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 complemen-

tary 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
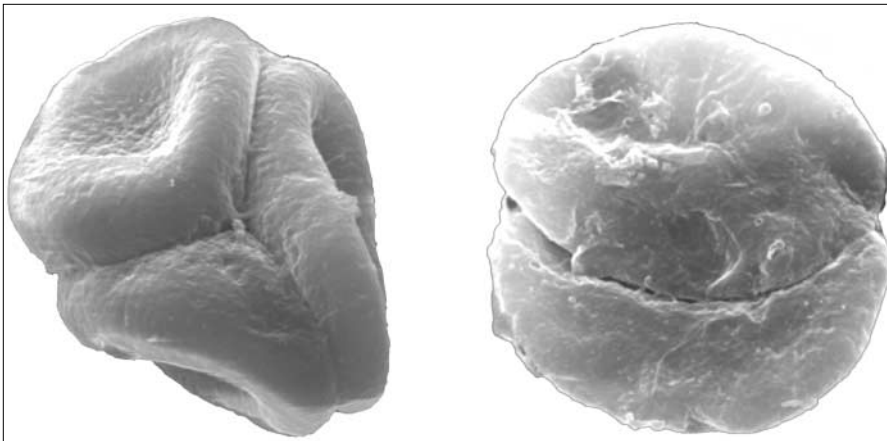
Figure 1 **What the first land plants left behind. Evidence of the earliest land plants comes from spores extracted from 440–470-million-year-old rocks in Oman. The nature of the plants that produced these grains has remained a mystery, but Wellman *et al.*[1] have now found evidence that the spores were produced by minute land-dwelling plants that may have resembled liverworts. Unlike most of their modern counterparts, many of the earliest spores were dispersed in groups of four (tetrads; left) or in groups of two (diads; right). Spore diameter is 20** μm.

spore-extraction methods to recover organic residues from Ordovician sediments collected from a borehole in Oman. When they passed the insoluble organic material through a series of sieves designed to trap plant fragments and spores of various sizes, the authors found many well-preserved spores — but they also found something much more intriguing. Trapped in the sieve containing the largest pores were elongated, disc-shaped objects that, on closer inspection, proved to be clumps of spores packaged in a type of cuticle. These fossil fragments are exciting because they resemble the spore-bearing organs of later land plants. So Wellman and colleagues' trawl through organic residues had netted a catch of the tiny plants that produced the spores. Although far from complete, these specimens indicate that the Ordovician spores were indeed produced by land plants and not by algae. But what did these early plants look like, and how are they related to modern plant forms?

The plants that produced the spores were certainly minute and probably simple, but these frustratingly incomplete fragments tell us little else. In a hunt for further clues, Wellman and colleagues looked in detail at the structure of the spore wall. They found a laminate interior resembling that of some living liverworts, which is consistent with other evidence[7,8] pointing to liverworts as the closest living relatives of the earliest land plants. Although intriguing, the spore-wall data are unlikely to win over the sceptics[6]. What we need now are more complete specimens of these tiny plants, and Wellman and colleagues' recovery techniques are clearly promising ways to achieve this.

One further issue raised by the new study is the possibility that plant life existed on land even before the Ordovician period. Could signs of plant life be awaiting discovery in even older rocks? Maybe so, according

to one study[9]. These authors investigated the time of origin of land plants using a 'molecular clock' analysis, in which the timing of evolutionary divergence is inferred from comparisons of the gene sequences of living plant species. Controversially, this approach placed the common ancestor of all living land plants in the Precambrian period, around 700 million years ago. From a

palaeontological perspective, the existence of land plants this long ago seems very unlikely. For one thing, there is no unequivocal evidence for land-plant spores in rocks predating the Ordovician period. Given the ubiquity of such spores in near-shore marine sediments throughout later periods, this dearth of microfossil data is telling. And different clocks tell different times — a more recent molecular analysis placed the origin of land plants close to the time predicted from the spore findings[10]. If plant life on land did predate the Ordovician period then it is very well hidden indeed. ■

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Global change

Probing early atmospheres

Stephen J. Mojzsis

Information about atmospheric conditions far back in Earth's history is embedded in the isotopic composition of fossil microbes. Such studies are technically demanding, but hold considerable promise.

What were atmospheric CO_2 concentrations like during the Proterozoic eon, the interval of Earth's history between about 2,500 million and 543 million years ago? The issue is germane to studies of the ancient biosphere because, owing to the way in which the Sun's composition and other properties evolved, its luminosity is thought to have increased gradually over time. Aside from a small contribution from internal heating that is driven by radioactive decay, the surface temperatures of a planet are governed by the amount of solar radiation it receives and how this interacts with the atmosphere. The fact that greenhouse gases, chiefly CO_2 (but also water vapour and methane), re-radiate infrared radiation to the surface keeps the present average surface temperature some 33 K above what it would otherwise be. Models of solar luminosity[1] indicate that if the greenhouse had not been much greater early in Earth's history, global

glaciation should have held sway throughout the Proterozoic and the preceding Archaean eon, which stretches back to about 3,900 million years ago.

However, various lines of reasoning suggest that, over geological time, Earth has maintained surface pressures and temperatures that were conducive to the presence of liquid water, and thereby a global habitat for life. Carbon dioxide has always been an important greenhouse gas. But how much was present in the atmosphere during the Proterozoic, when the surface biosphere became transformed from a wholly microbial and anoxic world to an oxygenated domain poised for the emergence of diverse multicellular life?

On page 279 of this issue[2], Kaufman and Xiao describe their use of a novel approach to this question in comparing the carbon-isotope compositions of eukaryotic algal microfossils (acritarchs) to those of 'consanguineous carbonate' — that is, carbonate

249