its current level around 700 million years ago, coinciding with the cessation of snowball Earth conditions. This peak reflects a large increase in the marine phosphorus inventory that was sustained over tens of millions of years. Given that 'modern' marine phosphorus has a residence time of tens of thousands of years, it is hard to imagine ocean conditions in which sustained high levels of phosphorus were not driven by a step-change in the global phosphorus mass balance.

The thinking about the consequences of such high phosphorus levels then runs as follows. The result of the phosphorus-driven marine productivity was sustained algal blooms in the ocean, much like those found today in ponds and streams near areas of heavy fertilizer application. The death and settling of these blooms caused long-term, enhanced organic-carbon burial, which (via the mass-balance relationship between carbon and oxygen[9]) resulted in the addition of oxygen to the ocean–atmosphere system (Fig. 1). This increase in atmospheric oxygen controlled the evolutionary patterns of oxygen-dependent metazoans. Such a scenario provides a plausible link between the roles of snowball Earth glaciations and late Proterozoic oxygenation in leading to the explosion in metazoan diversity.

The implications of the new results[4] for understanding glacially induced phosphorus weathering on landscapes are also interesting. We are beginning to appreciate how glacial dynamics affects phosphorus weathering on land and transport to the oceans[10]. In the modern 'rooted' world, in which soil development is generally mediated by plants, most of the weathered phosphorus is mobilized and transported from landscapes in a narrow time window after a glacier retreats. Continental records[11] indicate that this large flux of phosphorus occurs in about 10,000 years in most landscapes (probably faster in low-relief/high-rainfall landscapes and slower in high-relief/low-rainfall landscapes). In a modern landscape with its considerable plant coverage, maintenance of a sustained increase in phosphorus delivery to the oceans would require periodic removal of weathered and phosphorus-depleted soils, and exposure of fresh material for further soil development.

In late Proterozoic time, however, the absence of land plants meant that there would have been little soil development to stabilize landscapes, or to convert mineral-based phosphorus forms on pristine mineral surfaces to the organically and oxide-bound phosphorus found in modern soils. Presumably, phosphorus stripping from rocks was much more extensive, as the landscapes themselves were much less stabilized because of the lack of flora. Thus, in this case, the present is not a key to the distant past. Without the systems to stabilize phosphorus, the phosphorus cycle in the late Proterozoic would have been permanently revved up — that is, until rootedness came into play several hundred million years later. A test of this hypothesized mechanism of enhanced phosphorus stripping from landscapes would be to identify deltaic or other sedimentary-basin environments from the late Proterozoic, and to use proxy estimates of phosphorus loss (for example, the phosphorus/aluminium ratio) to determine whether values for this time interval are lower than expected given the source material. Such analyses would provide independent evidence of high phosphorus weathering rates.

Meanwhile, with this paper[4] and use of the phosphorus/iron proxy, there is now another way to look at nutrient variations in the ancient oceans. No proxy is perfect, however. In this instance, the weaknesses are both obvious (the limited spatial and temporal range of the proper rock types for analysis) and less obvious (variations in original iron-oxide composition that are now masked by mineral maturation). Nevertheless, thanks to Planavsky and colleagues[4], we have a picture of the marine phosphorus cycle through deep time. We can begin to develop informed hypotheses about how variations in the phosphorus cycle are driven, and what impact they have on the global carbon cycle, oxygen levels and the evolution of marine ecosystems. ■

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CANCER

Genomic evolution of metastasis

Prognosis for patients with pancreatic cancer is bleak, often owing to late diagnosis. The estimate that at least 15 years pass from tumour initiation to malignancy offers hope for early detection and prevention. SEE LETTERS P.1109 & P.1114

E. GEORG LUEBECK

Radiocarbon dating and comparative analyses of skeletal anatomy have informed the theory of human evolution; similarly, DNA sequencing of tumour cells coupled with dissection of the molecular anatomy of chromosomal aberrations is beginning to yield deeper insight into the evolution of cancer. In this issue, two papers[1,2] present findings from sequencing the protein-coding regions (exons) of more than 20,000 genes from the genomes of patients with metastatic (stage IV) pancreatic cancer. The findings are unprecedented, providing the first high-resolution image (at the level of single base pairs) of the non-germline mutational spectrum of pancreatic tumours and their metastatic descendants.

It has long been recognized that genomic instability is a hallmark of cancer. However, its significance in cancer progression has been the subject of debate for just as long. To shed light on this, Campbell *et al.*[1] (page 1109) performed a DNA-sequence-based study of chromosomal rearrangements. They find that specific chromosomal rearrangements known as fold-back inversions occur in almost all of a patient's metastatic lesions. What's more, unlike other chromosomal rearrangements, which seem to occur either in the primary, parental tumour or in the metastatic lesion, Campbell *et al.* detect fold-back inversions in both primary and metastatic tumours. The authors therefore argue that fold-back inversions occur early in tumorigenesis and are probably a crucial driver of pancreatic-cancer progression.

The precise origin of fold-back inversions is unknown. It could be that DNA-replication-related erosion of the telomeres (the chromosome ends) — potentially because of suppressed or dysfunctional activity of the enzyme telomerase — triggers recurrent breakage–fusion–bridge (B/F/B) cycles[3,4], which, in turn, cause progressive gains and losses of genetic material and so genomic instability. Intriguingly, telomerase activity seems to be restored in the invasive tumours, which might have a stabilizing effect on the abundance of B/F/B-induced rearrangements,

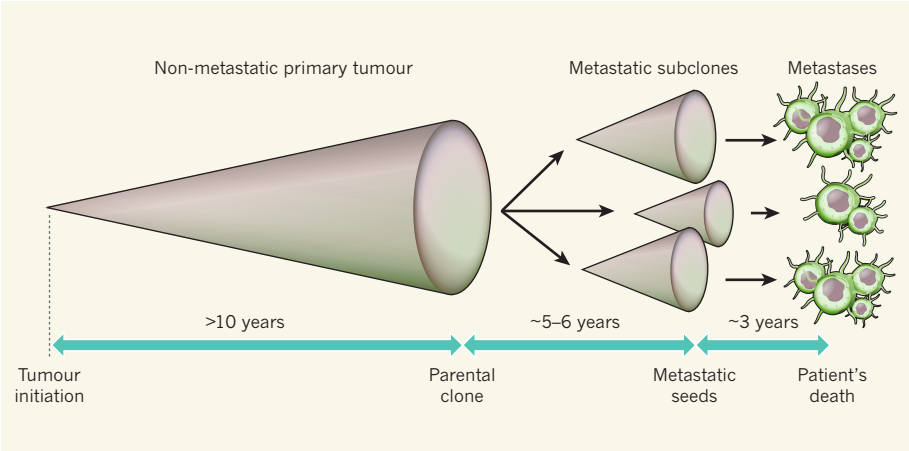

Figure 1 | The pancreatic-cancer timeline. Mathematical analyses of tumour-DNA sequence data from two collaborative studies[1,2] suggest that it probably takes more than 10 years from the initiation of a pancreatic tumour to the birth of the parental clone that results in pancreatic cancer. However, this clone does not have metastatic potential, and the subclones with the ability to spread to other tissues develop over an additional 5–6 years. The metastases, which are soon followed by the patient's death, occur over roughly the next 3 years.

but not on other rearrangements.

Campbell and colleagues' results affirm the presence of genomic instability in the development of pancreatic cancer. But because of extensive differences in the number, type and position of the rearrangements among patients — and even between the metastatic deposits in the same organ of a single patient — the functional consequences of this instability remain unclear. Studies using next-generation sequencing technologies on a larger number of patients are likely to fill in the missing pieces and pinpoint the driving forces in tumour progression and metastatic dissemination across different types of cancer.

In a separate study, Yachida *et al.*[2] (page 1114) address the clinically relevant issue of the timescales associated with tumour progression. These authors also carry out genomic sequencing of pancreatic-cancer metastases and examine their phylogenetic relationship with their respective, previously sequenced, primary tumours in seven patients. They thus derive estimates of three timescales: the time from tumour initiation to the birth of the founder cell of the parental (non-metastatic) clone; the sojourn time between the parental clone arising and its acquisition of metastatic potential; and the time from metastatic dissemination to the patient's death (Fig. 1).

Remarkably, the authors estimate that the time from tumour initiation to metastatic dissemination is at least a decade — a conclusion that suggests that there is a window of opportunity for medical intervention before the cancer spreads to distant organs. This finding is not inconsistent with that inferred from quantitative analyses of the age-specific incidence of pancreatic cancer in the general population[5]. On the basis of a general mathematical description that recognizes the random nature of both mutation accumulation and clonal expansion in pancreatic cancer, the earlier, population-based analysis[5] estimated that the mean sojourn time from the tumour-initiating mutation to clinical diagnosis may be as much as five to six decades.

On the surface, the population-based estimate seems much longer than Yachida *et al.* conclude. It should be kept in mind, however, that the present sequence-based time estimates[2] are not general: they do not refer to the average of all pancreatic lesions with cancerous and metastatic potential in the tissue, but rather refer to the one lesion in the tissue which, by chance, leads to the first primary tumour in that tissue. Thus, Yachida and colleagues' estimate must be considered a lower bound for the mean sojourn time of pancreatic lesions, such as pancreatic intraepithelial neoplasia, that have the potential to cause invasive and metastatic cancer. From a clinical perspective, what matters is the prospective disease risk, which may involve multiple lesions individually evolving towards cancer. Thus, the time estimates of Yachida *et al.* are conservative and so clinically relevant.

These two studies[1,2] are a bellwether, and are among the first to explore the biological and clinical implications of sequence data for individual tumours. As the sequencing technology moves forward — and it does so at a blinding speed — more exciting details of the evolutionary processes involved in tumour progression are likely to be unearthed. It is to be hoped that such information will not only deepen our understanding of the cancer process, but also lead to new approaches to early cancer detection, better prognosis and, ultimately, prevention. ■

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STEM CELLS

The intestinal-crypt casino

Stem cells can renew themselves indefinitely — a feature that is often attributed to asymmetrical cell division. Fresh experimental and mathematical models of the intestine provide evidence that begs to differ.

MICHAEL P. VERZI & RAMESH A. SHIVDASANI

Certain tissues, such as the skin, blood and intestinal lining, replenish millions of lost cells every day. The burden of renewal falls on small populations of stem cells, which can make exact copies of themselves, as well as generate all the resident cell types that differentiate and eventually die. This rare dual ability, a defining property of all stem cells, is exemplified by the asymmetrical division of germ cells[1] and neuronal precursors[2] in the fruitfly. Nonetheless, as long as the total stem-cell pool in a tissue remains roughly constant, in principle there is no reason why individual stem cells should not divide symmetrically, to generate either two identical stem cells or two daughters that exit the pool to differentiate. Indeed, two reports published in *Science*[3] and *Cell*[4] demonstrate that, in the normal course of tissue renewal, intestinal stem cells divide symmetrically.

In the small intestine, stem cells lie at visually identifiable positions within pocket-like crypts, and their progeny migrate in predictable streams (Fig. 1a, overleaf). In mice, two cell populations manifest the capacity for both prolonged self-renewal and multi-lineage