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Regenerative Engineering for Knee Osteoarthritis Treatment: Biomaterials and Cell-Based Technologies

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ABSTRACT

Knee osteoarthritis (OA) is the most common form of arthritis worldwide. The incidence of this disease is rising and its treatment poses an economic burden. Two early targets of knee OA treatment include the predominant symptom of pain, and cartilage damage in the knee joint. Current treatments have been beneficial in treating the disease but none is as effective as total knee arthroplasty (TKA). However, while TKA is an end-stage solution of the disease, it is an invasive and expensive procedure. Therefore, innovative regenerative engineering strategies should be established as these could defer or annul the need for a TKA. Several biomaterial and cell-based therapies are currently in development and have shown early promise in both preclinical and clinical studies. The use of advanced biomaterials and stem cells independently or in conjunction to treat knee OA could potentially reduce pain and regenerate focal articular cartilage damage. In this review, we discuss the pathogenesis of pain and cartilage damage in knee OA and explore novel treatment options currently being studied, along with some of their limitations.

1. Introduction

Osteoarthritis (OA) is a chronic, debilitating, and painful disease, and is the most common form of arthritis in the world. It is a complex disease that involves the entire synovial joint, including the articular cartilage, synovium, and subchondral bone [1,2]. The disease involves the release of pro-inflammatory factors in the joint, leading to structural derangements (Fig. 1). Importantly, OA is the leading cause of disability due to pain; it accounts for approximately 70% of arthritis-related hospital admissions and 23% of clinic visits for arthritis [3]. Knee OA is the most common form of OA, given the anatomical position, since the knee bears most of the weight of the body. Older adults above the age of 50 are at an increased risk for knee OA, possibly due to hormonal changes or senescence of chondrocytes [3,4]. With an estimated one-third of US adults living with obesity, two-thirds of these individuals are at risk of developing knee OA in their lifetime [1,5,6]. This risk could be due to increased weight bearing on the joint or to the

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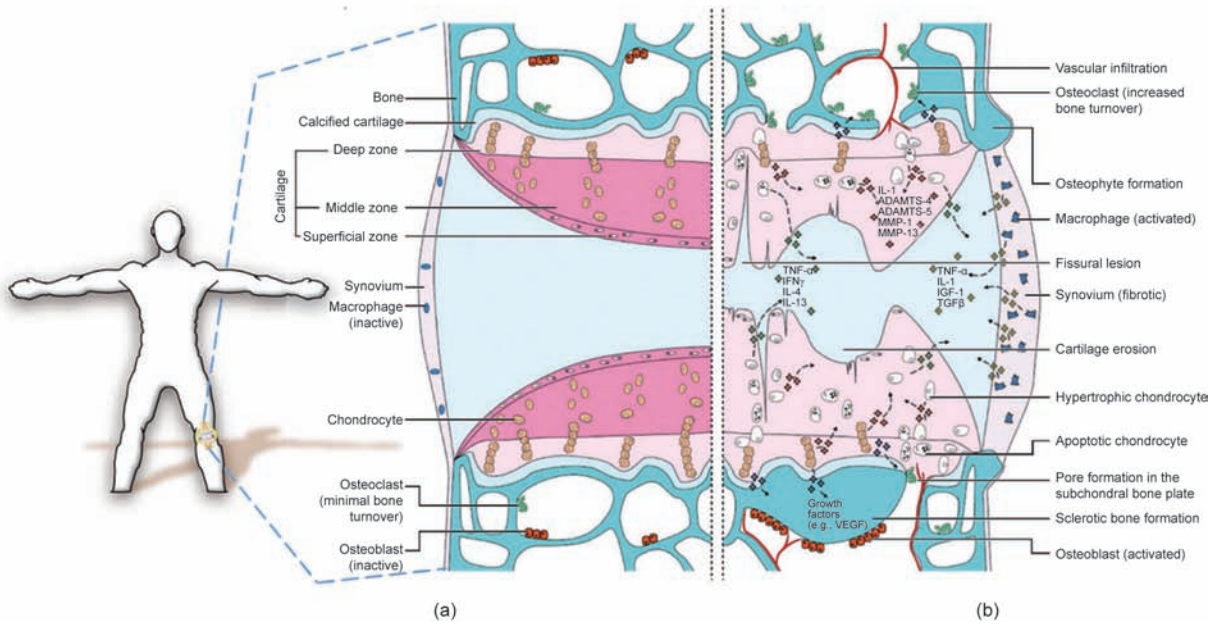

Fig. 1. Structural changes between (a) a healthy joint and (b) an OA joint. Expression of matrix proteinase plays an important role in inducing OA. (Adapted with permission from Ref. [2])

release of adipokines, which are cytokines released from adipose tissue. In the US, 27 million adults were estimated to have OA in 2008, with the number of adult arthritis patients projected to rise from 47.8 million in 2005 to more than 67 million by the year 2030 [7,8]. However, the number of individuals seeking medical help is predicted to increase even further through care programs such as the Affordable Care Act [9]. The total cost of the treatment of knee OA for each individual diagnosed with the disease exceeds $6000 USD per year, with a lifetime cost of over $100 000 USD [10,11]. This number is still modest, however, as the true cost of OA has not been taken into account. These additional costs include the loss of hours from work and the effect on the patient's quality of life due to disability from pain [12]. Thus, OA is a very significant health problem that poses a physical burden to patients and an economic burden to both patients and the healthcare system.

The end-stage surgical solution for knee OA, which accounts for most of the cost of OA treatment, is total knee arthroplasty (TKA) [3,10,11]. TKA involves replacement of the knee joint with prostheses made of metallic alloys and polymers. This procedure gives relief from pain, improves physical functions, and improves quality of life for most patients. However, it is not uncommon for revision surgeries to be necessary for failed joint replacements. It is projected that more than 3 million TKA procedures will be demanded by the year 2030, along with a nearly concomitant increase in revision surgeries [13]. This is an increase from 450 000 TKA procedures in 2005. With this increasing prevalence and cost of the management of knee OA, it is important to develop newer, less-invasive, and more cost-efficient therapeutic intervention for the disease. These treatments should also postpone or eliminate the need for a TKA.

Due to the increasing efforts of researchers, surgical procedures with varying success rates have already been developed. One notable example of such innovations is the less-invasive procedure of subchondroplasty. This involves the use of calcium phosphate bone substitutes to treat bone marrow lesions (BML), which are associated with the development of end-stage OA; thus, the procedure prevents severe OA and the need for TKA [14,15]. Despite the usefulness of this procedure, some patients do not fare well due to variability in patients [14]. In addition, the use of subchondroplasty is limited to BML. Hence, novel regenerative engineering strategies utilizing the latest advancements in biomaterial science, stem cell science, aspects from developmental biology, and physical forces will enable the development of translational therapies for knee OA treatment. "Regenerative engineering" has been defined as the convergence of advanced material science, stem cell science, physics, developmental biology, and clinical translation for the regeneration of complex tissue and organ systems [16,17].

In this review, we discuss the pathogenesis of the OA disease and current biomaterial and cell-based technologies to treat knee OA.

2. Osteoarthritis pain and treatment modalities

Pain is the number one reason for a patient's visit to the clinic when symptoms of knee OA arise [3]. This pain can occur without simultaneous radiographic evidence of knee OA [3,18]. The pain may be dull and constant with intermittent intense exacerbations. The etiology of OA pain is complex, with several modifiable and non-modifiable factors involved. Modifiable risk factors include weight, structural derangements, biological processes such as inflammation, and sociocultural factors [3,19]. Non-modifiable factors include patient genetics. We discuss the effects of inflammation, structural pathology such as articular cartilage damage, and other factors on pain in subsequent sections.

2.1. Osteoarthritis pain

The biological mechanisms that contribute to knee OA pain are patient dependent and not fully understood. Chondrocytes and other cell types present in the knee joint produce inflammatory mediators and degradative enzymes, leading to cellular apoptosis. The inflammatory process is induced by cytokines such as pro-inflammatory interleukins and tumor necrosis factor-α (TNF-α) [20]. These mediators may be recognized by receptors of nerve terminals present in the synovial joint. Such noxious stimuli can activate high-threshold ion channels, resulting in the propagation of pain signals from peripheral tissues to the central nervous system [21]. The cytokines produced in the osteoarthritic joint may act on the innervating joint nociceptors (myelinated or unmy-