The hypoxic cancer secretome
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Once a primary tumour spreads to distant sites in the body and establishes a secondary tumour, the consequences are devastating, and mostly lethal. Bone is a typical site for cancers to spread to (most commonly breast, prostate, lung, kidney, thyroid and colon cancer) – however why cancer cells preferentially home to bone over other organs in some cancers, but not all, is not fully understood. There is increasing evidence that modulation of the extracellular matrix (ECM) plays an important role in the lethal progression from a primary to metastatic bone tumour. Yet it is not known which occurs first, abnormal extracellular matrix (ECM), which supports secondary tumour formation, or the arrival of cancer cells into the bone that create abnormal ECM. Recently it has been shown that tumour-derived factors, the so-called “hypoxic cancer secretome” circulate the body and exert effects on ECM remodelling within distant organs, creating pre-metastatic niches.

One such factor is Lysyl oxidase (LOX), which is highly expressed by invasive/metastatic cancer cells, enhances tumour progression and is high in patients with lower metastasis-free survival. LOX is critical for pre-metastatic niche formation in soft-tissue (lungs, liver and brain) enhancing bone marrow-derived cell invasion and thereby enabling colonisation of metastasising tumour cells. Recently we have begun to unravel the role of LOX in the bone pre-metastatic niche, in particular the early events governing osteolytic lesion formation. Using multiple in vitro and in vivo models, and a large clinical cohort, we show that LOX gene expression is significantly correlated with osteotropism and bone relapse. We show that high expression of LOX in primary breast tumours or systemic delivery of LOX in vivo leads to osteolytic lesion formation, and that silencing or inhibition of LOX activity abrogates this. The enzymatic activity of tumour-secreted LOX affects both osteoclasts and osteoblasts, disrupting normal bone homeostasis leading to bone lesion formation. These changes and lesions occur prior to tumour cell arrival in the bone and act to provide the initial foothold for circulating tumour cells to colonise the niche and form bone metastases.

In summary, by using novel approaches to interrogating the hypoxic secretome we have uncovered a novel step in bone metastasis and mechanism of bone homeostatic regulation, opening up new opportunities for therapeutic intervention with important clinical implications.

Relevant references/further reading:
References
ECTS PhD TRAINING COURSE, 2-5 JULY 2016

SPEAKER ABSTRACTS