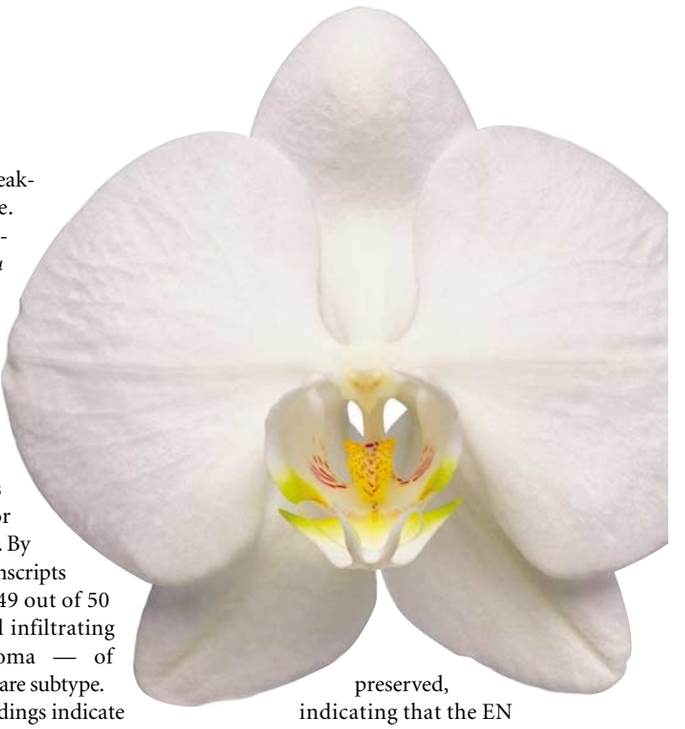
HIGHLIGHTS

TRANSLOCATIONS

Rare simplicity



Single genetic lesions underlying transformation are seldom found in epithelial cancers because of the genetic complexity of the disease. However, Tognon *et al.* now report a translocation event that forms a dominantly acting oncogene and causes a rare form of breast cancer — secretory breast carcinoma (SBC).

Secretory carcinoma accounts for less than 1% of all breast cancers and occurs in patients as young as 3 years old — patients are usually cured, but a mastectomy or chemotherapy is often required. It is generally accepted that specific fusion genes are associated with specific tumour types, but when the authors saw that a translocation — which they had previously identified in paediatric mesenchymal tumours — was the only karyotypic abnormality in an SBC in one 6-year-old patient, they decided to investigate other cases.

The translocation — between the *ETV6* transcription factor on chromosome 12 and the protein tyrosine kinase domain of the neurotrophin-3 receptor *NTRK3* on chromosome 15 — results in constitutive activation of wild-type NTRK3, which activates the RAS–mitogen-activated protein kinase and the phosphatidylinositol 3-kinase–AKT pathways for mitogenesis and cancer survival.

The authors detected *ETV6–NTRK3* fusion transcripts in tumour specimens from 11 out of 12 further patients with SBC, all of whom had the identical breakpoint sequence. Dual-colour fluorescence *in situ* hybridization (FISH) analysis showed that all samples of SBC that were available for analysis were positive for the fusion gene. By contrast, no transcripts were found in 49 out of 50 cases of typical infiltrating ductal carcinoma — of which SBC is a rare subtype.

So, these findings indicate that the *ETV6–NTRK3* gene fusion is a non-random rearrangement in SBC, but does the translocation product (EN) cause transformation? Tognon and colleagues transfected two immortalized non-transformed mouse epithelial cell lines — the Scg6 cell line has mesenchymal features, and Eph4 has a stable epithelial phenotype — with an *ETV6–NTRK3* retroviral construct. Both cell lines expressed the construct and showed a transformed phenotype, whereas cells transfected with vector alone did not. In addition, when these cells were injected into nude mice, the EN-expressing cells formed tumours, whereas the cells transfected with vector alone did not. Histopathology showed that the original phenotype was preserved, indicating that the EN product — which had only been associated with mesenchymal malignancies before — does not block epithelial differentiation potential.

The authors have established that *ETV6–NTRK3* is a dominantly acting oncogene in SBC. Furthermore, this research challenges the dogma that fusion genes are only associated with one of the three germ layers, as the EN product has been previously found in mesenchymal tumours, and now in an epithelial malignancy.

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References and links

ORIGINAL RESEARCH PAPER Tognon, C. *et al.* Expression of the *ETV6-NTRK3* gene fusion as a primary event in human secretory breast carcinoma. *Cancer Cell* **2**, 367–376 (2002)