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search for tumour-associated mutations in developmentally important genes would seem likely to bear fruit.

One might question whether lessons learned from malignancies in blood-cell production will generalize to solid tumours. But there is little evidence, if any, that blood malignancies are in any way unique. For example, chromosomal translocations, which were initially thought to be a curiosity of acute leukaemias, are now known to be common in prostate cancer. Mutations that activate protein-kinase enzymes, and that frequently cause them to become oncoproteins, were again initially associated with leukaemia, but are now commonly recognized in solid tumours. And cancer stem cells, now detectable in breast cancers, and in brain and other tumours, were at first seen as relevant only to leukaemia. Cancer pathogenesis seems to follow a largely common path, regardless of the type of cell in which it originates.

Finally, we are left with an obvious challenge: devising strategies for fixing the defects in cellular differentiation caused by recurrent loss-of-function mutations. Treatment with all-*trans* retinoic acid is an effective 'differentiation therapy' for acute promyelocytic leukaemia, although this has been generally regarded as relevant only to that subtype of leukaemia. But if defects in differentiation underlie many (or possibly all) cancers, a broader exploration of such treatments should perhaps be entertained. Whereas a clear path has been established for developing anticancer drugs that inhibit the increased activity of oncoproteins such as kinases, approaches to restoring lost function in tumour-suppressor proteins are less obvious. And the pharmacological modulation of transcription factors is in large measure uncharted territory.

Innovative approaches to chemical screening and drug discovery are likely to be needed. But the fact that *PAX5* abnormalities in ALL seem to exist mainly in the haploinsufficient state may make the problem easier — finding small molecules that augment the expression or activity of the residual *PAX5* allele is probably feasible.

In any event, we have a challenge that we should be pleased to tackle. Trying to develop better therapies for cancer without knowing the underlying genetic causes would be utterly impossible. ■

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BIOPHYSICS

Quantum path to photosynthesis

Roseanne J. Sension

Knowing how plants and bacteria harvest light for photosynthesis so efficiently could provide a clean solution to mankind's energy requirements. The secret, it seems, may be the coherent application of quantum principles.

The Sun bombards Earth with a steady stream of energy — about 10^{17} joules per second, on average[1]. If we could convert this energy efficiently to a chemically useful form, our reliance on fossil fuels and nuclear power — and so our production of climate-change agents and hazardous waste materials — could be substantially reduced. But how can we achieve such efficiency?

Of course, the photosynthesizing organisms on Earth already have the answer. In higher plants and certain bacterial systems, the initial steps of natural photosynthesis harness light energy with an efficiency of 95% or more — values that we can only aspire to with artificial photocells. Elsewhere in this issue, Engel *et al.*[2] (page 782) take a close look at how nature, in the form of the green sulphur bacterium *Chlorobium tepidum*, manages to transfer and trap light's energy so effectively. The key might be a clever quantum computation built into the photosynthetic algorithm.

Photosynthesis is initiated by the excitation, through incident light, of electrons in pigment molecules — chromophores — such as chlorophyll. This electronic excitation moves downhill from energy level to energy level through the chromophores before being trapped in a reaction centre, where its remaining energy is used to initiate the production of energy-rich carbohydrates. In natural light-harvesting systems, chlorophyll pigments are arranged together in an 'antenna', sometimes with elegant symmetry and sometimes with apparent randomness, but always with a precise structure that is supplied by a protein scaffold (Fig. 1). Many studies indicate[3–6] that this strictly defined structure, together with the close proximity of the chromophores, is essential for the strong absorption of light, fast

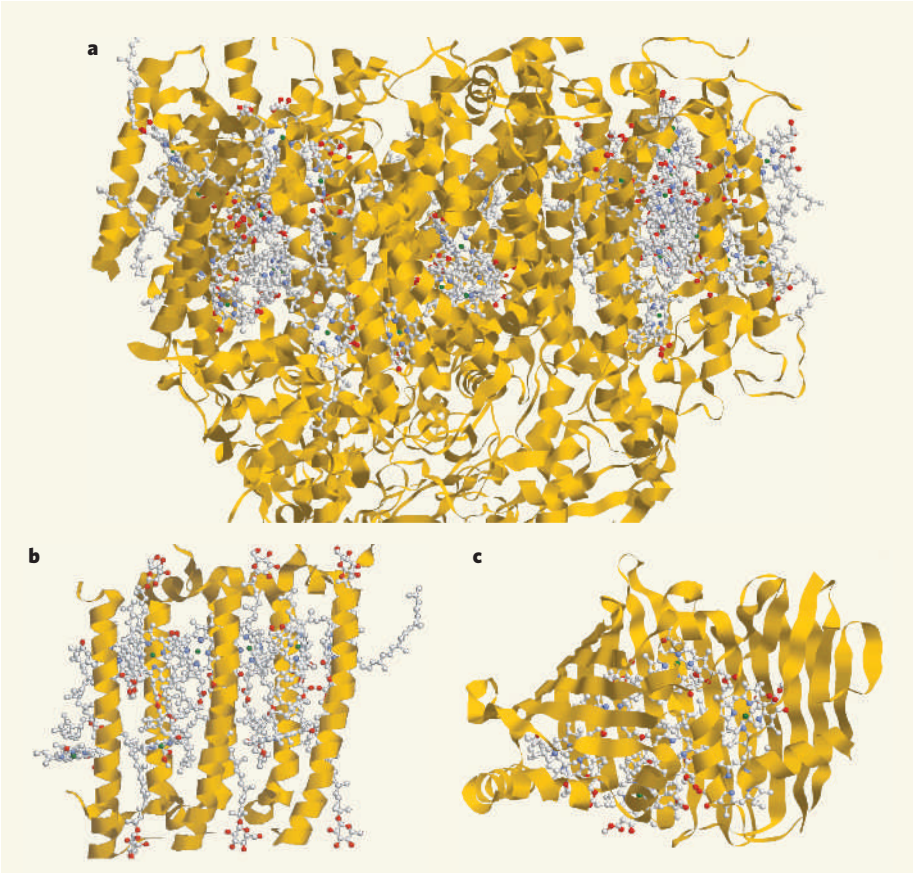

Figure 1 | Complex complexes. Three representative pigment protein complexes involved in natural photosynthesis. **a,** Photosystem II, found in oxygenic photosynthetic organisms[8]. **b,** Light-harvesting complex 2, found in purple bacteria[9]. **c,** The Fenna–Matthews–Olsen antenna complex[10], the bacteriochlorophyll complex investigated by Engel *et al.*[2]. Yellow, protein; white, chromophores.

downhill energy transfer and efficient trapping of the electron excitation in a reaction centre, all of which are characteristic of natural photosynthesis.

But where does quantum mechanics, let alone quantum computing, fit in here? The mechanism of energy transfer through chromophore complexes has generally been assumed to involve incoherent hopping — that is, seemingly uncoordinated movement in a 'random walk' with a general downhill direction — either between individual chromophores, or between modestly delocalized energy states spanning several chromophores. The energy transfer is determined by quantum-mechanical states and their overlaps, to be sure, but there is nothing inherently 'quantum' or wave-like in the process itself.

Engel *et al.*[2], however, performed two-dimensional Fourier transform spectroscopy of the bacteriochlorophyll Fenna–Matthews–Olsen antenna complex, and discovered regular variations in the intensity of their signal. These 'quantum beats', which persist for hundreds of femtoseconds, are characteristic of coherent coupling between different electronic states. In other words, the electronic excitation that transfers the energy downhill does not simply hop incoherently from state to state, but samples two or more states simultaneously. The data also suggest that the protein scaffold might itself be structured to dampen fluctuations that would induce decoherence of the electronic excitation.

Coherent energy transfer allows the 'wave-like' sampling of the energy landscape to establish the easiest route for the electronic excitation to the reaction complex much faster than the semi-classical hopping mechanism allows — indeed, it does so almost instantaneously. The process is analogous to Grover's algorithm in quantum computing, which has been proved to provide the fastest possible search of an unsorted information database[7].

Although the data were acquired at low temperature (77 kelvin), the observation of electronic coherences in such a complex system is remarkable. Assuming that the effect is general — that similar coherences occur in many different natural light-harvesting systems, and are observed at non-cryogenic temperatures — we may find that nature, through its evolutionary algorithm, has settled on an inherently quantum-mechanical process for the critical mechanism of efficient light harvesting. This is an interesting lesson to be considered when designing artificial systems for this purpose. ■

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CELL BIOLOGY

Fraternal twins

Franck Duong

A popular route for protein transport into and across cell membranes is through the Sec channel. This channel seems to function by forming a dimer of two identical units, where each has a distinct role.

The transmembrane Sec channel, or Sec translocon, is a major protein-transport route across the endoplasmic reticulum of higher organisms and the cell membrane of bacteria. This essential machinery ensures the correct distribution of cellular proteins, and catalyses the translocation, and membrane integration, of hundreds of different proteins that carry a specific targeting signal called the signal sequence. To mediate transport, the Sec channel associates with different partners in the cell's internal fluid, or cytosol, that supply the driving force for translocation. For example, during protein translation, the ribosome — the factory for all protein production — feeds nascent polypeptide chains directly into this channel. In bacteria, the channel also associates with an enzyme called SecA (or SecA ATPase), which, following translation, 'pushes' the protein substrate into the channel. A report by Osborne and Rapoport[1], published in *Cell*, provides a view of how SecA and the Sec channel work together.

The fact that the Sec channel forms both a membrane conduit for polypeptides and a binding site for its translocation partners has been rationalized through structural analysis of its evolutionarily conserved core component — the heterotrimeric SecY–SecE–SecG complex, called SecY for short[2]. The atomic structure of the Sec channel revealed four domains: an hourglass-shaped, hydrophilic conduit located in the body of the SecY complex; a constricted 'pore ring', which seals the conduit in the middle; a 'plug' domain that lies on top of the constricted region when the channel is inactive; and a 'lateral gate' serving as both the binding site for the signal sequence and an escape route towards the lipid layer for transmembrane protein domains (Fig. 1, overleaf). On the part of the complex facing the cytosol, at least two large loops that extend out of the plane of the membrane serve as a docking site for either SecA or ribosomes. Biochemical analyses using a translocation system reconstituted *in vitro* have provided experimental support for some of the proposed functions of these structural domains[3–5].

From such structural information, one would predict that a single SecY copy would be enough to perform the transport task. But that possibility had already been ruled out by numerous observations of membrane-embedded and solubilized SecY complexes that naturally form oligomers containing two (dimer) or four (tetramer) copies of the complex. Although there now seems to be a consensus that the bacterial Sec channel exists as a dimer, and that its mammalian counterpart is tetrameric when interacting with ribosomes[6,7], the underlying reason for the oligomerization of SecY complexes had remained a puzzle. Experimentally, it is difficult to monitor the oligomeric state of membrane proteins and the function of their different states. But Osborne and Rapoport[1] have now provided substantial insights into this problem.

By cross-linking the polypeptide substrate to cysteine amino-acid residues strategically engineered and positioned in the complex, the authors first demonstrated that the lateral gate and the plug domain of only one SecY complex simultaneously make contact with the translocating polypeptide chain and its signal sequence. This confirms the structural prediction that a single SecY copy in the SecY translocon forms the protein-conducting channel.

Next, the authors reasoned that, if two SecY copies work together but each has a distinct function, an inactive SecY complex should be rescued on interaction with its active counterpart. This result would indeed prove that the oligomers are involved in translocation. To facilitate such analysis, two *secY* genes have previously been fused in tandem, resulting in the production of a covalently linked SecY dimer[8]. Using this approach, Osborne and Rapoport showed that an inactivating mutation in one SecY copy does not prevent protein translocation as long as a normal copy of this complex is also present in the tandem construct.

It remains conceivable that one SecY copy forms an active unit by interacting with another SecY copy, but without the contribution