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Potentiation of anti-angiogenic activity of heparin by blocking the ATIII-interacting pentasaccharide unit and increasing net anionic charge

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ABSTRACT

Heparin, a potent anticoagulant used for the prevention of venous thromboembolism, has been recognized as a tumor angiogenesis inhibitor. Its limitation in clinical application for cancer therapy, however, arises from its strong anticoagulant activity, which causes associated adverse effects. In this study, we show the structural correlation of LHT7, a previously developed heparin-based angiogenesis inhibitor, with its influence on VEGF blockade and its decreased anticoagulant activity. LHT7 was characterized as having average seven molecules of sodium taurocholates conjugated to one molecule of low-molecular-weight heparin (LMWH). This study showed that the conjugation of sodium taurocholates selectively blocked interaction with antithrombin III (ATIII) while enhancing the binding with VEGF. This resulted in LHT7 to have negligible anticoagulant activity but potent anti-angiogenic activity. Following up on this finding, we showed that the bidirectional effect of sodium taurocholate conjugation was due to its unique structure, that is, the sterane core hindering the ATIII-binding pentasaccharide unit of LMWH with its bulky and rigid structural characteristics while the terminal sulfate group interacts with VEGF to produce stronger binding. In addition, we showed that LHT7 was localized in the tumor, especially on the endothelial cells. One explanation for this might be that LHT7 was delivered to the tumor via platelets.

1. Introduction

Angiogenesis is a crucial step in tumor progression by which tumor grows and survives beyond the certain size; on the other hand, tumor that has inadequate blood supply turns necrotic or apoptotic [1]. Among many pro-angiogenic growth factors that are involved in angiogenesis, VEGF is known as the key regulator at the initial stage of tumor angiogenesis, affecting survival, migration and proliferation of endothelial cells [2]. Therefore, it has been regarded as the most attractive therapeutic target in inhibiting angiogenesis.

Heparin, a member of highly sulfated endogenous glycosaminoglycan family, is a promising mother molecule candidate for broad-spectrum angiogenesis inhibitor. Although heparin is clinically approved as a potent anticoagulant agent, its other physiological functions such as ability to interact with various endogenous proteins are also shown by many studies. Many of these proteins, including VEGF, FGF1, FGF2, PDGF, HB-EGF, heparanase, MMPs and selectins are crucially involved in many stages of tumor progression [3–5]. However, direct clinical application of heparin for cancer therapy has limitations because of its strong anticoagulant activity and relatively weak anticancer effect. Therefore, many efforts have been made to develop heparin-based anticancer agents by various approaches, including the use of non-anticoagulant fractions of heparin [6], chemical modification of heparin [7,8] or synthesizing

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