CANCER

Lipoxygenase makes a leaky tumour

By transporting tumour cells around the body, the lymphatic system has a key role in cancer metastasis. Now, Kerjaschki *et al.* have found that arachidonate 15-lipoxygenase (15LOX) and its product, the eicosanoid 12(*S*)-HETE, are important in this process in mammary carcinomas. Writing in the *Journal of Clinical Investigation*, the authors present evidence that 12(*S*)-HETE may act by creating defects in the endothelium surrounding the lymphatic system, which could allow tumour cells to pass through it.

The mechanism by which tumour cells colonize the lymphatic system and lymph nodes is not well understood. It may, for example, involve the formation of intermetastatic lymphatic vessels, which are made with cancer cells that have already spread rather than primary tumour cells. The authors began, therefore, by examining real tumours together with their associated lymph nodes. With the help of immunohistochemical staining, they observed discontinuities in the intrametastatic lymphatic walls through which tumour cells had penetrated.

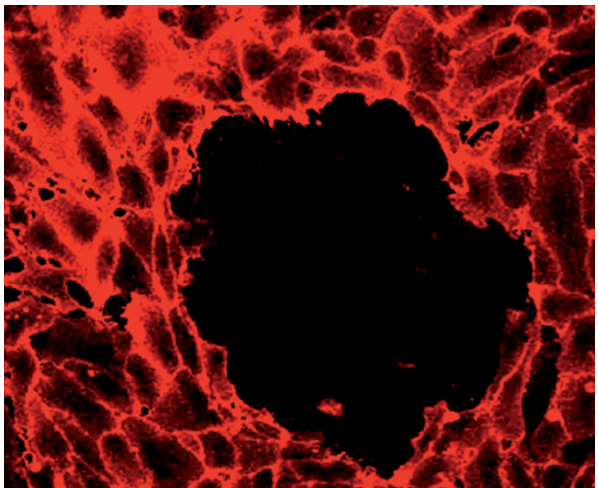

Image courtesy of D. Kerjaschki, Medical University of Vienna, Austria.

To explore how such discontinuities might form, they turned to *in vitro* studies using spheroids of MCF7 human mammary carcinoma cells. To simulate real clusters of tumour cells on the lymphatic endothelium, the spheroids were placed on a monolayer of human dermal lymphatic endothelial cells. Defects occurred immediately below the spheroids and resembled the discontinuities seen in real tumours. The authors showed that cell migration, rather than apoptosis, was likely to be the cause of these defects.

Meanwhile, the team discovered that 15LOX was one of several proteins that were expressed at higher levels in the MCF7 spheroids than in MCF7 monolayers. Because its product — 12(*S*)-HETE — is known (in certain systems) to be involved in the migration of tumours and in endothelial cell motility, they suspected that these species might be involved in defect formation. To test this, they inhibited 15LOX using either nordihydroguaiaretic acid or the traditional Asian anticancer drug baicalein; up to 90% reduction in defects was observed with the latter. The role of 12(*S*)-HETE was confirmed by using an antibody to selectively block its effect.

Next, the authors tested whether these results could be reproduced *in vivo* by knocking down the 15LOX gene (*ALOX15*) in MCF7 cells and transplanting these cells into mice. After 63 days, 100% of control mice had developed tumours, but only 5% of knockout mice. Furthermore, the tumour lymphatic vessels in the knockout mice appeared to be collapsed and devoid of tumour cells. Finally, the authors presented a correlation between *ALOX15* expression in real tumours and clinical outcome.

In summary, these results support the concept that the production of 12(*S*)-HETE by 15LOX is important in the induction of lymph node metastases and the bulk invasion of lymphatic vessels by tumour cells through discontinuities in the endothelium. However, further studies are needed to determine the mechanisms mediating the effects of 12(*S*)-HETE. These results also suggest that inhibition of 15LOX might interfere with lymphatic dissemination, and that it could be a promising approach to evaluate in clinical trials for mammary carcinomas.

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ORIGINAL RESEARCH PAPER
Kerjaschki, D. *et al.* Lipoxygenase mediates invasion of intrametastatic lymphatic vessels and propagates lymph node metastasis of human mammary carcinoma xenografts in mouse. *J. Clin. Invest.* **121**, 2000–2012 (2011)