WHARTON'S JELLY

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What is regenerative medicine?

In recent years, regenerative medicine therapies using biologic applications, such as stem cell products and platelet-rich plasma treatments, have gained the attention of many researchers and clinicians due to encouraging experimental evidence. Of the various stem cells formed by the body, mesenchymal stem cells (MSCs), also known as stromal cells, are arising as a promising therapeutic application for musculoskeletal injuries and conditions such as osteoarthritis and intervertebral disc degeneration. Stem cells are cells which have the ability to transform into specialized cell types through interactions with signaling factors called growth factors and cytokines (1). The exact signaling molecules and their associated mechanisms of action are not fully understood, but current research suggests that these signaling factors induce stem cells to divide, differentiate, and proliferate into specialized cell types (1). The regenerative properties of stem cells provides an exciting opportunity to expand the available treatment options for complications associated with organ transplantation, diabetes, neurological conditions, cardiovascular diseases, and bone and cartilage conditions (2). Recent research has indicated the potential for stem cell therapies in treatment of conditions such as intervertebral disc degeneration, osteoarthritis and chronic tendinopathy (4, 5, 6, 8, 23). As such, stem cell therapies are at the forefront of research in regenerative medicine.

What is Wharton's Jelly?

The regenerative potential of stem cell therapies has demonstrated immense promise in pain management techniques for musculoskeletal injuries and diseases, such as intervertebral disc degeneration. Specifically, ongoing clinical trials exploring the benefits of therapies containing umbilical cord-derived MSCs from Wharton's jelly region show encouraging therapeutic potential for reducing pain and inflammation and enhancing healing (2, 3).

Recent studies have demonstrated that MSCs derived from Wharton's Jelly may have the potential to reduce the apoptosis of intervertebral disc cells, called nucleus pulposus cells (NPCs), that results from disc compression (4). Further, co-culturing MSCs derived from Wharton's Jelly with nucleus pulposus cells from degenerative intervertebral disc cells can induce MSC differentiation into NPCs and can activate favorable gene expression in degenerative NPCs (5). Clinically, MSCs derived from Wharton's jelly have been utilized in treatments aimed at repairing spinal cord, liver and heart tissue injuries and in the treatment of immune-mediated diseases (6).

Wharton's jelly is a gelatinous substance obtained from the connective tissue of human umbilical cords. In the umbilical cord, Wharton's jelly has several functions: to provide structural and protective support of the umbilical blood vessels and to provide a developing fetus with oxygen, glucose and amino acids while facilitating removal of waste products. Clinically, MSCs derived from Wharton's jelly may have the ability to stimulate cellular regeneration while eliciting little host immune response, as well as reducing pain and promoting healing through secretion of factors involved in immunomodulation. Regenerative medicine literature suggests the distinctive composition of Wharton's jelly may play an important role in it's anti-inflammatory, pain-reducing, and enhanced healing capabilities (7).

Although MSCs can be isolated from myriad tissue types such as bone marrow and connective tissue of the umbilical cord, and are able to differentiate into osteoblasts, chondrocytes, adipocytes, and supported hematopoietic stroma, Wharton's jelly has been shown to contain the highest concentration of harvestable MSCs of allogenic tissues (2, 8). MSCs derived from umbilical cord Wharton's jelly region secrete factors thought to be involved in the regenerative and immunomodulatory abilities of MSCs (9). Further, the MSCs found in Wharton's jelly may also secrete factors that improve wound healing through enhanced intracellular communication (9).

In addition to the high concentration of MSCs, Wharton's jelly contains significant amounts of growth factors, cytokines, hyaluronic acid and exosomes (7). These constituents directly impact signaling pathways that contribute to the downstream anti-inflammatory, pain-reducing and enhanced healing effects of Wharton's jelly. Notably, recent research has demonstrated that decellularized Wharton's Jelly matrix (i.e. excluding MSCs) can promote cell differentiation of degenerative intervertebral disc cells towards a discogenic phenotype and can improve the phenotype of degenerative intervertebral disc cells (8). Further, decellularized Wharton's Jelly matrix was shown to maintain the viability of these discogenic cells (8). These remarkable findings demonstrate the regenerative capacity of Wharton's Jelly for treatment of intervertebral disc injuries (8).

Important growth factors found in Wharton's jelly include insulin-like growth factor-1 (IGF-1) carrier proteins that are known to improve osteogenic differentiation and induce MSCs into cell lines that develop into cartilaginous tissues, growth factors which are ligands for epidermal growth factor receptor (EGFR) and thus encourage growth and survival of osteogenic cells, and signaling proteins which are involved in bone remodeling called vascular endothelial growth factor (VEGF) (7, 11). The presence of such growth factors suggests the potential role of Wharton's jelly in regenerative medicine and is specifically applicable to designing pain management therapies to repair damaged tissues without the need for surgery. The growth factors found in Wharton's jelly may be involved in modulating cellular mechanisms that combat chronic pain, joint and spine degeneration, and other musculoskeletal conditions due to their orthopedic-related nature. At present, many clinical and preclinical studies are investigating the potential of Wharton's jelly for treatment of various orthopedic conditions (12).

Additionally, many immunomodulatory cytokines found in Wharton's jelly are relevant to the field of regenerative medicine. Cytokines are substances that are produced by cells of the immune system and are often classified as either pro-inflammatory cytokines or anti-inflammatory cytokines. As the classification suggests, anti-inflammatory cytokines play critical roles in inhibiting inflammation, preventing hyperalgesia, and promoting wound healing. Important anti-inflammatory cytokines found in Wharton's jelly include chemokine ligand 5 (CCL5) which is associated with downstream signaling that leads to increased bone formation and a promoter of osteogenic differentiation called interleukin 6 receptor (IL-6R) (7, 13, 14). Pro-inflammatory cytokines are often associated with harmful inflammatory responses, but studies have also indicated that pro-inflammatory cytokines may play a role in initiating regenerative function of osteoclasts (7, 15). Such pro-inflammatory cytokines, called macrophage colony-stimulating factor (MCSF) and macrophage stimulating protein 1-alpha (MIP1-α), are found in Wharton's jelly (7).

Furthermore, studies have demonstrated that Wharton's jelly contains significant amounts of hyaluronic acid (HA) (7). HA is found in many areas of the body and is relevant to various aging and musculoskeletal disorders, such as epidermal atrophy and knee osteoarthritis. Specifically, HA is an important component of synovial fluid, which acts as a lubricant in joints, and is produced by connective tissue cells such as chondrocytes and fibroblasts. As many musculoskeletal diseases like osteoarthritis are associated with reduced HA concentrations, conventional treatment of these diseases often includes HA injections called viscosupplementation injections (16). Recent literature has suggested that the combination of components in Wharton's jelly may provide improved efficacy as a treatment for knee osteoarthritis compared to HA injections alone, and currently there are clinical trials investigating this hypothesis (17).

In addition, the significant levels of extracellular vesicles including exosomes found in Wharton's jelly provides further insight into the potential therapeutic advantages of Wharton's jelly in regenerative medicine (7). Extracellular vesicles are essential to intercellular communication, but their functions extend far beyond this purpose. Extracellular vesicles relate to regenerative medicine through their role in MSC paracrine signaling and through their ability to release specific RNA species which can alter gene expression by modulating the epigenetic landscapes of target cells (18). Exosomes are a type of extracellular vesicle secreted from most stem cells and have been found to be significant secretory products of Wharton's jelly-derived MSCs. Studies suggest that the extracellular vesicles derived from Wharton's jelly show promising therapeutic avenues for numerous conditions ranging from myocardial ischemia/reperfusion injury to chronic kidney disease to knee osteoarthritis (10, 19, 20, 21)

Regenerative medicine research and preliminary clinical study data suggests that the amalgamation of the varied composition of Wharton's jelly, including the high concentration of MSCs and the presence of growth factors, cytokines, hyaluronic acid, and extracellular vesicles including exosomes, shows promising evidence that Wharton's jelly may exert anti-inflammatory, pain-reducing and enhanced healing effects in many diseases and conditions.

Notably, the MSCs found in umbilical cord-derived Wharton's jelly entail fewer ethical and safety concerns compared to stem cells isolated from adult tissue because they are harvested after birth, have a reduced likelihood of recipient rejection due to improved immunoprivilege, and demonstrate enhanced proliferation and maintenance of multipotency (5, 22).

Prior to the recent interest in regenerative medicine, the treatment of many musculoskeletal diseases relied heavily on surgical intervention. Although minimally invasive injections and procedures have become more common, these practices are not cures. As the field of regenerative medicine continues to grow, it is essential to consider that developing regenerative therapeutics for musculoskeletal diseases, such as MSCs derived from Wharton's jelly, may serve as a promising and non-surgical alternative to conventional treatments.

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