Abstract

The lymphatic system is a major route for the spread of cancer cells. The recent discovery of lymph vessel specific marker proteins helped to advance the research on the lymphatic system. One of these marker proteins is the lymphatic hyaluronan receptor LYVE-1, which is mainly expressed on lymphatic endothelial cells. The biological function of LYVE-1 is yet unknown. LYVE-1, a close homologue of the hyaluronan receptor CD44, is a member of the link protein super-family. CD44 has an important influence on the behaviour of cancer cells. Especially the soluble ectodomain of CD44 is involved in the regulation of tumour progression. Here we demonstrate that LYVE-1 is present both as a full length plasma membrane bound and as a soluble ectodomain form in tissues. Hence, soluble LYVE-1 (sLYVE-1) was also detected in mouse sera. Using an orthotopic xenotransplantation tumour model, we investigated the influence sLYVE-1 on breast cancer progression in athymic nude mice.

Our results showed that LYVE-1 is a strong inhibitor of breast cancer progression. Over-expression of sLYVE-1 as well as systemic administration of recombinant sLYVE-1/Fc reduced the tumour growth significantly in independent orthotopic tumour studies. The underlying mechanism of LYVE-1 activity in tumour inhibition is not yet clear. Our results suggest that the inhibition is not directly on the tumour cells per se, but rather via their binding partners. We suggest that sLYVE-1 might interfere with the CD44 hyaluronan interaction through the binding to hyaluronan. The binding of LYVE-1 to hyaluronan was verified by surface plasmon resonance measurements. To further elucidate the influence of LYVE-1 on the tumour progression we established a transgenic mouse model in which sLYVE-1 is strongly over-expressed in the basal keratinocytes of the epidermis. The transgenic mice did not show any general morphological changes in the skin. To further investigate the modulating role of LYVE-1 in tumourogenesis, we plan to cross-breed our transgenic mice with HPV8-expressing mice which spontaneously develop non-melanoma skin cancer, or to induce cancer in the sLYVE-1-over-expressing mice through classical two-step carcinogenesis.