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Short Communication

Significance of Notch Inhibition in the Treatment of Leukemia

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DESCRIPTION

The pantheon of "cancer hallmarks," core characteristics that all cancer cells share, has recently included metabolic reprogramming of cancer cells to it. The Warburg effect, which drives cancer cells to rely on glycolysis for energy and anabolic metabolism even when oxygen levels are adequate for oxidative phosphorylation, may be the finest of these metabolic changes. When you consider that cell growth is based on the biosynthesis of cellular building blocks from metabolic intermediates, which are largely provided by the glycolytic and Tricarboxylic Acid (TCA) pathways, this seemingly paradoxical use of fuel makes more sense. Increased cellular uptake of glucose and glutamine, a "hunger" that can be visualized clinically by Positron Emission Tomography (PET) scanning, primes these pathways in cancers and rapidly growing normal tissues [1]. Many oncogenic stimuli now appeared to have an impact on metabolic circuits that promote Warburg metabolism. One of these is the Notch pathway, which is activated by mutations in NOTCH1 in the majority of human T-ALLs (T cell Acute Lymphoblastic Leukaemia).

The authors show that T-ALLs with activating mutations of NOTCH1 employ glutamine as the dominating source of intermediates for priming the TCA cycle using murine models and xenografted primary human T-ALL (so-called primagrafts) (a process referred to as anapleurosis). Following pharmacologic inhibition or genetic ablation of Notch phosphorylation, glutamine intake drops rapidly.

Whereas lymphoblasts are protected from Notch inhibition by the expression of glutaminolytic enzymes (e.g., the M2 isoform of pyruvate kinase PKM2 and glutaminase (GLS). Herranz, et al. [2] also show that combining notch and glutaminolysis inhibitors is an effective medication in mice having T-ALL primagrafts, supporting therapeutic strategies that target pathways that enable Warburg metabolism in this illness. The relationship between notch and glutamine metabolism in T-ALL is similar to previous work revealing that MYC, a major regulator of glutaminolysis, is a critical downstream target of NOTCH1 in this cellular context [3,4]. The importance of Notch/MYC signaling axis is supported by the finding that mice engineered to express MYC in T cell progenitors develop Notch-independent T-ALLs and that T-ALL cells addicted to conditional MYC transgenes can be rescued from transgenic MYC withdrawal by notch *via* upregulation of the endogenous MYC locus [4].

MYC is still a difficult protein to target directly, however the notch pathway can be targeted using small molecules (gamma-secretase inhibitors) and blocking antibodies, which are both being tested in clinical trials. This seems to be an ideal scenario for the development of a rational tailored therapy, but the results so far have been underwhelming. While notch inhibitor treatment decreases lymphoblast counts in the most of T-ALL patients, only a tiny portion of those with NOTCH1-mutated T-ALL achieve major hematologic responses (approximately 5%-10%). The field's primary translational issue stems from this experience, and it's simple to express but difficult to answer: how do T-ALL cells finally be free from notch dependency? Herranz, et al. [2] present two scenarios, both of which involve metabolic changes. It has long been recognized that reducing Notch from human T-ALL cells causes a reduction in cell size and cell-cycle arrest, but no cell death, and that these changes are accompanied with autophagy stimulation. Herranz demonstrate that notch inhibitor-treated leukaemia cells show related genes features, and they go on to show that T-ALL cells with autophagy defects due to ATG7 loss are more responsive to Notch inhibitors. As a result, autophagy appears to assist Notcha-dependent T lymphoblasts in surviving in the face of notch inhibition and food limitation. Other notch-mutated T-ALLs (and other cell lines) have been shown to proliferate unabated also when Notch is inhibited. Herranz provide compelling evidence that upregulation of PI3K/AKT signaling and higher reliance on glycolysis (instead of glutaminolysis) for anapleurosis is one mode of metabolic escape.

Upregulation of PI3K/AKT signaling was achieved in Herranz 2015 models by removing the tumor suppressor PTEN, which encodes a lipid phosphatase that acts as a brake on PI3K/AKT signaling. PTEN loss-of-function mutations are found in about 20% of human T-ALL patients [5], and Herranz report that PTEN is also downregulated in lymphoblasts following Notch withdrawal, though the mechanisms are unknown. PTEN loss was related to change in expression of genes involved in glycolysis utilization.

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PI3K/AKT signaling has the ability to improve MYC function by enhancing MYC mRNA translation and other mechanisms [6].

This "rewiring" of signaling inputs and metabolic outputs appears to free cells of notch dependency, providing a plausible (though unproven) explanation for Notch inhibitors' failure to elicit deep and sustained responses in patients. Even before exposure to notch inhibitors, our research suggests that heterogeneity in the Notch/MYC signaling axis and cellular metabolic circuits may exist in T-ALL [7]. This is consistent with past findings in other human cancers that have shown that certain cells rely more on Warburg metabolism or oxidative phosphorylation. In tumor cells, where central necrosis and poor vascularization are common, this variability has been attributed in part to deprivation of oxygen and nutrients, however, in leukemias, which lie in the bone marrow and have ready access to the vasculature, such anatomic variables are not as obviously engaged. Herranz found a way to target different metabolic states in T-ALL by combining notch inhibitors with PI3K/AKT inhibitors, for example Notably, other tiny little bit tumours, such as breast cancers and certain B cell neoplasms, appear to have the Notch/ MYC signaling axis.

CONCLUSION

As a result, the principles described may have much further implications for the use of targeted agents targeting notch. It will be interesting to see if notch inhibition promotes similar metabolic changes in cancers other than T-ALL, and if so, if they are also dependent on PI3K/AKT signaling.

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