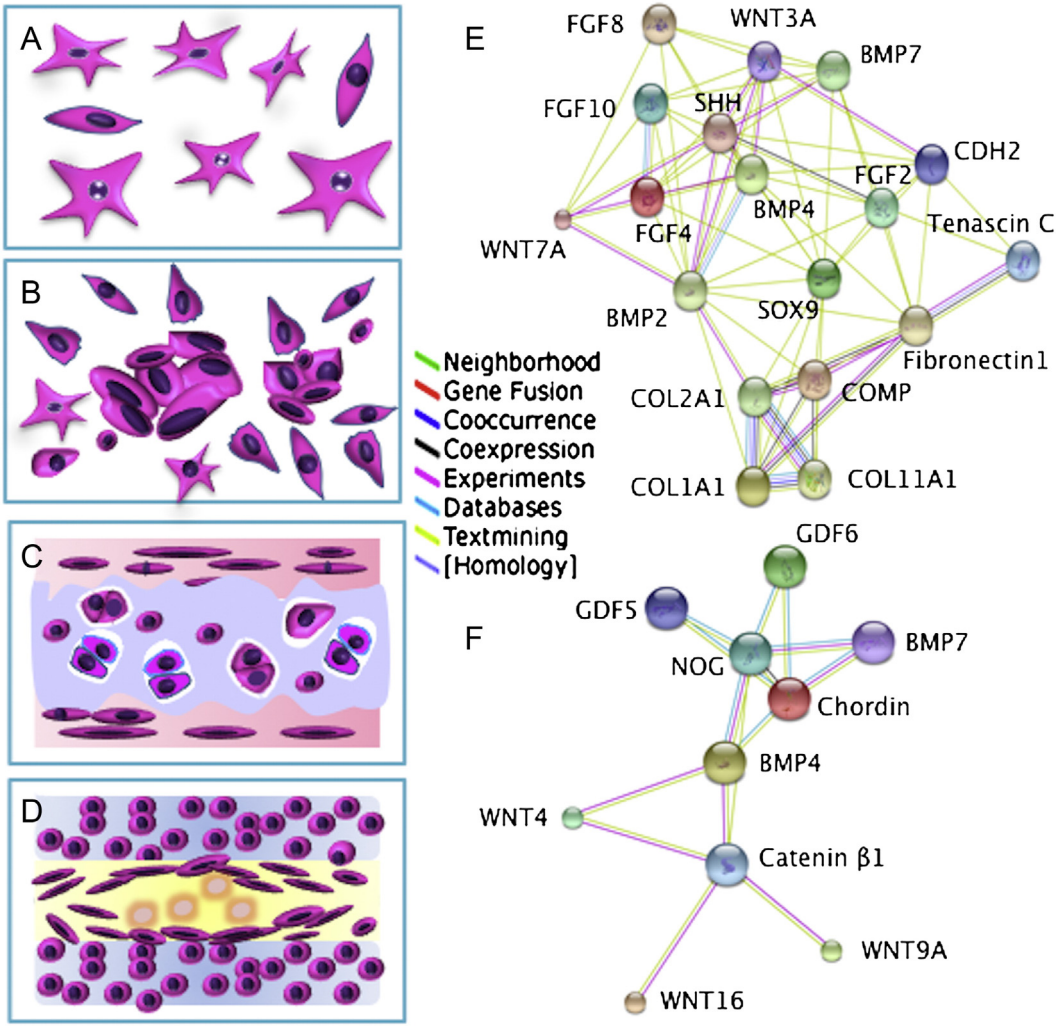

Fig. 1. (A) Undifferentiated mesenchymal cells. (B) Cellular aggregation. (C) Chondrocytes located in matrix lacunae. (D) Formation of interzone with flattened cells. (E) Protein–protein interaction involved in mesenchymal condensation phase of cartilage development. (F) Protein–protein interaction involved in interzone formation and cavitation of cartilage development.

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