Nature Reviews Drug Discovery | AOP, published online 26 May 2006; doi:10.1038/nrd2066

CANCER

Blocking LOX prevents cancer spread

The main cause of mortality among cancer patients is generally secondary, or metastatic, tumours, but few selective drugs have been identified that specifically target metastasis itself. Now, an exciting report from Erler and colleagues describes the involvement of the monoamine oxidase lysyl oxidase (LOX) in several stages of the migration of malignant cancerous cells from their primary tumour formation site, establishing a new therapeutic target for preventing and treating metastases.

Whether metastases develop is determined by the interactions between various factors, but it is not always clear how these factors contribute to the mechanisms that drive this multi-component process. Cancer cells that are capable of spreading throughout the body often originate and can thrive in hypoxic (low oxygen) environments, and hypoxic tumours are clinically linked to poor patient outcome. Previous investigations of hypoxic tumour physiology established a link between hypoxia and elevated LOX expression. Building on these findings, Erler and colleagues analysed breast, head and neck cancer studies, and found that hypoxic breast cancer cells had elevated levels of LOX expression, with a lower probability of survival for those patients whose tumour cells expressed higher levels of LOX.

To investigate the therapeutic potential of blocking LOX activity, the authors implanted mice with tumours grown from human breast cancer cells engineered to produce significantly less LOX than normal cells. Metastatic cancer cells were detected in the lungs and liver of control animals that received wild-type tumours. However, mice that received modified tumours expressing lower levels of LOX had fewer metastatic cells in their lungs and none in their liver. Metastasis was completely abolished by giving the control mice β-aminoproprionitrile, an irreversible LOX inhibitor. This response was also achieved using an antibody against LOX.

Cellular invasion, acquisition of motility and cellular adhesion are just three components of the metastatic process. Erler and colleagues identified roles for LOX in all three phases. To investigate the role of LOX in invasion, the authors used collagen gels to recreate the cellular environment necessary for growth. Control cancer cells incubated on the gel had a branched appearance, showing invasion capabilities, but cells expressing lower levels of LOX were completely immobile, retaining a spherical shape. Next, immunofluorescent imaging of these cells revealed that LOX is concentrated at the leading edge of motile cancer cells, particularly in hypoxic conditions. Linked to motility, the authors also found that LOX, through activation of focal adhesion kinase, is required for formation of cellular adhesion interactions that are essential for cancer cell migration. The involvement of LOX in various steps of the metastatic process underscores its potential as a key therapeutic target for the treatment of cancer.

Samantha Barton

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