The attitude to international research also varies among tropical countries, being determined by the opposing forces of cosmopolitanism and parochialism. An index of the ease of doing biodiversity research, analogous to the World Bank's index of the ease of doing business[15], should be developed to rank the competitiveness of tropical countries vying for the limited pool of international expertise and research funds. The 2014 Nagoya Protocol for the Convention on Biological Diversity was meant to enhance international scientific collaboration by ensuring benefit sharing. Unfortunately, over-regulation has produced the opposite effect, stifling much-needed biodiversity research in the tropics[16]. Paradoxically, this might open up an opportunity for Papua New Guinea. Unlike Indonesia, Papua New Guinea is not a signatory to the Nagoya Protocol, and this might aid its efforts to become one of the most biodiversity-research-friendly countries in the tropics.

The authors' plant list for New Guinea is an excellent start on a long journey towards obtaining a full inventory of New Guinean biodiversity — a necessary tool for ensuring plant conservation and sustainable use. It is crucial that New Guineans themselves, as the custodians of this biodiversity, should forge the path towards achieving this goal.

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Immunology

A dendritic cell multitasks to tackle cancer

Marianne Burbage & Sebastian Amigorena

Learning how immune cells target tumours is crucial for cancer immunotherapy. The finding that a type of dendritic cell activates two sorts of T cell and coordinates their crosstalk sheds light on immune responses to tumours. **See p.624**

The generation of an efficient immune response against cancer is a multifaceted, multistep process. Ferris *et al.*[1] reveal on page 624 that a type of immune cell called a dendritic cell is more versatile than was previously thought in its ability to orchestrate tumour targeting.

A key feature of the process in which immune cells target cancer is the activation of CD8 T cells. These immune cells can recognize antigens, short peptide fragments that derive from tumour cells. The initiation of antitumour responses also requires the action of dendritic cells (Fig. 1), which ingest and capture tumour-derived proteins, and process them into antigens. Dendritic cells display these antigens on their surface, bound to major histocompatibility complex (MHC) molecules, and present them to the T-cell receptor (TCR) on T cells.

Another type of T cell, called a CD4 (or helper) T cell, recognizes antigens displayed on a category of molecule termed class II MHC molecules. CD4 T cells provide accessory signals that allow CD8 T cells, which are primed by antigens presented on class I MHC molecules, to kill tumour cells (CD8 T cells that have developed this capacity are also called cytotoxic T cells). CD8 T cells can then establish long-lasting protection against tumour recurrence. Knowing how CD4 and CD8 T cells are stimulated, and by which type of dendritic cell, is central to understanding and manipulating antitumour immune responses in the clinic[2].

Most of what we know about immune responses, including antitumour responses, comes from studies of infection rather than of cancer. During viral infections, two types of dendritic cell, called DC1s (also known as conventional type I dendritic cells) and DC2s, initially activate CD8 and CD4 T cells, respectively. The two types of activated T cell then sequentially or simultaneously recognize antigens on DC1s, and CD4 T cells provide effective 'help' to CD8 T cells[3,4]. For example, CD4 T cells secrete molecules that directly support CD8 T cells. CD4 T cells also induce DC1s to express molecules that further boost the activation of CD8 T cells, a process referred to as licensing.

Whether the interactions of CD4 and CD8 T cells with DC1s are simultaneous or sequential is debated. Either way, previous results[3,4] are consistent with the model that DC1s must present antigens on both class I and class II MHC molecules to generate an immune response against an infectious agent. A microscopy method for studying cells in living animals, called intravital imaging, has already provided spectacular evidence that DC1s act as platforms that support simultaneous interactions with CD4 and CD8 T cells[3,4]. However, many studies have shown that DC1s present antigens on class I MHC molecules to CD8 T cells, whereas DC2s present antigens on class II MHC molecules to CD4 T cells[5]. Even though the selective presentation of antigens on class I and class II MHC molecules by distinct types of dendritic cell is widely accepted, it is not easy to reconcile this view with the platform model for how help from CD4 T cells occurs, because in this model the same dendritic cell needs to present antigens to both CD4 and CD8 T cells.

The platform model of DC1s enabling CD8 T cells to get help from CD4 T cells has not received definitive genetic support from *in vivo* experiments. Ferris and colleagues now report such evidence. First, the authors assessed the role of the help provided by CD4 T cells at different stages of antitumour immune responses in mice, using a type of mouse cancer, called fibrosarcoma, that is known to induce strong immune responses. One month after surgical removal of primary fibrosarcoma tumours, the authors injected cancer cells of the same type and monitored tumour growth. In control animals, these secondary tumours were rejected — destroyed by immune cells with 100% efficiency. However, antibody-mediated removal of either CD4 or CD8 T cells during the immune response against the primary tumour, or the memory immune response against the secondary tumours, abolished immune-system control of the secondary tumour. This indicates that CD4

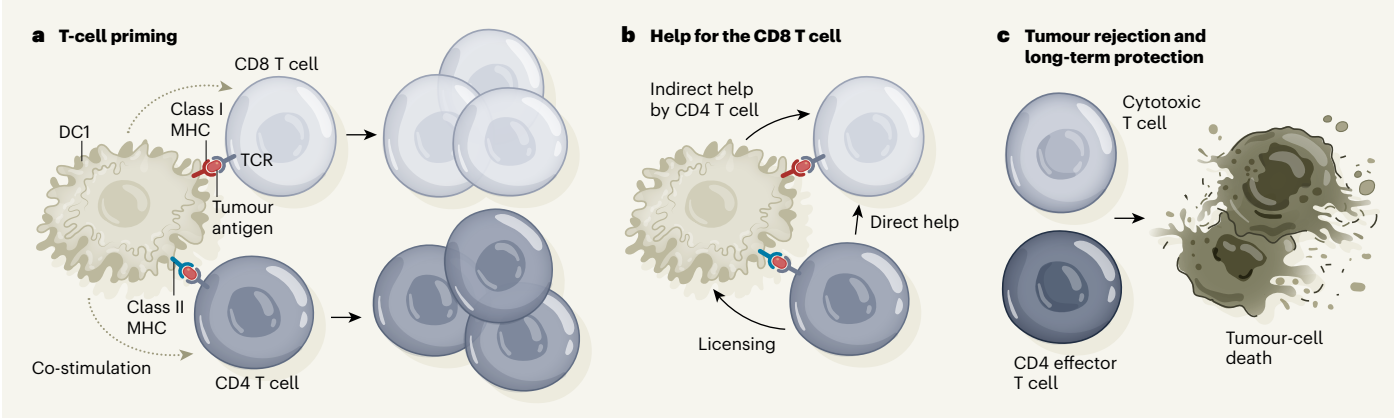

Figure 1 | How a dendritic cell helps T cells to target tumours. a, An immune cell called a conventional type 1 dendritic cell (DC1) ingests pieces of tumour cells and processes them to generate peptide fragments called antigens. These then bind proteins called major histocompatibility complex (MHC) molecules. Class I MHC molecules present antigens to a type of immune cell called a CD8 T cell, whereas class II MHC molecules present antigens to a CD4 T cell. If a T-cell receptor (TCR) on a T cell recognizes an antigen, the cell is activated and it divides. Until now, it has mainly been thought that DC1s provide such priming signals only to CD8 T cells. However, Ferris *et al.*[1] show in mice that DC1s also stimulate CD4 T cells. **b**, Activated T cells then interact with a DC1, which acts as a 'platform' for a CD4 T cell to directly interact with a CD8 T cell and boost its activation. The CD4 T cell also indirectly helps in readying the CD8 T cell by 'licensing' the DC1-mediated activation of the CD8 T cell. **c**, CD8 and CD4 T cells that are capable of launching immune responses (termed cytotoxic and effector cells, respectively) drive tumour rejection and provide a memory capacity that offers long-term protection against tumour regrowth.

T cells are needed for both types of response in this system.

Ferris and colleagues engineered fibrosarcoma cells to express the egg-white protein ovalbumin, which provides a model system to monitor immune responses. Wild-type mice efficiently rejected these engineered tumour cells. To track the activation of CD4 T cells, the authors took CD4 T cells engineered to express a TCR that recognizes the ovalbumin antigen, and transferred them into tumour-bearing mice. After a few days, the authors collected immune cells in lymph nodes, structures in which material draining from the tumour is brought into contact with immune cells. The engineered CD4 T cells were actively proliferating, indicating that they had been stimulated by interacting with ovalbumin antigen from the tumour. By contrast, taking the same experimental approach in mice lacking DC1s revealed a clear lack of stimulation of CD4 T cells, suggesting that DC1s are necessary for this.

Using genetic approaches either to selectively remove class II MHC molecules from DC1s or to restrict class II MHC expression to DC1s, the authors provide direct evidence that class II MHC molecules on DC1s prime CD4 T cells to respond to a tumour antigen. Importantly, and consistent with previous research[6], the authors show that DC1s are not necessary for activating CD4 T cells after injection with soluble ovalbumin, indicating that different types of dendritic cell present the antigens expressed on tumour cells and those found in soluble proteins.

The authors show that the priming of CD8 T cells is compromised after disruption of the expression of class II MHC molecules on DC1s, supporting the idea that the stimulation of CD8 T cells requires direct interactions between DC1s and CD4 T cells. Indeed, mice selectively lacking class II MHC molecules on DC1s fail to reject tumours engineered to express ovalbumin. How do DC1s support the activation of both CD8 and CD4 T cells? Using genetic manipulation, Ferris *et al.* show that expression of the receptor protein CD40 in DC1s is essential for the activation of CD4 T cells, effective priming of CD8 T cells and tumour rejection.

This study provides compelling genetic evidence that DC1s support CD4 T cells in providing help for tumour-specific immune responses by CD8 T cells. Unlike previous reports, the work shows that the initial activation of CD4 T cells by tumour antigens is mediated by DC1s. Where and when these interactions take place in the lymph node, and whether the initial activation of both CD4 and CD8 T cells is mediated by the same DC1 population, remains to be investigated.

The evidence from the genetic removal of CD40 in DC1s indicates the protein's role in enabling CD4 T cells to aid the responses of CD8 T cells. However, the authors did not analyse the details of how CD4 T cells influence and license DC1s to activate CD8 T cells. In particular, it would be interesting to study whether interactions between DC1s and CD4 T cells modulate the expression of key immune-cell regulators, such as checkpoint proteins or soluble molecules called cytokines.

Might DC1s have a similarly central role in aiding antitumour immune responses in humans? Both DC1s and DC2s are clearly evolutionarily conserved in humans, and mouse and human DC1s have numerous shared functions and express some similar proteins[7]. However, there are some species differences. IL-12 protein is a cytokine needed for immune responses by CD8 T cells. In mice, DC1s make more IL-12 than do DC2s, but in humans, the opposite is true[8,9]. Whether, similar to mouse cells, human DC1s are more efficient than DC2s at presenting antigens to CD8 T cells is a matter of debate, with research reported that supports either view[10].

Despite many publications suggesting that DC1s are crucial for antitumour immune responses in humans, the evidence is still indirect and debated[11,12]. Establishing the role of human DC1s is of utmost importance, and the outcome will have major consequences for developing immunotherapies in the clinic. For now, it is probably wiser to temper enthusiasm with caution when discussing possible immunotherapy strategies based exclusively on targeting DC1s in humans.

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