

nature REVIEWS

quick search **GO**

advanced search

◀ article ▶

table of contents

archive

issues

highlights

reviews

perspectives

Nature Reviews Cancer 2, (2002)

SIGNALLING

Cryptic clues about metastasis

Kristine Novak

Many of the signals that regulate tumour growth, metastasis and neovascularization are derived from interactions between cancer cells and the extracellular matrix. Heparan sulphate glycosaminoglycans (HSGAGs) are heavily glycosylated polysaccharides that are present at the cell surface and extracellular matrix, and that bind to and regulate the activities of signalling molecules such as growth factors and cytokines. Now, researchers report that enzymes that cleave these polysaccharides expose cryptic sites that can promote or inhibit tumour growth and metastasis.

Alterations in HSGAG structure have previously been observed on tumour cells, but it was not known whether these changes were a cause or a consequence of tumour progression. It is difficult to study the biological effects of different HSGAGs, as these highly charged polysaccharides are variably sulphated and modified by heparanases. Heparanase genes have been cloned from tumour cells, however, and differences in their expression patterns have been correlated with metastatic potential. In the 22 January issue of *Proceedings of the National Academy of Sciences*, Dongfang Liu *et al.* show that treatment of mice with two different heparanase enzymes has opposite effects on tumour growth and metastasis.



Heparanase I (Hep-I) cleaves highly sulphated regions of HSGAGs, whereas Hep-III cleaves only the undersulphated region of the polysaccharide chain. In both melanoma and lung carcinoma models, tumour growth was accelerated in mice injected with Hep-I — characterized by increased tumour-cell proliferation, decreased apoptosis and neovascularization. Hep-III treatment of mice, on the other hand, significantly inhibited tumour growth. Hep-III-treated cancer cells were also less invasive in *in vitro* migration assays, whereas Hep-I treatment increased the ability of cells to migrate by twofold. But does heparanase treatment directly affect growth and metastatic ability of tumour cells, or do these enzymes release bioactive saccharide fragments?

To investigate the role of HSGAG fragments in modulating tumour progression, the authors treated melanoma cells with either Hep-I or Hep-III and isolated the resulting products. Structural analysis of the fragments released by Hep-I or Hep-III treatment confirmed that these were compositionally different and structurally distinct. The different enzymatic products were injected into tumour-bearing mice, and found to recapitulate the biological effects of Hep-I and Hep-III treatment. This indicated that the effects of enzyme treatment were indeed caused by the release of bioactive HSGAG fragments.

But how do these saccharide fragments function? Specific HSGAG structures have previously been shown to bind and modulate fibroblast growth factor 2 (FGF2) activity, and FGF2 signalling has been associated with melanoma

progression. So, the authors set out to determine whether these HSGAG fragments also affected FGF2 activity. Hep-III treatment prevented FGF2 stimulation of the extracellular-signal-related kinases [Erk1](#) and [Erk2](#) in melanoma cells, whereas treatment with Hep-I activated Erk1/2 signalling and promoted FGF2-mediated proliferation. Exposure of primary tumours to Hep-III (or its products) also inhibited phosphorylation of the FGF receptor-1 ([Fgfr1](#)) and [focal adhesion kinase](#) activation, whereas Hep-I did not.

These findings indicate that HSGAGs can have either a positive or negative effect on tumour growth, depending on their composition. Liu *et al.* conclude that the ability of cells to change the composition or 'signature' of their polysaccharide coat provides them with a mechanism to fine tune the signalling response to the extracellular matrix. Furthermore, a study by Mattias Belting *et al.* in the 8 January issue of *Proceedings of the National Academy of Sciences* reports that heparan sulphate proteoglycans are also involved in polyamine internalization, and that glycosaminoglycan (GAG)-deficient tumours grow more slowly *in vitro* and *in vivo*. Together, these studies reveal that GAGs might be good targets for anticancer therapeutics.

References and links

ORIGINAL RESEARCH PAPER

Liu, D., Shriver, Z., Venkataraman, G., El Shabrawi, Y. & Sasisekharan, R. Tumor cell surface heparan sulfate as cryptic promoters or inhibitors of tumour growth and metastasis. *Proc. Natl Acad. Sci. USA* **99**, 568-573 (2002) | [PubMed](#) |

FURTHER READING

Belting, M. *et al.* Tumor attenuation by combined heparan sulfate and polyamine depletion. *Proc. Natl Acad. Sci. USA* **99**, 371-376 (2002) | [PubMed](#) |

WEB SITE

[Ram Sasisekharan's lab](#)

 [back to top](#)

NATURE REVIEWS | [CANCER](#)

Nature © Macmillan Publishers Ltd 2002 Registered No. 785998 England