METASTASIS

Stopping the spread

Hypoxic conditions have been correlated with both metastasis and poor outcome in cancer patients. Amato Giaccia and colleagues have now shown that the enzyme lysyl oxidase (LOX), which is highly expressed in hypoxic tumour cells, is crucial for hypoxia-induced metastasis.

The LOX enzyme is important for extracellular matrix (ECM) formation. It oxidizes lysine residues in collagen and elastin, therefore stabilizing and strengthening the fibres. This, combined with the expression of LOX in

“
LOX might promote metastasis through remodelling the ECM.
”

hypoxic tumour cells, led Giaccia and colleagues to propose that LOX might be involved in remodelling the ECM to promote metastasis.

The authors first showed that LOX expression is regulated by the transcription factor hypoxia-inducible factor 1 (HIF1) in human cancer cell lines. They then used mouse models to confirm a role for LOX in promoting metastasis. Decreasing LOX expression with LOX short-hairpin RNA (shRNA) in the MDA231 breast cancer cell line decreased the incidence of metastasis when the cells were grown as orthotopic tumours in nude mice. In addition, mice with MDA231 tumours that were treated with a specific LOX inhibitor or an anti-LOX antibody had fewer metastases, which demonstrates the therapeutic potential of inhibiting LOX.

How does LOX induce metastasis? Hypoxia-induced invasion of several cancer cell lines *in vitro* was reduced by LOX inhibition. The LOX enzyme can function both intracellularly and extracellularly, but only inhibition of extracellular LOX reduced invasion, and conditioned medium from cells that expressed LOX increased invasion. Cell migration, which is required for invasion, was also reduced in LOX shRNA MDA231 cells. So, mechanistically, how might extracellular LOX affect cellular motility and invasion?

Cell migration requires several processes such as the formation of pseudopodia at the leading edge, and activation of integrin ECM receptors and downstream signalling pathways that regulate the actin cytoskeleton and ECM remodelling. One role of LOX is to increase collagen fibre formation in the ECM. The authors proposed that collagen, which is a ligand for β_1 -integrin, might increase cell motility through the activation of focal adhesion kinase (FAK). Indeed, LOX shRNA cells had a reduced level of phosphorylated FAK, and LOX transfection restored FAK phosphorylation, which could in turn be blocked by β_1 -integrin-inhibiting antibodies. Immunofluorescent staining of extracellular LOX was observed at the leading edge of MDA231 cells, particularly under hypoxic conditions, which provides further evidence that LOX might promote metastasis through remodelling the ECM.

Giaccia and colleagues also showed that increased expression levels of LOX correlated with decreased survival in patients with breast cancer or head and neck cancer, a finding that further supports LOX as a therapeutic target to prevent metastasis.

Sarah Seton-Rogers

ORIGINAL RESEARCH PAPER Erler, J. T. et al. Lysyl oxidase is essential for hypoxia-induced metastasis. *Nature* **440**, 1222–1226 (2006)

RESEARCH HIGHLIGHTS ADVISORS

AVI ASHKENAZI Genentech, Inc.,
South San Francisco, CA, USA
JOSE BASELGA
Vall d'Hebron University Hospital,
Barcelona, Spain
ANTON BERNIS
Netherlands Cancer Institute,
Amsterdam, The Netherlands

MARIA BLASCO
Spanish National Cancer Centre
(CNIO), Madrid, Spain
RON DEPINHO Harvard Medical
School, Boston, MA, USA
GLENN DRANOFF
Dana-Farber Cancer Institute,
Boston, MA, USA

RAKESH JAIN
Massachusetts General Hospital,
Boston, MA, USA
CHRISTOPH LENGAUER
Novartis Institute for Biomedical
Research Inc., Cambridge, MA, USA
LANCE LIOTTA National Cancer
Institute, Bethesda, MD, USA

JOHN D. POTTER
Fred Hutchinson Cancer
Research Center, Seattle,
WA, USA
DAVID SIDRANSKY
Johns Hopkins University
School of Medicine, Baltimore,
MD, USA

BERT VOGELSTEIN
The Sidney Kimmel Comprehensive
Cancer Center, Baltimore, MD, USA
ROBERT WEINBERG
Whitehead Institute for Biomedical
Research, Cambridge, MA, USA
ZENA WEBB University of California
at San Francisco, CA, USA