

Bio Disc Homologous Application

Bio Disc represents the first placental matrix allograft specifically designed for application as a protective barrier around the nucleus pulposus. Engineered to set a new standard in the management of annular tissue compromise, Bio Disc provides circumferential coverage of the nucleus pulposus and supports the integrity of the annulus fibrosus following injury or intervention. Comprised predominantly of type I and type III collagen, this placental-derived allograft is structurally homologous to the native annulus fibrosus, offering a biologically compatible solution for tissue covering and protection.

1. BACKGROUND

The intervertebral disc (IVD) consists of three major components: the outer or annulus fibrosus (AF), the inner or nucleus pulposus (NP), and the cartilaginous endplates (CEPs) that anchors the discs to adjacent vertebrae [1].

The NP is a gel-like structure that sits at the center of the IVD and accounts for much of the strength and flexibility of the spine. It is made of 66% to 86% water, with the remainder consisting primarily of type II collagen (it may also contain type VI, IX, and XI) and proteoglycans. The proteoglycans include the larger aggrecan and versican that bind to hyaluronic acid and several small leucine-rich proteoglycans. Aggrecan is largely responsible for retaining water within the NP. This structure also contains a low density of cells. While sparse, these cells produce the extracellular matrix (ECM) products (aggrecan, type II collagen, etc.) and maintain the integrity of the NP [1].

The AF is a ring-shaped disc of fibrous connective tissue that surrounds the NP. This structure is highly organized, consisting of 15 to 25 stacked sheets, or "lamellae," of predominantly collagen, with interspersed proteoglycans, glycoproteins, elastic fibers, and the connective tissue cells that secrete these ECM products. Each lamella contains collagen uniformly oriented in a plane that differs in orientation to the adjacent lamella by about 60 degrees. This alignment leads to the parallel orientation of alternate lamella. This "radial-ply" formation provides exceptional strength compared to an entirely longitudinal setup and has been mimicked in the construction of products such as car tires. The lamellae are interconnected through translamellar bridges. The number of translamellar bridges per unit area is set to achieve a balance between strength and flexibility. A greater number of bridges would provide greater resistance to compressive forces but would limit flexibility and vice-versa. The AF contains an inner and an outer portion. They differ primarily in their collagen composition. While both are primarily collagen, the outer annulus contains mostly type I and type III collagen, while the inner has predominantly type II. The inner annulus also contains more proteoglycans than the outer. The ratio of type I to type II changes gradually; as the distance from the NP increases, the amount of type II collagen decreases, while the amount of type I increases. Another major difference between the two segments is the morphology of the connective tissue cells that secrete ECM. The cells of the inner annulus are described as round, while the outer annulus has a more oblong, fibroblast-like appearance [1][2].

2. Annular Tear or Fissure

There are three types of annular tears: circumferential tear, also known as delamination; annular rim tear; and radial tear. Histological studies of annular tears in painful discs have revealed the entire process of AF healing, including inflammatory cell infiltration, granulation tissue formation, and tissue remodelling, suggesting that the annulus fibrosus is actually torn and undergoes an active healing process. However, the healing process in disc tissue differs from that of normal tissues. In most tissues, healing progresses from deep to superficial layers, while in the intervertebral disc, the repair process moves from the vascularized outer layer of the annulus to the inner layer along the tear or injury. If the tear occurs in the inner layers of the annulus or NP, the healing process is not initiated. Healing of the torn AF is extremely difficult, possibly not only because a sparse cell population is unable to break down large bundles of collagen fibers from the annulus and replace them

with new bundles, but also because of insufficient blood supply [3].

Pre-clinical studies have shown that AF injury leads to increased production of proinflammatory molecules, including interleukin (IL)-1 β , IL-6, IL-8, tumor necrosis factor-alpha (TNF- α), and NGF [3]. In addition, increased levels of inflammatory cytokines TNF- α , IL-6, and IL-8 and matrix metalloproteinases (MMP)-3, MMP-10, and MMP-13 have been observed [3]. The secretion of pro-inflammatory cytokines, such as MMPs, is regulated by the mechanical microenvironment of the cells and can predispose the IVD to further mechanical damage and the generation of a number of characteristic lesions primarily in the AF [4].

3. Amniotic Membrane

Amniotic membrane (AM), innermost layer of the fetal membranes, is composed of three histologically distinct layers: the epithelial layer, the basement membrane and mesenchymal/stromal layer.

The epithelial layer comprises a flat, cuboidal and columnar cells uniformly disposed on the basement membrane, which consists mainly of collagen IV, elastin, fibronectin, laminin and proteoglycans. AECs are known to manufacture hepatocyte growth factor, epidermal growth factor, keratinocyte growth factor, and fibroblast growth factor. Through the production of these factors, AECs have been shown to promote epithelization, inhibit angiogenesis, inhibit fibroblast activation through the inhibition of transforming growth factor- β , promote neural differentiation, provide immunosuppression via inhibition of both innate and adaptive immune systems, promote tenocyte proliferation, as well as possess the capability for trilineage cell differentiation, or differentiation into all 3 germline lineages [5-7].

The mesenchymal layer is a vascular layer that abuts the chorion and contains 3 distinct sublayers: the compact, fibroblast, and spongy layers. The fibroblast layer provides for the structural integrity via type I and III collagen, arranged in parallel bundles, and contains the embryonic mesoderm derived mesenchymal stromal cells (AMSCs). AMSCs have shown capabilities for trilineage cell differentiation. In addition to a higher proliferative rate than adult-derived MSC sources, AMSCs have been found to promote angiogenesis through the expression of proangiogenic factors and suppress the innate and adaptive immune systems. The spongy layer is abundant in proteoglycans and glycoproteins, particularly hyaluronic acid, which is thought to serve as a primary inhibitor of transforming growth factor- β , resulting in cessation of scar formation. Additionally, the spongy layer possesses a loose, nonfibrillar collagen network connecting it to the adjacent chorion, which is exploited for tissue separation for various commercial graft products that are isolated amnion [5-7].

4. Some points to consider

- a. The AF consists primarily of Collagen (Collagen I and III on outside) along with other ECM components, such as proteoglycans, glycoproteins, elastin etc. The histologic composition of AM is similar and thus, its application can be considered as homologous use.
- b. The AF is a circumferential, collagen based barrier that surrounds the NP. The AF (the outer layer of the intervertebral disc) is a crucial barrier to prevent disc herniation. A herniated disc occurs when the soft, jelly-like center (nucleus pulposus) pushes through a weakened or damaged AF [11].
- c. A lumbar disc herniation cannot typically exist without a defect in the AF. For a herniation to occur, the nucleus pulposus (the inner, gelatinous part of the disc) must protrude through the outer layer of the disc, the AF. This protrusion requires a tear or fissure in the barrier or covering to the NP, namely a tear or fissure in the AF, which then allows the nucleus pulposus to extend beyond its normal boundaries.
- d. AM patching on injured tissue has shown low incidence of side-effects [4].
- e. Clinical studies have shown significant improvements in PROMs in patients post application of AM.
Example:
 - i. Clinical study has shown significant improvement in functional outcomes in patients in the AM group compared to the control group post lumbar microdiscectomy [9].
 - ii. Clinical study has shown significant improvement in the pain score in patients in the AM group compared to the control group during lumbar decompression [10].

wf. Lumbar microdiscectomy requires a surgical defect be made in the AF to resect extruded, protruded or herniated disc material [12].

g. Recurrent herniation occurs in 7% to 18% of patients following discectomy [13].

h. A large defect in the annulus fibrosus after surgery is a major risk factor for reherniation [14].

h. Application of cryopreserved Amniotic Membrane to the AF as a barrier or covering to the NP was found to be superior in both cost saving analysis, and recurrent disc herniation rates to standard of care in disc herniation surgery over a 2 year study [15].

Conclusion:

- *There is evidence based precedent that AM is homologous in structure to the AF.
- *There is evidence based precedent that AM, like the AF, is homologous as a barrier or covering to the NP.
- *There is evidence based precedent that the application of AM as a barrier or covering around the NP is safe and effective.
- *There is evidence based precedent that when AM is applied as a barrier or covering around the NP, the incidence of recurrent disc herniation declines.
- *There is evidence based precedent that when AM is applied as a barrier or covering around the NP, the cost of care declines.

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