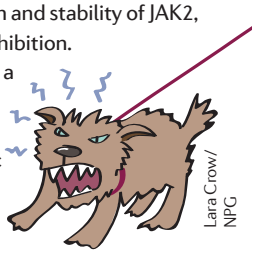
THERAPEUTICS

Holding JAK back

Janus kinase 2 (JAK2) is commonly activated by somatic mutations in myeloproliferative neoplasm (MPN). However, JAK2 inhibitors have only limited effectiveness in treating patients with MPN, and a new study might now explain why: inhibited JAK2 can form heterodimers with other kinases to maintain oncogenic signalling.

Ross Levine and colleagues sought to elucidate the drug-tolerance mechanisms that develop during chronic exposure of JAK2-mutant haematopoietic cells to JAK2 inhibitors. DNA-sequencing analyses of haematopoietic cell lines treated *in vitro*, and clinically treated patient MPN samples, found no evidence for second-site kinase mutations, which are a known mechanism of resistance to some kinase inhibitors. Despite this apparent continued sensitivity of the JAK2 protein to inhibition of its catalytic autophosphorylation activity, chronically treated cells retained JAK2 phosphorylation and hyperactive signalling downstream of JAK2.

How do cells rewire their signalling to overcome JAK2 inhibition? The authors reasoned that other kinases might associate as heterodimers with JAK2 to provide the activating phosphorylation. In haematopoietic cells *in vitro*, as well as in mouse models and patients with MPN, chronic treatment with JAK2 inhibitors increased the association of JAK2 with the JAK1 and TYK2 kinases. As evidence of functional relevance, expressing constitutively active JAK1 resulted in JAK2 phosphorylation and activation of downstream signalling, even in the presence of JAK2 inhibitors. Furthermore, treatment studies of cells, mice and patients indicated that cells also respond by upregulating the expression and stability of JAK2, possibly to buffer the effects of JAK2 inhibition.



Lara Crow/NPG

Collectively, these findings suggest a model by which inhibited JAK2 carries out an important scaffold function to allow continued oncogenic signalling in the absence of its own catalytic activity; indeed, knockdown of JAK2 in chronically treated cells decreased JAK2 downstream signalling and cell proliferation.

Interestingly, JAK2 inhibitor sensitivity was gradually restored following drug removal, implying that intermittent treatment might be worthy of clinical investigation.

Can the tolerance mechanisms be overcome with rational therapeutic strategies? Heat shock protein 90 (HSP90) inhibition, which causes the destabilization of various proteins including JAK2, was found to reduce signalling downstream of JAK2. Also, switching treatment to the novel JAK2 inhibitor BBT-594, which has a superior ability to remain bound to inactivated JAK2 compared with other JAK2 inhibitors, decreased JAK2 downstream signalling and cell proliferation, perhaps by blocking heterodimerization. Furthermore, knockdown of JAK1 or TYK2 resensitized cells to multiple JAK2 inhibitors.

Therefore, combination strategies targeting both JAK2 and relevant bypass mechanisms may hold therapeutic promise.

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ORIGINAL RESEARCH PAPER Koppikar, P. *et al.* Heterodimeric JAK–STAT activation as a mechanism of persistence to JAK2 inhibitor therapy. *Nature* 22 Jul 2012 (doi:10.1038/nature11303)