in a movable nanomechanical mirror that is a microgram in weight. The high-temperature entanglement envisaged by Galve *et al.* could be achieved by coupling two such mirrors to one another. I and colleagues[4] have shown, using a different theoretical approach to that of the present study[1], that such nanomechanical entanglement should persist at temperatures of about 20 kelvin. The hope now is that, by using Galve and colleagues' new ideas, the temperature can be pushed upwards to, say, 100 kelvin. This would eliminate the current need for expensive and elaborate cryogenics to cool the oscillators.

So, OK, we can in principle entangle nanomechanical oscillators at high temperatures. Physicists will no doubt get excited because this realization will strengthen the evidence for the universality of quantum mechanics. But why should anybody else care?

The most exciting macroscopic and 'hot' non-equilibrium systems we know are, of course, the living ones. We can, in fact, view any living system as a Maxwell's demon, maintaining life by keeping its entropy low against the environmental noise — that is, by being far from equilibrium. The father of thermodynamics, Ludwig Boltzmann, himself viewed living systems in this way. Here is what he said on the matter: "The general struggle for existence of living beings is therefore not a fight for energy, which is plentiful in the form of heat, unfortunately untransformable, in every body. Rather, it is a struggle for entropy that becomes available through the flow of energy from the hot Sun to the cold Earth. To make the fullest use of this energy, the plants spread out the immeasurable areas of their leaves and harness the Sun's energy by a process as yet unexplored, before it sinks down to the temperature level of our Earth, to drive chemical syntheses of which one has no inkling as yet in our laboratories."

We have actually learnt a little bit about that "unexplored" process — photosynthesis — since Boltzmann. And as it happens, recent experiments[5] show a quantum effect leading to entanglement[6] in some photosynthetic complexes. Such entanglement might yield an increased efficiency in the transfer and processing of energy in photosynthesis. The overall mystery of photosynthesis remains, but there is now evidence that quantum physics has something to do with it in a profound way. And there are other instances in biology in which quantum entanglement could be important[7]. If this is a general trend in the biological world (and it is a big 'if'), maybe Boltzmann was only half right: could it be that life does not just keep its entropy low, but rather, also aims to keep its quantum entanglement high if and when needed for an increased efficiency of energy transport? For now, the jury is still out. ■

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CANCER

Tumour stem cells switch sides

Tumour stem cells are proposed to be the source of tumour cells. It now emerges that they also give rise to the endothelial cells that line the tumour vasculature, mediating tumour growth and metastasis. SEE LETTERS P.824 & P.829

VICTORIA L. BAUTCH

To grow, solid tumours need a blood supply. They recruit new blood vessels mainly by inducing the sprouting of endothelial cells from external vessels and promoting the cells' migration into the tumour. This ability, called the angiogenic switch, is required for tumour cells to invade surrounding tissue and metastasize to distant sites — the deadly hallmarks of cancer[1]. In this issue, Wang *et al.*[2] and Ricci-Vitiani *et al.*[3] show that, in addition to recruiting vessels from outside, brain tumours produce endothelial cells for vessel formation from within.

Recent research in tumour biology has focused on two main concepts. According to the first concept — vasculogenic mimicry — some tumour cells take on certain characteristics of vascular endothelial cells and line the tumour's blood vessels[4]. The origin of such tumour cells is ill-defined: whereas one study[5] suggested that tumour stem cells show vasculogenic mimicry, it is generally thought that tumour cells in the immediate environment of the nascent vessel are co-opted for the purpose. The co-opted cells are thought to retain most of their tumour-cell characteristics while acquiring a limited number of endothelial-cell features.

The second concept — that some tumours originate from a tumour stem cell — has been controversial. According to this idea, tumour stem cells are both refractory to most traditional therapies and capable of regenerating the tumour following treatment. The deadly brain tumour glioblastoma is thought to arise from tumour stem cells[6].

Wang *et al.*[2] (page 829) and Ricci-Vitiani *et al.*[3] (page 824) now reveal data that are relevant to both concepts, and provide strong evidence that a proportion of the endothelial cells that contribute to blood vessels in glioblastoma originate from the tumour itself, having differentiated from tumour stem-like cells.

Both groups note that a subset of endothelial cells lining tumour vessels carry genetic abnormalities found in the tumour cells themselves (Fig. 1). For instance, a comparable proportion of a cell population expressing endothelial-cell markers and a population of neighbouring tumour cells harboured three or more copies of either the *EGFR* gene or other parts of chromosome 7. Such cell populations also shared a mutated version of the oncogene *p53*. Another indicator of the tumour origin of some tumour-vessel endothelial cells is that, as well as expressing characteristic endothelial-cell markers — such as von Willebrand factor and VE-cadherin — they expressed the non-endothelial, tumour marker GFAP.

The researchers also present evidence that tumour-derived endothelial cells arise from tumour stem-like cells. They find that a glioblastoma cell population that could differentiate into endothelial cells and form blood vessels *in vitro* was enriched in cells expressing the tumour-stem-cell marker CD133. Moreover, Wang and colleagues show that a clone of cells derived from a single tumour cell, which expressed CD133 but not VE-cadherin, was multipotent: *in vitro*, the cells differentiated into both neural cells (which eventually form tumour cells) and endothelial cells.

On being grafted into mice, these cells formed highly vascularized tumours. Moreover, even the progenitor cells from these tumours continued to form tumours and tumour-derived endothelial cells, suggesting that the multipotential characteristic had been maintained. Ricci-Vitiani *et al.* gained further insights by generating undifferentiated cell aggregates from human tumour-derived CD133-expressing cells and grafting them into mice. The internal vessels of the resulting tumours expressed human vascular markers,

whereas more external vessels carried mouse-specific endothelial-cell markers. What's more, the authors found human endothelial cells in tumour vessels linking to the mouse vessels and delivering blood to the tumour.

Wang *et al.*[2] suggest that the differentiation of tumour stem-like cells into endothelial cells might be mediated by signalling pathways involving two proteins — vascular endothelial growth factor (VEGF) and Notch. The authors propose that Notch regulates the initial differentiation of tumour stem-like cells to endothelial progenitor cells, whereas VEGF selectively affects the differentiation of endothelial progenitors to tumour-derived endothelial cells (Fig. 1).

Another team[7] has also investigated the source of cells contributing to tumour vessels, and has shown that tumour stem-like cells cultured from human glioma tumours form endothelial cells *in vitro*. The authors detected channels lined with tumour-derived cells in mice transplanted with human tumours — a process they classify as vasculogenic mimicry. However, their analysis of the original human tumours was limited to marker expression, and so they could draw no firm conclusion about the relationship between the tumour cells and the endothelial cells. Similarly, other groups[8,9] have presented evidence of genetic abnormalities common to tumour cells and endothelial cells, but their data did not distinguish among several potential mechanisms for the observations.

What is the functional significance of a tumour origin for vascular endothelium? To address this question, Ricci-Vitiani *et al.*[3] generated tumours in which the tumour-derived vessels were susceptible to drug-mediated destruction. Following drug treatment, these tumours were smaller than control tumours and had fewer blood vessels. This indicates that blood vessels derived from tumours are crucial for tumour survival.

The new work[2,3] also defines the relationship between a tumour and the blood vessels with which it interacts. If a dedicated compartment of some tumours provides a niche for stem cells that can give rise to functional blood vessels, there may be a less urgent need for tumour cells to undergo the angiogenic switch to recruit vessels, and stronger selective pressure on them to differentiate into endothelial cells.

Moreover, these observations challenge the assumption that tumour endothelial cells are normal cells, and therefore lack the genetic instability that may be the basis of drug resistance in tumour cells. Consistent with this suggestion, earlier studies[10,11] showed that tumour endothelial cells over-duplicate centrosomes — cellular organelles involved in cell division — and possess elevated levels of chromosome abnormalities. Moreover, there seems to be a link between increased activity of the signalling cascades that promote blood-vessel formation and chromosome abnormalities in endothelial cells[12]. Tumour cells may therefore promote genetic instability in tumour endothelial cells through two distinct mechanisms: by giving rise to them directly, or by sending a signal to a nearby endothelial cell. Thus, not only the tumour compartment, but also genetically unstable tumour endothelial cells, may contribute to drug resistance.

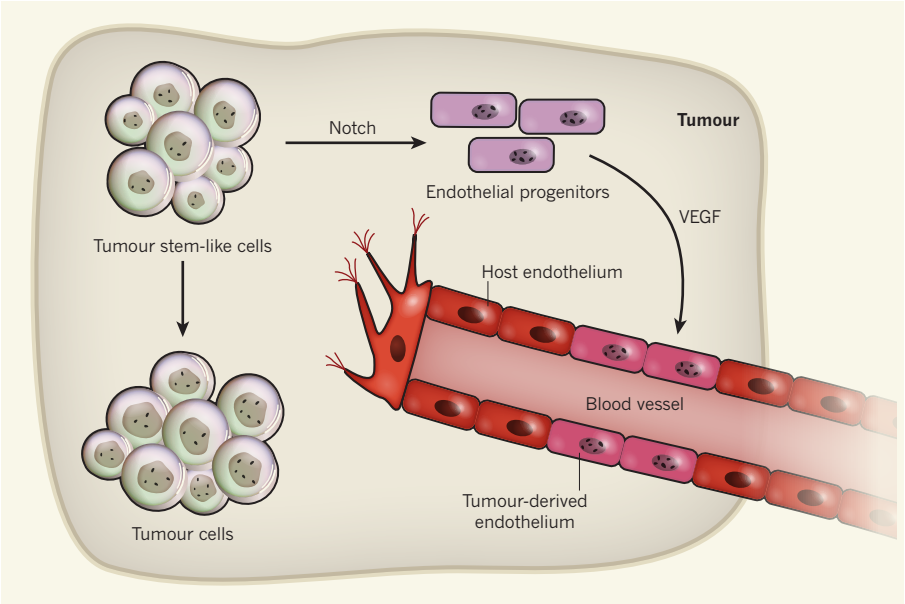

Figure 1 | Tumour stem-like cells are multipotent. Tumour-derived stem cells are thought to give rise to tumour cells. Wang *et al.*[2] and Ricci-Vitiani *et al.*[3] propose that a portion of the vascular endothelium that lines the tumour vessels in glioblastoma also arises from tumour stem-like cells. They show that the genetic abnormalities (dots) seen in the tumour cells are also present in endothelial cells isolated from the tumours. It seems that tumour stem-like cell differentiation to endothelial-cell progenitors occurs through Notch-mediated signalling, and that further differentiation of endothelial-cell progenitors into endothelial cells is mediated by the VEGF signalling pathway.

Several compelling questions arise from the latest data[2,3]. First, how general is the differentiation of tumour stem-like cells into endothelial cells? Both studies focused on glioblastomas, and so the relevance of this pathway in other tumours of suspected stem-cell origin must also be determined. Other cell types of the underlying support tissue (stroma), such as fibroblasts, also play a part in tumour formation and progression. Do tumour stem cells contribute to these non-endothelial stromal lineages, and, if so, under what conditions?

It is also necessary to define the conditions that promote the differentiation of tumour stem-like cells to endothelial cells, and to determine the prevalence of this process within a given tumour environment. For example, does local shortage of oxygen trigger this differentiation? The present studies examine the molecular pathways that regulate the formation of tumour-derived endothelium at a superficial level. Defining the relevant mechanisms thoroughly is an essential prelude to the design of new therapies.

Finally, it will be crucial to determine how tumour-derived endothelial cells and vessels differ from their non-tumour counterparts in both morphology and function. Other studies[13] have reported that, when cultured, endothelial cells isolated from tumours exhibit some properties of stem cells, with the assumption that these properties were acquired by signals from the tumour environment. In light of the present work, an intriguing alternative possibility is that endothelium derived from tumour stem-like cells contributes to the observed cell characteristics. This work[2,3] therefore highlights yet another of the numerous ways in which tumours evade destruction: by contributing to their own support system. ■

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