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Review

The knee meniscus: Structure–function, pathophysiology, current repair techniques, and prospects for regeneration

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ABSTRACT

Extensive scientific investigations in recent decades have established the anatomical, biomechanical, and functional importance that the meniscus holds within the knee joint. As a vital part of the joint, it acts to prevent the deterioration and degeneration of articular cartilage, and the onset and development of osteoarthritis. For this reason, research into meniscus repair has been the recipient of particular interest from the orthopedic and bioengineering communities. Current repair techniques are only effective in treating lesions located in the peripheral vascularized region of the meniscus. Healing lesions found in the inner avascular region, which functions under a highly demanding mechanical environment, is considered to be a significant challenge. An adequate treatment approach has yet to be established, though many attempts have been undertaken. The current primary method for treatment is partial meniscectomy, which commonly results in the progressive development of osteoarthritis. This drawback has shifted research interest toward the fields of biomaterials and bioengineering, where it is hoped that meniscal deterioration can be tackled with the help of tissue engineering. So far, different approaches and strategies have contributed to the *in vitro* generation of meniscus constructs, which are capable of restoring meniscal lesions to some extent, both functionally as well as anatomically. The selection of the appropriate cell source (autologous, allogeneic, or xenogeneic cells, or stem cells) is undoubtedly regarded as key to successful meniscal tissue engineering. Furthermore, a large variation of scaffolds for tissue engineering have been proposed and produced in experimental and clinical studies, although a few problems with these (e.g., byproducts of degradation, stress shielding) have shifted research interest toward new strategies (e.g., scaffoldless approaches, self-assembly). A large number of different chemical (e.g., TGF-β1, C-ABC) and mechanical stimuli (e.g., direct compression, hydrostatic pressure) have also been investigated, both in terms of encouraging functional tissue formation, as well as in differentiating stem cells. Even though the problems accompanying meniscus tissue engineering research are considerable, we are undoubtedly in the dawn of a new era, whereby recent advances in biology, engineering, and medicine are leading to the successful treatment of meniscal lesions.

1. Introduction

Six decades ago, the discovery that removing the meniscus from the knee joint—then commonly seen as the sole technique for treating sports-related injuries—resulted in the deterioration of articular cartilage and the gradual development of arthritis, radically changed the approach for treating meniscus-related problems [1]. In 1982, partial meniscectomy was suggested as an alternative to complete meniscectomy [2], while the first published account of a meniscus transplant dates back to 1989 [3]. These studies are landmarks in understanding the anatomical and functional utility of the knee meniscus, and have since resulted in numerous investigations into different treatment approaches.

The current prevailing trend in repairing meniscus-related lesions is to maintain the tissue intact whenever possible [4–6]. However, the inability of surgeons to restore the tissue—both anatomically and functionally—in cases of complex or total traumatic lesions continues to present challenges. The simultaneous inability to delay the progressive development of osteoarthritis presents a similar motivation to search for new therapeutic avenues.

This review will cover current knowledge regarding anatomical and biochemical characteristics of the knee meniscus, and discuss the tissue's biomechanical and functional properties. The review will also address the causal pathologies precipitating the need for

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meniscus treatment, and the effectiveness of current tissue repair methods, among different age groups. Finally, current therapeutic developments in repairing the meniscus will be discussed, focusing especially on the field of tissue engineering. Within this topic, special emphasis will be placed on advances in scaffolds and scaffold-free approaches to regenerate meniscal tissue. Finally, perspectives for the future of meniscus repair will be given.

2. Structure and function of the knee meniscus

2.1. Meniscus anatomy

The knee joint contains the meniscus structure, comprised of both a medial and a lateral component situated between the corresponding femoral condyle and tibial plateau (Fig. 1) [7]. Each is a glossy-white, complex tissue comprised of cells, specialized extracellular matrix (ECM) molecules, and region-specific innervation and vascularization. Both menisci are critical components of a healthy knee joint [7–12]. The main stabilizing ligaments are the medial collateral ligament, the transverse ligament, the meniscofemoral ligaments, and attachments at the anterior and posterior horns (Fig. 2) [8]. The meniscofemoral ligaments, also known as the Humphrey and Wrisberg ligaments, connect the posterior horn of the lateral meniscus to a location near the insertion site of the posterior cruciate ligament on the medial femoral condyle. Though only 46% of people have both of these ligaments, 100% of people have at least one of them [8]. The meniscus surface appears smooth upon both gross inspection and microscopically [9]. Human medial and lateral menisci have distinctly different dimensions: lateral menisci are approximately 32.4–35.7 mm in length and 26.6–29.3 mm wide, while medial menisci are 40.5–45.5 mm long and 27 mm wide [10,11]. Though both menisci are roughly wedge-shaped and semilunar, lateral menisci display greater variety in size, shape, thickness, and mobility than medial menisci [12,13]. Lateral menisci also cover a larger portion of the tibial plateau (75–93% laterally) in comparison to medial menisci (51–74% medially) [13].

Vascularization in this tissue is of high relevance. From prenatal development until shortly after birth, the meniscus is fully vascularized. Afterward, however, vascularization appears to subside. At 10 years of age, vascularization is present in around 10–30% of the meniscus, and at maturity the meniscus contains blood vessels and nerves only in the peripheral 10–25% of the tissue [13]. Subsequently, two distinct regions of the meniscus can be distinguished: the outer, vascular/neural region (red-red zone), and the inner, completely avascular/aneural region (white-white zone). These two areas are separated by the red-white region, which presents attributes from both the red-red and white-white regions (Fig. 3). Critically, the healing capacity of each area is directly related to blood circulation, leaving the white region susceptible to permanent post-traumatic and degenerative lesions [14].

2.2. Biochemical content

Regarding composition by wet weight, the meniscus is highly hydrated (72% water), with the remaining 28% comprised of organic matter, mostly ECM and cells [15]. In general, collagens make up the

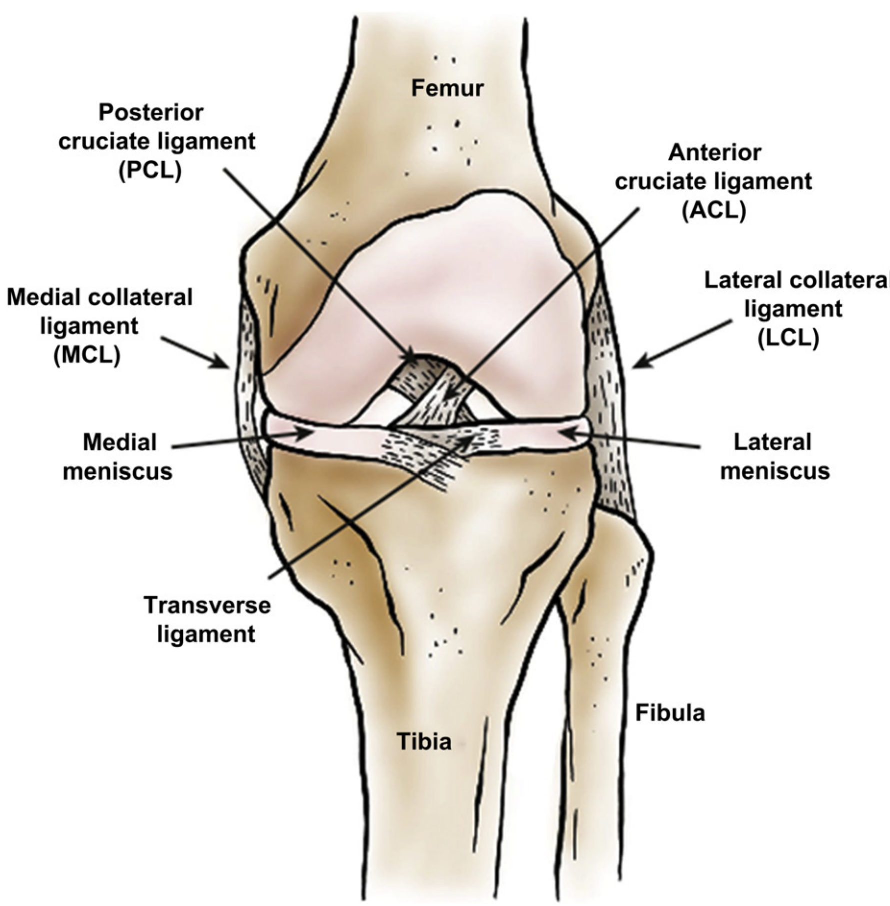

Fig. 1. Anatomy of the knee joint: anterior view. The knee meniscus is situated between the femur and the tibia. Crossing the meniscus are various ligaments, which aid in stabilizing the knee joint.