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Review

Hyaluronate and its derivatives for customized biomedical applications

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ABSTRACT

Since hyaluronate (HA) was firstly isolated from the vitreous of bovine eyes in 1934, HA has been widely investigated for various biomedical applications. As a naturally-occurring polysaccharide, HA has been used for joint lubrication and ocular treatment in its intact form due to the excellent biocompatibility, viscoelasticity, biodegradability, and hygroscopic properties. HA can be easily functionalized via the chemical modification of its carboxyl and hydroxyl groups. Recently, a variety of biological functions of HA have been explored and a number of customized applications have been investigated taking advantages of the interaction between HA and biological tissues. HA has been used for drug delivery to enhance the blood circulation time of drugs with target-specificity to HA receptors in the body. HA has been also used to prepare tissue engineering hydrogel scaffolds for the spatiotemporal control of encapsulated cells. In this review, we describe the key biological functions of HA in the body in terms of its structure, physical properties, biodistribution and interaction with HA receptors. After that, we describe unique advantages that allow HA to be applied in various biomedical fields. Finally, we report the conventional and newly emerging applications of HA and its derivatives under commercial development stages.

1. Introduction

Hyaluronate (HA) is a naturally occurring anionic polysaccharide with disaccharide repeating units of D-glucuronic acid and N-acetyl-D-glucosamine linked via alternating β (1 → 4) and β (1 → 3) glycosidic bonds [1]. HA was isolated from the vitreous of bovine eyes for the first time in 1934 and subsequently characterized for its unique properties in the body [2]. After that, HA has been considered for a wide variety of biomedical applications [3–5]. In the early stage, HA isolated from human umbilical cords [6] and rooster combs [7] was used for biomedical applications without further modification. HA was used as a vitreous supplement during eye surgery [8,9] and a supplement in the synovium of osteoarthritic joints [10,11]. Since HA was able to be produced efficiently through a large scale microbial fermentation process [12,13], it has been extensively applied to diverse biomedical fields. According to the medical needs for various therapeutic applications, HA derivatives have been developed to construct different platforms including hydrogels [14], nanoparticles [15], drug conjugates [16] and so on.

HA has distinct advantages for biomedical applications compared to widely used synthetic polymers such as poly(ethylene glycol) (PEG) and poly(lactic-co-glycolic acid) (PLGA). First, because HA is a natural ubiquitous polysaccharide, it avoids controversial safety issues [17,18]. For comparison, despite the FDA approval of PLGA, it is limited to certain medical applications mostly due to the acidified surrounding tissues after its degradation in the body [19]. Although chitosan is a promising natural cationic biopolymer, some studies indicate that its intravenous administration at high doses can cause significant adverse effects due to the fatal blood aggregation [20,21]. In contrast, HA is relatively free from the risk of toxicity or immunogenicity, and various HA products have been commercialized after FDA approval in the forms of dermal filler [22], intraarticular injection [23], ophthalmic solution [17] and so forth. Second, HA is easily degraded in the human body by enzymatic degradation of hyaluronidase (HAse) [24]. Although there are

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several commercialized PEGylated drugs with a prolonged half-life [25,26], the slow clearance of high molecular weight (MW) PEG has raised critical concerns about its potential adverse effects after repeated administrations for chronic diseases [27,28]. On the other hand, HA exhibits rapid clearance in its natural form, and its degradation rate can be controlled by chemical modification [29,30], accelerating commercial development and FDA approval of its related products. Third, HA has inherent interaction via HA receptors with cells and tissues in the body, enabling unique biological functions. For example, HA can be selectively accumulated in liver tissues without targeting moieties because of its abundant receptors on the liver cells [31,32]. In contrast, other polymers such as PEG, PLGA, and poloxamer should be modified with targeting ligands for the same purpose. Owing to these superior properties, HA has been recognized as one of the best polymers for various biomedical applications.

This review provides a comprehensive description for biological characteristics of HA and its derivatives for customized biomedical applications. We first present biological functions of HA in the body from a few different points of views including structural properties, biological fate after administration, and specific interaction with its receptors. After that, we describe customized biomedical applications of HA and its derivatives according to the diverse biological properties of HA in various fields including drug delivery and tissue engineering. Finally, we describe perspectives on HA as a re-emerging historic biopolymer which may provide a clear cue for current unmet medical needs.

2. Biological functions of HA in the body

The clear understanding of key biological functions of HA is the important starting point for its customized biomedical applications. As shown in Fig. 1, HA has hydrophilic groups including hydroxyl groups, carboxyl groups, and acetamido groups which not only form hydrogen bonds each other but also interact with water molecules, providing high water solubility and hydrophilicity to HA [33,34]. Remarkably, unlike typical hydrophilic polymers, HA contains axial hydrogen atoms (C–H) as shown in red color in Fig. 1, which form an extensive hydrophobic patch domain [35]. Because highly hydrophilic groups and hydrophobic patches coexist on the backbone of HA, it exhibits a unique amphiphilic property. When HA is externally administered into the body, for example, by intravenous injection, HA disappears with a half-life of a few min during circulation and most of HA is delivered to the liver. HA is internalized and subsequently degraded by liver sinusoidal endothelial cells (LSECs) in the liver and its degradation products are detected in the circulation only 20 min after injection. The half-life of injected HA in other tissues is 12 h in skin and joints, 1–1.5 h in the anterior chamber of eyes, 70 days in the vitreous body (Fig. 1) [36].

After accumulation in various organs, HA has been known to interact with its receptors, such as cluster determinant 44 (CD44), receptor for hyaluronate-mediated motility (RHAMM), HA receptor for endocytosis (HARE), and lymphatic vessel endothelial HA receptor-1 (LYVE-1) [16]. These HA receptors are distributed in several organs as shown in Fig. 1 and play pivotal roles in regulating cell proliferation, migration, and differentiation by activating signaling cascades as well as endocytosis and degradation of HA [37]. Among them, CD44 is the most intensively investigated receptor due to its wide distribution in a variety of cells. The binding of HA to CD44 results in cell adhesion, cell migration, induction of hematopoietic differentiation, and interactive signaling for cell activation [38]. The binding of HA to RHAMM is reported to regulate angiogenesis associated with endothelial cell proliferation in addition to cellular responses of fibroblasts and smooth cells to growth factors [37,39]. Both HARE and LYVE-1 play important roles in receptor-mediated endocytosis and degradation of HA in the lymphatic system [40,41]. Due to the broad distribution of HA receptors in the body and their unique interaction with biological tissues, HA has been successfully applied as a targeting ligand for drug delivery and tissue engineering.

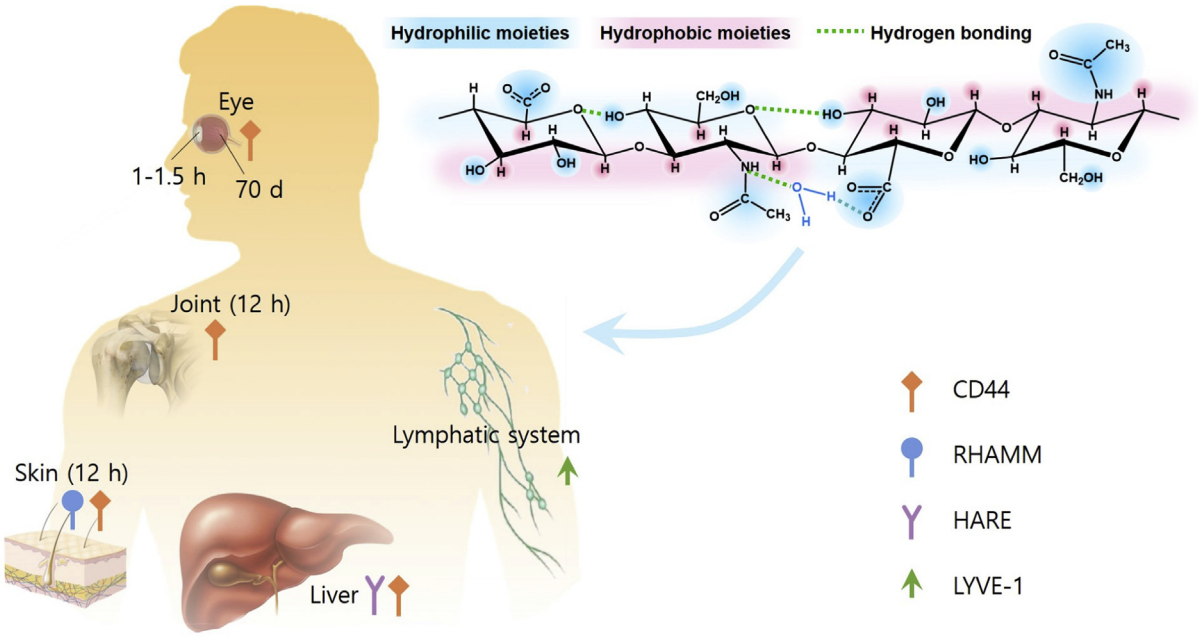

Fig. 1. Chemical structure of hyaluronate (HA) and distribution of HA receptors in the body. The half-life of HA is described after injection into various tissues. In the chemical structure, hydrophilic (blue) and hydrophobic (red) moieties are indicated, and the hydrogen bonding is represented by green dashed lines. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)