METASTASIS

A sweet sabre promotes cell invasion


CORBIS

Tumour cells invade their surrounding tissue and degrade the extracellular matrix (ECM) glycosaminoglycan component hyaluronan. Hyaluronan fragments can also promote tumour cell invasion through a mechanism involving the cell surface glycoprotein CD44. Reporting in *Cancer Research,* Sugahara *et al.* show that specific forms of chondroitin sulphate, another ECM glycosaminoglycan component, also contribute to tumour cell invasion.

The glycosaminoglycan chondroitin sulphate type E (CSE) consists of repeating units of disulphated *N*-acetylgalactosamine linked to glucuronic acid and is known to bind to the cell motility regulators selectin and CD44. Using a new CSE-specific antibody, Sugahara *et al.* detected CSE in various mouse models of spontanous pancreatic cancer.

Cleavage of the extracellular domain of CD44 by metalloproteinases is induced by hyaluronan fragments and leads to the translocation of the intracellular domain of CD44 to the nucleus, resulting in the transcription of genes that support tumour progression, including *CD44*. When migrating pancreatic cancer cells were incubated with CSE, the authors found that the extracellular domain of CD44 was cleaved only in the presence of low-molecular-mass fractions of CSE that had been extracted from the tumours. Replicating the hyaluronan–CD44 interaction, low-molecular-mass CSE also dramatically enhanced CD44-dependent tumour cell motility. A synthetic low-molecular-mass CSE produced similar results, which were abolished upon treatment with chondroitinase or a CD44-neutralizing antibody. These findings identify CSE as a component of the tumour microenvironment and indicate that CSE fragments promote tumour motility by cleaving CD44 in a manner similar to that of hyaluronan fragments. Whether CSE is generated by tumour metalloproteinases or other unknown mammalian chondroitinases remains to be determined.

This study adds to our knowledge about the way in which molecules from the tumour cell microenvironment interact with proteins on the cancer cell surface in carcinogenesis. Future studies might show whether blocking the interaction between glycosaminoglycans and cancer cell proteins can abrogate tumour progression.

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ORIGINAL RESEARCH PAPER Sugahara, K. N. *et al.* Chondroitin sulphate E fragments enhance CD44 cleavage and CD44-dependent motility in tumour cells. *Cancer Res.* **68**, 7191–7199 (2008).