Tumour biology

A metabolic vulnerability of pancreatic cancer

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Unusual metabolic pathways used by cancer cells offer possible targets for the development of clinical treatments. One such pathway, involving molecules called polyamines, has been found for pancreatic cancer. See p.339

Does pancreatic cancer have metabolic vulnerabilities that might offer therapeutic opportunities? On page 339, Lee *et al.*[1] identify a pathway of interest.

Pancreatic cancer is the third leading cause of cancer-related deaths in the United States[2], and it has the lowest five-year survival rate of any cancer[3]. Pancreatic ductal adenocarcinoma (PDAC), a highly aggressive form of this malignancy, represents more than 90% of pancreatic cancer cases[4]. Although therapeutic options for PDAC have grown, surgery and chemotherapy still provide the best chance of remission. There is a strong clinical need to find new therapeutics for PDAC and to gain a greater understanding of the biology of this disease.

Mutations in the cancer-promoting gene *KRAS* are found in 90% of all PDAC cases[5], and mutations in other genes, including *TP53,* are frequently involved in driving PDAC development and spread (metastasis). PDAC-associated mutations transform the biology of pancreatic cells in a variety of ways that typically serve to facilitate a high rate of cell division and adaptation to life in an often-hostile tumour microenvironment. The ability of PDAC cells to grow in such settings is mainly achieved by the reprogramming of cellular metabolism to sustain proliferation even in nutrient-poor environments. However, therapeutic efforts to target PDAC metabolism have yet to yield success.

One metabolic pathway that is commonly dysregulated across cancer subtypes is that of the synthesis of molecules called polyamines, which have essential roles in nearly all living organisms. In mammals, putrescine, spermidine and spermine are key polyamines. Polyamines have been implicated in a wide range of biological functions, including differentiation, immune-system function and the cell cycle. Despite our current level of understanding, we have scarcely begun to unveil the importance of these molecules across nature and in human disease.

Like many types of cancer, PDAC requires high levels of polyamines to sustain malignant tumour growth, and gene-expression of polyamines correlates negatively with survival[5]. The pervasiveness of heightened polyamine metabolism across many cancers probably stems from the regulation of this pathway by notable cancer-promoting genes. For example, both *KRAS* and *MYC*, a cancer-promoting gene that is active in 70% of human cancers, can transcriptionally regulate the gene expression needed for polyamine synthesis[6].

These observations have made polyamine biosynthesis an attractive target for cancer therapy. However, the most successful polyamine inhibitor so far has shown limited success as a single anticancer agent[7,8]. Therapeutic approaches that combine inhibition of polyamine synthesis with polyamine transport blockade have shown promise in various animal studies[9]. But our limited understanding of polyamine transport makes optimizing such an approach challenging. Therefore, gaining insight into the mechanics of polyamine metabolism and transport in cancer cells and understanding how these molecules serve tumour growth has clear potential clinical utility.

"The work suggests a specific approach to target pancreatic cancer with the potential for minimal effects in healthy tissues."

Lee *et al.* shed light on the role of polyamine metabolism in pancreatic cancer cells. The amino acid ornithine can be the substrate for the first step of polyamine synthesis, and it is converted to putrescine by the enzyme ODC1 (Fig. 1). Cells have many options available for how to generate ornithine, and the amino acid arginine acts as the main source of ornithine and subsequently putrescine. Using impressive *in vivo* metabolic-tracing experiments in mice, Lee and colleagues reveal that PDAC tumours have an unusual approach for fuelling ornithine and polyamine production.

The authors' analysis of PDAC cells reveals these cells' reliance on the amino acid glutamine to fuel ornithine and polyamine production. The interconversion of glutamine and ornithine is a bidirectional pathway controlled by the enzyme OAT. However, this reaction commonly favours the pathway direction from ornithine to glutamine, placing PDAC in a relatively small club of scenarios and environments — including early infancy, the fasting intestine and specific subsets of immune cells — in which ornithine and polyamines are mainly made from glutamine.

Lee and colleagues show that preventing the conversion of glutamine to ornithine through OAT deletion was alone sufficient to deplete polyamines in PDAC cells, and this approach was as efficient at preventing polyamine synthesis as was the loss of ODC1, which is a rate-limiting enzyme for polyamine synthesis. Notably, genetic and pharmacological targeting of polyamine metabolism through OAT removal reduced tumour growth in samples of cells from people with PDAC that were transplanted into mice. These results position OAT as a new target for polyamine modulation in pancreatic cancer. Some further key experimental observations by the authors support the attractiveness of this approach.

Cellular metabolism is a highly dynamic system that is adept at responding to changes in local conditions. Often, the dearth of a given metabolite molecule can be compensated for by re-routing other pathways to replenish substrate pools. Fascinatingly, no such compensatory effect is seen in PDAC cells, in which under OAT loss there is seemingly an inability to re-route arginine into ornithine in an attempt to preserve ornithine and polyamine synthesis. This gives added credence to OAT-mediated polyamine synthesis as a potential metabolic vulnerability for pancreatic cancer.

Questions remain as to why PDAC cells rewire their metabolism to favour glutamine-derived polyamine synthesis. Observations by Lee *et al.* demonstrating an arginine-depleted tumour microenvironment that limits access to arginine, combined with a rise in OAT levels if pancreatic cells become PDAC cells, suggest that this acts as a selective force. But this does not explain why cultured PDAC cell lines are also biased towards OAT-driven polyamine synthesis when arginine is available to them in the culture medium. Perhaps a type of gene regulation called an epigenetic effect in these cells maintains this metabolic route, or perhaps using glutamine to fuel polyamine metabolism has benefits we have yet to appreciate. These experiments raise the question of whether polyamines sourced

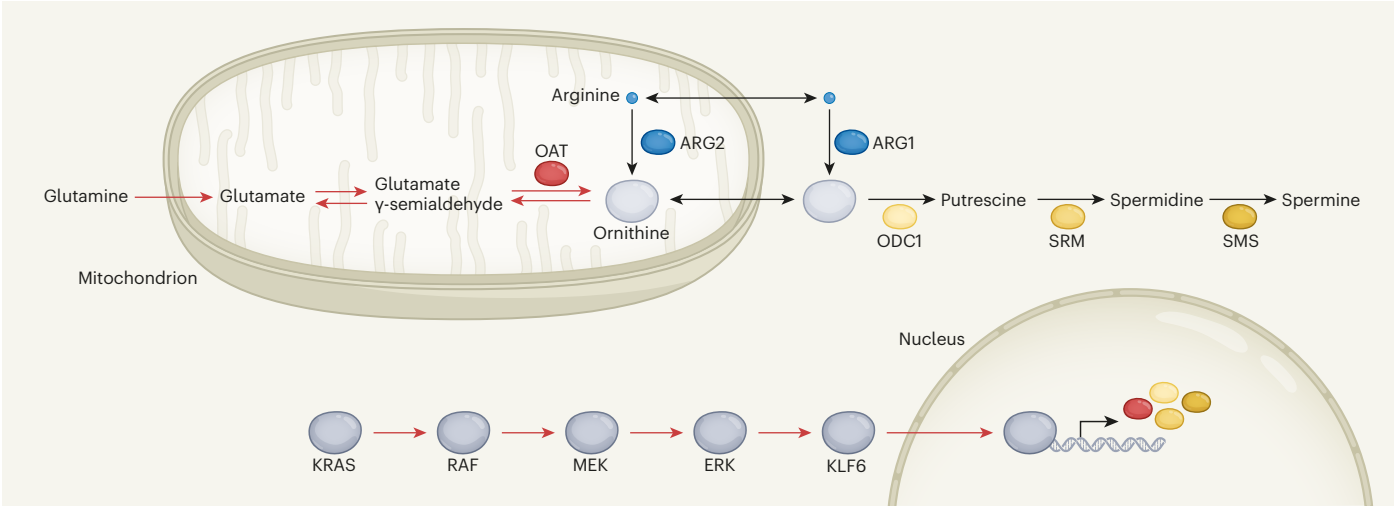

Figure 1 | Pathways to produce polyamine molecules. Polyamines (such as putrescine, spermidine and spermine) have a variety of roles, including aiding cell division. In most adult human cells, polyamine production requires the amino acid arginine, which might enter an organelle (a mitochondrion), and this pathway requires the enzymes ARG1 or ARG2, ODC1, SRM and SMS. Lee *et al.*[1] report that cells of a type of cancer called pancreatic ductal adenocarcinoma (PDAC) make polyamines by boosting various pathways (red arrows). The alternative route requires the amino acid glutamine and the enzyme OAT. PDAC cells commonly have a mutant version of the protein KRAS, which uses a pathway that contains the proteins RAF, MEK and ERK and the transcription-factor protein KLF6 to drive the expression of proteins needed for polyamine production. These findings might help in the search for new clinical targets.

from different substrates carry out distinct functions.

KRAS has previously been implicated as an upstream regulator of polyamine metabolism in cancer[10,11]. Lee and colleagues demonstrate transcriptional control of OAT and polyamine-synthesizing enzymes by *KRAS*. Removal of mutant *KRAS* in human and mouse PDAC cells diminished OAT expression as well as levels of ODC1, and the enzymes spermine synthase (SMS) and spermidine synthase (SRM), suggesting potent regulatory control of polyamine synthesis by *KRAS*. Indeed, inducible deletion of *KRAS* suppressed glutamine-derived, but not arginine-derived, ornithine and putrescine synthesis in PDAC cells, placing *KRAS* at the centre of this metabolic remodelling.

These observations were emulated using inhibitors of the KRAS substrate MEK, suggesting that KRAS signalling might mediate transcriptional regulation of polyamine synthesis. The authors identified KLF6 as a potential transcription factor downstream of KRAS that facilitates this control, and KLF6 silencing diminished protein levels of OAT and other polyamine-synthesizing enzymes. Indeed, KLF6 suppression was sufficient to diminish glutamine-derived polyamine production, revealing a KRAS–MEK–KLF6 axis governing polyamine metabolism in pancreatic cancer.

How these factors operate together to direct this switch in polyamine dynamics is unclear because loss of *KRAS* does not substantially perturb KLF6 levels, suggesting post-transcriptional regulation of KLF6 in PDAC. Lee *et al.* demonstrate that OAT inhibition results in transcriptional alterations in PDAC cells and provide data, obtained using the sequencing technique ATAC-seq, to suggest an epigenetic basis for these changes. Many differentially regulated genes connected to pathways needed for tumour growth, such as for the cell cycle and the response to environments with limited nutrients, were implicated.

This study reveals a way to target polyamine metabolism in pancreatic cancer — the effective manipulation of this pathway has been a long-standing goal of cancer therapy. The work suggests a specific approach to target pancreatic cancer with the potential for minimal effects in healthy tissues.

It is interesting to note that *in vivo* pharmacological inhibition of OAT had limited effects on immune cells in the tumour microenvironment. This highlights the potentially selective nature of OAT targeting. One advantage of current polyamine-blockade therapies (commonly ODC 1 and polyamine transport co-inhibition) is their ability to remodel the tumour immune-cell landscape towards anti-tumour programs. Therefore, future studies might investigate incorporating OAT targeting into polyamine-blockade regimens tested in animal models of PDAC.

Lee and colleagues' work provides a reminder that we must also begin to try to understand how polyamines exert such potent effects on gene expression and epigenetics. A major function of polyamine metabolism is a modification (hypusination) of the translation factor protein eIF5A. Other work has demonstrated potent regulatory effects of the polyamine–eIF5A–hypusine axis on epigenetics[12].

Teasing apart the direct ability of polyamines to modulate epigenetic effects, perhaps through binding of DNA and histone proteins, from the indirect effects mediated by hypusinated eIF5A, and the overlapping or disparate roles of the individual polyamines in this regard, is challenging. However, this will be necessary to gain a deeper understanding of why polyamine synthesis is a metabolic dependency for many tumours.

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