IN BRIEF

METASTASIS

Awakening a sleeping giant

Metastatic recurrence of breast cancer years after successful treatment of the primary tumour is an important clinical problem, but the molecular events that control the activation of dormant micrometastases are poorly understood. Using a mouse model that recapitulates the transition from indolent micrometastases to overt bone metastasis, Lu *et al.* found that aberrant expression of vascular cell adhesion molecule 1 (VCAM1) in metastatic tumour cells recruits monocytic osteoclast progenitors through the VCAM1 receptor α4β1 integrin, thus increasing osteoclast activity and bone resorption. VCAM1 expression was partially dependent on activation of the nuclear factor-κB pathway. Furthermore, antibodies directed against VCAM1 or α4 integrin inhibited the progression of bone metastases in mice, and higher VCAM1 expression correlated with earlier relapse in patients with breast cancer. Therapeutically targeting this pathway may help to prevent metastatic recurrence of breast cancer.

ORIGINAL RESEARCH PAPER Lu, X. *et al.* VCAM-1 promotes osteolytic expansion of indolent bone micrometastasis of breast cancer by engaging α4β1-positive osteoclast progenitors. *Cancer Cell* 30 Nov 2011 (doi:10.1016/j.ccr.2011.11.002)

METABOLISM

Working around defective mitochondria

Although some tumour cells have normally functioning mitochondria and use oxidative metabolism to generate precursors (such as citrate) for the synthesis of macromolecules (such as lipids), it is unknown how tumour cells that carry mutations in components of the citric acid cycle or electron transport chain (ETC) produce such precursors. Mullen *et al.* show that tumour cells with mutations in complex I or complex III of the ETC use glutamine-dependent reductive carboxylation to form citrate using mitochondrial and cytosolic isoforms of $NADP^+$/NADPH-dependent isocitrate dehydrogenase. Patient-derived renal carcinoma cells with mutations in fumarate hydratase also use this metabolic pathway to support their growth, as do tumour cells with normal mitochondria treated with pharmacological ETC inhibitors.

ORIGINAL RESEARCH PAPER Mullen, A. R. *et al.* Reductive carboxylation supports growth in tumour cells with defective mitochondria. *Nature* 20 Nov 2011 (doi:10.1038/nature10642)

MELANOMA

An exchange factor drives metastasis

Signalling pathways that control the migration of melanoblasts during development are thought to contribute to melanoma metastasis. Using mice, Lindsay *et al.* show that loss of *Prex1*, which encodes a guanine nucleotide exchange factor (GEF) specific for RAC, results in a defect in melanoblast migration during development. Furthermore, when $Prex1^{-/-}$ mice were crossed to a mouse model of melanoma in which the mice express mutant NRAS ($Nras^{Q61K}$) and lack the tumour suppressor INK4A, those lacking PREX1 were resistant to metastasis. PREX1 was also upregulated in primary human melanomas and melanoma cell lines, and silencing of PREX1 expression or blocking its GEF activity inhibited invasion *in vitro*.

ORIGINAL RESEARCH PAPER Lindsay, C. R. *et al.* P-Rex1 is required for efficient melanoblast migration and melanoma metastasis. *Nature Commun.* 22 Nov 2011 (doi:10.1038/ncomms1560)