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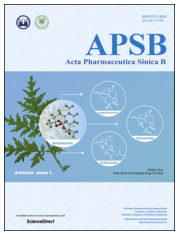

REVIEW

Targeting hyaluronan for the treatment of pancreatic ductal adenocarcinoma

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Abstract Progression of cancer is often associated with interactions between cancer cells and extracellular matrix (ECM) surrounding them. Increasing evidence has suggested that accumulation of hyaluronan (HA), a major component of ECM, provides a favorable microenvironment for cancer progression. Pancreatic ductal adenocarcinoma (PDAC) is characterized typically by a dense desmoplastic stroma with a large amount of HA, making this molecule as an attractive target for therapy. Several studies have shown efficacy of inhibitors of HA synthesis or signaling for the treatment of PDAC. Recent studies have also demonstrated substantial improvements in the effects of chemotherapy by a targeted depletion of stromal HA in PDAC using an enzymatic agent. Thus, targeting HA has been recognized as a promising therapeutic strategy to treat this highly aggressive neoplasm. In this review article, we summarize our current understanding of the role of HA in the progression of PDAC and discuss possible therapeutic approaches targeting HA.

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1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most aggressive and intractable solid tumors, which often invades surrounding stromal components, including lymphatic, vascular, and perineural systems, ultimately metastasizing to distant organs. Despite recent advances in the clinical management, the survival rate in patients with PDAC remains the lowest among all cancer types, emphasizing the need for a better understanding of its biology. In particular, identification of molecular mechanisms underlying the aggressive behaviors of PDAC can provide the basis for the development of targets for therapeutic intervention[1]. Although substantial progress has been made in our understanding of the genetic and epigenetic alterations in PDAC, the identification of these molecular defects in cancer cells has led to little progress in developing new treatment strategies[2,3].

The progression of cancer is governed by complex mechanisms and is significantly accelerated by tumor microenvironment composed of extracellular matrix (ECM), such as collagen, fibronectin, laminin, and hyaluronan (HA)[4]. Among the ECM components, HA has been extensively studied in its relation to cancer initiation and progression. HA, a large polysaccharide composed of repeating disaccharides of glucuronic acid and *N*-acetyl-glucosamine, plays a critical role in a variety of cellular processes[5]. HA regulates cell adhesion, migration, and proliferation by interacting with specific cell surface receptors including CD44 and receptor for HA-mediated motility (RHAMM)[6]. HA is synthesized by hyaluronan synthases (HAS, including HAS1, HAS2, and HAS3) and is degraded by hyaluronidases (such as HYAL1 and HYAL2)[5,7,8]. In normal physiological conditions, the amount of HA is controlled by a balance between synthesis and degradation; however, HA has been shown to be abundantly accumulated in the surrounding stroma of malignant tumor[9,10]. The HA-rich microenvironment may promote tumor progression by enhancing cell proliferation, migration, invasion, metastasis, angiogenesis, and resistance to chemotherapeutic agents[9,10].

Because PDAC is characterized typically by a dense desmoplastic stroma containing a large amount of ECM, it is highly probable that HA is involved in the malignant properties of this tumor type. In fact, several studies have shown increased expression of HA and its receptors in PDAC[11–16]. In an experimental model of PDAC, accumulation of extracellular HA by HAS overexpression accelerated tumor growth[17]. These findings strongly suggest that HA could be a therapeutic target in PDAC. Only a few studies, however, have addressed the effects of HA inhibitors for the treatment of PDAC[18–20]. More recently, two studies have shown that inhibition of HA by PEGPH20, an HA-targeting enzymatic agent, substantially augments the effect of chemotherapy with gemcitabine in animal models[21,22]. These findings suggest a novel therapeutic approach to combat the chemoresistance of PDAC by targeting HA. In this review article, we summarize the current understanding of the role of HA in PDAC and discuss its potential therapeutic applications.

2. Role of HA in the progression of PDAC

HA is a large, linear glycosaminoglycan that consists of repeating disaccharide subunits of glucuronic acid and *N*-acetylglucosamine produced by HA synthases (HAS1, HAS2, and HAS3) and degraded by hyaluronidases (mainly HYAL1 and HYAL2)[5]. In normal physiological conditions, the amounts of HA in tissues are tightly regulated by a balance between synthesis and degradation. In certain cancers, HA is often increased or highly concentrated in tumor cells and, particularly, in their surrounding ECM. There have been several studies investigating the degree of HA concentration and/or pattern of HA expression in PDAC. For example, a previous study showed that HA is secreted from cultured human pancreatic cancer cell lines[11]. In addition, the amount of HA is increased in human PDAC tissues (12-fold increase) as compared to the normal pancreas[14]. Using a biotinylated HA-binding protein isolated from bovine cartilage, Fries et al.[12] demonstrated that in primary PDAC tissues, HA was found predominantly in the connective tissue immediately around tumor cells or at the border between the tumor and normal pancreatic tissue. A comprehensive analysis of the HA content in a variety of human malignant tumors revealed that PDAC had the highest incidence of detectable HA content, which was predominantly associated with the desmoplastic stroma rather than with tumor cells[21]. We also used immunohistochemistry to analyze the expression of HA and its regulators (including HAS2 and HYAL1) in primary PDAC[16], and demonstrated that HA is strongly expressed in 80% of primary PDAC tissues with a staining being detected both in tumor and stromal components (Fig. 1). Importantly, strong HA expression was an independent prognostic factor in patients with PDAC undergoing resection, suggesting a prognostic significance of HA in PDAC[16].

Little is known about the mechanism by which HA is aberrantly accumulated in PDAC. One possible mechanism is increased production of HA from cancer cells themselves through its accelerated synthesis. In fact, our previous study demonstrated overexpression of one of the HA synthases, HAS2, in PDAC tissues[16]. We and other researches also demonstrated that cultured PDAC cells secrete a certain amount of HA into conditioned media[23,24]. Furthermore, we recently discovered that epigenetic mechanism (namely DNA methylation) is involved in the regulation of HA synthesis in PDAC cells[24]. Another mechanism may be related to the enhanced secretion of HA from stromal cells, including fibroblasts. In support of this, it has been shown that HA staining was predominantly associated with the desmoplastic stroma rather than with tumor cells in human PDAC tissues[15,21]. Interestingly, Knudson et al.[25] demonstrated that direct coculture between tumor cells (including PDAC cells) and normal fibroblasts promotes the production of HA into the culture medium.

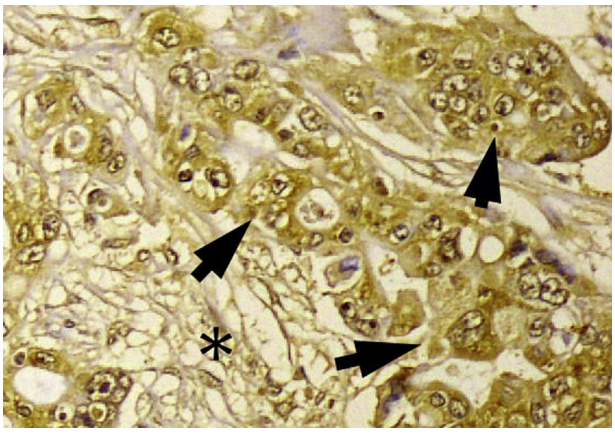

Figure 1 Overexpression of hyaluronan in human pancreatic ductal adenocarcinoma tissue by immunohistochemical staining. Strong staining is observed mainly in tumor cells (arrows) but is also present in stroma (*).