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Review - Human and Animal Health

Decellularized Wharton's Jelly: Biomaterial Potential for Regenerative Medicine Applications - A Mini-Review

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HIGHLIGHTS

- Wharton's Jelly (WJ) can stimulate cellular response.
- WJ promotes cell proliferation, adhesion, differentiation, and migration.
- WJ 3D printing scaffold can increase the healing tissue potential.
- WJ contains a variety of growth factors that promote tissue regeneration.

Abstract: The use of Wharton's Jelly (WJ) as a biomaterial is currently undergoing an appearance in the regenerative medicine field. The biomaterials applications focus on the aspects of cellular growth or delivery of proteins capable of stimulating cellular response. However, the basic knowledge about Wharton jelly and decellularization processing technology combined with understanding the physical-chemical properties of this biomaterial is necessary for proper application in regenerative medicine. This mini-review article summarizes information on the composition of WJ, application of drug delivery, in medicine and discusses recent

developments with a special focus on its use for regenerative medicine. The most successful and stimulating applications are studies in regenerative medicine and tissue engineering, for wound healing to treat burns, tumor treatment, nanoparticle carriers, and drug delivery systems.

Keywords: cell seeding; decellularized Wharton's jelly matrix; natural scaffolds; tissue decellularization; Wharton's jelly matrix.

INTRODUCTION

Over the past few, sundry regenerative medicine (RM) and nanotechnology approaches have been proposed as potential innovative strategies for many diseases [1,2]. Biologics presently used in medicinal applications involve platelet-rich plasma, bone marrow aspirate, adipose tissue aspirate, amniotic fluid, amniotic membrane, umbilical cord-derived Wharton's jelly, and cord blood [3,4].

Wharton's Jelly (WJ) tissue is a potential biomaterial with increasing use in RM through its decellularization. WG is a fetal tissue composed of mucoid connective tissue around the umbilical cord (UC) composed of collagen, hyaluronic acid (HA) and chondroitin sulfate, and proteoglycans [3]. In this scenario, decellularized WJ constitutes important progress in this research area, as an ideal system to deliver drugs and nanoparticles with growth factors among others and provide a fair environment for cell and tissue regeneration [5].

Decellularization is a technique that uses chemical, enzymatic methods, or physical means to extract cellular elements from natural tissues to acquire an acellular extracellular matrix (ECM) scaffold. The product of this process is a three-dimensional (3D) structure of ECM that can be utilized as a biological support (scaffold) for employment in tissue engineering and RM [5]. Scaffolds need to be biocompatible, bioabsorbable and with physical and chemical properties that allow cell adhesion, proliferation and differentiation [6].

Decellularization processes propose to minimize the tissue potential damage and thus preserve its native mechanical and biologic properties [7]. Thus, tissue engineering uses 3D printing with similar properties, different methods, and materials that have remarkable potential applied in tissue implantation. This article intends to resume information on the composition of WJ, its application in medicine, in drug delivery and to debate up to date with emphasis on its use for regenerative medicine.

Characteristic and preparation of Wharton's jelly

1. Structure

WJ is composed of a layer of mucoid connective gelatinous ECM of the UC. It is composed of a layer of simple amniotic epithelium and matrix elements such as collagen (types I, III, IV, and V), HA, and various sulfated glycosaminoglycans that surround the UC vessels. The structural integrity of these components does not alter after the current decellularization process (Figure 1) [8,9].

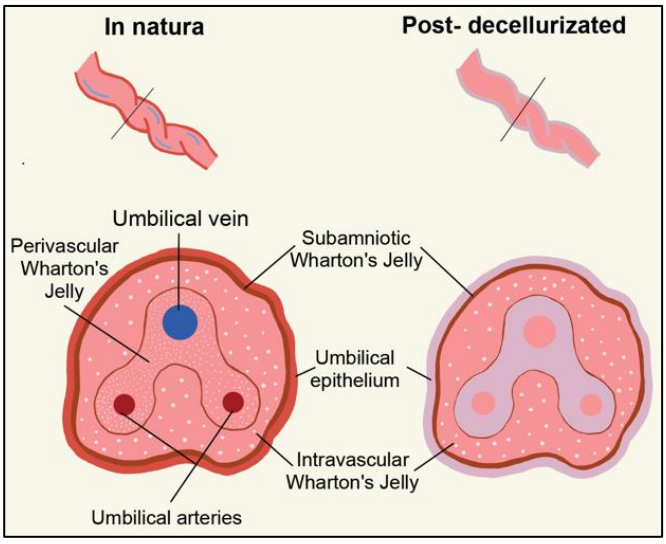

Figure 1. The structural integrity of Wharton's Jelly before and after the decellularization process.

2. Properties

Wharton jelly mesenchymal stem cells have several functions in tissue reconstruction in ophthalmologic surgery and wound treatment. Biomechanically, its resistance and elasticity provide biochemical structure and protection to the epithelial cells. Biologically, promote osteogenic and chondrogenic cells' adhesion, differentiation, and migration, and stimulates extracellular matrix production in vivo. Moreover, it has the properties of pro-inflammatory and anti-inflammatory cytokines with are essential for proper tissue healing [10]. Recent studies show that WJ, expressed growth factor-1 (IGF-1), but also platelet-derived growth factor (PDGF), vascular endothelial growth factor (VEGF), and TGF-α, (transforming growth factor – α [11].

With its immunomodulatory effect, GW can stimulate different tissues. IGF-1 induces osteogenic and chondrogenic differentiation of mesenchymal stem cells and improves extracellular matrix propagation [3]**.** Transforming growth factor (GF), through its receptor, promotes proliferation and survival of osteoprogenitors and plays an anabolic role in bone metabolism [4]. PDGF exhibits chemotactic properties toward human osteoblasts, and its downregulation is related to cartilage deterioration [12]. VEGF, a signal protein that induces angiogenesis, is included in tissue remodeling and bone formation [11].

Furthermore, several pro-inflammatory cytokines associated with healing in wounds were identified in the WG. The intercellular adhesion molecule-1 (ICAM-1) promotes leukocyte accumulation in the wound site and has immunosuppressive effects on dendritic cells and T cells, which may aid in the treatment of graft versus host diseases [13,14]. The expression of monocyte chemotactic protein1 (aka CCL2), a cytokine, induces wound healing as well, including in diabetic wounds as demonstrated in a previous study [15].

Umbilical cord WJ seems to be an optimal biomaterials source for cell culture systems and in the application as three-dimensional scaffolding. Since studies validated that it is a biocompatible matrix that permits cellular attachment, development, and proliferation with satisfactory properties in vitro and in vivo. Furthermore, it can be painlessly harvested in abundance in several births around the world without generating morbidity to the donor [16,17].

3. Preparation, sterilization, and preservation

a. Preparation

The method of umbilical cord (UC) preparation was as previously described by Bartolucci. In brief, the donor patience of the placenta is selected by serological tests to exclude human immunodeficiency virus (HIV), hepatitis B, hepatitis C, or syphilis). The placenta is broadly flushed in sterile PBS containing 200 U/mL penicillin and 200 µg/mL streptomycin. Then the WJ was sectioned into small-scale parts (1–2 mm), implanted in 100-mm culture plates. This method is used in various studies with few changes [18].

b. Sterilization

The UC is collected under sterile conditions. Normally, to maintain the UC and WJ under sterile conditions are used antibiotics and antimycotics cover gram-positive and negative bacteria and fungi to prevent microbial proliferation from contamination during processing. Additionally, it is pointed out immediately refrigeration at 4 ^{o}C after the sterilization process. It is also reported the initiation of the decellularization process within 72h after UC collection [19].

c. Preservation

Previous research showed that the protocols for cryopreservation are the most common method of preservation of the decellularized umbilical cord segments. Thus, the cryopreservation substance consists of saline without cryoprotectants. It is utilized in > 20 volume excess to the volume of fresh material at a cooling rate of 1 °C/min, and before it is stored at − 20°C [20,21]. Most effective protocols utilize CryoStor CS10 (which contains 10% DMSO), freezing to − 80 °C, storage in liquid nitrogen for 1 month and rapid thawing at 37 °C. Also, decellularized WJ can be preserved using a lyophilized technique (freeze-drying) [12].

4. Clinical Applications of WJ in surgical treatment

Wharton's jelly is a connective gelatinous umbilical cord tissue. Tissue engineering aims to use the principles and technologies for obtaining scaffolds useful for regeneration medicine applications. Wharton's jelly in medical applications is extensively used because it has good biocompatibility and low cost. Even after the decellularization process, the matrix of WJ retains a diversity of bioactive substances like GF, collagen,

laminin, fibronectin, and polysaccharide. Wharton's jelly-derived mesenchymal stem cells (WJ-MSCs) in situ transplantation promoted functional cardiac recovery after AMI [22,23].

In the same manner, Hashemi and coauthors 2019 in observed that (WJSCs) seeded on an amniotic membrane could promote a healing effect in diabetic wounds [24]. The application of WJ-MSCs enclosed with PF-127/SAP also promoted cell proliferation, neovascularization, and wound diabetic healing in rats [25].

Wang and coauthors 2013, in a previous study, demonstrated that the WJ-MSCs utilization improved the neurological function in rats with spinal cord injury [26]. Furthermore, a multi-center trial study has shown excellent results concerning the safety and efficacy of transplanted WJ-MSCs in patients with knee osteoarthritis [27]. The advantage of WJ-MSCs for cartilage healing gives indications to be the most promising utilization for this biomaterial, given the similarities between chondrocytes, WJ cells and the cellular matrix of cartilage [28].

In addition, a preliminary in vivo study demonstrated that WJ-MSC can differentiate into neuron-like cells, endothelial-like cells, myocyte-like cells, insulin-producing cells, and hepatocyte-like cells. However, there are still few studies correlating the potential of WJMSCs with mesenchymal stem cells came of other tissue origins [29].

A systematic review compared WJ-MSCs with other sources of MSCs in the treatment of cancer and showed that WJ-MSCs have more antitumorigenic effects. Despite that, there are still no clinical tests using WJ-MSCs for that purpose. Since, albeit 88% of the research showed that the WJ-MSCs allow for reducing cancer cell proliferation, 12% of the papers, which are all in vitro studies, reported contradicting results whereby WJ-MSCs improved cancer spreading [30].

CONCLUSION

Several publications have suggested that the application of WJ accelerates the onset of the cell proliferative in chronic diabetic wounds. Experimental studies using WJ after acute myocardial infarction have described promising results in cardiac function in recent years.

Finally, we note that experimental and clinical trials have intensively explored Wharton's jelly mesenchymal stem cells as a matrix for promising three-dimensional scaffolding migration, proliferation, and cell differentiation in regenerative medicine.

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