Tumour biology

Metabolic diversity drives cancer cell invasion

Sanjeethan C. Baksh & Lydia W. S. Finley

The migration and growth of cancer cells at sites far from the initial tumour is usually fatal. Metabolic heterogeneity — variable expression of an enzyme in the initial tumour — is identified as an early step in this deadly process. **See p.747**

Cancer becomes life-threatening when cells in the initial (primary) tumour spread and grow in distant organs, a process termed metastasis. Metastasis is inefficient — only a subset of cells in a primary tumour can invade the bloodstream, survive in the hostile foreign environments of the circulatory system and distant organs, and manage to resume growth in alien tissues. How cells acquire this metastatic potential, and why only a small portion undergo metastasis, remain largely unknown[1].

Metabolism is implicated in several steps of metastasis: cellular metabolism supports tumour growth in primary and secondary sites and facilitates cancer-cell survival in the bloodstream and distant organs. Whether these stage-specific metabolic requirements demand accompanying metabolic flexibility, and whether variable (heterogeneous) metabolic profiles of cancer cells in the primary tumour underlie the cells' differential propensity for metastasis, is mostly a mystery[2]. Rossi *et al.*[3] reveal on page 747 that variable expression of a metabolic enzyme is a driver of early-stage metastasis.

The metabolic enzyme phosphoglycerate dehydrogenase (PHGDH) initiates synthesis of the amino acid serine (Fig. 1) using the molecule 3-phosphoglycerate. The gene that encodes this enzyme is frequently present at higher-than-normal numbers of copies in several types of human cancer, and PHGDH suppression restrains the growth of primary tumours[4]. Rossi and colleagues report that human tumours with uniformly high expression levels of PHGDH were more likely to undergo primary-tumour growth, but were paradoxically less likely to metastasize than were tumours with heterogeneous or low levels of PHGDH expression. In mouse models of breast cancer, cells with low PHGDH expression in the primary tumour were more likely to metastasize than were cells with high expression. Intriguingly, tumour growth at secondary sites required PHGDH re-expression. Thus, high expression of this enzyme supports proliferation of cancer cells in primary and metastatic tumours, but a period of low expression is required for efficient metastasis.

To understand why low PHGDH expression supported early metastasis, the authors assessed gene expression in cells with and without PHGDH. This revealed that cells lacking the enzyme had higher expression of genes associated with migration, invasion and partial transition to what is termed a mesenchymal-cell state, which is a frequently observed characteristic of metastatic cells[5]. In human tumours, cells with the lowest levels of PHGDH expression had the highest expression of these genes, directly linking metabolic heterogeneity with gene-expression programs associated with metastasis. The authors found consistently that cells with low PHGDH were more migratory than were cells with high PHGDH from the same tumour, demonstrating that low levels of the enzyme are sufficient to induce aggressive features in cancer cells.

Surprisingly, other enzymes of the serine synthesis pathway were expressed at a constant level in tumours, and their loss did not increase migration, suggesting that PHGDH regulates aggressive behaviour independently of its ability to provide serine. Rather, Rossi and colleagues found that PHGDH altered cell migration by directly binding to an enzyme called phosphofructokinase (PFK), which is a key component of the glycolytic pathway, in which glucose is converted into the molecule pyruvate. PHGDH binding stabilized PFK, boosting the use of glucose through this pathway. However, the loss of PHGDH destabilized PFK, and redirected the PFK substrate, fructose-6-phosphate, from the glycolytic pathway to a pathway that synthesizes sialic acid (Fig. 1). This molecule modifies cell-surface proteins that facilitate migration, and blocking sialic acid synthesis reversed the effects of low PHGDH on cancer-cell migration and metastasis.

It is tempting to speculate that the 'moonlighting' function of PHGDH — stabilizing PFK — also ensures a continuous supply, downstream of PFK, of the glycolytic intermediate 3-phosphoglycerate, which is required for serine synthesis. In addition, PHGDH might do more to support proliferation than provide

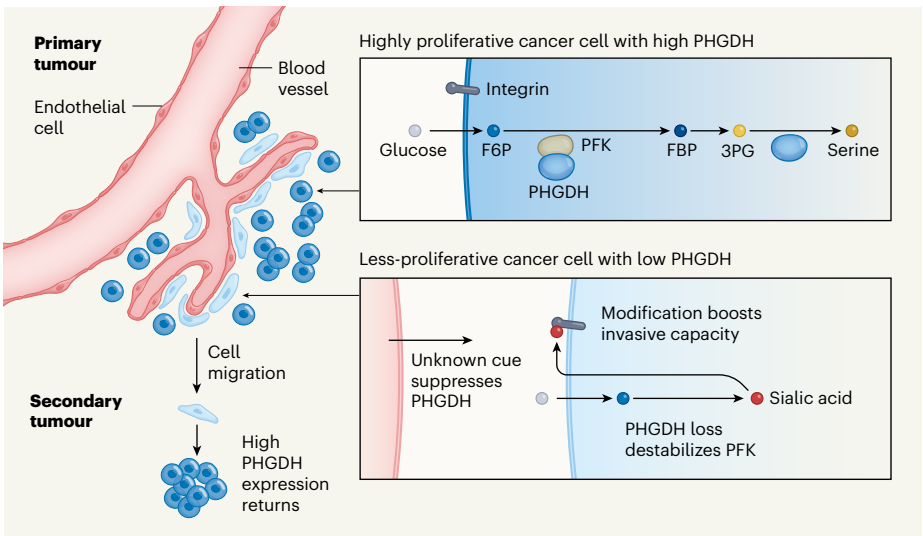

Figure 1 | A metabolic rollercoaster as a tumour spreads from its primary site. Rossi *et al.*[3] analysed mouse and human breast cancer cells. Cells with high levels of the enzyme phosphoglycerate dehydrogenase (PHGDH) are highly proliferative. These cells have limited capacity to invade other tissues, because they lack components needed to migrate, such as modified versions of integrin receptors. Cells with high PHGDH produce the amino acid serine through a pathway that uses the molecule glucose. Glucose is converted to fructose-6-phosphate (F6P), which is converted by the enzyme phosphofructokinase (PFK) to fructose 1,6-bisphosphate (FBP). PHGDH stabilizes PFK. FBP is metabolized to produce 3-phosphoglycerate (3PG), which PHGDH converts to serine. Some breast cancer cells suppress PHGDH expression through a mechanism that requires endothelial cells but is not fully understood. Cancer cells with low PHGDH have a low proliferative capacity, and convert glucose to sialic acid, a version of which coats integrins and facilitates invasion by cancer cells. These cells can populate a distant secondary site. Tumour cells at the secondary site can regain high levels of PHGDH, thereby boosting their proliferative capacity.

serine — breast cancer cells with high levels of PHGDH cannot tolerate PHGDH loss[4] even with abundant serine available, indicating that PHGDH must have a function beyond providing serine if loss of PHGDH can't be compensated for by serine supplementation. Determining whether or not moonlighting functions or other PHGDH-interacting partners have a role in this phenomenon is an area for future investigation.

What induces a subset of tumour cells to suppress PHGDH? Strikingly, the authors found that cells with low levels of the enzyme tended to cluster near vascular tissue. Factors secreted by the endothelial cells that line vascular tissue were sufficient to suppress PHGDH expression, thereby coupling proximity to the vasculature to acquisition of invasiveness. Because cells of the vasculature can also supply amino acids, Rossi and colleagues' work raises the possibility that endothelial cells induce a metabolic state in which tumour cells can tolerate a reduction in their usual capacity for serine synthesis. Distance from the vasculature, or intercellular nutrient exchange and competition, have been implicated in the establishment of metabolic heterogeneity in cells of the same tumour[6]. Although the specific factors that suppress PHGDH remain to be elucidated, Rossi and colleagues' work establishes a new driver of metabolic heterogeneity — one in which signalling from endothelial cells directly affects the expression of a metabolic enzyme in tumour cells.

Metabolism is thought to affect specific steps in tumour formation. By showing that metabolic heterogeneity itself is important for tumour progression, the authors' work underscores the contribution of metabolic variation throughout the course of cancer development. Targeting a given metabolic pathway might therefore have stage-specific effects: for example, inhibiting the synthesis of sialic acid might suppress early metastatic spread.

More broadly, whether metabolic heterogeneity can be exploited therapeutically remains to be explored. If cells with high levels of PHGDH rely on their ability to make serine, and cells with low PHGDH levels rely on serine obtained from outside the cells, then PHGDH inhibitors and a dietary approach of serine starvation might work synergistically to eliminate both proliferative and invasive cells in a tumour. Indeed, this approach is highly effective in models of colorectal cancer[7], and such a strategy might be essential if cells deficient in PHGDH are the most aggressive cells in a tumour[8].

Uncovering metabolic heterogeneity across time and space will provide key insights into how metabolism supports tumour formation. Although methods for studying bulk tumour metabolism and inter-tumour heterogeneity exist, these approaches cannot detect transient or unusual metabolic states that might be found in rare cell populations in specific niches. Advances in techniques such as mass spectrometry imaging should allow spatial evaluation of metabolism[9]. This should, in turn, boost our understanding of the role of metabolic heterogeneity in cancer, and might point towards new avenues for targeting diverse tumour-cell populations.

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The authors declare no competing interests.
This article was published online on 18 May 2022.