PROGNOSTIC MARKERS

Two are worse than one

Most cases of breast cancer are dependent on oestrogen for tumour progression, and treatment with tamoxifen, which modulates the oestrogen receptor (ER), has been successful in considerably reducing deaths from breast cancer. However, many patients become resistant to tamoxifen and C. Kent Osborne and colleagues now show that overexpression of an oestrogen receptor co-activator, AIB1, together with high expression of a member of the epidermal growth-factor-receptor family, ERBB2 (also known as HER2/neu), in ER-positive breast cancer patients is associated with resistance to tamoxifen.

Osborne *et al.* examined tumour samples from 316 breast cancer patients with long-term follow-up. In the 187 patients who had received adjuvant tamoxifen, high AIB1 expression was associated with poorer prognosis and shorter disease-free survival (DFS).

ERBB2 signalling through MAPK (mitogen-activated protein kinase) activates both the ER and AIB1, and some studies have indicated that high ERBB2 expression is associated with tamoxifen resistance, so do ERBB2 and AIB1 interact to affect the response of a tumour to tamoxifen? The authors found that untreated patients with high ERBB2, regardless of the level of expression of AIB1, had worse prognosis than those with low ERBB2. However, high ERBB2 plus high AIB1 in patients who had received adjuvant tamoxifen was an even worse prognostic factor. DFS in these patients was 42% versus 70% in patients with any other combination of ERBB2 and AIB1 expression.

So, these results confirm laboratory findings that ER co-activators can enhance the ER-agonist activity of tamoxifen — the drug is less effective in patients with high AIB1 levels. The role of AIB1 in tamoxifen resistance might explain why correlations in previous studies in which only ERBB2 was measured in tamoxifen-treated patients have been inconsistent.

Ezzie Hutchinson

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TUMOUR SUPPRESSORS

Sticky situation

Tumour invasion is commonly associated with increased cell migration and extracellular-matrix destruction. In a search for genes that are disrupted during tumour formation, Vijay Yajnik *et al.* discovered that loss of intercellular contact structures called 'adherens junctions' can also contribute to tumour invasiveness.

Yajnik *et al.* used representational difference analysis (RDA) — a screening method for detecting homozygous deletions in genomic DNA — to identify genes that were deleted during tumour progression in the $Nf2^{+/-}$ $Trp53^{+/-}$ mouse cancer model, which gives rise to tumours with high metastatic potential. One of the genes that is lost in osteosarcomas from these mice encodes Dock4, a member of the CDM family of proteins. These proteins are regulators of the small GTPases that control cell motility, cell adhesion and invasion. Analysis of human cancer samples revealed that inactivating *DOCK4* mutations were also present in a variety of human cancer cells, but not in any of the 200 control samples tested.

Yajnik *et al.* showed that reconstitution of mouse osteosarcoma cells with *Dock4* led to pronounced morphological changes. These cells developed a flattened morphology and grew to a lower cell density at confluence than the parent cell line, indicating contact inhibition. *Dock4* re-expression also caused the cells to form adherens junctions — strong mechanical attachments between adjacent cells.

Formation of such cellular structures is typically regulated by the activity of small GTPases. Yajnik *et al.* found that re-expression of Dock4 was correlated with activation of the Rap GTPase, but not with Rac, Rho or Cdc42 GTPase activity. Furthermore, co-expression of *Dock4* with a dominant-negative form of Rap prevented adherens juction formation and contact inhibition in osteosarcoma cells. Mouse osteosarcoma cells engineered to re-express Dock4 were less likely than their parent cells to produce colonies in soft agar, and produced much smaller tumours when injected into mice. These tumours also failed to infiltrate surrounding tissues, indicating that adherens junctions can somehow prevent tumour-cell invasiveness.

Further research is required to determine the mechanisms by which Rap controls adherens junction formation, and how these cellular structures regulate cell migration.

Kristine Novak

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