EARLY DETECTION

Tiny signals

In patients with breast cancer, biopsies for lymph node metastases are usually performed to determine the patient prognosis — those who test positive are considered as candidates for adjuvant therapy. However, up to 30% of patients that are free of lymph node metastases still develop metastatic disease. In the *New England Journal of Medicine*, Stephan Braun *et al*. report that the detection of disseminated tumour cells in bone marrow samples is a more reliable determinant of metastasis and patient survival.

Unlike other tumour types, such as head and neck cancers, breast tumour cells frequently bypass the lymph nodes and disseminate directly through the blood to distant organs. This haematogeneous dissemination of cancer cells has been shown to be an early event in tumour progression. Small numbers of disseminated tumour cells can be detected in bone marrow samples by sensitive immunocytochemical assays for proteins such as cytokeratin and epithelial mucins, so Braun *et al*. set out to determine their prognostic significance. In a pooled meta-analysis of data from 9 studies involving 4,703 patients with stage I, II or III breast cancer, the authors evaluated the association between detection of bone marrow micrometastases and patient outcome over a 10-year period.

The study compared the effects of different factors, such as tumour size, grade, bone marrow metastasis, lymph node metastasis and hormone receptor expression, and revealed that the presence of micrometases in bone marrow were the best predictors of outcome (survival, disease recurrence and metastasis to other organs) within the first 5 years after diagnosis. Bone marrow micrometastases were detected in over 30% of patients and these patients were found to develop larger tumours with a higher histological grade that more

STRUCTURE

InhibitABL

Although the kinase activity of BCR–ABL is inhibited by imatinib, the onset of drug resistance has prompted the search for further intervention strategies. Aside from its increased tyrosine kinase activity, the primarily cytoplasmic localization of the fusion protein is thought to contribute to its leukaemogenic properties. Because the F-actin binding domain (FABD) in the carboxy terminus of BCR–ABL is thought to, in part, regulate this localization, Oliver Hantschel and colleagues have analysed its three-dimensional structure.

ABL localizes to both the nucleus and the cytoplasm — this is dependent on environmental cues. However, BCR–ABL does not, but both proteins have identical carboxy terminal domains that govern the localization of the protein. These include three nuclear localization signals that enable the import of the kinase into the nucleus, a putative nuclear export signal that is part of the FABD, and the FABD itself. The authors determined the 3D structure of the FABD of human ABL by heteronuclear nuclear magnetic resonance spectroscopy. They found that the FABD folds into a compact bundle of four antiparallel α-helices and the 3D structure of this domain shows strong homology to other cytoskeletal proteins, some of which also bind F-actin. In contrast to previous observations, the authors show that the nuclear export signal is non-functional and is part of the hydrophobic core of the FABD, unless artificially exposed as an isolated peptide.

How does the FABD affect the localization of ABL and BCR–ABL? To address this, the authors made 21 mutant ABL and BCR–ABL proteins based on the structure of the FABD and examined their localization in cultured cells and their interaction with purified F-actin in a cell-free system. Their results indicate that loss of the FABD in ABL causes nuclear localization, but this does not occur in BCR–ABL. As both FABD are the same, there must be another property of the fusion protein that keeps it tethered in the cytoplasm. The authors' preliminary evidence indicates that the increased kinase activity of the fusion protein is not sufficient to exclude BCR–ABL from the nucleus, but that the coiled-coil domain of BCR is important.

Irrespective of the precise mechanism, previous data have indicated that disrupting the FABD domain of BCR–ABL limits its oncogenicity. The authors mapped the F-actin binding site to a few conserved residues in an α-helix. Based on this and their structural data, the authors conclude that pharmacological disruption of these conserved residues is a plausible approach for inhibiting BCR–ABL.

Nicola McCarthy

References and links

ORIGINAL RESEARCH PAPER Hantschel, O. *et al*. Structural basis for the cytoskeletal association of Bcr–Abl/c-Abl. *Mol. Cell* **19**, 461–473 (2005)

FURTHER READING Ruibao Ren. Mechanisms of BCR–ABL in the pathogenesis of chronic myelogenous leukaemia. *Nature Rev. Cancer* **5**, 172–183 (2005)

WEB SITE

Giulio Superti-Furga's lab: http://www.cemm.oeaw.ac.at/?cont=people&sub=gsf