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Hyaluronan as a therapeutic target in human diseases☆

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ABSTRACT

Accumulation and turnover of extracellular matrix is a hallmark of tissue injury, repair and remodeling in human diseases. Hyaluronan is a major component of the extracellular matrix and plays an important role in regulating tissue injury and repair, and controlling disease outcomes. The function of hyaluronan depends on its size, location, and interactions with binding partners. While fragmented hyaluronan stimulates the expression of an array of genes by a variety of cell types regulating inflammatory responses and tissue repair, cell surface hyaluronan provides protection against tissue damage from the environment and promotes regeneration and repair. The interactions of hyaluronan and its binding proteins participate in the pathogenesis of many human diseases. Thus, targeting hyaluronan and its interactions with cells and proteins may provide new approaches to developing therapeutics for inflammatory and fibrosing diseases. This review focuses on the role of hyaluronan in biological and pathological processes, and as a potential therapeutic target in human diseases.

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Abbreviations: HA, hyaluronan or hyaluronic acid; HAS, hyaluronan synthase; HYAL, hyaluronidase; HMW, high molecule weight; LMW, low molecule weight; HMMR, hyaluronan-mediated motility receptor; HARE, hyaluronan receptor for endocytosis; LYVE1, lymphatic vessel endothelial hyaluronan receptor 1; TNFIP6, tumor necrosis factor α-induced protein 6; CEMIP, cell-migration induced protein, hyaluronan binding; IPF, idiopathic pulmonary fibrosis; COPD, chronic obstructive pulmonary disease; BOS, bronchiolitis obliterans syndrome; 4-MU, 4-methylumbelliferone; IBD, inflammatory bowl disease; DSS, dextran sulfate sodium.

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1. Introduction

Hyaluronan (hyaluronic acid, HA) is a major component of extracellular matrix and is a non-sulfated glycosaminoglycan composed of repeating polymeric disaccharides D-glucuronic acid and N-acetyl-D-glucosamine linked by a glucuronidic β(1 → 3) bond. In humans, HA exist in all tissues and is abundant in the vitreous of the eye, the umbilical cord, synovial fluid, heart valves, skin, and skeletal tissues. HA can be produced by many cell types [1,2], although mesenchymal cells are believed to be the predominant source of HA [3]. HA has multiple functions in normal biological states, such as space filling, hydration, lubrication of joints, and provision of a matrix through which cells can migrate [3]. HA is actively produced during tissue injury [4], regulating tissue repair and disease processes, such as activation of inflammatory cells to mount an innate response to injury [5] and regulation of behavior of epithelial cells [6–10] and fibroblasts [11,12]. HA has been investigated in a wide range of biological and medical fields, and the research articles referring to HA have grown exponentially in recent years (Fig. 1).

There are many excellent reviews on the roles of HA in different fields, such as in angiogenesis [4], reactive oxygen species [13], HA digestion [14], cancer [3,15,16], cancer therapeutics [17], cancer metastasis [18], chondrocytes [19], lung injury [20–22], wound healing [23], diabetes [24], leukocyte trafficking [25], and in immune regulation [5,26,27]. The current review will summarize the role of HA in biological and pathological conditions, and will emphasize the role of HA in human diseases.

1.1. HA synthases

HA is synthesized by membrane-bound synthases, and there are three mammalian hyaluronan synthases (HAS1–3) [28]. All three proteins are bona fide HA synthases. In vitro transfection experiments showed that HAS1 and HAS3 generated HA with broad size distributions (molecular masses of 2 × 105 to approximately 2 × 106 Da), whereas HAS2 generated HA with a broad but extremely large size (average molecular mass of > 2 × 106 Da) [29]. Subsequent studies suggested that all three HAS enzymes drive the biosynthesis and release of high molecular weight (HMW) HA (1 × 106 Da) [30]. Deletion of murine Has1 [31] or Has3 [12] or Has1–Has3 double knockout [32] did not reveal a significant phenotype under homeostatic conditions, whereas Has2 deletion generated an embryonic lethal phenotype due to impaired cardiac development [33]. With tissue injury, both Has1 [32] and Has3 deletions [12,32] showed dysregulated tissue repair. Wound closure was significantly faster in Has1 and Has3 double null mice [32]. HAS2 protects skin fibroblasts against apoptosis induced by environmental stress such as UV exposure and serum starvation [34]. Furthermore, Has3 deficiency causes reduction in brain extracellular space leading to altered neuronal activity and seizures [35]. These studies generate important insights into the roles of hyaluronan in disease states.

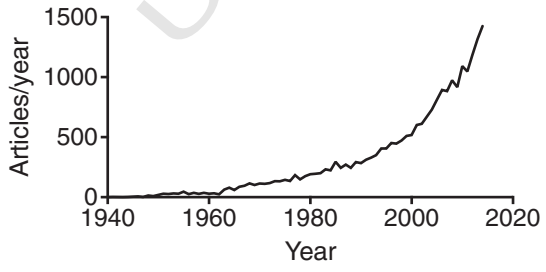

Fig. 1. Scientific articles published referring to "hyaluronan" from 1940 to 2014. The number of articles published in each of the past years from 1940 to 2014 was identified by searching the PubMed database (http://www.ncbi.nlm.nih.gov/sites/entrez) using the search terms (hyaluronan OR hyaluronic acid) queried on August 8, 2015.

1.2. HA degradating enzymes

Hyaluronidases (also called hyaluronoglucosaminidases) hydrolyze the hexosaminidic β(1–4) linkages between N-acetyl-D-glucosamine and D-glucuronic acid residues in HA and release disaccharide D-glucuronic acid-N-acetyl-D-glucosamine or HA fragments. In humans, there are six members of a gene family containing hyaluronidases identified: hyaluronidases 1–4, PH-20, and HYALP1 [14,36]. Although Hyal1 deficient mice are viable, fertile and show no gross abnormalities, these mice do develop osteoarthritis [37]. HA fragments control dendritic cell migration from the skin, and HYAL1 expression activated migration and promoted loss of dendritic cells from the skin [38].

Hyal2 deficient mice displayed a significant increase in plasma HA and increased HA in the interstitial extracellular matrix of atrial cardiomyocytes [39,40], suggesting that HYAL2 is essential for the breakdown of extracellular HA. Hyal2 deficient mice showed severe cardiopulmonary dysfunction [40]. Platelet-derived hyaluronidase 2 cleaves HA into fragments that trigger monocyte-mediated production of pro-inflammatory cytokines [41].

Hyal3 deficient mice showed a subtle change in the alveolar structure and extracellular matrix thickness in lung-tissues at 12–14 months-of-age, although there was no evidence of HA accumulation, suggesting that HYAL3 may not play a major role in constitutive HA degradation [42].

PH20 is elevated in demyelinating lesions and increased PH20 expression is sufficient to inhibit oligodendrocyte progenitor cell maturation and remyelination [43] (Table 1). Q3

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