SPECIAL ARTICLES

Effects of Sulfated Polysaccharides on Tumour Biology

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ABSTRACT

Sulfated polysaccharides can act not only as anticoagulants but also as tumour inhibitors. Recent studies suggest that sulfated polysaccharides could affect tumour cells directly. Sulfated polysaccharides could inhibit the metastasis and proliferation of tumour cells by binding to growth factors and cell adhesion molecules. Moreover, sulfated polysaccharides could inhibit heparanase, which cleaves heparan sulfate chains of heparan sulfate proteoglycans and cause release of growth factors sequestered by heparan sulfate chains. Some sulfated polysaccharides can induce apoptosis and differentiation of tumour cells, but the mechanism is uncertain. In addition, sulfated polysaccharides can enhance the innate and adaptive immune response for tumour cells. Thus, the anti-tumour mechanism of sulfated polysaccharides can be explained, at least partly, through the effects on tumour biology directly.

Efectos de los Polisacáridos Sulfatados en la Biología Tumoral

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RESUMEN

Los polisacáridos sulfatados podrían actuar no solamente como anticoagulantes, sino también como inhibidores del tumor. Estudios recientes sugieren que los polisacáridos sulfatados podrían afectar directamente las células tumorales. Los polisacáridos tumorales podrían inhibir la metástasis y la proliferación de las células tumorales por medio de la unión con los factores de crecimiento y las moléculas de adhesión celular. Además, los polisacáridos sulfatados podrían inhibir la heparanasa, que rompe las cadenas de heparán-sulfato del proteoglicano de heparán-sulfato, dando lugar a la liberación de los factores de crecimiento secuestrados por las cadenas de heparán-sulfato. Algunos polisacáridos sulfatados podrían inducir la apoptosis y diferenciación de las células tumorales, pero el mecanismo es incierto. Además, los polisacáridos sulfatados podrían mejorar la respuesta inmunológica innata y adaptativa frente a las células tumorales. De este modo, el mecanismo antitumoral de los polisacáridos sulfatados pudiera explicarse – al menos parcialmente – a partir de los efectos sobre la biología tumoral directamente.

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INTRODUCTION

Sulfated oligosaccharides, such as heparan, heparan sulfate, chondroitin 4-sulfate, chondroitin 6-sulfate and dermatan sulfate, are important ingredients of extracellular matrix (ECM). Recently, many sulfated polysaccharides have been extracted from bacteria, plants and animals. Patients with cancer have an increased risk of venous thromboembolic complications (1). Clinical trials have suggested that low molecular weight heparin (LMWH) provides a survival advantage for cancer patients with established thrombosis (2, 3). Furthermore, some experimental studies suggested that the anti-thrombotic activity play an important role in the anti-tumour effects of sulfated polysaccharides. Sulfated polysaccharides could suppress the proliferation and metastasis of tumour cells by the inhibition of tissue factor, thrombin, thrombus formation and platelet aggregation (4).

However, other studies suggested that the anti-metastatic and anti-thrombotic activities of sulfated polysaccharides were unrelated (5, 6). Clinical trials have indicated that sul-

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fated polysaccharides influenced the survival in animals and patients with advanced malignancy favourably but without venous thromboembolism (7, 8). Besides thrombin, sulfated polysaccharides bind to a wide range of proteins, such as growth factors and cell adhesion molecules. As a consequence, it is more likely that the anti-cancer mechanisms of sulfated polysaccharides are not purely an anti-thrombotic effect. In the present review, we evaluated the anti-cancer effect of sulfated polysaccharides on tumour biology.

Inhibit Metastasis

In addition to providing structural integrity of ECM, heparan sulfate proteoglycans act as storage depot for a variety of heparan sulfate-binding proteins. Heparanase is an endo-glucuronidase that hydrolyze internal glycosidic linkages of heparan sulfate in cell surface and ECM, thus causing release of growth factors sequestered by heparan sulfate chains. Heparanase is over-expressed by most cancer cells and accelerate tumour growth and metastasis. The anti-metastatic effect of sulfated polysaccharides is partly attributed to their heparanase-inhibiting activity (4, 9, 10). In addition, sulfated oligosaccharides could bind vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF) but are unable to present VEGF and FGF to their high-affinity receptors. As a result, sulfated oligosaccharides inhibit VEGF- and FGF-mediated angiogenesis (12–18).

Some components of the ECM, such as collagen, laminin, fibrinogen, fibronectin and vitronectin, possess heparin-binding domains, which have affinities for heparins or heparin-like molecules. Interactions between heparin-like molecules on the cell surface and heparin-binding domains on fibronectin, vitronectin or laminin can enhance cell migration, whereas soluble heparins inhibit such interaction and consequently lead to inhibition of migration of tumour cells (2, 19).

Inhibit Proliferation

It is controversial whether sulfated polysaccharides could affect the proliferation of tumour cells (18, 20–24). Heparins inhibit the growth of human hepatoma HepG2 cells, whereas heparan sulfates had no effect on the growth of HepG2 cells. Neither heparins nor heparan sulfates had any effect on the growth of poorly differentiated and highly metastatic hepatoma cell lines, SK-Hep-1 and PLC/PRF/5 (21). In addition, heparins and LMWH inhibit the proliferation of rat hepatoma cell lines, FAO (25). Therefore, inhibition of proliferation may be mediated by the chemical properties of sulfated polysaccharides and the species of tumour cells.

Heparanase causes release of growth factors sequestered by heparan sulfate chains. Sulfated polysaccharides can inhibit heparanase and directly bind to growth factors to inhibit the growth of tumours (21, 25–27). Angiogenesis is a process that is critical for tumour growth. The anti-proliferative effect of sulfated polysaccharides is partly attributed to anti-angiogenesis. In addition, fucoidan and sulfated heteropolysaccharide isolated from the red alga *Schizymenia dubyi* have anti-proliferative activity with a block observed in the G_1 phase (23, 28).

Induce Apoptosis

PI-88, a sulfated oligosaccharide, induces apoptosis of pancreatic islet carcinoma (18). B-1, a sulfated polysaccharide isolated from the culture filtrate of marine *Pseudomonas spp*, induces apoptosis of human leukaemic cells (U937) **(**29). Internalized sulfated glycosaminoglycans interfere with transcription factor function and subsequently induce apoptosis of murine melanoma cells (30). Fucoidan-induced apoptosis in human lymphoma HS-Sultan cell lines is accompanied by the activation of caspase-3 and down-regulation of extracellular signal-regulated kinase pathway (24).

Induce Differentiation

Sulfate polysaccharide structures change during cell differentiation and sulfated polysaccharide-growth factor interactions may be affected by such changes. Human colon carcinoma cells (CaCo-2) undergo spontaneous differentiation in culture when grown on semi-permeable supports. A greater proportion of 2-O-sulfated iduronic acid units and a smaller amount of 6-O-sulfated glucosamine units exist in differentiated than in undifferentiated cells. The structural changes affect the binding of heparan sulfate to the long isoform of platelet-derived growth factor A chain but not to FGF2 (31). Significant alterations in the charge, size and sulfation pattern of heparan sulfate in PC12 phaeochromocytoma cell accompany nerve growth factor-induced differentiation and neurite outgrowth (32). The sulfated heteropolysaccharide isolated from the red alga *Schizymenia dubyi can* induce the terminal maturation of non-small-cell bronchopulmonary carcinoma cells (NSCLC-N6) and arrest cells in the G_1 phase (33).

Immune Regulation

Most studies support that sulfated polysaccharides can enhance the innate immune response by promoting the tumoricidal activities of macrophages and natural killer cells (34–37). Antigen-presenting cells migrate into and out of tumour tissue to present tumour antigen to T- helper cells, as well as to produce cytokines, such as interleukin-1 beta and TNF-alpha that stimulate T-helper cells. As a result, T-helper cells promote the activity of cytotoxic T-cell, which has the strong cytotoxic effect on tumour cells. Sulfated polysaccharides can enhance the adaptive immune response by promoting such process (36, 38–40). Recent studies have implicated that sulfated polysaccharides recognize a range of cell adhesion systems. Sulfated polysaccharide could bind to CD_2, CD_3 and CD_4 in T lymphocytes and enhance the proliferative response of T lymphocytes (41–43).

CONCLUSION

Besides thrombin, sulfated polysaccharides bind to a wide range of proteins, such as growth factors and cell adhesion molecules. As a consequence, sulfated polysaccharides could affect the proliferation, differentiation, apoptosis and metastasis of tumour cells. In addition, sulfated polysaccharides could enhance the innate and adaptive immune response to tumour cells.

Thus, the anti-tumour mechanism of sulfated polysaccharides could be explained, at least partly, through the effects on tumour biology directly.

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