Heparanase, A Key Target for Gene Therapy against Human Malignancies

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Invasion and metastasis are key features of many human malignant tumors. In the process of invasion and metastasis, tumor cells must break through the barrier of the extracellular matrix (ECM) and the basement membrane (BM). The key in this procedure is the ECM-degrading enzymes secreted by tumor cells. The major component of ECM and BM is heparan sulfate proteoglycan (HSPG), which is mainly composed of a protein core and several heparan sulfate (HS) side-chains[1]. Heparanase, an endoglycosidase, is a novel ECM-degrading enzyme that cleaves HS at several sites. It induces the degradation of the ECM and BM, facilitates the migration of tumor cells, and releases HS-bound active fibroblast growth factor (FGF) and vascular endothelial growth factor (VEGF), and, therefore, promotes tumor invasion, metastasis, and angiogenesis[2,3]. Heparanase is aberrantly expressed by many human malignancies, such as gastrointestinal carcinoma, hepatocellular carcinoma, breast carcinoma, metastatic melanoma, and carcinomas of ovary, prostate, bladder, and pancreas[4,5,6,7,8,9,10,11]. In addition, the heparanase expression level is closely correlated to the invasive and metastatic potency of the tumor cells and the prognosis of the cancer patients[7,8,9,10,11]. By virtue of its important roles in the process of tumor progression, heparanase has been considered a key target for antitumor drug development[1,2,3].

It has been reported that nonanticoagulant species of heparin, several sulfated oligosaccharides, and sulfated polysaccharides can inhibit the enzymatic activity of heparanase and, therefore, inhibit tumor invasion, metastasis, and angiogenesis[12,13,14,15]. One representative of these inhibitors, a sulfated oligosaccharide named PI-88, is being tested in multicenter clinical trials[14]. However, recent studies indicate that heparanase can also promote tumor progression independently by its nonenzymatic activity through activating phosphatidylinositol 3-kinase (PI3 K)/protein kinase B (PKB/AKT) and p38 signaling pathways, inducing the expression of cyclooxygenase 2 (COX-2), VEGF, and FGF2, or promoting adhesion of tumor cells to ECM[16,17,18,19,20]. These nonenzymatic functions of heparanase may contribute to the limited efficiency of heparanase enzymatic inhibitors in cancer therapy.

Due to the potential nonspecific and enzymatically limited inhibitory activities of these inhibitors, as well as the great difficulties in identifying efficient inhibitors, genetic approaches targeting heparanase have been regarded as promising alternatives[21,22,23,24,25]. Uno et al. constructed an adenoviral vector carrying an antisense, full-length, human heparanase cDNA and found that the heparanase expression, the in vitro invasiveness, and in vivo metastasis of human lung cancer A549 cells were specifically
inhibited[22]. A similar study also found that the inhibition of heparanase expression was efficacious in the prevention and treatment of melanoma metastasis[23]. A recent study by Zhang et al. shows that genetic inhibition of human heparanase by specific antisense oligodeoxynucleotide (AS-ODN) or small interfering RNA (siRNA) can efficiently regress the invasion, metastasis, angiogenesis, and in vivo tumor growth of human hepatocellular carcinoma[24]. Together with another report demonstrating that AS-ODN against human heparanase inhibits the expression of heparanase and the in vitro invasiveness of human mammary carcinoma cells in a dose-dependent manner[25], accumulating evidence have suggested that small inhibitory genetic molecules (e.g., AS-ODN and siRNA) targeting heparanase are of great value in the control and treatment of human malignancies.

Although the genetic blocking molecules have been shown to inhibit the expression of heparanase and regress tumor progression, the methods of stable transfection of these molecules have some limits for clinical application, such as gene integration, expression efficiency, and drug withdrawal difficulties. Alternatively, the transient transfection of some small genetic molecules, such as AS-ODN and siRNA, is more similar to the regular drug administration. For example, they can be easily synthesized, administered, and withdrawn[26,27,28]. AS-ODN is a potential therapeutic agent that can inhibit gene expression in a sequence-specific manner[26,27]. RNA interference (RNAi) is a post-transcriptional mechanism of gene silencing through chromatin remodeling, inhibition of protein translation, or direct mRNA degradation[28]. Data from the recent studies have demonstrated that down-regulation of the expression of heparanase by either AS-ODN or siRNA can efficiently inhibit the invasion and metastasis, as well as angiogenesis of human hepatocellular carcinoma and mammary carcinoma[24,25]. Therefore, AS-ODN and siRNA specific for human heparanase may be of potential value in the treatment of human cancers.

The genetic blocking methods employing AS-ODN and siRNA are powerful technologies that hold great promise in cancer therapy. Nevertheless, further investigations are required to overcome the obstacles for their successful clinical application, such as the delivery efficiency, nonspecific immune responses, incomplete gene suppression, and even the off-target effects.

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REFERENCES

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