ONCOGENES

Nothing but a G thing

As targeted therapies continue to furrow their way into the heart of cancer treatment, finding the clinically relevant, 'actionable' mutations is becoming more and more of a priority.

With this in mind, a team led by Andrew A. Lane and David M. Weinstock set out to find actionable mutations in blastic plasmacytoid dendritic cell neoplasm (BPDCN), an aggressive leukaemia with poorly understood biology. They started by transducing mouse BaF3 cells that expressed the *BCL-2* oncogene with a BPDCN patient-derived cDNA library. Three clones grew out in an interleukin-3 (IL-3)-independent manner, and they were all found to contain a mutant version of the *GNB1* gene, which encodes a β subunit of heterotrimeric G proteins.

> “disrupted Gα–Gβ interactions lead to unrestrained signalling”

Lara Crow / NPG

Mutations in G protein-β (Gβ) subunits had not been previously characterized in human cancers, so Yoda *et al.* probed further. A database search revealed different *GNB1* mutations across a spectrum of haematological malignancies. Intriguingly, certain mutations were associated with myeloid-derived malignancies, whereas others were more frequently found in B cell malignancies. The authors forged ahead with a series of bone marrow transplantation experiments. Their *in vitro* observations were confirmed by showing that donor cells transduced with mutant *GNB1* could give rise to either myeloid-derived or B cell-derived leukaemias in recipient mice. In both cases, leukaemogenesis was dependent on the presence of a partner mutation in the donor cells — deletion of cyclin-dependent kinase inhibitor 2a (*Cdkn2a*).

How did mutations affect signalling downstream of heterotrimeric G proteins? Signalling via G proteins triggers the dissociation of Gα and Gβ subunits, which activates downstream effector proteins. Immunoprecipitation experiments revealed that mutant GNB1 dissociated from the complex in the absence of an upstream signal. Next, proteomic analysis showed that cells expressing mutant GNB1 also had increased activation of the AKT, mTOR and ERK pathways. These observations suggest that disrupted Gα–Gβ interactions lead to unrestrained signalling cascades downstream of G proteins, driving transformation.

But were GNB1 mutations actionable? Administration of BEZ235 — a small-molecule inhibitor of the PI3K and mTOR pathways — markedly improved survival of mice with mutant *GNB1*-induced myeloid leukaemia. Together, these data strongly suggest that targeting *GNB1* might have therapeutic benefits.

Things became even more interesting when they looked at human tumour samples. Recent studies have linked G protein activation with resistance to the BRAF inhibitor, vemurafenib, in melanoma, so the authors asked whether Gβ mutations were involved. Tellingly, they found that a mutant form of a second Gβ protein, GNB2, drove resistance to vemurafenib in A375 melanoma cells. Next, they widened the net to include other kinase inhibitors and found that overexpression of mutant GNB1 could mediate resistance to the ABL1 inhibitors nilotinib and imatinib, as well as to the Janus kinase 2 (JAK2) inhibitor ruxolitinib. Therefore, not only might GNB1 mutations have a role in haematological transformation, but they might also propel resistance to different kinase inhibitors.

These are intriguing results, but many questions remain unanswered. Will targeting Gβ be a much-needed panacea for certain haematological malignancies, and will we be able to harness these findings to help to tackle drug resistance, a growing problem in cancer treatment? Only time will tell.

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