spacing, and has units of bits per second per hertz (bit s^{-1} Hz^{-1}).

Reaching the spectral-efficiency limits calculated by Mitra and Stark requires coherent optical detection, which involves interfering the received signal with a reference signal at an identical or slightly different frequency. Current systems use a simpler method, which detects the intensity of the received optical signal. In the absence of amplifier noise and nonlinearities, capacities of optical fibres can be calculated rigorously for systems using intensity detection[3,4]. We don't know what the limits are for a nonlinear amplified DWDM system using intensity detection, but in the linear regime the maximum spectral efficiency of a DWDM system using intensity detection[5] is roughly 1 bit s^{-1} Hz^{-1} less than half that with coherent detection (for example, 2 and 1 bit s^{-1} Hz^{-1} compared with 6 and 4 bit s^{-1} Hz^{-1}, respectively).

Mitra and Stark[1] now show that for a typical nonlinear DWDM system, assuming coherent detection, the spectral efficiency limit exceeds 3 bit s^{-1} Hz^{-1}. For comparison, the next-generation commercial DWDM systems are expected to use 40 Gbit s^{-1} channels with 100-GHz spacing — equal to a spectral efficiency of only 0.4 bit s^{-1} Hz^{-1}. All current DWDM systems use 'on–off keying', a way of encoding bits by the presence or absence of light. Using a binary modulation technique such as on–off keying, spectral efficiency cannot exceed 1 bit s^{-1} Hz^{-1} (this limit is reduced to 0.67 bit s^{-1} Hz^{-1} by assuming more realistic system parameters). So a system approaching Mitra and Stark's spectral-efficiency limits would require a non-binary encoding technique, such as multilevel intensity or phase modulation.

When calculating the effects of CPM, Mitra and Stark have implicitly assumed a modulation technique involving time-varying intensity. It is already known that using a constant-intensity modulation technique, such as phase or frequency modulation, can eliminate CPM. The fibre's refractive index varies slightly with the wavelength of light, which tends to convert phase or frequency modulation to intensity modulation. This wavelength dispersion must be carefully compensated for to maintain constant intensity. If we follow the same calculations as Mitra and Stark, and constant intensity is maintained, then the spectral-efficiency limit should increase with transmitted power, in contrast with their results. In reality, as the power increases, spectral efficiency would eventually be limited by other nonlinear effects, such as four-wave mixing.

As Mitra and Stark point out, nonlinearities such as CPM can be cancelled out, in principle, by using a number of clever tricks[6,7]. Better optical fibres can also help — for example, hollow fibres with air cores have a reduced nonlinear response[8]. In ordinary optical fibres, light can propagate in two orthogonal polarizations — that is, with electric field lines along two perpendicular directions. A simple way to double spectral efficiency is to send two independent signals with these different polarizations and use polarization-resolved detection. Even without polarization-resolved detection, sending neighbouring signals with perpendicular polarizations is a well-known method to reduce nonlinearities.

Mitra and Stark's work is a useful step towards working out the limits to the spectral efficiency of optical fibres. Nonetheless, our understanding of the ultimate limits, and how to approach them in practice, will continue to evolve. ■

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Immunology

T cells and tumours

Drew Pardoll

The immune system's response to new tumours is complicated but seems to depend on where and when tumours develop. This will have to be much better understood to enlist a patient's immune defences in fighting cancer.

Does the immune system see tumours more as 'self' or as 'foreign'? The answer is complex, as is plain from papers published here in April[1] and on page 1058 of this issue[2]. They show that the immune response probably depends on the location and properties of tumour cells early in their development.

Quantum engineering

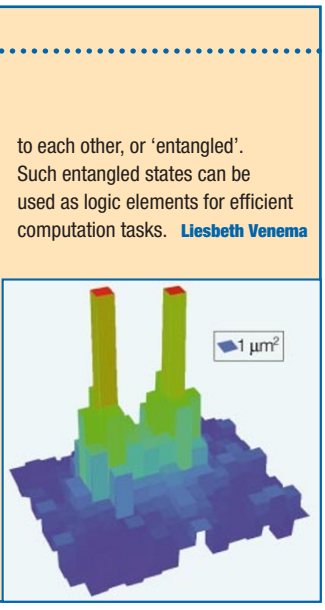
Catch the atom

Two groups have independently succeeded in confining single atoms in microscopic traps (N. Schlosser *et al.*, *Nature* **411,** 1024–1027; 2001, and S. Kuhr *et al.*, *Science*, 14 June 2001, 10.1126/science.1062725). This feat opens the way to designing experiments in which various quantum-mechanical effects can be exploited. Several techniques already exist to manipulate individual particles, such as photons and ions, but it has been notoriously difficult to pin down neutral atoms.

The two groups developed methods to attract cooled-down atoms towards spots of high electric-field intensity in traps formed by laser beams. Schlosser *et al.* find that the individual rubidium atoms entering their traps scatter enough photons to image them with a CCD camera. The images show that the traps are occupied by either no atoms or just one at a time. Moreover, once an atom is caught, it can be kept trapped for up to 2 seconds — a veritable lifetime in quantum mechanics.

Kuhr *et al.* exerted their control over chilled caesium atoms and designed traps that can catch any desired small number of atoms. Intriguingly, they also found that these atoms can be catapulted into free flight from the trap, raising prospects of an 'atom on demand' delivery service.

As a final flourish, Schlosser *et al.* have positioned two traps, each containing a single atom, close to each other as shown here in the CCD image. In this set-up, the internal states of the two atoms can be intimately related to each other, or 'entangled'. Such entangled states can be used as logic elements for efficient computation tasks. **Liesbeth Venema**



First, some background. In the 1950s, the immune-surveillance hypothesis was formulated. According to this idea, the immune system surveys the body for specific antigens expressed by newly arising tumours, most of which are rapidly eliminated. Progressive cancer was seen as a rare occurrence in which tumours evade immune surveillance, ostensibly through specific resistance or 'cloaking' mechanisms. This view was supported by findings that cancers have various ways of making themselves resistant to the immune system, one tactic being inactivation of an afflicted cell's major histocompatibility complex (MHC)[3,4], or its associated machinery[5,6]. This would allow the cell to evade recognition by T cells. Recognition of diseased cells and their execution by T cells, after presentation by the MHC of foreign antigens at the cell surface, is one of the main immune defence mechanisms.

The immune-surveillance hypothesis ran into trouble, however, as various findings emerged. The common, non-virus-associated cancers (breast, lung and so on) do not arise any more frequently in people with a defective immune system than in those with a fully functioning system[7]. Likewise, nude mice — which have impaired T-cell and B-cell (antibody) immunity — have tumour incidences equivalent to those of normal mice[8]. Finally, studies of transgenic mice, in which specific T cells for tumour-associated antigens could be marked and monitored, showed that tumour cells can induce immune tolerance[9–11]. In some cases, T cells were activated, but only transiently. In others, the tumour-specific T cells were rendered unresponsive (anergic). These findings all support an opposite view to that of the immune-surveillance hypothesis — that the immune system sees tumours more as self than as foreign.

The new papers by Shankaran *et al.*[1] and Ochsenbein *et al.*[2] show that the truth lies somewhere between these two views. Shankaran *et al.* evaluated the incidence of tumour formation in immunodeficient mice that provide 'cleaner' subjects than the nude strain (which have residual T- and B-cell function). The authors used mice in which the RAG and/or STAT-1 genes had been deleted, enabling them to analyse responses of the innate arm of the immune system as well as the adaptive (antigen-mediated) arm that depends on T and B cells. RAG 'knockout' mice cannot rearrange the genes that are central to adaptive immunity. STAT-1 knockout mice lack the pathways, mediated by γ-interferon, that are essential for both the adaptive and innate responses.

Cancer incidence in both of these types of mice was clearly higher than in normal mice. But the type and location of tumours depended on which components of the immune response were absent. RAG-deficient mice largely suffered from cancer of epithelial tissue in the intestine. Double RAG/STAT-1 knockouts developed analogous breast cancers as well, so innate immunity may suppress tumours at certain sites. Both types of mice particularly developed spontaneous tumours from around one year of age and beyond (this, by mouse standards, is senior-citizen status). So, even without important elements of the immune system, the mice did pretty well, showing that its role in limiting tumorigenesis is more subtle than implied by the classic surveillance hypothesis.

Shankaran and colleagues' findings support a highly modified version of immune surveillance in which the immune system can act as an 'extrinsic suppressor' of tumours in certain locations or tissues. This is analogous to the classic intrinsic suppressors, such as that encoded by the *p53* gene,

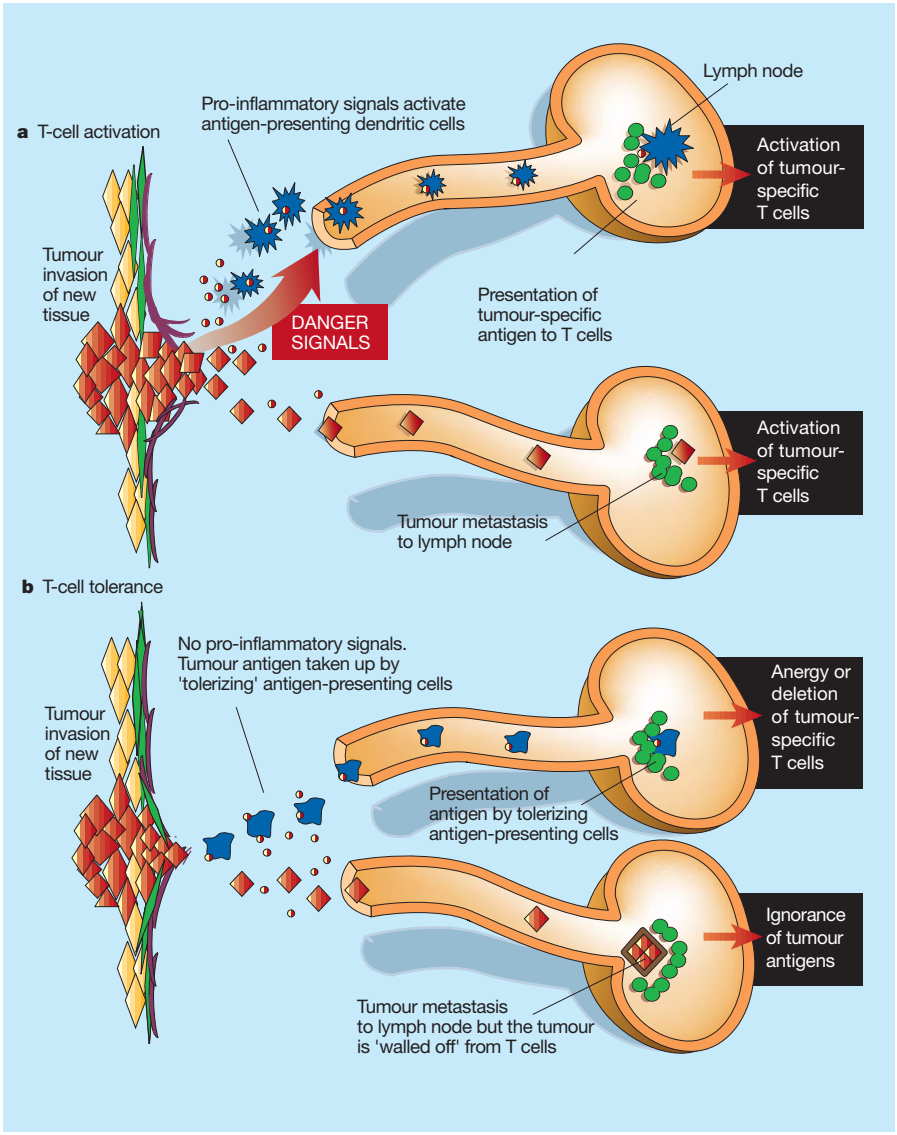


Figure 1 **T-cell responses to tumours in different circumstances. Tumour invasion across normal tissue barriers and metastasis can lead to** a, **T-cell activation, or** b, **T-cell tolerance.** a, **As shown in the upper pathway, the tumour may disrupt the intercellular matrix, which can result in the generation of pro-inflammatory signals. These signals cause progenitor cells from the bone marrow to differentiate into antigen-presenting dendritic cells. When carried into the lymph nodes, the dendritic cells present the tumour-specific antigen to T cells, which become activated. Alternatively** (a, **lower pathway), some tumours may metastasize to lymph nodes and directly activate T cells.** b, **Some tumours can invade new tissue and metastasize without generating pro-inflammatory signals. Here (upper pathway), 'tolerizing' antigen-presenting cells can take up tumour antigen and, after passing into lymph nodes, present the tumour-specific antigen to T cells and make them tumour-tolerant in one of two ways: by anergy (in which the T cells are rendered unresponsive) or deletion (in which the T cells are destroyed). Alternatively** (b, **lower pathway), although a tumour may metastasize to the lymph nodes, it becomes 'walled off' from T cells, which therefore remain ignorant of the tumour antigens.**

which must be inactivated or bypassed to allow tumour progression.

In their paper, Ochsenbein *et al.*[2] describe how they have correlated the ability of tumours to migrate into secondary lymphoid organs — lymph nodes and spleen — with the activation of T-cell responses against tumour antigens. The significance of these organs is that they are the main places where T cells await activation.

Ochsenbein *et al.* looked at several different mouse tumours and found that some metastasizing tumours that fail to 'seed' lymph nodes and spleen are 'ignored' by the immune system. They also found that when tumours were injected into secondary lymphoid organs, they segregated into two types. One type — 'immunogenic' tumours that elicited a strong immune response — circulated in lymphoid regions, intermingling with T cells and allowing direct antigen presentation to T cells and activation of anti-tumour immunity. Another, indirect pathway to T-cell activation is well characterized (Fig. 1a, upper pathway): antigen-presenting cells known as dendritic cells take up tumour antigens, carry them to lymph nodes and present them to T cells[12,13]. The circumstances under which the direct or indirect pathway predominates remain to be identified.

The second type of tumour identified by Ochsenbein *et al.* was only weakly immunogenic. This type grew as nodules, 'walled off' from the immune system by barriers that prevented activation of anti-tumour immunity. So even if tumour antigens make their way to secondary lymphoid organs, this is not necessarily enough to activate immunity. It is indeed likely that this second kind of tumour represents most human tumours. As any oncologist will tell you, lymph-node metastases are usually a poor prognostic sign, indicating a high likelihood of cancer spread to elsewhere. Presumably, tumours that directly activate T cells in lymph nodes are eliminated before becoming clinically detectable.

How, then, can one reconcile the evidence that tumours can either activate the immune system or make it tolerate them? Possible answers are outlined in Fig. 1. At certain points in their development, tumours must become invasive and create their own blood supply. These severe disruptions of cellular processes and tissue architecture may provoke pro-inflammatory signals, which can convert immune toleration to activation through induction of dendritic cells[14] (Fig. 1a, upper pathway). Dendritic cells can ingest tumour antigens; after migration to the lymph nodes, and with certain co-stimulatory molecules, they can activate T cells quite efficiently. Alternatively, tumour cells may migrate to lymph nodes and activate T cells directly (Fig. 1a, lower pathway).

In other circumstances, despite causing serious disruption, it seems that a tumour may fail to generate pro-inflammatory signals. The immune system then probably views a tumour as 'self' tissue and tolerates its antigens. This tolerance can take the form of 'ignorance', as outlined by Ochsenbein *et al.*[2], in which the immune system is never made aware of the tumour (Fig. 1b, lower pathway). Or it can result from active processes such as T-cell anergy or deletion (Fig. 1b, upper pathway). These processes involve transfer of tumour antigens to 'tolerizing' antigen-presenting cells, which develop in bone marrow, carry antigens to lymph nodes and, in the absence of co-stimulatory signals, present them to T cells. The result is T-cell anergy or deletion[15–17].

Against this background, the ultimate immune response may depend on where and when tumour-specific antigens form. If the tumour does not generate a new antigen during the pro-inflammatory phases of its development, then immune tolerance dominates. But if the tumour is unlucky enough (from the tumour's perspective) to generate a strong antigen just when it is generating a pro-inflammatory response, the outcome will be a vigorous anti-tumour response. These tumours will be eliminated naturally unless they have developed specific resistance mechanisms, such as downregulation of MHC or the antigen-processing machinery.

Overall, we can conclude that tumours that reach the stage of being clinically detectable are likely to have done so in one of two ways. They will either have generated tolerance in the immune system or have developed ways of resisting immune recognition. In terms of cancer treatment, we need to identify ways to break tolerance or circumvent resistance mechanisms. ■

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Daedalus

Phones and the brain

One of the problems of using a mobile phone is that the brain is sensitive to microwaves. Daedalus points out that each brain cell has many inputs (dendrites) and one main output (its axon). All these fibres go to other brain cells. Nerve pulses from a specific combination of dendrites fire (or inhibit the firing of) an impulse down the axon. So each brain cell acts as a logical gate; it learns from experience. It alerts the dendrites which receive each pulse, so that they fire or inhibit its resulting output. This changing sensitivity stores our memories and abilities.

It is reasonable that the substances which do all this are proteins. They seem well adapted as the ultimate storers of knowledge. A protein molecule may, in one configuration, inhibit a brain cell; in another, it may potentiate it. And the energies that separate the protein configurations are in the microwave region, below the infrared band which holds bond-stretching itself.

This theory, says Daedalus, explains the great plasticity and learning capacity of the brain, and also its sensitivity to microwaves. Reconfiguration of protein structure must require the absorption of microwaves to shift the amino-acid moieties from one configuration to another. Hence the fears that children educated under microwave towers, and mobile-phone users, may suffer memory loss. A single frequency, as from a mobile phone, could at best scramble only one or two protein transitions; it could still leave gaps in a memory. The more complex transmissions from a microwave tower, at many frequencies, could be more troublesome.

So Daedalus is exploiting the recent culturing of nerve cells in a special medium. His idea is that in a Petri dish the cells can be exposed to much stronger microwaves than in any brain. The way they link together by their dendrites, or draw apart, will reveal the effects of the microwaves. Some frequencies may turn out to be particularly dangerous. They may trigger many changes of state in the dendrites. Other frequencies may turn out to be well clear of the brain's operating frequencies. These will be the ones to use for mobile-phone use. And, of course, a simple design change will reduce the phone's impact on its user by a factor of about four. Put the irradiating antenna at the microphone end, projecting from the jaw-line, well clear of the ear and the brain.

David Jones