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Commentary

Ability of Heparin in Pro-Tumorigenic Activity of Cancer Cell Exosomes and Its Associated Improvement in Cancer Prognosis

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DESCRIPTION

Cancer-associated thrombosis is a major cause of mortality in cancer patients, with death commonly arising from Venous Thromboembolism (VTE), a resultant of the ability of cancer cells to activate the blood coagulation cascade as well as other prothrombotic properties of host cells. The anticoagulant heparin is widely used in these circumstances for the prevention of thrombosis and the associated conditions such as pulmonary embolism and atrial fibrillation [1].

As a member of the heparin sulfate proteoglycan family, heparin can also modulate the proliferation, adhesion, angiogenesis, migration and invasion of cancer cells *via* multiple mechanisms. Thus, heparin may improve outcomes in patients with cancer by reducing the risk of venous thromboembolic disease as well as a direct anti-tumour effect, in which it was established that it also exerts an anti-cancer effect presumably by acting as a modulator of the multiplicity of ways by which it can control cell genotype and phenotype [2].

Tumor cells actively shed exosomes into their surrounding microenvironment and growing evidence indicates that these vesicles have pleiotropic functions in the regulation of tumor progression, promoting immune escape, tumor invasion, neovascularization, and metastasis [3]. Exosomes are small extracellular vesicles (diameter, 30-90 nm), produced by a wide variety of cell types including reticulocytes, epithelial cells, neurons, and tumor cells [4]. Because of their bioactive contents (proteins, mRNA, miRNA), exosome constitute concentrated carriers of genetic and proteomic information, which vary in properties and functionality according to cell type from which they originate as well as the particular physiological and pathological conditions in existence at the time of their packaging and secretion. By shuttling molecules between cells, exosomes promote intercellular communication and alteration in the function of target cells and, thereby, are considered to be involved in modulating a wide range of cellular processes.

In one of our previous studies, we observed that heparin exerted a broadly anti-tumorigenic effect when added to cultures of breast cancer cells by reducing the expression of pro-tumorigenic proteins as well as the level of activation of multiple key cell signalling pathways [5]. This anti-tumorigenic effect was observed to be partially reversed upon the replacement of fresh medium without heparin. Exosomes have also been identified in body fluids and blood, indicating that the exchange of information between organs may also occur *via* exosomes, which led us to consider whether a more persistent effect could be achieved by treatment of the cells with exosomes produced by heparin treated cells, since exosomes are known to act as intracellular messengers and are remarkably stable in body fluids [6].

This proved to be the case when we analysed the tumorigenicity of MCF-7 and MDA-MB231 breast cancer cells cultured with exosomes purified from the culture medium of heparin treated cells. The results showed a reduction of tumorigenicity of the cells cultured in the presence of heparin derived exosomes compared to that of cells cultured in the presence of exosomes from untreated cells. These heparin derived exosomes were also observed to exert an anti-tumorigenic effect compared to the control cells in terms of the level of expression of pro-tumorigenic and cell cycle regulatory proteins as well as signalling activities. The anti-tumorigenic activity of the heparin-derived exosomes may arise from observed changes in the miRNA content or from heparin, itself, since it was observed to be bound to the exosomes [7].

When these results are compared to the levels of heparin used in the clinic, the therapeutic dosage of heparin used routinely in cancer patients is 150-300 units of heparin per kilogram of body weight administered once daily by subcutaneous injection. In our study, we observed that the maximum binding of heparin by the cancer cell cells occurred at 1 μg/ml (equivalent to around 0.4 units of heparin/ml), similar to the levels observed in blood during heparin therapy, a concentration which will be efficacious for internalization by cancer cells, thereby may contribute to the beneficial anti-tumor effect of heparin during cancer therapy [7]. We have previously also observed that necrotic tumor cells also bind heparin due to heparin binding histone and ribosomal proteins that become exposed during

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necrosis [8]. Thereby, heparin is able to act as an anti-inflammatory agent and attenuate histone-induced inflammatory response in whole blood [9].

As exosomes are remarkably stable in bodily fluids, and able to interact with the surrounding tissues in both intercellular and extracellular domains, the exosomal heparin may also constitute a relatively stable reservoir allowing heparin activity to persist in the circulation even after therapy has been discontinued, which could be considered as a special additional pharmacological characteristic of heparin following clinical administration.

The use of heparin as an antitumor agent is limited due to its potent anticoagulant activity. Non-anticoagulant heparins can be obtained either by removing chains containing the antithrombin-binding sequence, or by inactivating critical functional groups or units of this sequence. Non-anticoagulant heparins are preferable for potential clinical use because they can be administered at high doses, thereby fully exploiting the antimetastatic component of heparin, and also can be used more safely in cancer patients with bleeding complications [10]. Therefore, it worth to inquire whether the beneficial antitumorigenic effect of heparin binding to exosomes will probably also be observed with non-anticoagulant heparin (since it arises from the primary biological role of heparin as a cell surface polyanionic glycosaminoglycan). It is possible therefore to envisage long term anti- cancer benefits of treatment with non-anticoagulant heparin to modulate the protumorigenic role of cancer exosomes over the longer term but with minimal bleeding risk.

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