Involvement of Heparanase in Tumor Metastases: A New Target in Cancer Therapy?

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Ultimately, the cause of death for many cancer patients is the presence of metastases, the spread of the cancer from primary to distant sites. One of the critical steps in metastasis is the ability of tumor cells to degrade basement membrane structures that underlie the epithelial and endothelial cell layers, and much research has focused on the identification of genes that contribute to this process. Consequently, several distinct classes of proteases, including collagenases, cathepsins, serine proteases, and endoglycosidases, contribute to the dissolution of the basement membrane. Heparanase, the predominant enzyme in the endoglycosidase class, degrades heparan sulfate glycosaminoglycan—the principal polysaccharide component of the basement membrane. Cleavage of this substrate by heparanase has two effects: 1) the loss of integrity of basement membrane structure, and 2) the release of heparan sulfate–bound bioactive angiogenic and growth-promoting factors. In addition, heparanase may have other activities that contribute to tumor progression. For example, a recent study (1) demonstrated that this endoglycosidase induces endothelial cell migration via activation of the protein kinase B/Akt signaling pathway and in a manner independent of its endoglycosidase activity.

Previous studies have sought to determine the role of heparanase in tumor progression. However, such investigations, especially the earlier ones, relied on the use of heparin-mimicking molecules to inhibit heparanase activity. Because the reagents used in those previous studies lacked specificity, the conclusions drawn from the studies are somewhat debatable. However, subsequent to the simultaneous cloning of the cDNA-encoding heparanase by two independent groups (2,3), Goldshmidt et al. (4) found that the overexpression of the cDNA-encoding heparanase conferred a metastatic phenotype in lymphoma cells. Nevertheless, the ability of increased heparanase levels to induce a metastatic phenotype does not necessarily imply that tumors make use of this endoglycosidase to drive tumor dissemination. In this issue of the Journal, Edovitsky et al. (5) have attempted to address this shortcoming by using ribozyme and small interfering RNA (siRNA) technology to knock down the levels of endogenous heparanase. The authors convincingly show that, in models of experimental and spontaneous metastases, these strategies attenuate the ability of diverse tumor cells, including melanoma, mammary adenocarcinoma, lymphoma, and glioma cells, to invade in vitro and to colonize distant sites including the liver and lungs. This study (5) corroborates an earlier study (6) showing that an adenoviral-delivered antisense heparanase could inhibit the pleural dissemination of lung cancer cells.

Experimental data from Edovitsky et al. (5) and Uno et al. (6) provide strong support for a role for heparanase in the metastatic process. Moreover, these studies can be used to rationalize the development of anti-heparanase strategies for cancer patients. Nevertheless, some caution should be exercised in predicting clinical efficacy on the basis of these impressive laboratory results. Indeed, tumor cells have a remarkable system of redundant mechanisms that can efficiently overcome targeting of single molecules (7), and this redundancy is probably one of the contributing mechanisms underlying the lack of clinical benefit seen with metalloproteinase inhibitors in cancer patients (8). To be fair, the endoglycosidase family (9) has fewer members than the metalloproteinase family, making the redundancy issue less likely to be a problem in targeting heparanases than it is in targeting metalloproteins. Nevertheless, some of the data in the article by Edovitsky et al. (5) are suggestive of redundancy. For example, the authors demonstrate that, although MDA-MB-435 mammary adenocarcinoma cells stably transfected with the anti-heparanase ribozyme showed no enzymatic heparanase activity, residual in vitro invasiveness was still evident. Of course, it may be that the amount of heparanase enzyme is simply below the detection limits of the assay or that the contribution of this endoglycosidase to in vitro invasion is independent of its enzyme activity, as shown recently by Gignis-Velitski et al. (1). An experimental approach that would overcome the confounding effect of residual heparanase would be to use heparanase-null mice bearing genetic or carcinogen-induced tumors. Would tumors null for this enzyme still be able to spread to secondary sites? Obviously, a complete abrogation of tumor spread would argue for an indispensable role of heparanase in tumor dissemination. Conversely, a reduced but residual rate of tumor spread would suggest redundant proteolytic mechanisms that can compensate for the absence of heparanase. Indeed, the idea of redundant proteolytic mechanisms has a precedent, albeit in wound healing (a physiologic paradigm of tumor invasion): Lund et al. (10) demonstrated, in an elegant study, that tissue repair was dependent on a functional overlap between serine proteases and collagenases.

An equally important issue relating to the utility of anti-heparanase therapies in cancer treatment concerns the fact that, at the time of presentation, the majority of patients already have disseminated disease. Consequenly, treatment of such patients with anti-heparanase regimens might be akin to closing the barn door after the horse has bolted. Thus, how could a knock-out punch against heparanase be useful in the treatment of cancer patients? There are two possibilities. First, with increasing public awareness, and as cancer screenings become more prevalent in the general population, the number of patients diagnosed with early-stage disease should increase. By definition, such tumors are still localized and are therefore more amenable to therapy with anti-metastasis agents. Second, considering the proangiogenic effects of heparanase documented in the study by

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See “Note” following “References.”

DOI: 10.1093/jnci/djh256

Journal of the National Cancer Institute, Vol. 96, No. 16, © Oxford University Press 2004, all rights reserved.
Edovitsky et al. (5), anti-heparanase drugs may have a static effect on distant tumor lesions by preventing the establishment of tumor vasculature necessary for tumor growth beyond 1 mm³.

In conclusion, the findings in the study by Edovitsky et al. (5), together with those from previous studies make for a compelling case for a role of heparanase in tumor progression. The extent to which this information can be exploited in novel therapies will depend on the development of specific inhibitors that target heparanase and the blockade of redundant mechanisms that compensate for the loss of the endoglycosidase in cancer.

REFERENCES


NOTE

M. Nakajima conducts research sponsored by Novartis Pharma.