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Cancer

Cues for migration

René Bernards

Lack of oxygen causes the cells of certain tumours to spread to new locations. It also activates a homing mechanism that enables the migrating cells to target specific organs.

The ability of tumour cells to metastasize — to spread to other parts of the body — is perhaps the main reason that certain types of cancer are often fatal. But how do tumours acquire this characteristic? Starving tumour cells of oxygen seems to be one trigger for metastasis, and researchers are beginning to uncover the molecular pathways that underlie this phenomenon[1,2]. Writing on page 307 of this issue, for instance, Staller and co-workers[3] reveal that a gene called *CXCR4* is activated by the lack of oxygen, and that this activation causes tumour cells to migrate and to home in on a specific set of organs.

Highly aggressive tumours rapidly outgrow their blood supply, leaving the cells starved of oxygen — a condition known as hypoxia. Tumour cells adapt to hypoxia by increasing their synthesis of a protein named HIF (hypoxia-inducible factor), which in turn binds to and activates several genes[4]. The proteins encoded by these HIF-responsive genes have a variety of functions. Some increase tissue oxygenation — such as vascular endothelial growth factor (VEGF), which stimulates the outgrowth of new blood vessels — and some enhance cellular glucose uptake and metabolism to allow energy generation when oxygen is scarce.

Our understanding of how levels of HIF are upregulated during hypoxia is growing rapidly[4]. The protein encoded by the von Hippel–Lindau tumour suppressor gene (pVHL), which is frequently mutated in cancer, is central to this process. The normal VHL protein is part of a complex that, when oxygen is abundant, targets the α-subunits of HIF (HIF-α) for degradation. Recognition of these subunits by pVHL depends on a modification of HIF-α that can occur only in the presence of oxygen. When oxygen is scarce, this modification does not occur and so HIF-α escapes destruction, causing an increase in HIF levels and enhancing expression of the hypoxia-inducible genes. Mutations of the *VHL* gene produce an effect rather like hypoxia — mutant forms of pVHL found in cancer cannot destroy HIF-α, and as a result, the hypoxia-inducible genes are persistently activated[4] (Fig. 1).

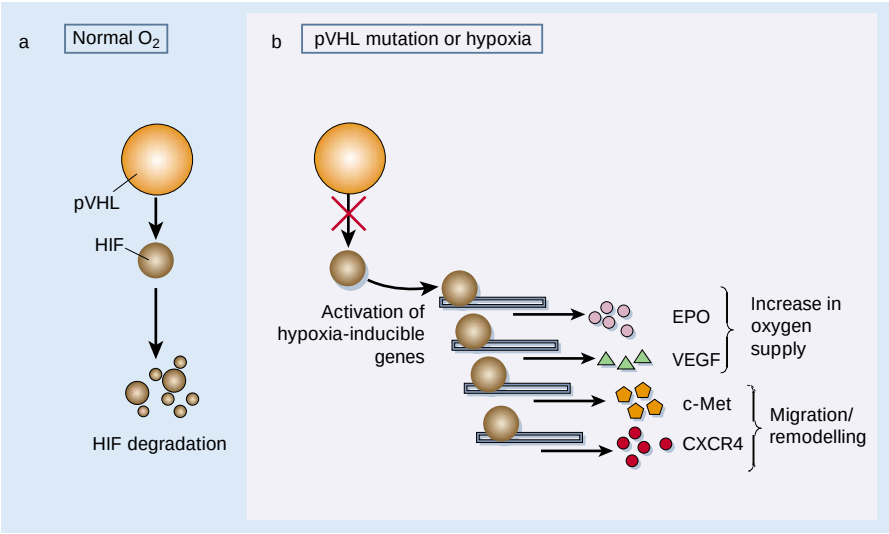

Figure 1 **The hypoxic response.** a, **Under conditions of normal oxygen, the von Hippel–Lindau tumour suppressor protein (pVHL) modifies the protein HIF, which leads to its destruction.** b, **When oxygen is scarce (hypoxia), or when pVHL is mutated, HIF accumulates inside cells and activates the expression of certain genes. This triggers two complementary responses. First, tissue oxygenation is stimulated through the activation of genes such as VEGF (which stimulates the outgrowth of new blood vessels) and erythropoietin (EPO, which stimulates the production of red blood cells). Second, tumour cells are stimulated to move away from the site of hypoxia through the activation of genes such as *c-Met,* which enhance cell motility and invasion. Now, Staller *et al.*[3] show that the gene *CXCR4* is also activated by HIF. CXCR4 not only stimulates migration, it also enables tumour cells to home in on specific, distant organs.**

In the new study, Staller *et al.*[3] searched for genes that are regulated by pVHL. They introduced *VHL* into renal carcinoma cells (which lack a normal copy of this gene) and then, using DNA microarray analysis, they looked for changes in the activity of thousands of other genes, under non-hypoxic conditions. Unexpectedly, they found that normal pVHL dramatically reduced the production of a receptor protein called CXCR4. This receptor binds chemokines — secreted proteins, rather like growth factors, that allow migrating cells (immune cells, for example) to navigate to specific organs[5]. The binding of chemokines to receptors such as CXCR4 on the surface of migrating cells stimulates both cell adhesion and motility, and causes the cells to move towards the source of the chemokine.

But how does pVHL regulate the production of CXCR4? As the authors expected, it does so by downregulating HIF. The authors found a functional HIF-binding site in the regulatory region of the *CXCR4* gene. They also found that cells containing normal pVHL produced more CXCR4 when exposed to hypoxia. So *CXCR4* seems to be a bona fide hypoxia-inducible gene.

The connection between CXCR4 and hypoxia is revealing, because several studies have indicated that 'chemoattraction' through CXCR4 contributes to organ-specific metastasis in certain forms of cancer. For instance, human breast cancer cells often contain high levels of CXCR4, and these cells preferentially metastasize to sites that produce large amounts of the chemokine SDF-1α (the binding molecule, or ligand, of the CXCR4 receptor), such as the lungs and bone marrow[6]. In fact, *CXCR4* is part of a small set of genes that cooperate to promote bone metastases from breast cancer[7].

But why does hypoxia induce CXCR4? Presumably, it doesn't matter to a tumour cell where it migrates. An answer to this question can be deduced from the characteristics of mice that are genetically engineered to lack this gene. Such mice show defects in the branching and/or remodelling of certain blood vessels[8]. So the activation of CXCR4 in blood-vessel cells might be part of an integrated hypoxic response that allows

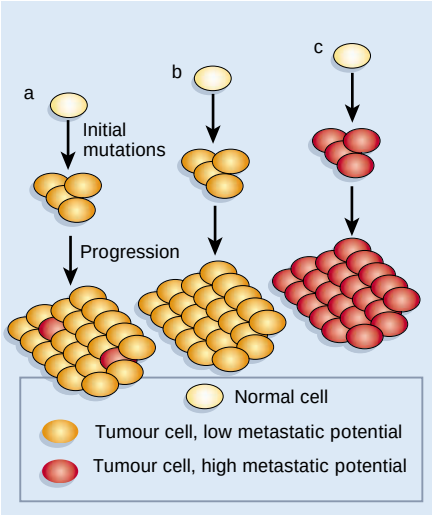

Figure 2 **The development of metastatic capability in cancer cells.** a, **The classical view is that tumour cells with a high metastatic capability arise at low frequency within the primary tumour. These rare variants give rise to metastases.** b, c, **DNA-microarray-based gene-expression profiling has indicated, however, that some tumours are homogeneously of 'good prognosis' and others are uniformly of 'poor prognosis'. One way of explaining these data is to assume that some tumours start off on the wrong foot, their initial mutations predisposing them to become highly metastatic after additional mutations have been acquired[12,13]. Other incipient tumours have initial mutations that make progression to a metastatic phenotype unlikely. The work of Staller *et al.*[3] provides support for the situation indicated in** c. **Mutations in the *VHL* gene may not only stimulate uncontrolled cell division (an early step in cancer development), but also, as the authors show, promote cell motility, invasion and homing to distant organs.**

both the generation of new vessels (through the induction of VEGF) and the remodelling of existing vessels (through CXCR4 induction). The finding that VEGF induces expression of *CXCR4* supports the view that CXCR4 plays a part in remodelling the vasculature during hypoxia[9].

CXCR4 might be needed to promote the survival of tumour cells in a hypoxic environment[10], and it enhances cell motility, allowing the tumour cell to migrate away from areas of low oxygen. Hypoxia-induced metastasis also occurs through other signalling pathways — for instance, the gene encoding the c-Met receptor was recently identified as being hypoxia-inducible[1]. This receptor protein enhances both cell motility and invasion through binding its ligand, hepatocyte growth factor. But the CXCR4 pathway is different because it enables the migrating cells to navigate to specific organs. So, apart from the well-known effects of hypoxia on blood-vessel growth, it also seems to trigger a second and complementary response, enabling cells to migrate away from areas of low oxygen and to home to specific, distant organs (Fig. 1). That *CXCR4* expression stimulates homing to distant sites is probably not relevant to the physiological response to hypoxia, but only an unfortunate side effect of tumour-cell hypoxia. This side effect could, however, explain the generally worse prognosis of patients with a hypoxic tumour[2]. Consistent with this, Staller *et al.* show that clear-cell renal cancers that harbour a mutant form of *VHL* express high levels of *CXCR4*, which correlates with poor survival[3].

The new study also contributes to the continuing debate over whether the ability of tumour cells to metastasize is acquired early or late[11,12] (Fig. 2). The data of Staller *et al.* enable us to envisage how tumour cells might be poised early on to spread to other parts of the body. Incipient tumour cells that acquire a mutation in the *VHL* gene early on may be predestined to spread to secondary sites at a later stage — when they have acquired additional growth-promoting mutations — as the activation of genes such as *c-Met* and *CXCR4* endows them with the ability to migrate, invade and home in on specific tissues. So as well as providing clues about how tumours metastasize, Staller and colleagues' findings edge us closer to an understanding of the timing of tumour progression. ■

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Palaeobotany

Fishing for the first plants

Paul Kenrick

Sifting of organic residues from ancient rocks has netted a catch of tiny fossils that provide clues about when plant life first appeared on land.

The significance of microscopic spores entombed in rocks dating from about 440–470 million years ago has puzzled investigators of early life. Are these spores proof that plant life existed on land long before the time suggested by other forms of fossil evidence? And, if so, what sorts of plants do they represent? On page 282 of this issue, Wellman *et al.*[1] present direct evidence of the life forms that produced these enigmatic spores, and their findings lend credence to the notion that minute plants existed on land 470 million years ago.

Spores are produced by land plants in prodigious quantities. These robust, decay-resistant particles can become incorporated into sediments, providing a record of floral change through geological time. Careful study of rocks dating from the Ordovician period, 443–489 million years ago, has revealed an unexpected diversity of spores that are much older than the fossilized remains of plants that could have produced them[2,3]. These minute grains might represent evidence of the earliest land flora, but how can we be sure that these spores came from bona fide land plants, and what can they tell us about the nature of this early flora?

Answering these questions is difficult because the most ancient spores are rather odd. Instead of being dispersed as single grains, many are fused in pairs or in groups of four, and some are enclosed in an extra membrane[2,3] (Fig. 1). These so-called permanent diad and permanent tetrad configurations are unlike the spores of most living plant species, but they do bear some resemblance to the spores of certain present-day liverworts. Diad and tetrad spores have also been found in land-plant fossils dating from an early part of the Devonian period (400–417 million years ago)[4,5].

So, one school of thought holds that the tetrads and diads of the Ordovician period are evidence of land plants that are related to living bryophytes (liverworts, mosses and their kin)[2–5]. Others contend, however, that the data linking these spores to bryophytes are too tenuous[6]. The spore-producers might be close relatives of land plants, but that does not necessarily make them bryophytes. It is conceivable that in both ecological and physiological terms they were little more than aquatic algae. Direct evidence of the life forms that produced the Ordovician spores could settle this matter, but so far this has proved elusive.

Wellman *et al.*[1] take us a step closer to resolving this controversy. They used standard