NEWS & VIEWS

CANCER STEM CELLS

Here, there, everywhere?

Connie J. Eaves

Can every tumour cell propagate human cancers or is this property exclusive to an elite subset? Findings are divided. The latest set shows that — depending on circumstances — both perspectives can be correct.

A long-standing goal of both researchers and oncologists is to establish a framework for understanding how many and which tumour cells must be eliminated for treatment to be successful. One framework that has received much attention recently attempts to understand cancers as perturbed versions of the normal tissue in which they arise, with retention of many tissue-specific developmental features. The 'cancer stem cell' hypothesis is a derivative of this framework, and states that cancer cell populations have a hierarchical developmental structure in which only a fraction of the cells — the cancer stem cells — can proliferate indefinitely. If this concept is correct, it could have implications for cancer treatment. But Quintana *et al.*[1] report on page 593 of this issue that, for at least one type of human cancer, the reality may be more complex.

What is the evidence for cancer stem cells in human tumours? The creation of mice that are sufficiently immunodeficient to tolerate the growth of primary human cells in them has only recently allowed this idea to be examined experimentally, and so far only a few tumour types have been investigated[2–7]. All of these studies suggest that only a tiny subset of cells (0.0001–0.1%) have the ability to generate a new tumour in most immunodeficient mice that were available at the time of each study. The earlier studies also found that the features of cells with tumorigenic potential differ from those of the bulk of the tumour cells but are often shared with the normal stem cells of the same tissue. Together, these findings supported the idea that human cancer cells that can produce tumours in immunodeficient mice represent a biologically distinct set with stem-cell-like properties.

Quintana *et al.*[1] transplanted single human cancer cells into highly immunocompromised mice — more so than the animals used previously — and used rigorous procedures to measure the frequency of tumorigenic cells in different strains of mice. They demonstrate that as many as one in four tumour cells derived from a type of human skin cancer called melanoma can initiate a tumour. Moreover, tumour cells capable of producing a new tumour can have many different features, most of which are common to some, but not all, of the tumorigenic cells, and none of which shows a particular association with tumorigenic potential[1].

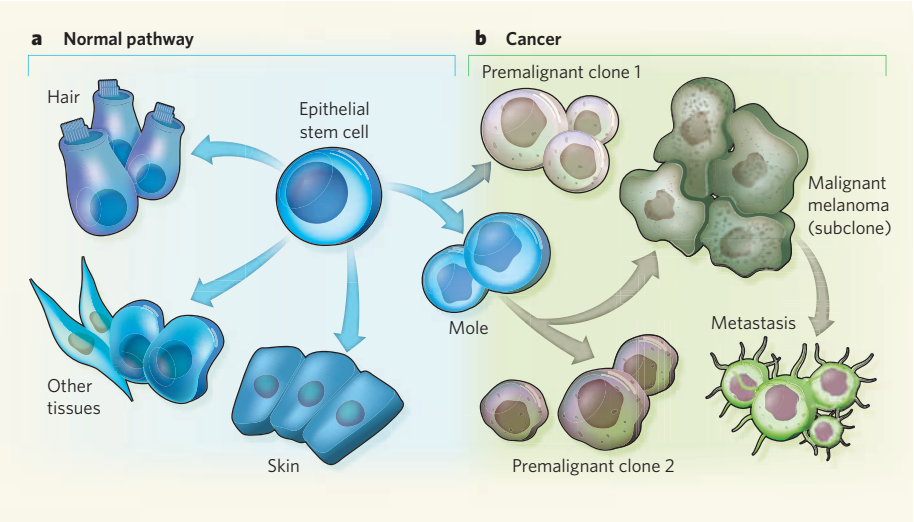

Figure 1 | Oncogenesis is a sequential process. a, Normally, stem cells (in the example shown, epithelial stem cells) give rise to various differentiated cells such as hair and skin cells. **b**, In cancer, however, it is thought that these stem cells must undergo a specific set of rare changes to produce a population that is frankly malignant. Such a sequential process allows many subclones to develop along the way, each characterized by more aggressive features.

How can these surprising findings be reconciled with the earlier observations[2–7]? One explanation could be that the process of oncogenesis typically involves an accumulation of many rare events that leads to altered control of growth and differentiation. The first of these events is likely to occur in normal stem cells because these are the only cells that undergo sufficient rounds of cell division to accumulate the particular combination of changes necessary for a malignant cell to evolve (Fig. 1). Evidence for both a clonal origin of tumours and their evolution through an accumulation of genetic mutations has been around for decades. But linking these observations to the idea that malignant cells ultimately originate from a stem-cell population is less well established.

A big impetus for the concept of cancer stem cells comes from studies of a type of blood cancer called chronic myeloid leukaemia. Here, a small abnormal chromosome called the Philadelphia chromosome is found in several types of blood cell and in their most primitive precursors. The chronic-phase clone becomes dominant because the mechanisms controlling how many mature cells should be produced are highly deregulated, without affecting the ability of the cells to execute normal differentiation programs. If the disease is not adequately treated, more aggressive subclones, characterized by additional mutations that disrupt the differentiation process, arise, and these subclones then produce a rapidly fatal acute leukaemia. This sequence of events illustrates how premalignant stem-cell-driven cell populations may precede the appearance of a frankly malignant subclone that could contain a high proportion of cells with tumorigenic activity (Fig. 1b). The more aggressive the subclone, the faster it is likely to grow, quickly diluting the original premalignant population and making its identification difficult.

A second explanation may involve the possible influence of the environment in which the tumour cells are trying to grow. Increasing evidence suggests that non-malignant host-cell

populations have a significant role in tumour growth[8]. Quintana *et al.*[1] report that, when they used the same *in vivo* assay protocol as was used in a previous study[7], they detected the same low (one in a million) frequency of tumorigenic human melanoma cells. Nonetheless, the authors[1] found that many more cells could form tumours when various aspects of the original protocol[7] were altered. These included prolonging the observation period, injecting the tumour cells into an extract rich in extracellular-matrix components such as laminin to improve tumour-cell viability, and using more highly immunodeficient strains of mice as hosts.

If the growth potential of a cancer does depend on a rare subset of cancer stem cells, it seems important to know how to eradicate these particular cells. Similarly, assessing the ability of a candidate therapy to destroy these cells would seem crucial to predicting its efficacy. But even these assumptions are being challenged by some experimental findings. For example, the outcome of treating patients in the chronic phase of chronic myeloid leukaemia with the drug imatinib mesylate — before the acute phase has begun — suggests that selective and effective killing of the differentiating cells in the premalignant clone may be sufficient to prevent this cancer's progress for many years, even though the treatment has little ability to destroy the chronic-phase stem cells[9,10].

Research into human cancer stem cells is still gathering steam, so it is not clear how unusual or clinically relevant Quintana and colleagues' observations[1] are. It is possible that their findings are unique to a subset of tumours, to specific types of mutation, to certain states of cancer progression, to distinct factors within the tumour environment, and/or to the states of innate and acquired immunity of the host. Equally possible is that these observations are more commonly applicable. Either way, this study provokes healthy scepticism in the absolute value of any tumour-initiating cell measurement and points to the need for careful studies designed to test new biomarkers and therapeutics. ■

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See also Abstractions, page xiii, and News, page 553.

MATERIALS SCIENCE

Clear leap for superconductors

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Electric fields offer an innovative means of controlling condensed-matter systems. The approach has been applied to nanoscale oxide interfaces, for studying the physics of two-dimensional superconductors.

In recent years, the ability to engineer the interface between two oxides on the nanoscale with atomic-layer precision has led to remarkable advances in our knowledge of the electronic phenomena occurring at these interfaces. For instance, the transfer of charge at the interface between two ordinary oxide insulators, $LaAlO_3$ and $SrTiO_3$ (ref. 1), gives rise to a conducting two-dimensional gas of electrons that, at low temperatures, is a superconductor (it conducts electricity without resistance)[2]. Now Caviglia *et al.*[3] (page 624 of this issue) show that an electric field can be used to modify the electron concentration of a transparent (clear) electron gas that forms at the $LaAlO_3$/$SrTiO_3$ interface (Fig. 1), allowing the emergence of two-dimensional superconductivity to be examined in unprecedented detail.

A major challenge in the study of these interfaces is identification of the source of the charge carriers (the electrons). One possible source is a 'polar catastrophe', in which the change in net layer charge (positive or negative) between the last TiO_2 layer of the $SrTiO_3$ structure and the first LaO layer of the $LaAlO_3$ structure, drives an electronic reconfiguration that introduces charge carriers into the system[1]. Alternatively, they might be produced in a more mundane fashion by means of oxygen defects or the interdiffusion of cations between the $LaAlO_3$ and $SrTiO_3$ layers[4]. Caviglia and colleagues' work does not address this issue definitively, but it is not germane to the fundamental physics that they elucidate here.

Caviglia *et al.*[3] use an electric field to reversibly pump charge carriers into or out of the interface, a process called charge doping. Impressively, this allows the authors to map out a region of the phase diagram of the interface state — a plot of temperature versus charge-carrier concentration that shows the phase boundary between the insulating state and the superconducting state. Because electric-field doping introduces no chemical or structural disorder at the interface, unlike chemical doping (in which the chemical composition is altered to introduce charges into the system), the authors are able to study the charge physics of a 'clean' system, without the obscuring, undesirable effects of disorder.

Interestingly, Caviglia *et al.* find no evidence of magnetism at the $LaAlO_3$/$SrTiO_3$ interface over the entire range of carrier concentrations studied, including densities of about 10^{13} electrons per cubic centimetre, for which a magnetic state was previously identified[5]. What they find instead is a superconducting, dome-shaped region in the phase diagram (see Fig. 3 on page 625), occurring over a range of charge-doping levels and temperatures that is consistent with the range over which doped $SrTiO_3$ is known to be superconducting.

Caviglia and colleagues' pivotal finding is that this clean, disorder-free doping approach allows them to identify the quantum critical point that separates the superconducting state from the insulating state as a function of charge density. A detailed analysis of this critical region suggests quantum phase fluctuations that are reminiscent of insulator–superconductor quantum phase transitions, tuned by electric fields, seen in other two-dimensional systems[6].

But where do we go from here? One clear role for the authors' approach of using an electric field to control superconductivity will be in elucidating the nature of phase transitions in other systems, particularly in systems in which the symmetry is broken by the presence of the interface. What's more, this approach will facilitate the development of nanoscale superconducting circuits, including the creation of rewritable arrays of Josephson junctions (two superconductors separated by a thin, non-superconducting region).

The authors' method will find even more wide-ranging applications. First, the electric-field control of interface properties, combined with the nearly unlimited possible combinations of oxides displaying diverse electronic properties, will allow other physical phenomena to be probed, including magnetism, orbital ordering and charge ordering[7]. The present interest in this approach is also partly due to its potential for achieving charge-mediated magnetoelectric coupling in composite multiferroic systems. These materials allow magnetism to be controlled in the solid state using electric fields. Furthermore, in its search for an eventual replacement for the transistor, the semiconductor industry is looking at exotic phenomena in various solid-state systems, including the control and manipulation of exotic ground states in novel, artificially structured materials. Electric-field control of these ground states could form the basic logic states ('0' and '1') of future information-processing technologies.

But most notably, Caviglia and colleagues' work[3] marks the dawn of a new era in the design of superconductors consisting of materials created with atomic-layer precision. In these