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Review article

An overview of hydrogel-based intra-articular drug delivery for the treatment of osteoarthritis

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ABSTRACT

Drug administration by intra-articular injection is an emerging popular treatment for knee osteoarthritis (OA). This method of drug administration minimizes the toxic effects of the drugs administered systemically, and maximizes local effects. However, traditional oral drugs delivered *via* intra-articular injection are limited by the lack of sustained release. Injectable materials such as hydrogels or hydrogel microspheres have been extensively studied for their applications as intra-articular injection for the treatment of OA, which is attribute to their minimally invasive manner, extended drug retention time and high loading efficiency. In this review, we summarized hydrogel types and hydrogel characteristics for intra-articular injection, and the drugs, proteins and cells used in the injectable delivery systems. Through this review, we hope to inspire researchers to construct novel hydrogel-based delivery system for the intra-articular injection treatment of knee OA.

Contents

1. Introduction

Osteoarthritis (OA) is a progressive destructive joint disease that initially features as degenerated cartilage and secondary changes in the subchondral bone and synovium, which subsequently leads to osseous overgrowth and loss of motor function in the affected joints [1]. OA, frequently found in hip, knee, distal phalangeal and

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intervertebral joints [2], is a severe clinical and public health problem, causing pain, disability and a heavy health care burden for the society and family [3]. Symptomatic knee OA makes a significant impact on society, with 44.7% of people suffered from developing disability in their lifetime [4]. Despite the growing numbers of clinical treatments available for patients with OA, none of them is able to reverse disease progression [5]. Oral medications commonly used to manage OA are usually nonsteroidal anti-inflammatory drugs or opioids [6], which have the disadvantages to cause a wide variety of adverse effects, such as gastrointestinal reactions, obesity, and osteonecrosis, resulting in limited clinical applications. Traditionally, surgery is required for severe OA patients showing symptoms such as debilitating pain and major functional limitation (impaired walking, daily activities, and ability to sleep or work), as well as X-ray evidence of narrowing joint space [7]. However, such surgery often leads to additional complications and further repair surgery is often required, increasing the patient's dilemma on treatment options [8,9].

The joint capsule in the synovial joint constitutes a discrete anatomical compartment that allows the possibility of intra-articular drug administration, especially for knee OA patients. The local efficacy and system safety of intra-articular administered drugs, such as corticosteroids (CS) and hyaluronic acid (HA), have been reviewed, indicating their applicability for the treatment of knee OA [10]. Intra-articular injection treatments can specifically target drugs only to the affected joints while minimizing overall systemic exposure. However, the low retention time limits the application of intra-articular injection treatments. It has been found that articular cartilage possesses hydrogel-like mechanical properties with a compressive modulus of 0.7–0.8 MPa, a shear modulus of similar magnitude (0.69 MPa), and a tensile modulus of 0.3–10 MPa, which are reminiscent of that of hydrogel [11].

Hydrogel contains a three dimensional polymer network cross-linked chemically, physically or ionically, with water as the predominant dispersion medium [12]. Their classification may be based on the source (natural or synthetic hydrogels), the nature of cross-linking (covalent or physical hydrogels), the nature of the inner networks (homopolymer networks, copolymer networks, interpenetrating networks, or double networks), and their fate *in vivo* (degradable or non-degradable hydrogels) [13]. Biocompatibility, biodegradability, nontoxicity and non-immunogenicity are basic characteristics for hydrogels used in intra-articular injection [14]. Viscosupplementation (VS) is a recommended intervention in intra-articular injection treatment of knee OA [5]. Hyaluronic acid (HA) is not only an abundant material in the synovial fluid, but also a natural material to form hydrogels. Based on the knowledge and researches of HA and HA-based hydrogel, researchers began to investigate other hydrogels with chemical constructions resembling HA for VS treatment, such as chitosan-based hydrogels [15] and alginate-based hydrogels [16]. In order to improve retention time of the aforementioned hydrogels in knee joint, researchers have made chemical modification of their molecular structure. Furthermore, hydrogels may afford to carry the burden of various drugs due to the internal networks formation during gelation. They could be used as vehicles to effectively deliver drugs into joints, and localize the curative constituents. Recent studies have constructed local delivery systems capable of long-term sustained release of drugs, proteins, and cells to treat knee OA [11,17]. Moreover, microspheres and nanospheres made from different kinds of materials have been introduced into hydrogels. These newly formed injectable delivery systems have revealed the superiority of hydrogels and increased efficacy of OA "drugs" local treatment by avoiding systemic side effects.

This review is focused on hydrogel-based delivery system in association with drugs, proteins, and cells which could relieve symptoms or change progression of OA. The modification of hydrogel materials and the mode of delivery system would be listed and analyzed based on the categories of hydrogels. We hope to inspire researchers to develop novel hydrogel-based delivery systems to treat knee OA.

2. Articular cartilage and osteoarthritis

The normal knee joint (top two panels) is organized into distinct structural elements, including the two articulating bones (femur and tibia), the articular cartilage covering the adjacent bone surfaces, and the synovial lining of the joint cavity [18]. Serving as osteochondral unit, alteration in the composition or structure of any individual components of the articular cartilage, subchondral bone and calcified cartilage results in the disruption of joint integrity and the loss of function, which is known as clinical syndrome of osteoarthritis (OA) [19]. Researches in animal models and clinical analysis of cartilage specimens from patients with OA reveal sequence of pathological changes in the cartilage matrix associated with OA initiation and progression [20]. In early stage of OA, pathological changes include swelling and degradation of cartilage matrix in the superficial zone of the cartilage, and increases of metabolic activity of chondrocytes. With the progression of OA, cartilage matrix lose proteoglycans and collagen network erodes, the synthesis of degradative enzymes (such as matrix metalloproteinase 13, metalloproteinase with thrombospondin motifs-5) further exacerbates the breakdown of articular cartilage. In addition to cartilage degeneration, synovial membrane always suffers inflammation due to the mechanical changes in OA cartilage, and makes OA disease more debilitating. In late stage of OA, the penetration of vascular elements, sensory and sympathetic nerves into the osteochondral layer is evident. Osseous outgrowths called osteophytes often form at the joint margins as well as subchondral bone sclerosis. The revealed details of OA progression inspire clinical physicians and fundamental researchers explore proper treatment strategies to tackle symptomatic OA.

3. OA intra-articular injection treatment strategies

Due to the closure of inner space of articular cavity, it is possible to localize the treatment agents inside articular cavity for a time. It avoids or minimizes side effects of oral administered drugs, such as gastrointestinal complications for nonsteroidal anti-inflammatory drugs (NSAIDs) [21], potential toxicity for acetaminophen [22], nausea and vomiting for opioid analgesics [23].

HA is the most abundant glycosaminoglycan in mammalian tissue. In the human body, the largest reservoir of HA is the synovial fluid (SF) of the diarthrodial joints with HA concentrations ranging from 0.5 to 4 mg/mL [24,25]. The high concentration of HA in SF is essential for normal joint function, wear reduction, and articular cartilage attrition during joint motion. In normal joints, HA (molecular weight, Mw, ranging from 2×10^6 to 10×10^6 Da) forms a network, which allows the reciprocal flow of water and small solutes between articular cartilage and capillaries in the synovium to adapt to the various pressures induced by diarthrodial joints movement [26,27]. OA responds to the decrease in the concentration and reduction in the molecular weight of hyaluronan in the SF [28]. Intra-articular injection of hyaluronic acid (HA) is known as viscosupplementation. Basic studies have shown that the molecular weight of HA varies from 0.5×10^6 to 1×10^6 Da with HA possessing high viscoinduction capacity, and that the oligosaccharides of HA trigger endogenous HA synthesis, thus high-Mw HA is involved in viscosupplementation [29,30]. HA has a short half-life (1–2 days) in the tissue, limiting its applications as a biocompatible, biodegradable and non-immunogenic polymer [31]. Chemical modification and cross-linking of HA have increased the retention