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Prionace glauca skin collagen bioengineered constructs as a promising approach to trigger cartilage regeneration

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ABSTRACT

Representing a strategy of marine by-products valorization, based on isolation of biocompounds and assessment of biomedical applicability, the potential of blue shark (*Prionace glauca* (PG)) skin collagen to induce chondrogenic differentiation of human adipose stem cells (hASC) was investigated, with and without exogenous stimulation. For that, a cryogelation method was applied to produce highly interconnected porous 3-dimensional (3D) constructs made of collagen and collagen:hyaluronic acid (20:1). *In vitro* studies reveal that hASC adhere abundantly to the constructs which then suggests the early chondrogenic differentiation of those cells. These findings are supported by the mRNA expression encoding chondrogenic-related markers like Coll II and Sox-9 that are markedly upregulated at an early stage for both conditions, with and without exogenous stimulation. The introduction of hyaluronic acid (Hya) seems to play a crucial role at later time points, as shown by the evident immunodetection of aggrecan (ACAN), even without exogenous stimulation. It is hypothesized that the PG collagen itself can support chondrogenic differentiation at early time points, but exogenous stimulation is required to ensure phenotype maintenance. The present work highlights the relevance of using blue shark collagen biopolymer as a building block to produce highly effective temporary matrices for cartilage applications.

1. Introduction

Considering the avascular nature of the human native cartilage, injuries and degenerative conditions seriously compromise its intrinsic functionalities [1,2]. Generally, cartilage damages are physiologically irreversible, requiring specific treatments. Many different approaches have been used to treat cartilage lesions including perforations and microfractures; osteochondral autografts, mosaicplasty and allografts transplantation; and autologous chondrocyte implant (ACI) or mesenchymal stem cells (MSCs). ACI approaches can be also used in combination with 3D matrices (matrix-induced autologous chondrocyte implantation, MACI) [3–5].

The standard treatments are inspired in bone marrow stimulation techniques since they are straightforward, fast, and inexpensive. However, in more severe cases wherein the total replacement of the tissue is needed, mesenchymal stem cells stimulation itself is not sufficiently effective [6,7], with ACI and MACI techniques emerging as promising alternatives to treat larger defects, generally larger than 2.5 cm^2 [3].

Over the past years, bioactive substitutes based on Tissue Engineering (TE) strategies have been thus proposed and developed. Despite the large efforts on the subject, the clinical use of TE 3D structures is still limited to a few commercially available products with the best natural matrix being Chondro-Gide® (Geistlich Pharma AG, Wolhusen, Switzerland) [8]. Chondro-Gide® is a porcine collagen-based matrix established as a first-line treatment when combined with the microfracture technique [9]. It is considered a cost-effective one-step technique for the treatment of traumatic cartilage defects offering a helpful environment for mesenchymal stem cells differentiation and new cartilage formation [10]. It can be also used as an MACI approach

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