Nature Reviews Cancer | AOP, published online 15 March 2012; doi:10.1038/nrc3254

METASTASIS

Multitasking hyaluronic acid

> The STAB2 antibody also prevented spontaneous metastasis

The presence of the glycosaminoglycan hyaluronic acid (HA) in the extracellular matrix (ECM) or pericellular region has been implicated in promoting tumour cell proliferation, invasion and motility. However, how circulating serum HA affects metastasis is not known. Circulating HA levels are controlled by scavenger receptors that are expressed on hepatic sinusoid endothelial cells (HSECs), and the primary HA scavenger is thought to be stabilin 2 (STAB2); so, Atsushi Miyajima and colleagues created *Stab2*$^{-/-}$ mice. These mice were normal except for very high levels of serum HA, owing to reduced endocytosis of HA by *Stab2*$^{-/-}$ HSECs.

IT STOCK

The high HA levels in *Stab2*$^{-/-}$ mice prompted the authors to investigate metastasis in this system. Tail vein injection of B16F10 melanoma cells resulted in nodule formation on the lungs of wild-type mice at 14 days, which was surprisingly reduced in *Stab2*$^{-/-}$ mice. This did not seem to be a result of changes in tumour cell proliferation, and imaging of B16F10 cells that expressed firefly luciferase indicated early inhibition of metastasis in *Stab2*$^{-/-}$ mice (7 days post-injection). The authors confirmed these results by treating wild-type mice with an antibody against STAB2, which increased serum HA levels and suppressed B16F10 cell nodule formation in the lungs. The STAB2 antibody also prevented spontaneous metastasis of two breast cancer cell lines following transplantation into the mammary fat pad.

How might high circulating HA concentrations inhibit metastasis? Using B16F10 cells that expressed luciferase, the authors analysed whether HA levels can affect the homing of tumour cells to the lungs. Six hours after tail vein injection, luciferase activity was significantly reduced in the lungs of *Stab2*$^{-/-}$ mice and in wild-type mice treated with the STAB2 antibody. Elevation of serum HA levels for several hours (by tail vein injection of HA) was sufficient to reduce luciferase activity of B16F10 cells in the lungs. Furthermore, co-culture of pulmonary endothelial cells (ECs) and B16F10 cells under conditions that mimicked physiological flow (such as might occur when tumour cells are disseminated in the blood) indicated that tumour cells attach to HA on the surface of ECs when circulating HA levels are low, but high circulating HA concentrations block the EC–tumour cell interaction, probably by competing with HA on ECs for tumour cell binding.

Therefore, the role of HA in metastasis may depend on its location (ECM, pericellular region or circulating) and concentration, and these data suggest that inhibition of STAB2 might be used therapeutically to prevent metastasis.

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ORIGINAL RESEARCH PAPER Hirose, Y. *et al.* Inhibition of stabilin-2 elevates circulating hyaluronic acid levels and prevents tumor metastasis. *Proc. Natl Acad. Sci. USA* 27 Feb 2012 (doi:10.1073/pnas.1117560109)