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New findings of heparanase in human diseases

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Abstract. – OBJECTIVE: This mini-review aims to discuss research works about heparanase published in 2017 and 2018 and provide a direction for therapy methods targeting heparanase.

PATIENTS AND METHODS: The relevant data were searched by using keywords "heparanase", "function", "diseases" and "inhibitors" in "PubMed, "Web of Science" and "China Knowledge Resource Integrated databases (CNKI)", and a hand-search was done to acquire peer-reviewed articles and reports about heparanase.

RESULTS: Except for tumor progression, pathological processes including procoagulant activities, preeclamptic placentas, inflammation and so on are all verified to be associated with heparanase activity. Also, these newly-found functions are closely connected to certain cellular activities, including epithelial to mesenchymal transition (EMT).

CONCLUSIONS: It could be concluded that heparanase would be a potential and valuable therapeutic target.

Key Words:
Heparanase, Function, Diseases, Inhibitors.

Introduction

As a component of the extracellular matrix (ECM), heparan sulfate (HS) chains have a significant metabolic function. They consist of heparan sulfate proteoglycans (HSPG), which take an important part in numerous biological processes, including keeping the structural matrix stable, forming basement membranes and binding to the receptors of various signaling molecules[1]. A large number of biological processes in diseased and healthy conditions are associated with HS and HSPG. Considering the vital role of HS and HSPG, enzymes regulating HS and HSPG should also be emphasized. Among the regulating enzymes, heparanase is an outstanding one[1]. Heparanase could degrade HS specifically and in this way, it could affect a lot of biological processes.

The distinctive role of heparanase has been widely researched and heparanase's function in tumor progression, angiogenesis and many other pathological activities have been already verified. This mini-review aims to report new findings of heparanase's function in the last two years and tries to promote the clinical application of heparanase inhibitors.

EMT

Epithelial-mesenchymal transition (EMT) was a change in cell phenotypes which has been demonstrated to have an effect in the process of tumorigenicity[2]. Heparanase has already been verified to play a role in fibroblast growth factor-2-induced EMT, accompanied by syndecan-1.

In 2017, Masola et al[3] demonstrated that in mesothelial cell EMT, heparanase also plays a central part. Via an *in vitro* study which employs several biomolecular strategies, their experiment proved that pharmacological inhibition of heparanase could reverse EMT and minimize fibrosis. They verified that heparanase inhibitors had become a valuable therapeutic method for patients on peritoneal dialysis. Gastric signet-ring cell adenocarcinoma (SRCA) is a particular gastric carcinoma that has notable fibrosis, fast-speed invasion and also frequent metastasis. Shah et al[4] showed that in SRCA, heparanase has a close relationship with EMT-related fibrosis. Heparanase gene expression and EMT-related molecular gene expression are consistent in SRCA tissues. Their

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study provided a promising therapeutic target in the treatment of SRCA.

Procoagulant Activity

The procoagulant activity of heparanase has been discussed by Vlodavsky et al[5]. Their study showed that in heparanase-over-expressed transgenic mice and leukemia patients, the increase of tumor vascularity was correlated with the up-regulation of heparanase. They presumed that a peptide that corresponds to the heparin-binding domain exerted the pro-coagulant function of heparanase and angiogenic factors were released by heparanase from the ECM to induce an angiogenic response *in vivo*.

In 2017, Crispel et al[6] identified the heparanase procoagulant domain and the peptides were derived from this domain. In the experiment, bleeding time was significantly shortened, and wound healing was enhanced by the peptides.

On the other hand, Bayam et al[7] published a relevant paper in 2018. They described the auto-action of heparanase in a thrombus burden and thromboembolism. Their study showed that the inhibition function of heparanase's procoagulant domain could be a therapeutic target for tumors and sepsis.

However, heparanase's procoagulant function could be affected in several particular situations. In 2018, Matan et al[8] proved that the procoagulant ability of heparanase would decrease during sepsis. Moreover, the procoagulant activity of heparanase would return to normal levels immediately once the patient recovered. Although the particular mechanism of this phenomenon needs further exploration, this finding may be of great value in predicting severe sepsis risk.

Protumor

Marker of Poor Prognosis

The protumor function of heparanase has long been recognized and has been observed in a variety of human tumors, including tumors of the head and neck, bladder, breast, pancreas, cervix, colon, ovary, endometrium, thyroid, liver and so on[1]. In 2017, some new findings supplemented this theory.

In the review article of Barbosa et al[9], heparanase's function in cleaving HS could promote the physiopathological process of prostate ECM turnover and the progress of prostate cancer. Goldberg's experiment[10] in breast carcinoma also verified heparanase's pro-tumor function. In that study, heparanase promotes breast tumorigenesis in patients with hyperinsulinemia. In the 2017 study of Vornicova et al[11], heparanase could be an indicator in the early diagnosis of breast cancer and help determine the treatment type of breast cancer. Sun et al[12] demonstrated that heparanase overexpression suggested poor prognosis of breast cancer. Spyrou et al[13] showed that heparanase promotes the aggressiveness of pediatric brain tumors. In the paper of Barash et al[14], both preclinical and clinical data showed that heparanase is of great significance in mesothelioma progression.

From this study, we may regard heparanase as a therapeutic target for patients with cancer

Promotes Tumor Metastasis

In 2018, Yang et al[15] showed that heparanase plays an important role in mitotic spindle regulation. According to their study, chromosomes would become unstable when heparanase lost its function on the microtubule organization center (MTOC). After that, oncogenesis would develop.

Wei et al[16] suggested that heparanase is able to mediate cell adhesion, which contributes to the circulating tumor cell (CTC) clusters. CTC would also mediate metastasis.

Putz et al[17] were the first to report that heparanase plays an important part in the invasion of NK cells and promotes the progression of tumors. On the other hand, it could be indicated that heparanase inhibitors may be able to restrict NK cell infiltration.

Promotes Tumor Angiogenesis

In 2018, Zechendorf et al[18] indicated that heparanase played a role in septic cardiomyopathy. In the study of Lv et al[19], heparanase combined with IL-17A, contributed to the tumor angiogenesis in cervical cancer through the nuclear factor kappa-B (NF-κB) signaling pathway.

Inflammation

A notable example of heparanase's pro-inflammatory function is the study by García et al[20]. In their research, heparanase overexpression was detected in the inflammatory condition of keratoconic corneas. The role of heparanase in inflammation could also be depicted by Changyaleket et al[21]. Their experiment illustrated that heparanase

could mediate the neuroinflammatory response in subarachnoid hemorrhage (SAH). SAH-related neurological deficits could be promoted by heparanase, leading to early brain injury.

Normal and preeclamptic placentas

Hambruch et al[22] indicated that heparanase might be involved in bovine placental maturation. They showed that heparanase helped to reduce fetomaternal adhesion by degrading the matrix, thus promoting the post-parturition membrane separation.

Che et al[23] observed that heparanase can be a potential predictive biomarker for preeclampsia at an early stage of pregnancy and represents a promising therapeutic target for the treatment of preeclampsia.

Renal Disease

Szymczak et al[24] showed an increase in heparanase activity in patients with lupus nephritis and membranous nephropathy. Heparanase could be a marker of membranous nephropathy and lupus nephritis. In the study of Abassi et al[25], heparanase was regarded as an important factor in renal injury development and kidney dysfunction promotion. The inhibition of heparanase could be an effective therapeutic method for acute kidney injury. Masola et al[26] also found that heparanase contributed to kidney damage by regulating pro-fibrotic factors.

Viral Infections

Neel et al[27] pointed out the role of heparanase in viral pathogenesis. They verified that the expression of heparanase will be upregulated in viral infections, including Herpes simplex virus, dengue virus, human papillomavirus, respiratory syncytial virus, adenovirus, hepatitis C virus, and porcine respiratory and reproductive syncytial virus. They concluded that heparanase played a significant role in viral infections.

To better understand heparanase's role in Herpes simplex virus-1 (HSV-1), Agelidis et al[28] demonstrated that heparanase may be the trigger for HSV-1 infection and heparanase was upregulated by HSV-1 infection in human corneal epithelial cells. The upregulated heparanase moved to the nucleus and promoted viral spread afterward. Their findings suggested that heparanase could serve as a driver of the viral spread of HSV-1 infection.

Liver Fibrosis

Secchi et al[29] drew the conclusion that heparanase could affect liver fibrosis along with macrophages. Their work suggested that inflammatory macrophages are significant sources of heparanase and heparanase contributes to the macrophage-mediated activation of hepatic stellate cells. They suggested that heparanase was involved in early liver damage. Heparanase-targeting compounds could be promising in liver fibrosis treatment.

Nervous System

Xiong et al[30] demonstrated that heparanase could promote the differentiation of embryonic stem (ES) cells into neural lineage cells. In their study, heparanase-overexpressed ES cells had a more rapid growth rate than normal ES cells. Erk and Akt phosphorylation caused by heparanase overexpression played an important role.

Garcia et al[31] discovered a relationship between heparanase expression and Alzheimer's Disease (AD). They found that in the brain tissue of AD patients, heparanase and heparanase-2 could be detected in degenerated neurons and core-fragmented neuritic plaques. In the work of Changyaleket et al[32], the role of heparanase in stroke, multiple sclerosis and glioma growth has also been clarified.

Heparanase was also indicated to attenuate axon degeneration which was caused by sciatic-nerve-transection by regulating the Schwann cell injury response and axon-glia support. This finding may lead to a new therapy method[33].

Inhibitors of Heparanase

In 2017, Rondanin et al[34] investigated an arylamidonaphtalene sulfonate compound with anti-angiogenic and anti-metastatic properties was named FCE27266. The results suggested that FCE27266 had strong heparanase inhibition activity and no cytotoxic effects. These similar abilities were also found in SST0546NA1 (17a, an FCE27266 analogue)[34].

An experimental demonstration of CircHIPK3's inhibition effect was first carried out by Li et al[35] in 2017. In their paper, the "microRNA

sponges" role of CircHIPK3 was described and the treatment role of CircHIPK3 in malignant bladder carcinoma was evaluated.

The first study illuminating that aspirin could be a therapy target was reported by Dai et al[36] in 2017. Aspirin could prevent cancer metastasis and angiogenesis in this way. In 2017, Loka et al[37] conducted a series of computational researches to extract HS-heparanase interactions. Afterward, they used the interactions as a template to design HS-mimicking glycopolymers. Finally, they confirmed that a 12-repeating-units glycopolymer was the most potent inhibitor that had a strong heparanase-binding ability.

Another heparanase inhibitor was observed by Poupard et al[38] in 2017. They demonstrated 11 kDa RD-GS-λ-Carrageenan as an effective heparanase inhibitor and a potential anti-angiogenic agent. A zinc ionophore called pyrithione was found to have an inhibition effect on heparanase in the research of Guo et al[39] in 2017. Pyrithione could restrict the release of the virus by inhibiting heparanase and reducing the replication of the virus. Baburajeev et al[40] discovered that 1,2,4-triazolo-1,3,4-thiadiazoles could be a promising heparanase inhibitor in humans.

Among the recently discovered heparanase inhibitors, arctigenin is a special one that is extracted from the seeds of *Arctium lappa* L. Lou et al[41] demonstrated that arctigenin could downregulate heparanase expression and consequently prevent MDA-MB-231 cells' invasion and migration, even though the mechanism remains to be clarified. Another inhibitor of heparanase named roneparstat was described by Rossini et al[42] in 2018. They concluded that roneparstat could modulate and enhance the microenvironment during anti-lymphoma therapy. Particularly, a kind of bionic nanodevice (Beijing, China) exploiting heparanase, which is tumor cell-selective, showed a good effect in combating breast carcinoma. The nanodevice was invented by Lang et al[43] and provided a promising method for treating breast cancer.

Conclusions

Studies have shown that heparanase plays an important role in tumor development. However, new features of heparanase still need to be explored, since the mechanisms of heparanase's functions are still not totally clarified. With the discovery of heparanase's new functions, a wider range application of heparanase inhibitors in clinical medicine would be possible. Considering the role of heparanase in human diseases, the inhibitors of heparanase are promising targets in treatment.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Data access and responsibility

All authors had full access to all the data in the study and Prof. Min Cui takes responsibility for the integrity of the data and the accuracy of the data analysis.

Author contributions

Hao Jin and Min Cui drafted the manuscript. Shixiong Hu undertook critical revision of the manuscript for important intellectual content.

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