Tumour biology

Mutation and lineage lead to organ-specific cancer

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Cancer-promoting mutations tend to result in tumours arising only in certain organs, but the reasons for this specificity are not fully understood. The analysis of human kidney cancer provides clues to solving this mystery. **See p.999**

A conundrum that cancer researchers have grappled with for decades is the consistency with which certain mutations drive cancer in specific organs, even though the pathways that are activated by the mutations seem to be universally relevant and commonly deployed in non-cancerous cells in other organs. On page 999, Patel *et al.*[1] report that this consistency can be driven by cell-type-specific factors that work in sync with the cancer-promoting mutations to promote tumour growth in a tissue-specific manner.

Tissue specificity has been observed for cancers caused by spontaneous mutations (termed somatic mutations) in cells in a tissue, as well as for tumours caused by inherited mutations (called germline mutations) present in cells throughout the body. Cancers caused by germline mutations often display tissue specificity, which is a surprising observation given these mutations' widespread presence[2]. For example, germline mutations of the genes *BRCA1* and *BRCA2* cause major disruptions to DNA repair, yet they result in cancer that originates mainly in the breasts and ovaries. Similarly, *BRAF* mutations are associated with the skin cancer melanoma, *APC* mutations are a hallmark of colon cancer, and loss of the gene *VHL* is a characteristic of a kidney cancer termed clear cell renal cell carcinoma. These genes also have crucial functions in a much wider array of cell types than those that are associated with cancer risk[3].

These observations make one wonder whether this specificity is driven by unique attributes of the organs in which cancer occurs. Previous research[4] has shown that 80–90% of the genes that promote cell growth differ between types of cancer. This suggests that the tissue specificity of cancer is a result of different contexts in which cancer-promoting mutations might or might not trigger disease, although what these contexts are remains unclear[4]. Another example of a specificity phenomenon is provided by the gene encoding the protein TGF-β, mutations of which are cancer-promoting in some contexts and tumour-suppressive in others[5].

Furthermore, cancers that occur in different organs, but that share a cancer-promoting mutation, can respond differently to the same therapy that targets the shared abnormality. For example, melanomas can be treated with inhibitors of BRAF protein, whereas colon cancer cells with the same type of mutation affecting BRAF are not treated with these inhibitors because of treatment-resistance pathways in these cells[6].

To address what enables particular mutations to cause cancer in a tissue-specific manner, Patel and colleagues identified transcription-factor proteins that support the growth of human cell lines of clear cell renal cell carcinoma involving a mutation in *VHL* (Fig. 1). Surprisingly, this work pointed to PAX8, a transcription factor associated with normal kidney cells, and which has a role during development in the formation of a kidney structure called the proximal tube. The authors found that PAX8 is part of protein complexes that form with the protein HIF2A, a key component of the response to low oxygen levels (hypoxia). In addition, they found that a complex containing HIF2A and PAX8 is stabilized when *VHL* is lost.

To evaluate the function of PAX8 in clear cell renal cell carcinoma, the authors depleted PAX8, and found that this led to a reduction in the levels of proteins required for the cell cycle, a decrease in signalling mediated by the protein MYC (which leads to reduced cell proliferation), and a drop in hypoxia-associated signalling. The authors used the gene-editing technique CRISPR to gain a more detailed view of this process in kidney cells, and identified a genomic region of interest (termed an enhancer) that drives gene expression. They found that this enhancer functions to promote tumour formation and that HIF2A and PAX8 bind to it (Fig. 1).

This enhancer is flanked by the gene *CCND1*, which encodes the protein cyclin D1. This positive regulator of the cell cycle is activated in multiple cancers, including clear cell renal cell carcinoma, in which its expression is controlled by a VHL–HIF2A complex. Furthermore, depleting PAX8 in kidney cells resulted in reduced *CCND1* expression. Patel *et al.* conclude that PAX8 boosts cancer-promoting signalling in an HIF2A-dependent manner.

The authors also show that PAX8 controls *MYC* expression by enlisting HNF1B, a protein that is a hallmark of clear cell renal

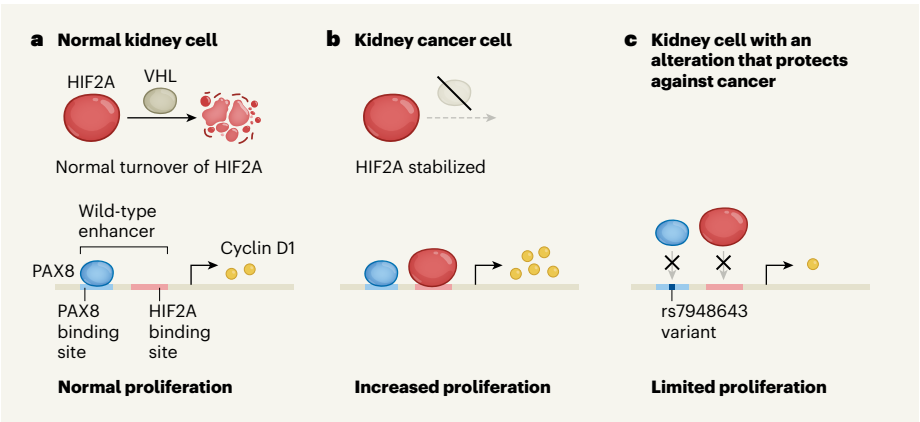

Figure 1 | Inherited mutations and kidney cancer. Patel *et al.*[1] analysed human kidney cancer to investigate why cancer-promoting mutations drive tumours specifically in this organ. Their findings implicate a transcription-factor protein called PAX8, which also functions during kidney development, as having a key role. **a**, In a healthy kidney cell, the protein VHL degrades the HIF2A protein. Expression of the gene encoding the protein cyclin D1 (which functions in proliferation) is regulated by a genomic region called an enhancer, which contains binding sites for PAX8 and HIF2A. In a normal cell, PAX8 helps to drive cyclin D1 expression. **b**, Loss of the gene encoding VHL is a hallmark of a type of kidney cancer called clear cell renal cell carcinoma, and this change results in a rise in HIF2A levels. HIF2A binds to the enhancer, in coordination with PAX8, to boost expression of cyclin D1, and thus drive proliferation. **c**, Some people have a version of the enhancer with a change at site rs7948643 that inhibits PAX8 binding, and thereby subsequently prevents HIF2A from binding. The result is limited cyclin D1 levels and limited proliferation.

cell carcinoma[7]. *MYC* expression is associated with the spread (termed metastasis) of kidney cancer to secondary sites[8], suggesting that PAX8 might have a key role in driving metastasis. Moreover, the depletion of PAX8 in non-cancerous cell lines of epithelial cells from the kidney resulted in reduced expression of *HNF1B* and *MYC*, and in less proliferation of normal epithelial kidney cells and of cancer cells, independently of the presence of VHL and HIF2A. The authors' results indicate that the expression of PAX8, HNF1B and MYC might be an evolutionarily conserved characteristic of cells of the kidney lineage when VHL is present.

Patel and colleagues have revealed that PAX8 is a requirement for cancer-promoting signalling downstream of the most-prevalent germline mutation (a mutation driving VHL loss) that is associated with clear cell renal cell carcinoma. As such, this study implicates lineage-specific transcription factors as being the key determinant of tissue-specific cancers caused by mutations. This revelation has many implications, not only for cancer research but also for application in the clinic.

Transcription factors acting in particular cell lineages are tissue specific, which opens the door to fresh approaches to create effective, organ-specific, targeted therapies. Therapies targeting such factors might offer a way to tackle the deadly metastatic spread of cancer, if the cells from metastasis retain the lineage factors specific to their cell of origin. In renal cell carcinoma, metastasis has already occurred for around 30% of people at the time of diagnosis (see go.nature.com/3x6nryn), and 20–40% of people who have an advanced primary tumour that hasn't yet metastasized will eventually develop local or distant tumours after surgical removal of the primary tumour at its first site of growth[9], highlighting the need for new therapies to tackle metastatic kidney cancer.

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Future studies are needed to determine whether lineage transcription factors have a role in cancer-promoting signalling in other types of tumour. If so, one might imagine a new class of anticancer therapeutic. If such approaches were developed and combined with genome sequencing of those at risk of inheriting cancer-promoting mutations, it would raise the question of whether it is possible to target lineage transcription factors for inhibition and thereby prevent the formation of cancers driven by inherited mutations. Patel and colleagues' study will certainly open the door to other investigations, and might ultimately lead to more anticancer therapeutics.

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