Cancer dependencies

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Hyperactivation of oncogenic driver pathways as a precision therapeutic strategy

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Many precision cancer therapies function by inhibiting oncogenic signaling pathways. A new study describes the counterintuitive finding that forced hyperactivation of the same pathways can also enable selective tumor targeting.

Genetic mutations that activate oncogenic signaling pathways increase the fitness of cancer cells. The fact that tumors with these mutations require constitutive oncogenic signaling for their survival — a concept known as oncogene addiction — explains the activity of many well-established oncogene-targeted therapies. In this issue of *Nature Genetics*, Chang et al.[1] show that forced hyperactivation of the same oncogenic pathways can also selectively impair cancer cell survival, which suggests that cancer cells can only tolerate a confined window of oncogenic signaling flux, and raises the possibility of a new class of targeted therapies (Fig. 1).

Several oncogene-targeted therapies exist, including inhibitors of well-established disease drivers such as BCR-ABL, EGFR, ALK and BRAF. In many cases, these agents have transformed disease management and substantially extended patients' lives. However, targeted therapies have well-known limitations. For example, in some cases, key nodes in oncogenic driver pathways have proven difficult to drug. Furthermore, even when potent and selective targeted therapies are developed, their application can be limited by challenges such as on-target, off-tissue toxicities[2] and the eventual development of resistance[3].

Constitutive oncogenic signaling, driven by the activation of an oncogene or loss of a tumor suppressor gene, can induce stress and lead to proliferative arrest in normal cells[4]. Recent studies have shown that an analogous concept may exist in cancer, in which tumor cells are unable to tolerate further activation of an already-activated oncogenic signaling pathway. For example, hyperactivation of ERK by withdrawal of mitogen-activated protein kinase (MAPK) inhibitors or the loss of ERK phosphatases DUSP4 and DUSP6 can inhibit the viability of *NRAS*- or *BRAF*-mutant tumor cells[5,6]. Similarly, tumor cells driven by fusion oncoproteins such as EWS–FLI and PAX3–FOXO1 are highly sensitive to even slightly increased levels of these oncoproteins[7,8].

To understand the generalizability of this concept on an enormous scale, Chang et al.[1] transduced pools of hundreds of DNA-barcoded cancer cell lines with activators of the oncogenic MAPK, phosphoinositide 3-kinase (PI3K) and WNT pathways. They validated the finding that ERK hyperactivation leads to growth inhibition, showing that these effects were most pronounced in *BRAF*-mutant and, to a lesser extent, *RAS*-mutant cell lines relative to receptor tyrosine kinase (RTK)-driven lines. Reverse-phase protein array analysis showed that sensitivity to ERK hyperactivation was directly correlated with the cell's baseline level of ERK activity, as measured by levels of phosphorylated MEK (p-MEK), with *BRAF*-mutant lines exhibiting the highest p-MEK levels. Similarly, the researchers found that fitness defects resulting from forced hyperactivation of the AKT pathway were increased in cell lines containing *PIK3CA* or *PTEN* mutations that drive oncogenic activation of this pathway. Interestingly, particularly strong fitness defects were observed in cell lines from tumors that contain double *PIK3CA* and *PTEN* mutations, which exhibited some of the highest baseline levels of AKT phosphorylation, a marker of pathway activity, in the cell line panel.

Finally, Chang et al.[1] discovered that forced hyperactivation of the WNT pathway by overexpression of β-catenin was selectively deleterious to subsets of colorectal cancers (CRCs) containing loss-of-function mutations in *APC*, a negative regulator of the pathway mutated in the tumors of approximately 80% of patients with this disease[9]. APC is a component of the β-catenin destruction complex, and tumors from patients with CRC containing wild-type *APC* often contain gain-of-function mutations in *CTNNB1*, which encodes β-catenin[9]. Surprisingly, overexpression of β-catenin decreased the viability of *APC*-mutant CRC cell lines but not *CTNNB1*-mutant lines, which suggests that the latter

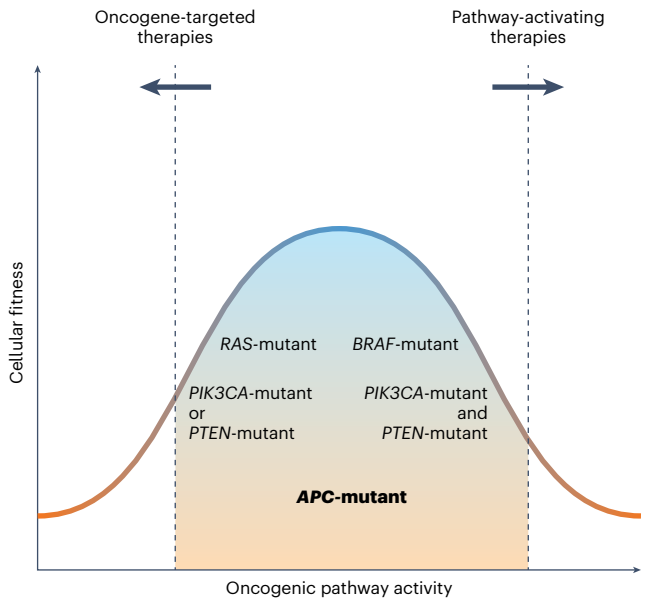

Fig. 1 | Schematic depicting the relationship between oncogenic pathway activity and cellular fitness. The results of Chang et al.[1] suggest that cancer cells achieve optimal fitness in the setting of moderate oncogenic pathway activity driven by mutations such as those indicated. Traditional oncogene-targeted therapies reduce fitness by reducing the activity of oncogenic pathways. A new class of pathway-activating therapies inspired by this work may instead reduce fitness by increasing pathway activity.

have adapted to high β-catenin levels. Furthermore, cell lines that were sensitive to β-catenin overexpression were selectively dependent on *APC* in CRISPR–Cas9 loss-of-function genetic screens performed by DepMap, even though these cells are enriched for *APC* mutations. This, together with evidence that sensitivity to loss of *APC* strongly correlated with sensitivity to loss of other members of the β-catenin destruction complex, suggests that *APC*-mutant cells may retain some level of activity of the destruction complex, and that this activity is essential for cell survival. In line with these findings, *APC* mutations often encode truncated forms of the protein that retain β-catenin-binding domains and the capacity to regulate its function[10–12]. Further experiments showed that β-catenin overexpression or *APC* knockout leads, as expected, to a marked upregulation of WNT target genes and a selective growth impairment in *APC*-mutant CRC cell lines, organoids and tumor xenografts. Finally, the authors demonstrated that WNT hyperactivation can be achieved by knockdown of *CSNK1A1*, which encodes the druggable casein kinase 1α, a member of the β-catenin destruction complex, highlighting the notion that inhibitors of this, or related proteins, may enable therapeutic WNT hyperactivation in vivo.

How hyperactivation of oncogene pathways exerts an anti-fitness effect on cancer cells is unclear, although clues exist. In normal cells, oncogene-induced growth arrest has been associated with diverse mechanisms that converge on RB and TP53 signaling[4]; in *BRAF*-mutant melanoma cells, ERK hyperactivation has been shown to drive JUNB- and p21-dependent cell cycle arrest[13,14]. In addition, the proteins whose pharmacological inhibition can drive optimal pathway hyperactivation-induced tumor targeting are unclear, and the development of drugs to modulate these targets will be subjected to the same druggability constraints that apply elsewhere.

The effect of pharmacological hyperactivation of oncogenic pathways on normal tissues remains to be determined, although there is evidence that patients treated with BRAF inhibitors that drive paradoxical MAPK activation in normal tissues experience manageable toxicities[15]. The viability of adults with germline mutations in genes encoding negative regulators of the MAPK, PI3K and WNT pathways provides further evidence that pharmacological pathway activation could be tolerable, particularly if applied discontinuously and with appropriate safety monitoring. Despite these concerns, the finding that forced activation of oncogenic driver pathways selectively impairs the survival of genetically defined tumor cell lines suggests possible new treatment strategies for tumors driven by these oncogenic pathways. These include potential therapies for tumors containing 'undruggable' WNT-activating *APC* mutations; tumors containing *PTEN* and *RAS* mutations that respond poorly to the inhibition of downstream kinases such as PI3K and MEK, respectively; and tumors that develop resistance to oncogene-targeted therapies.

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Competing interests

The author declares no competing financial interest.