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RESEARCH REVIEW

The Role of Hyaluronic Acid in Atherosclerosis and Intimal Hyperplasia

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Atherosclerosis is a chronic inflammatory condition of the blood vessel wall that can lead to arterial narrowing and subsequent vascular compromise. Although there are a variety of open and endovascular procedures used to alleviate the obstructions caused by atherosclerotic plaque, blood vessel instrumentation itself can lead to renarrowing of the vessel lumen through intimal hyperplasia, wound contracture, or a combination of the two. While the cell types involved in both atherosclerosis and vessel renarrowing after surgical intervention are largely characterized, current research has shown that components of the extracellular matrix are also important in the pathogenesis of the aforementioned processes. One such component is hyaluronic acid (HA). The objective of this review, therefore, is to examine the involvement of HA in these pathologic processes.

Literature on the structure and function of HA was reviewed, with particular attention given to the role of HA in the processes of atherogenesis, intimal hyperplasia, and wound contracture after blood vessel instrumentation.

HA interacts with vascular smooth muscle cells (VSMCs), endothelial cells (ECs), and platelets to promote atherogenesis. In particular, VSMCs manufacture large amounts of HA that form "cable-like" structures important for leukocyte adhesion and rolling. Additionally, transmigration of leukocytes across the EC layer is mediated by HA. Platelets cleave large molecules of HA into fragments that up-regulate leukocyte production of chemokines and cytokines. HA also has a role in both intimal hyperplasia and wound contracture, the two processes most responsible for vessel renarrowing after vascular instrumentation.

HA has a complex, and sometimes conflicting, role in the pathologic processes of atherogenesis and vessel wall renarrowing after surgical intervention.

Key Words: **hyaluronic acid; CD44; RHAMM; extracellular matrix; atherosclerosis; restenosis; vascular smooth muscle cells; endothelial cells; platelets; leukocytes.**

INTRODUCTION

Atherosclerosis is a chronic inflammatory disease of the blood vessel wall [1–3]. Disease progression eventually leads to plaque formation and narrowing of the vessel lumen [1, 2]. Medical therapy and lifestyle modification are the mainstays of treatment for atherosclerosis, but some atherosclerotic lesions progress to the point where surgical intervention is required [1]. Unfortunately, both percutaneous interventions and open surgical procedures also injure the vessel wall and can precipitate renarrowing of the vessel lumen secondary to intimal hyperplasia (IH), wound contracture, or both [4].

Early research intent on determining the pathogenesis of both atherosclerosis and renarrowing of the vessel lumen after surgical intervention mainly focused on the role of the platelets and cellular components in these processes, including vascular smooth muscle cells (VSMCs), macrophages, and endothelial cells (ECs) [1]. However, biologically active elements of the extracellular matrix (ECM) are also important in the vascular remodeling that takes place in both atherosclerosis and renarrowing of the vessel lumen after instrumentation [2, 5].

One such element of the ECM that is important in both of these processes is hyaluronic acid (HA), otherwise known as hyaluronan [2]. HA is a negatively-charged glycosaminoglycan (GAG) present in abundance in the

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body, especially in the skin, articular joints, vitreous humor of the eye, and the vasculature (Fig. 1A) [6]. Originally thought to be a mere "space-filler" in the ECM, it is now known that HA has important roles both structurally and as a signaling molecule [7]. Specifically, HA regulates cell adhesion, migration, and differentiation, and is involved in a host of cellular processes including morphogenesis, regeneration, and wound healing [5, 7, 8]. With regard to the pathogenesis of atherosclerosis and renarrowing of the vessel lumen after vascular instrumentation, HA is a key component of the lesions associated with both processes [4, 9]. Additionally, HA appears to interact with many cellular components involved in both atherosclerosis and vessel renarrowing after surgical intervention, most importantly VSMCs and leukocytes [2]. The purpose of this review, therefore, is to examine the role of HA in the pathogenesis of both atherosclerosis and the processes causing vessel renarrowing after surgical instrumentation.

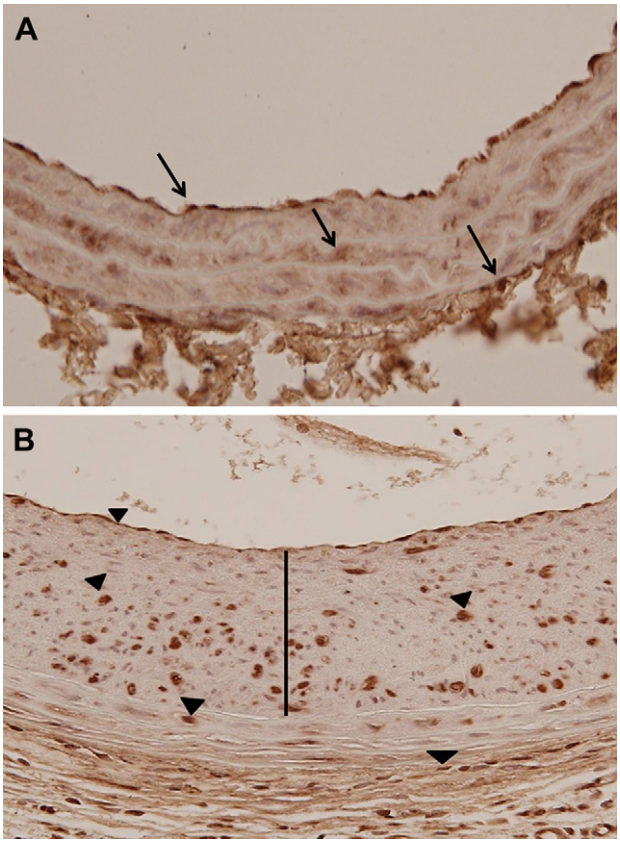

FIG. 1. (A) Immunohistochemistry staining showing the presence of HA in an uninjured carotid artery of a male Sprague Dawley rat. HA was detected with a polyclonal sheep primary antibody (1:200) and stained brown in color. HA (arrows) is present in the endothelial and smooth muscle cell layer but is most prominent in the connective tissue of the adventitia (×40). (B) Immunohistochemical staining showing the presence of HA after arterial injury by balloon catheter in a male Sprague Dawley rat. At 44 d after arterial injury, the area of intimal hyperplasia is pronounced at the lumen surface (solid black line). There is strong HA staining (arrowheads) now localized to the area of IH, with patchy distribution near smooth muscle cells in the medial layer (×40).

STRUCTURE, SYNTHESIS, AND DEGRADATION

Structure

HA is a straight-chain GAG of the ECM composed of repeating disaccharides of glucuronic acid and *N*-acetyl glucosamine linked by alternating β1-3 and β1-4 linkages (Fig. 2) [10, 11]. Interestingly, HA undergoes little chemical modification as no sulfated, acetylated, or phosphorylated variants of this molecule exist [10, 11]. The simple structure of HA is stable, allowing for rapid recovery after mechanical distortion or compression [10]. Furthermore, the structure of HA has osmotic properties important for maintenance of fluid volume in the joint space [12]. HA exists as both high molecular weight (3000–4000 kDa) and low molecular weight fragments (20 kDa) [13]. HA is synthesized in the high molecular weight form and the low molecular weight form is generated by degradation of the parent molecule (reviewed below) [13].

Synthesis

Unlike other GAGs that are synthesized at the Golgi apparatus and endoplasmic reticulum around a protein core, HA is synthesized on the cytoplasmic surface of the plasma membrane as a free linear polymer [7, 11, 14, 15]. The three known HA synthases (HAS)—HAS-1, HAS-2, and HAS-3— produce HA polymers of varying lengths [8, 11, 16], and expression of these three isoforms is cell- and tissue-specific [11]. The HA synthases are integral membrane proteins and they are able to translocate the growing HA polymer out of the cell as it is being synthesized [11, 17]. The energy expenditure for synthesizing an average length HA chain (about 10,000 disaccharide repeats) is significant—50,000 ATP molecules, 20,000 NAD cofactors, and 10,000 acetylCoA groups are required [7].

Degradation

Overall, the total body turnover of HA is on the order of several grams per day [15, 18, 19]. HA catabolism

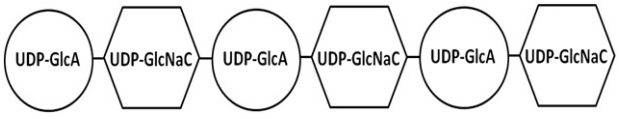

FIG. 2. Hyaluronic acid structure. Hyaluronic acid is composed of repeating disaccharides of glucuronic acid and *N*-acetyl glucosamine linked by alternating β1-3 and β1-4 linkages. UDP-GlcA = uridine diphosphate glucuronic acid; UDP-GlcNaC = uridine diphosphate *N*-acetyl glucosamine.