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.

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