CANCER

LOX does some prepping

Bones are the most common site of metastasis associated with breast cancer, but why are primary breast tumours attracted to bone? Cox *et al.* have shown that metastasis of certain breast cancers to bone can be enhanced by the enzyme lysyl oxidase (LOX), which induces bone lesions that provide a landing site for circulating tumour cells.

Tumour hypoxia is generally associated with increased metastases, so the authors analysed 344 hypoxic primary breast tumour samples from patients and found that hypoxia was correlated with increased bone metastases but only in oestrogen receptor (ER)-negative (ER^-) patients. To identify the factors underlying this specificity, Cox *et al.* analysed the proteins secreted under hypoxic conditions by a metastatic breast cancer cell line (ER^- MDA-MB-231) and found that LOX was upregulated in a subclone known to metastasize to bone. Indeed, a retrospective analysis of the patient samples showed that LOX expression is associated with metastasis and bone relapse in ER^- patients, but not in ER^+ patients.

Because the MDA-MB-231 cell line does not metastasize upon orthotopic implantation, the authors implanted ER^- 4T1 breast cancer cells — which spontaneously metastasize to bone and express high levels of LOX — into immune-competent BALB/c mice and demonstrated that LOX is secreted by hypoxic breast cancer cells and that it disrupts the balance between bone formation and destruction, such that there is greater overall bone loss. These sites of altered bone provided a favourable environment for disseminated breast cancer cells. Interestingly, such osteolytic lesions also appeared in tumour-free mice into which factors secreted by hypoxic breast tumour cells were injected. When mice were orthotopically injected with 4T1 cells with decreased LOX expression, the authors observed a reduced number of osteolytic lesions and metastases with no effect on primary tumour growth. Inhibition of LOX with a specific antibody also decreased osteolytic lesion formation, therefore confirming that systemic LOX, secreted by ER^- breast tumours, drives the formation of pre-metastatic niches in bones that precedes and facilitates the formation of metastases.

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Finally, the authors showed that LOX drives bone resorption by inducing the nuclear translocation of the transcription factor NFATc1, the master regulator of osteoclast formation, and that this mechanism is independent of the osteoclast differentiation and activation factor RANKL (receptor activator of nuclear factor-κB ligand).

Drugs that prevent osteoclast-mediated bone resorption — such as bisphosphonates and the RANKL-specific monoclonal antibody denosumab — are efficient therapies for preventing bone metastasis. Further studies may confirm whether LOX can provide a target for preventive treatment for patients at a higher risk of bone metastasis, as well as a biomarker to identify these patients. It would also need to be determined why the secretion of LOX by hypoxic breast cancer cells is predominantly linked to bone metastasis in patients with ER^- breast cancer but not those with ER^+ breast cancer.

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ORIGINAL RESEARCH PAPER Cox, T. R. *et al.* The hypoxic cancer secretome induces pre-metastatic bone lesions through lysyl oxidase. *Nature* **522**, 106–110 (2015)