METABOLISM

Flexible flux

Although it is well known that many tumours exhibit increased glycolysis, less clear is how associated metabolic pathways are affected and whether they contribute to cancer cell proliferation. Using unbiased functional genomics and metabolomics methods, two groups have demonstrated the importance of the serine synthesis pathway and the enzyme phosphoglycerate dehydrogenase (PHGDH) for tumorigenesis.

Locasale *et al.* used U-^{13}C-glucose labelling to analyse glucose-derived metabolites in HEK293T cells, and they found increased production of glycine. Increased glycine flux was also observed in a lung cancer cell line but not in non-transformed MCF10A mammary epithelial cells, and levels of glycine that had been synthesized from glucose directly correlated with PHGDH expression levels. They found that *PHGDH* was frequently amplified in a pool of 3,131 cancer samples, most commonly in melanoma, and amplification was correlated with protein overexpression. Glycine can be produced by the direct conversion of serine; the oxidation of the glycolytic intermediate 3-phosphoglycerate by PHGDH is the first step in serine biosynthesis that branches from glycolysis. The authors showed that melanoma cell lines with amplified *PHGDH* had increased flux through the serine pathway, and this, as well as their growth, was sensitive to short hairpin RNA (shRNA)-mediated knockdown of PHGDH. Analysis of 106 human tumour samples also confirmed a previous report that increased PHGDH protein levels correlated with triple-negative and basal breast cancers. Using inducible expression of PHGDH in MCF10A cells that were grown in Matrigel to form polarized three-dimensional acinar structures, they showed that PHGDH expression disrupted acinar organization and polarity, and enhanced proliferation and anchorage-independent survival; this depended on PHGDH catalytic activity.

> “diversion of glycolytic intermediates into the serine pathway may contribute to tumorigenesis”

In an independent study published at the same time, Possemato *et al.* compiled a list of 133 metabolic genes that are likely to be involved in tumorigenesis from available databases and developed a library of shRNAs against them. Screening this library for shRNAs that were depleted during the formation of tumours from a human breast cancer cell line (MCF10DCIS.com cells) in the mammary fat pad of mice revealed 16 genes that are likely to be essential for tumorigenesis. They found that one of these, *PHGDH*, was in a region of chromosome 1p that is frequently amplified in breast cancer and melanoma. They also confirmed that *PHGDH* mRNA is increased in oestrogen receptor (ER)-negative and basal breast cancers, and is associated with reduced 5-year survival rates; PHGDH protein was also strongly expressed in 23 of 32 ER-negative tumour samples. Breast cancer cells with amplified *PHGDH* had increased flux through the serine synthesis pathway, and PHGDH was required for proliferation. Importantly, the induction of shRNA against PHGDH in established mammary tumours in mice effectively reduced tumour growth. Interestingly, the suppression of PHGDH prohibited cell growth even in cells that were supplemented with serine, suggesting that the PHGDH pathway can promote cell proliferation by other mechanisms. Serine synthesis also results in the production of α-ketoglutarate (αKG), an intermediate of the tricarboxylic acid (TCA) cycle, from glutamine. PHGDH knockdown in MDA-MB-468 breast cancer cells reduced αKG levels but not serine levels, and U-^{13}C-glutamine labelling indicated that approximately 50% of the glutamine-derived αKG used in the TCA cycle comes from the serine synthesis pathway in cells with high PHGDH expression.

Both of these studies have highlighted that the diversion of glycolytic intermediates into the serine pathway may contribute to tumorigenesis, although the precise mechanisms responsible require further clarification. Existing data indicate that PHGDH suppression may not be toxic, so it could be a valid therapeutic target.

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ORIGINAL RESEARCH PAPERS Locasale, J. W. *et al.* Phosphoglycerate dehydrogenase diverts glycolytic flux and contributes to oncogenesis. *Nature Genet.* 31 Jul 2011 (doi:10.1038/ng.890) | Possemato, R. *et al.* Functional genomics reveal that the serine synthesis pathway is essential in breast cancer. *Nature* 14 Jul 2011 (doi:10.1038/nature10350)