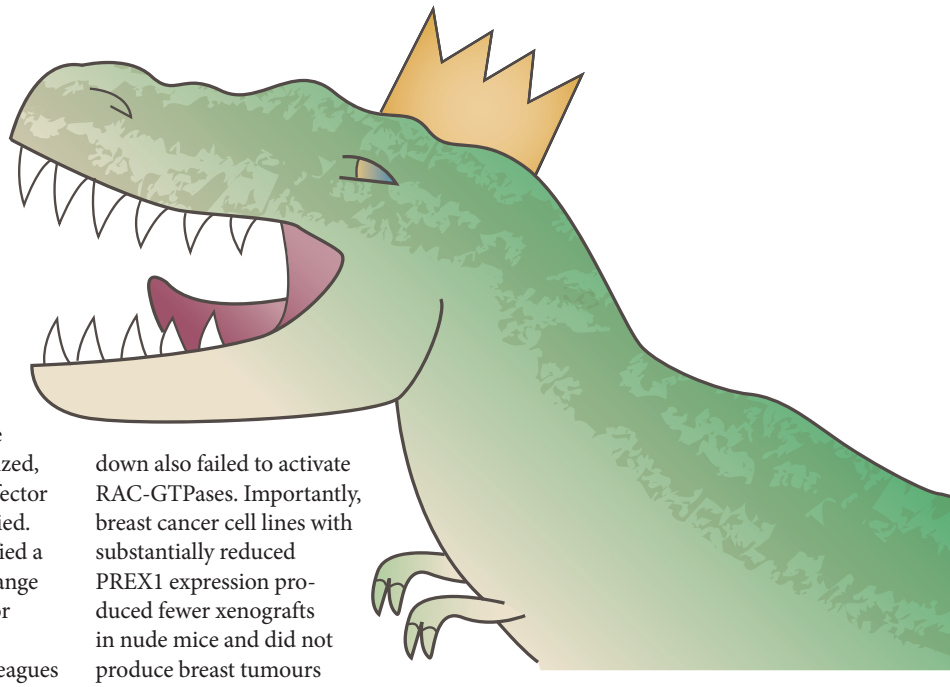

SIGNALLING

REX rules

Many of the signalling pathways that are disrupted in breast cancer, such as the ERBB family of tyrosine kinase receptors, have been characterized, but the precise downstream effector pathways are still being identified. Two recent papers have identified a RAC-guanine nucleotide exchange factor (GEF) that is required for breast cancer progression.

Marcelo Kazanietz and colleagues previously showed that RAC1 is activated in breast cancer cell lines in response to the ERBB ligands epidermal growth factor (EGF) and heregulin (HRG). To identify the specific GEF that is involved in activating RAC1, these authors designed an array to determine the expression levels of 26 RAC-GEFs and GEF accessory proteins in breast cancer cell lines. They found that phosphatidylinositol-3,4,5-trisphosphate (PtdIns(3,4,5)P_3))-dependent Rac exchanger 1 (*PREX1*) was highly expressed in luminal breast cancer cell lines. Analysis of a microarray of 295 human breast cancer samples also indicated that high-level *PREX1* expression was limited to luminal breast cancer subtypes. In addition, immunohistochemical staining of 165 breast cancer samples showed expression of PREX1 in 58% of the samples. Expression of PREX1 was significantly higher in patients who progressed to metastatic disease.

RNA interference (RNAi) showed that PREX1 was required for RAC1 activation in response to HRG and EGF, and that stable knock down of *PREX1* in various cell lines resulted in reduced migration in response to HRG. Overexpression of ERBB2 in cells in which *PREX1* was knocked down also failed to activate RAC-GTPases. Importantly, breast cancer cell lines with substantially reduced PREX1 expression produced fewer xenografts in nude mice and did not produce breast tumours after orthotopic injection.

PREX1 activity is controlled by both PtdIns(3,4,5)P_3, which is generated by PI3K, and Gβγ subunits that are released after activation of G protein-coupled receptors (GPCRs). Kazanietz and colleagues found that inhibition of Gβγ subunit release suppressed HRG-mediated activation of RAC1, and further experiments indicated that Gβγ resulted in the activation of PI3Kγ. GPCR activation has also been implicated in breast cancer progression, and these authors found that the GPCR CXCR4 is involved in cancer cell migration in response to HRG and that this requires the activation of both Gβγ subunits and PI3Kγ activity to activate PREX1 and RAC1.

Similar results were found by Atanasio Pandiella and colleagues. These authors had previously identified a role for the ERK5 pathway in HRG–ERBB signalling, and in additional studies aimed at identifying the importance of other pathways in HRG–ERBB signalling they observed that an antibody raised against a phosphorylated serine in AKT cross-reacted with another protein. Mass spectrometry analyses identified this protein as PREX1. These authors found that in response to HRG, PREX is phosphorylated on Ser605, Ser606 and Ser1169, and dephosphorylated on Ser313 and Ser319. They showed that this differential phosphorylation controls the activation of RAC1 by PREX1. Knock down of *PREX1* expression using short hairpin RNAs reduced migration and invasion of breast cancer cells in response to HRG and also reduced the proliferation of these cells — expression of a PREX1-Ser1169Ala mutant was unable to rescue this loss of proliferation. Analysis of human breast cancer samples also indicated that high expression of PREX1 correlated with a poor prognosis.

Overall, these findings indicate that PREX1 functions to integrate signals from both tyrosine kinase receptors and GPCRs to activate RAC activity, resulting in the proliferation and migration of breast cancer cells.

Nicola McCarthy

> “PREX1 functions to integrate signals from both tyrosine kinase receptors and GPCRs to activate RAC activity”

ORIGINAL RESEARCH PAPERS Montero, J. C., Seoane, S., Ocaña, A. & Pandiella, A. Rex1 participates in Neuregulin-ErbB signal transduction and its expression correlates with patient outcome in breast cancer. *Oncogene* 1 Nov 2010 (doi:10.1038/onc.2010.489) | Sosa, M. S. *et al.* Identification of the Rac-GEF P-Rex1 as an essential mediator of ErbB signaling in breast cancer. *Mol. Cell* **40**, 877–892 (2010)