ANGIOGENESIS

Showing the way home

Circulating bone-marrow-derived progenitor cells are known to home to actively remodelling tissues, such as a developing tumour. However, the mechanisms that are involved have been unclear. Judy Varner and colleagues now report that integrin $\alpha_4\beta_1$ promotes homing of these progenitor cells to the tumour neovasculature, and that the cells also actively participate in tumour growth.

First, human CD34$^+$ progenitor cells were labelled with a fluorescent dye and injected into the tail vein of nude mice implanted with mouse breast carcinoma spheroids on mammary fat pads. Real-time intravital microscopy was used to track the CD34$^+$ cells and showed that within a few minutes they were circulating in the tumour vasculature and, a few minutes later, they were arresting in blood vessels at the tumour periphery, but not in the tumour centre, surrounding normal fat pad or uninvolved mouse skin. These results discount non-specific leakage from tumour vessels because, if that were so, you would expect to find CD34$^+$ cells in central tumour vessels as well. CD34$^+$ progenitor cells were also seen within the tumour parenchyma near to blood vessels, implying that the cells migrated out of the vessel into the tumour tissue.

Adhesion proteins, such as integrins, are known to home haematopoietic cells to the bone marrow, so could the same mechanism be used to guide CD34$^+$ cells to neovasculature? All circulating CD34$^+$ cells expressed significant levels of integrin $\alpha_4\beta_1$. When fluorescently labelled CD34$^+$ cells were injected with anti-$\alpha_4\beta_1$ antibodies into nude mice bearing breast carcinomas, or into nude mice bearing lung carcinomas, no CD34$^+$-cell arrest was seen. Antagonists of other integrins did not prevent arrest.

To investigate whether $\alpha_4\beta_1$ promotes the participation of CD34$^+$ cells in blood vessel formation, Varner and colleagues isolated murine bone-marrow-derived progenitor cells, which had previously been shown to participate in blood-vessel formation, from enhanced green fluorescent protein (EGFP) mice. These cells expressed high levels of integrin $\alpha_4\beta_1$. EGFP$^+$ cells not only homed to tumours but also formed EGFP$^+$ blood vessels at the tumour periphery — both properties were inhibited by anti-$\alpha_4\beta_1$ antibodies. In addition, the integrin $\alpha_4\beta_1$ ligands, vascular cell adhesion molecule and fibronectin, were expressed in tumour endothelium, primarily at the tumour periphery.

This work identifies integrin $\alpha_4\beta_1$–ligand binding as a key mechanism regulating progenitor cell homing to target tissues. It also shows that once at the target site the cells can differentiate into endothelial cells. Antagonists of these bone-marrow-derived progenitors, or of integrin $\alpha_4\beta_1$ or its ligands, could form a useful part of anti-angiogenic tumour therapy.

Ezzie Hutchinson

ORIGINAL RESEARCH PAPER Jin, H. *et al.* A homing mechanism for bone marrow-derived progenitor cell recruitment to the neovasculature. *J. Clin. Invest.* **116**, 652–662 (2006)

BREAST CANCER

The X factor

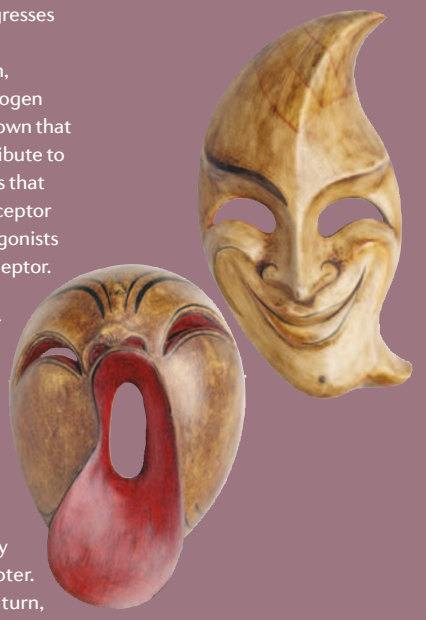
> “selection for the increased expression of a select number of X-chromosomal genes is likely to be a common characteristic of BLC.”

Recent research from the groups of David Livingston and Shridar Ganesan indicates that X chromosome abnormalities might function in the development of both sporadic and familial (BRCA1-negative) basal-like breast cancer.

Evidence indicates that loss of BRCA1 function disrupts the maintenance of the normal inactive X chromosome — BRCA1-mutant cell lines and cancers no longer have markers of a normal inactivated X chromosome. In addition, a loss of X-inactivation markers has been noted in breast cancers that are more likely to fail hormone treatment — a characteristic of basal-like cancers (BLCs). So, joint first authors Andrea Richardson and Zhigang Wang asked whether similar X chromosome abnormalities were common in sporadic cases of BLC.

PROSTATE CANCER

Switching roles



Prostate cancer invariably progresses from androgen-dependent to androgen-independent growth, causing resistance to anti-androgen therapy. Zhu *et al.* have now shown that infiltrating macrophages contribute to this process by releasing signals that convert selective androgen-receptor modulators (SARMs) from antagonists to agonists of the androgen receptor.

Nuclear hormone-receptors such as the androgen receptor bind both their normal hormone ligands and various modulators (SARMs in the case of the androgen receptor). The conformation of the receptor is determined both by its interactions with ligands and modulators, and by the conformation of the promoter. The receptor conformation, in turn, governs the assembly of regulatory