

# Oncogenes in context

**In certain types of gastrointestinal cell, mutations in the protein KIT give rise to gastrointestinal stromal tumours. Why are other cell types that express KIT not affected? The answer lies with a second protein. SEE LETTER P.849**

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**A**mong sarcomas — cancers of connective tissues — the gastrointestinal stromal tumour (GIST) is the most common in humans. In 80–85% of cases, GISTs are associated with gain-of-function mutations in the receptor tyrosine kinase KIT. On page 849 of this issue, Chi *et al.*<sup>1</sup> show that KIT has a partner in crime in the form of the transcription factor ETV1.

Most GISTs harbour non-germline mutations in KIT. In the rare familial GISTs, an activating KIT mutation is inherited. People carrying this mutation show diffuse, abnormal proliferation (hyperplasia) of a gastrointestinal cell type called the interstitial cell of Cajal (ICC), and are at high risk of developing GISTs throughout life<sup>2</sup>. ICCs are located in the muscular wall of the gut and function as pacemaker cells to regulate the process of peristalsis, whereby muscle contractions propel food through the digestive tract. GISTs are believed to originate from ICC stem/progenitor cells or from mesenchymal stem cells that give rise to ICC progenitors<sup>3</sup>.

In the gut wall, ICCs occur in several distinct anatomical locations, but GISTs arise from only two specific populations: myenteric ICCs and intramuscular ICCs. Notably, the hyperplasia seen in humans and mice with germline activating KIT mutations is also confined to these two ICC populations<sup>1,2,4</sup>. What's more, these humans and mice are strongly predisposed to developing GISTs, but do not commonly develop cancers in other tissues with high KIT expression — such as those containing melanocytes, germ cells or haematopoietic cells<sup>2,4</sup>.

So why is the pathogenicity of mutant KIT restricted to specific cell types? A tissue-restricted effect of oncogene activation — or of loss of tumour-suppressor genes — is a feature of many cancers. For example, the fused gene *BCR-ABL* functions as an oncogene in haematopoietic stem cells (most commonly causing chronic myeloid leukaemia) but not in other cell types<sup>5</sup>. In addition, loss of the *APC* tumour-suppressor gene is an initiating event in the formation of colonic polyp/adenocarcinoma but not other common solid tumours<sup>6</sup>. Like KIT, therefore, these genes act as 'gatekeepers' in specific cellular contexts, but what constrains their effects remains poorly understood.

Chi *et al.*<sup>1</sup> show that, where GISTs are concerned, ETV1 cooperates with mutated KIT

in a cell-specific way to cause tumours. ETV1 is a member of the ETS family of transcription factors, which has at least 29 members. All ETS transcription factors have an evolutionarily conserved 80-amino-acid-long DNA-binding domain, which binds to the consensus DNA sequence GGA(A/T). Individual ETS proteins regulate the activity of gene promoters directly through their intrinsic activation or repression domains, and/or by interaction with other proteins<sup>7</sup>.

Examining existing gene-expression profiles of GISTs and non-GIST sarcomas, Chi *et al.* show that ETV1 is part of the GIST expression signature. They report high expression of this protein, and of its messenger RNA, in all GIST samples tested, and show that reducing ETV1 expression decreases GIST-cell proliferation, as well as the tumorigenicity of GIST cells when these are injected into immunodeficient mice. The authors do not, however, find any evidence of genomic alteration affecting the *ETV1* gene.

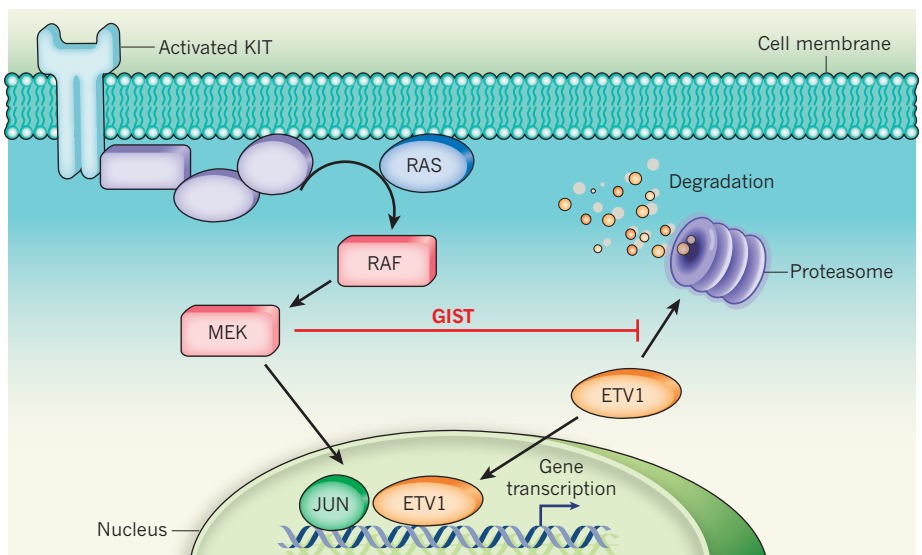
Chi and co-workers also show that, in mice carrying germline KIT mutations, ETV1 expression in the gut is restricted to only those subsets of ICCs that give rise to GISTs (myenteric and

intramuscular ICCs). In mice lacking ETV1, these specific subsets occur in lower numbers than in wild-type mice, indicating a requirement for ETV1 in these cells' development. Thus, ETV1 functions as a lineage-specific survival factor for the cells that give rise to GIST.

The authors' data also elucidate the signalling cascade that links KIT to ETV1. Chemically inhibiting KIT-dependent activation of the MAP-kinase enzyme resulted in a rapid loss of ETV1, suggesting that this transcription factor functions downstream of KIT. The ability of KIT or MEK inhibitors to decrease ETV1 levels was abrogated by inhibition of the protein-degrading machinery, the proteasome (Fig. 1).

Genomic alteration of ETS genes has been reported in several human cancers. For instance, translocation mutations affect ETS family members in Ewing's sarcoma (most commonly *EWS-FLI1*, but also *ERG*, *ETV1*, *ETV4* and *FEV*) and in prostate cancer (most commonly *TMPRSS2-ERG*, but also *ETV1*, *ETV4* and *ETV5*)<sup>7-9</sup>. Furthermore, mutations in the ETS protein SPI1 are associated with some cases of acute myeloid leukaemia, and high-level amplification of ETV1 has been reported in a significant minority of melanoma cancers<sup>7,10</sup>. Intriguingly, melanoma cell lines depend on ETV1 not just for proliferation, but also for growth independent of tissue anchorage. What's more, the ability of ETV1 to make melanocytes cancerous depends on constitutive activation of the MAP-kinase signalling pathway by gain-of-function mutations in the *BRAF* or *NRAS* proteins<sup>10</sup>.

What's surprising about Chi and colleagues' results is that they do not show ETS-dependent



**Figure 1 | Gastrointestinal stromal tumour at a cellular level.** Activation of the receptor tyrosine kinase KIT triggers the RAS/RAF/MEK pathway. This pathway ultimately results in changes in gene transcription mediated by activating specific transcription factors such as JUN. The transcription factor ETV1 acts downstream of the RAS/RAF/MEK pathway and can directly regulate gene expression. Chi *et al.*<sup>1</sup> find that ETV1 is essential for KIT-mediated development of gastrointestinal stromal tumours (GISTs). Normally, proteasomal degradation of ETV1 leads to a decrease in ETV1-dependent gene transcription. In GIST, signalling from mutant KIT leads to increased activity of MEK, which then blocks ETV1 degradation. The combination of MEK activation and developmental expression of ETV1 produces the gene expression profile that is characteristic of GIST.

oncogenesis related to a genomic alteration. Instead, the increased expression of ETV1 in GISTs seems to be a consequence of KIT signalling and the underlying gene-expression profile inherent to specific subsets of ICCs. In other words, to induce GISTs, KIT mutations act within the cellular context provided by ETV1 expression.

On the basis of this evidence<sup>1</sup>, ETV1 could not only be a useful diagnostic marker for GISTs, but also a drug target. The use of the anticancer drug imatinib and other KIT-kinase inhibitors has revolutionized the treatment of metastatic GISTs and increased the median survival of patients by 3–4 years. Imatinib, however, must be given continuously, because interrupted treatment with this drug is associated with rapid tumour re-growth<sup>11</sup>. Moreover, recent work indicates that, although differentiated GIST cells are KIT-dependent and imatinib-sensitive, the underlying GIST stem/progenitor pool is KIT-independent and imatinib-resistant<sup>3</sup>. Whether the survival of GIST stem/progenitor cells depends on ETV1 is therefore a pertinent question. If so, targeting ETV1 in GISTs may produce the cure that currently eludes KIT inhibitors such as imatinib.

More broadly, Chi and colleagues' data<sup>1</sup> suggest that tissue-specific expression of ETS family members may provide an oncogenic context for

other human cancers. Determining which ETS family members provide an oncogenic context for other cancers requires further research. ■

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**Competing interests** The authors declare competing financial interests. See online article for details.

#### ATMOSPHERIC CHEMISTRY

# Phase matters for aerosols

**Organic aerosol particles are ubiquitous in the atmosphere. In forests, such particles can occur in solid form — a finding that will lead to a re-evaluation of how they are formed, and their properties and effects. SEE LETTER P.824**

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Most schoolchildren, mischievous or not, know that a thrown egg sticks to a wall because it is predominantly liquid, but that a rock bounces because it is solid. Adults know this too, and, reporting on page 824 of this issue, Virtanen *et al.*<sup>1</sup> cleverly use this simple principle, along with electron microscopy, to determine the phase of much smaller airborne objects — atmospheric aerosol particles. Their measurements show that, contrary to conventional wisdom, the abundant microscopic organic particles that form in boreal forests by condensation of photo-oxidized tree emissions can be solid. This result has implications for understanding the formation and properties of these and other organic particles that are thought to affect both climate and human health.

The atmospheric aerosol is a complex mixture of primary and secondary material<sup>2</sup>. Primary aerosol is directly emitted in particulate form and consists of soil dust, sea spray, plant material and soot. Secondary aerosol consists of organic compounds and ammonium nitrates and sulphates — which form by condensation and particle-phase reactions of products of the atmospheric oxidation of volatile organic compounds, sulphur oxides and nitrogen oxides — and ammonia. Because of their mechanisms of formation, secondary and combustion-derived particles are typically less than about one micrometre in diameter, whereas most other particles are larger. Submicrometre-size particles can efficiently scatter and absorb radiation and serve as cloud condensation nuclei (CCN), thereby affecting climate, and can also be readily inhaled and thus adversely affect human health.