

Antimetastatic Potential of a Low Anticoagulant Heparin Derived from Bovine Intestinal Mucosa

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Introduction

Heparin is frequently used in the treatment of cancer-associated thromboembolism and several clinical studies indicate that it prolongs patients' survival. Such beneficial effect may arise from its attenuating effect on metastasis. However, the usefulness of heparin as an anticancer drug has been hindered by its anticoagulant effect. Pharmaceutical-grade heparin is commonly obtained from porcine intestinal mucosa, but in a few countries, bovine mucosa is also used. The latter exhibits approximately half anticoagulant effect of the first. Recently, we isolated a fraction from bovine heparin with very low-anticoagulant activity.

Objectives

The aim of this study is to evaluate the antimetastatic potential of a low anticoagulant heparin obtained from bovine mucosal heparin.

Material and Methods

Bovine heparin was fractionated on a Mono Q column coupled to a HPLC system using a step-wise NaCl gradient. The two fractions isolated (F1 and F2) showed differences in their structures and anticoagulant activities. To evaluate anti-metastatic effect of heparins, mice (8–12 weeks old) were intravenously administrated with PBS, bovine UFH or F1 (8 mg/kg) and injected with B16F10 melanoma cells 10 minutes later. Mice were terminated after 21 days and lungs were macroscopically evaluated for number of metastatic foci.

Results and Discussion

Fractions F1 and F2 were characterized according their chemical structure, molecular weight and anticoagulant activities. F1 displays a lower degree of sulfation and only 25% anticoagulant potency of bovine UFH. The experimental metastasis model showed that the number of metastatic foci was drastically reduced in bovine UFH or F1-treated animals comparing to controls.

Conclusions

The F1 fraction presents significant antimetastatic potential and low anticoagulant activity. Considering the high dependence of metastasis on P-selectin-mediated cell interactions, these data suggest a competitive ability of F1 fraction with ligands of P-selectin.

Keywords: porcine heparin, bovine heparin, antimetastatic effect.

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