Inhibition of manganese-mediated tumor cell migration by heparin analogs

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The metastatic disease accounts for over 90% of the deaths in cancer patients. Tumor progression is very complex, involving several molecular and cellular phenomena that occur at the primary tumor, inside blood vessel, at pre-metastatic niche and secondary tumor site. In all of them, dynamic interactions among tumor cells and the microenvironment are observed. Our hypothesis on tumor cell migration involves cell surface integrin and heparan sulfate proteoglycan forming a manganese-dependent macromolecular complex with extracellular fibronectin, leading to migration. In the presence of manganese, integrin undergoes a conformational change. Our data indicates that this change allows its interaction with heparan sulfate proteoglycans at the tumor cell surface, resulting in enhanced tumor cell migration. Heparin analogues are able to drastically attenuate this effect, both *in vitro* and *in vivo*. Circular dichroism and X ray fluorescence analyses suggest that manganese can be sequestered by heparin analogs, preventing it from binding to cell surface integrin. Additionally, an initial retrospective study on colon adenocarcinoma patients, carried out at Serviço de Patologia and Instituto de Pesquisas Biomédicas (Hospital Naval Marcílio Dias, Brazil), indicates that manganese is detected at the primary tumor, metastatic site and tumor-bearing lymph nodes, while it is not within detection range in tumor-free sites or lymph nodes.

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