OPINION

Creating immune privilege: active local suppression that benefits friends, but protects foes

Andrew L. Mellor and David H. Munn

Abstract | Natural regulatory mechanisms prevent inappropriate immune activation to self and innocuous foreign antigens. Here, we adapt the notion of immune privilege, which was originally applied to transplanted tissues, to consider how antigenic tumour cells and chronic pathogens might exploit natural regulatory mechanisms to become non-immunogenic. This conceptual approach reveals new mechanistic perspectives that may help to explain the paradoxical persistence of tumours and chronic pathogens, and suggests new opportunities to improve immunotherapy to treat these chronic inflammatory diseases.

The mammalian adaptive immune system is equipped with potent effector mechanisms to eliminate pathogenic organisms and infected cells. Counter-regulatory mechanisms keep immune effector cells under control during homeostasis and, when activated by inflammation, minimize collateral tissue damage caused by excessive or inappropriate immune activation. Loss of regulatory functions can be lethal or reveal other layers of regulation, attesting to the crucial need for multiple checks and balances to control immune effector-cell functions. Classically, unresponsiveness to self antigens that is acquired in primary lymphoid tissues and peripheral tissues results in systemic tolerance (that is, no self reactivity). Although contrary to the tenets of the classical self–non-self hypothesis, the immune system usually fails to mount effective immunity to innocuous (commensal) organisms and environmental allergens, which represent foreign antigens (FIG. 1). Active immunosuppression is crucial in these settings as unresponsiveness to foreign antigens is only partly explained by physical barriers that prevent antigen recognition. However, immunosuppressive mechanisms also provide opportunities for pathogens to block host immunity and a paradoxical lack of effective immunity is a contributory factor in chronic infectious diseases that affect many people; for some examples see BOX 1. Once established, chronic infections are notoriously refractory to natural and vaccine-induced immunity. Similar issues apply to cancer because most (and perhaps all) tumour cells express neo-antigens that are recognizable by T cells[1], yet established tumours are strikingly refractory to natural and vaccine-induced immunity.

How do these various antigenic insults achieve a privileged immune status? In this Opinion, we draw parallels with older observations from transplant biology showing that certain tissues display intrinsic immune privilege, defined as prolonged (or indefinite) survival of allografts that are placed at these anatomical sites compared with other locations. We adapt this original concept to encompass all tissues where local immune regulatory processes predominate over stimulatory processes when antigens are encountered. Our premise is that immunological unresponsiveness to cancer and persistent infections are, in part, indirect consequences of the need to control the potentially lethal consequences of unrestrained immunity to innocuous substances.

Key concepts in immune regulation

In this section, we consider key concepts that are relevant to locally acquired immune privilege, which will be applied when we discuss cancer and chronic infections later in this Opinion.

Antigenicity, immunogenicity and inflammation. Antigenicity (the ability to be recognized by the adaptive immune system) is necessary but not sufficient for immunogenicity (the response to an antigenic stimulus). Indeed, some antigenic challenges actively suppress immunity (FIG. 1). Although tissue inflammation stimulates adaptive immunity, certain types of inflammation — particularly excessive or chronic inflammation — paradoxically suppress immunity. In general, inflammation induces compensatory anti-inflammatory mechanisms (although with built-in delays) that are essential to limit potentially dangerous immune responses and reduce collateral tissue damage. Therefore, the traditional assumption that inflammation enhances immunogenicity needs qualification: in some contexts, inflammation stimulates active suppression.

Intrinsic and acquired immune privilege. The notion of intrinsic immune privilege was coined to explain observations that donor allografts elicited adaptive immunity of different potencies contingent on where grafts were physically placed on recipients[2]. Early studies focused on immune privilege in the eye, central nervous system, testes and placenta[3–7]. These sites were defined anatomically (that is, privilege was assumed to exist at these sites because of their anatomic location). Waldmann and colleagues applied the notion of immune privilege in considering mechanisms that enhanced allograft survival after immunotherapy[8]. We now build on this notion by applying the concept of acquired immune privilege to all local settings in which antigens elicit unexpectedly weak or no immune responses. Our hypothesis is that acquired immune privilege is maintained by active mechanisms that suppress responses to antigens in local tissues and associated lymph nodes. Although physical barriers that restrict antigen presentation may complement active regulation, even the classic 'anatomic'

© 2008 Nature Publishing Group

example of ocular immune privilege depends on anterior-chamber-associated immune deviation, an active suppressive process mediated by antigen-presenting cells (APCs) in the spleen[3,4]. Likewise, the placenta is not impermeable to cellular traffic, and the maternal immune system is actively suppressed to prevent rejection of the fetal 'allograft'[9–14]. Moreover, liver transplants elicit surprisingly weak alloresponses and may be actively tolerogenic[15], despite the absence of any physical barriers in this setting. Therefore, immune privilege is maintained by more than physical barriers, and applies to more than the few original sites.

By analogy to classical immune privilege, we propose that acquired immune privilege manifests locally (that is, the local site is privileged, not any particular set of antigens). However, acquired immune privilege is a functional state, accessible to a range of tissues, not an intrinsic physical attribute of certain tissues. Because it is local, immune privilege is distinct from systemic tolerance (long-term antigen-specific unresponsiveness of the entire immune system), although local suppression may create systemic tolerance over time. Some specialized tissues (such as the eyes) may be constitutively privileged to protect their functions. Other tissues may change status according to circumstances. Therefore, regional lymph nodes that drain mucosal surfaces may maintain suppressive niches during homeostasis[16–18] but permit immune responses during infections. Moreover, skin infections (or immunization) usually elicit potent immune responses, but skin becomes a suppressive niche during wound healing and tumour progression[19]. Hence, acquired immune privilege is not absolute, and may be selective and exhibit specificity by mechanisms that remain to be resolved. Nevertheless, we propose that the concept of acquired, local immune privilege offers helpful insight into certain otherwise puzzling aspects of the immunology of tumours and chronic infections.

Natural immune-regulatory mechanisms. As defined in this Opinion, acquired immune privilege is a set of local mechanisms that suppress mature lymphocyte responses to antigens encountered in peripheral tissues. We do not consider mechanisms that impose self tolerance during lymphocyte development (for example, thymic selection). Mature T cells may encounter self antigens and foreign antigens from innocuous sources, or from dangerous pathogens and tumours. The immune system must allow appropriate responses (but limit their extent and duration) while preventing inappropriate immune activation. Local suppressive mechanisms are particularly relevant in tissues with large mucosal surfaces because of the constant high risk of inappropriate immune activation to foreign antigens and commensal organisms encountered, even under homeostatic conditions[20]. By contrast, tissues of the central nervous system are not routinely exposed to foreign antigens and are highly sensitive to the damaging effects of inflammation. These considerations suggest that immune suppression — similar to effector mechanisms[21] — must be tailored and responsive to local conditions.

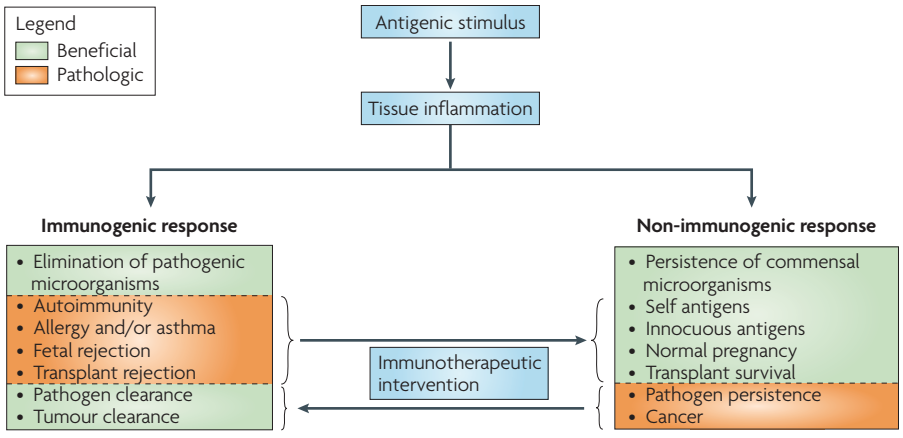

Figure 1 | **Immunogenic and non-immunogenic responses to antigenic stimuli.** Responses to tissue insults are accompanied by different types of inflammation that stimulate (immunogenic) or suppress (non-immunogenic) effective immune responses. Evolution has equipped the immune system with subtle mechanisms to discriminate between pathogenic and commensal microorganisms. These mechanisms may be beneficial or cause undesirable (pathologic) clinical syndromes if exploited by dangerous agents (cancers and pathogens), or if they become dysregulated (autoimmunity and allergic diseases). Horizontal arrows depict the goals of immunotherapeutic interventions to stimulate or suppress immunity in particular disease settings, leading to clinically desirable outcomes.

Mechanisms of acquired immune privilege

In this section we discuss potential checkpoints in the process of mounting an immune response (FIG. 2) when local immune privilege may be established and maintained by activating a range of regulatory mechanisms (TABLE 1). However, for the purpose of this discussion, we consider T-cell regulation only, focusing primarily on control mechanisms employed by regulatory dendritic cells (DCs) and forkhead box P3 (FOXP3)$^+$CD4$^+$CD25$^+$ regulatory T (T_{Reg}) cells.

Checkpoint 1: local inflammatory responses to tissue insults. Healthy tissues may act as *de facto* privileged sites because they lack pro-inflammatory or 'danger' signals[22,23]. In general, any tissue insult induces some degree of local inflammation, consisting of the influx and activation of immune cells, increased cytokine production, altered cell differentiation and metabolic stress responses, and perhaps unmasking of normally cryptic antigens. However, inflammation does not automatically promote an immune response — some forms of inflammation appear to actively suppress antigen-specific responses by the adaptive immune system.

For example, during infections, Toll-like receptor (TLR) ligands herald the presence of microorganisms. But the immune system must discriminate between pathogenic invasion and beneficial commensal microorganisms at mucosal surfaces[24] — both induce inflammation and introduce foreign antigens and TLR ligands, yet in some settings TLR ligands provoke immunosuppressive and tolerogenic responses[25,26]. This process of discrimination is not well understood, and may reflect subtle features of inflammation (for example, the type and variety of TLRs engaged), or modulation of outcomes by pathogen-specific T_{Reg} cells. From a functional standpoint, the dual ('yin–yang') nature of tissue inflammation may in part reflect a need for counter-regulation to restrain self-amplifying immune reactions. However, more fundamental processes may also be at work. Any healing wound inevitably releases self antigens and also generates inflammation. Yet a sterile healing wound, although inflamed, is nevertheless a site where tolerance to released self

© 2008 Nature Publishing Group

antigens must be maintained. Therefore, not all inflammation is immunogenic — some types may need to be suppressive.

Checkpoint 2: DC maturation and migration to local draining lymph nodes. When fully mature, DCs are uniquely specialized to present processed antigens (such as peptide–MHC complexes) to stimulate robust antigen-specific effector T-cell responses. Immature (or 'resting') tissue DCs also migrate to draining lymph nodes[27], but they exhibit weak T-cell-stimulatory functions[28], and may induce tolerance[29,30]. These attributes have classically been attributed to antigen presentation without co-stimulation ('signal 1 without signal 2'); however, as discussed by Reis e Sousa, even mature DCs with high expression of co-stimulatory molecules are sometimes suppressive and tolerogenic, implying a more active immunosuppressive role for DCs[27]. The molecular mechanisms underlying such active suppression have not been fully defined, but they include secretion of the regulatory cytokines interleukin-10 (IL-10) or transforming growth factor-β (TGFβ), expression of FAS ligand (FASL), programmed cell death 1 ligand (PDL1; also known as CD274) and PDL2, or intracellular enzymes with immunoregulatory effects, such as indoleamine 2,3-dioxygenase (IDO), arginase or inducible nitric-oxide synthase (iNOS) in certain settings[31–35].

Although DCs are present in all tissues (albeit in small numbers) they display distinctive features depending on the tissue type and their state of activation. In certain settings, small populations of specialized DCs acquire potent T-cell regulatory functions that can predominate over the stimulatory functions of all other APCs, including other DCs. For example, when suitably stimulated, some DCs in humans and mice are competent to express IDO (which catabolizes the essential amino acid tryptophan), and this endows DCs with potent T-cell regulatory functions[31]. Importantly, regulatory IDO$^+$ DCs do not sequester antigens or fail to present them. Instead, IDO activity in DCs alters the context in which antigens are presented, so that activated T cells die (by apoptosis), become anergic or differentiate into T_{Reg} cells instead of undergoing clonal expansion and differentiating into effector cells[36–39].

The underlying molecular mechanisms that modify T-cell responses to antigens are only starting to emerge. For example, amino-acid catabolism by certain APCs that express IDO or arginase can stimulate the cellular GCN2 (general control non-depressible 2)-kinase-dependent stress response in naive T cells and mature, functionally quiescent T_{Reg} cells (FIG. 3), leading to active bystander suppression[37–40]. These considerations highlight some of the complexities of DC immunobiology, especially when evaluating DC functions *in vivo*. Nevertheless, the key point is that DCs are specialized to collate local contextual information that determines how DCs present antigens to either suppress or stimulate immune responses.

Checkpoint 3: antigen presentation and T-cell activation in lymph nodes. T-cell priming occurs in tissue-draining lymph nodes and involves vanishingly small numbers of DCs, T cells and (in some settings) T_{Reg} cells. This event represents an ideal control point to maximize the impact on subsequent immune outcomes. Under homeostatic conditions, there may be an innate bias towards immune suppression in draining lymph nodes. For example, lymph nodes draining the pancreas or ovary contain T_{Reg} cells that potently suppress responses against pancreatic or ovarian antigens[16,17], and lymph nodes from mucosal surfaces may create constitutively suppressive niches[18]. However, little is known about how these lymph nodes are pre-conditioned to be suppressive.

An important factor controlling T-cell responses is the local balance of stimulatory versus suppressive APCs. Certain types of DCs, or DCs at particular differentiation states, present antigens in a manner that results in T-cell tolerance rather than immunity[41]. If the local balance of APCs favours suppression (particularly if active and dominant) then tissue antigens will not evoke an immune response — functionally, the tissue is immune privileged. One of the most potent ways in which DCs can create immunosuppression is by activating T_{Reg} cells[42,43]. Thus, DCs from tolerized allograft recipients or from tumour-bearing hosts can create potent immunosuppression by the activation of T_{Reg} cells[8,39,44]. Mice with chronic *Leishmania major* infection possess expanded T_{Reg}-cell populations in lesion-draining lymph nodes[45]. Similarly, tumour-draining lymph nodes contain increased numbers of T_{Reg} cells[46,47] and T_{Reg} cells are also crucial regulators of transplant rejection[48]. The mechanism by which certain DCs preferentially activate T_{Reg} cells is not well understood. It may reflect a preferential association between T_{Reg} cells and particular DCs, such as plasmacytoid DCs[49], or it may occur more generally when any DC presents antigen in a certain milieu (for example, in the presence of TGFβ, IL-10 or other regulatory cytokines). From the perspective of immune privilege,

Box 1 | **Selected human pathogens that may create immune privilege**

By creating immune privilege, pathogens can establish local microenvironments in which host immunity is not permitted, even if immunity to pathogenic antigens manifests systemically following natural infection or vaccine therapy. To eradicate chronic infections it might be necessary to block the local suppression that maintains immune privilege, as well as activate pathogen-specific immunity. However, interfering with mechanisms that allow a host–pathogen 'stand-off' could have undesirable effects, such as autoimmunity or excessive immunity leading to tissue pathology.

HIV-1 and hepatitis C virus

These viruses elicit robust immune responses that reduce viral loads but fail to eradicate the virus completely, even though the host remains fully immunocompetent for long periods after the initial infection. Certain types of virus-infected cells may form reservoirs that are highly refractory to natural and vaccine-induced immunity. Viral persistence causes chronic disease that is eventually lethal, destroying the immune system (HIV-1) or liver (hepatitis C virus).

Mycobacteria tuberculosis*, *Listeria monocytogenes* and *Toxoplasma gondii

These microorganisms typically infect mucosal tissues, forming granulomatous lesions with organized structures containing host cells, such as macrophages and dendritic cells. Granulomas may contain infections or protect pathogens from host immunity, or both. Disrupting granulomas to break immune privilege may re-activate dormant infections, which could make pathogens more vulnerable to immunotherapy, or allow excessive host immunity leading to tissue pathology.

Plasmodium* spp. and *Leishmania major

Some protozoan parasites of the genus *Plasmodium* can undergo a period of latency in the host's liver and can cause malaria relapse when re-activated. Immune privilege may help to protect parasites during latency, and weaken host immune responses during parasite re-activation. *L. major* propagates in highly localized skin lesions following insect (sandfly) bites, and may create local immune privilege involving host regulatory T-cell suppressor functions and interleukin-10-mediated suppression.

© 2008 Nature Publishing Group

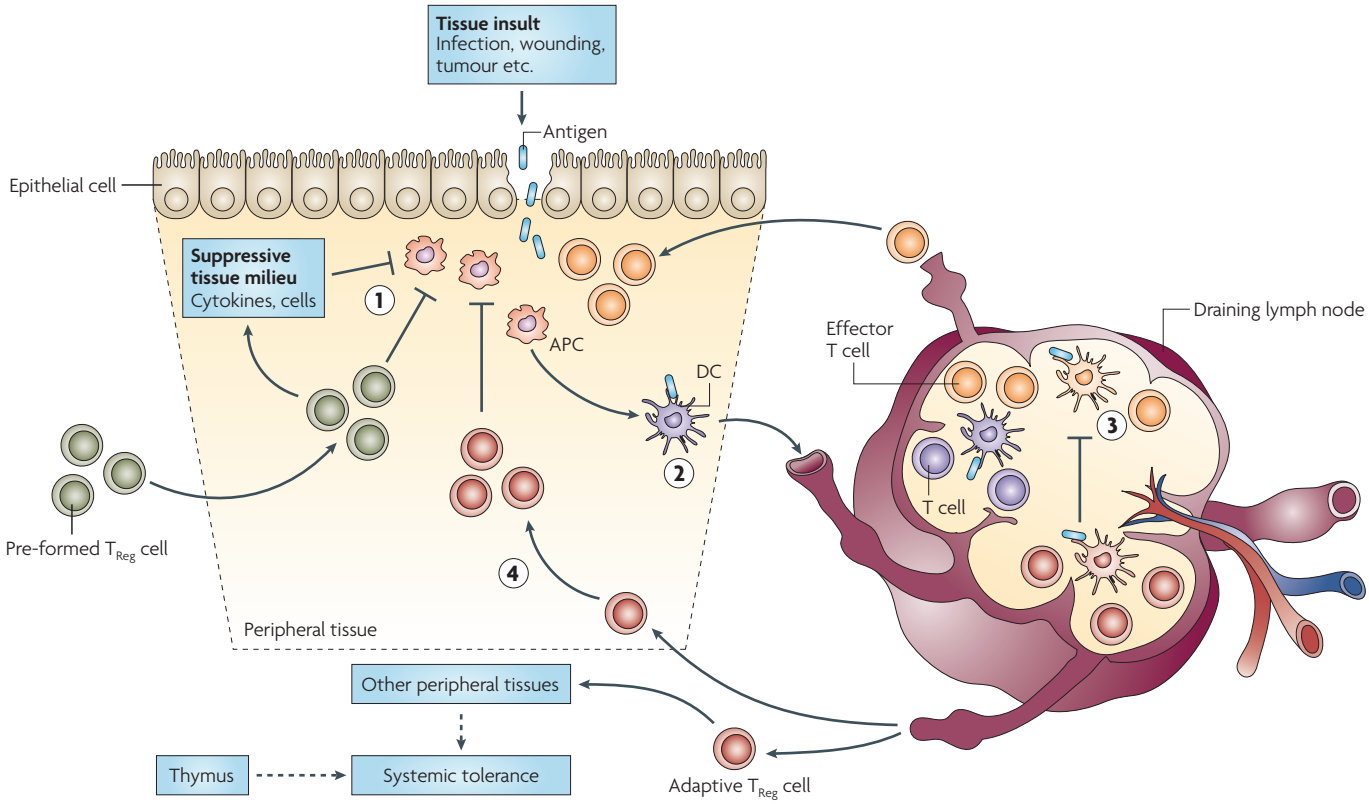

Figure 2 | **Potential regulatory checkpoints that create and maintain immune privilege in local tissue microenvironments.** Tissue insults induce the release of antigen that provokes downstream immune effector and regulatory responses. Immediate inflammatory responses may elaborate immune stimulatory and counter-regulatory mechanisms (checkpoint 1). Migratory dendritic cells (DCs) may deliver antigens to draining lymph nodes in an immune stimulatory or suppressive manner (checkpoint 2). Draining lymph nodes may be pre-conditioned to allow or suppress T-cell responses contingent on the established status of the lymph node and on inflammatory cues received from lesion sites (checkpoint 3). Once elicited, effector T cells that circulate back to tissue lesions may be prevented from functioning by trafficking barriers or physiologic blockade of T-cell effector functions by regulatory cells or suppressor factors (checkpoint 4). Systemic tolerance imposed by the thymus may contribute to local suppression via T_{Reg} cells that suppress autoimmunity or arise as a consequence of sustained local suppression. Potential checkpoints in which regulatory functions might predominate over effector functions to suppress afferent or efferent immune responses are indicated.

however, the key point is that even a small population of DCs may create potent and dominant local immunosuppression if they are able to activate T_{Reg} cells.

Checkpoint 4: regulation of effector cells at tissue sites. Even if immune effector cells are elicited and migrate to tissues, they may still succumb to dominant regulatory processes in these microenvironments. Local suppressive mechanisms may pre-exist, or may be elicited by inflammation. In the case of local suppression mediated by T_{Reg} cells, the effects may even include a degree of antigen specificity (that is, some local responses are allowed and some are suppressed), although how T_{Reg} cells achieve such discrimination is not understood[50]. Overall, the balance between regulatory and effector mechanisms may be finely tuned to local conditions. For example, at the centre of an active infection the balance may favour immunity, whereas at the margins of the infected area counter-regulation may predominate to limit collateral damage. The key point that is relevant to immune privilege is that robust systemic immunity will not be efficacious where it matters if local microenvironments exclude or inhibit effector cells.

Immune privilege in cancer and infections

In this section we apply the concept of acquired immune privilege to cancer and chronic infections. Viewing these disorders as pathologic examples of acquired immune privilege may provide new perspectives on therapeutic strategies.

Cancer. Tumours and associated parenchymal (stromal and recruited immune) cells establish robust immune privilege long before clinical manifestation, such that natural and artificial (vaccine induced) tumour-specific immunity can be completely blocked. Because immune surveillance mechanisms eliminate many developing tumours[51], those that survive to form mature tumours have evaded immune surveillance. As all solid tumours begin as small clusters of cells at one location, developing tumours do not need to create tolerance systemically — local immune privilege will suffice. Over time, local suppression may generalize, reducing systemic immunity to tumour antigens and thereby weakening immunological barriers that might otherwise protect against tumour metastasis. The key first step, however, and the hallmark of all successful tumours is local suppression of tumour-specific immune responses.

In terms of the checkpoints described above, developing tumours may provoke local inflammation, and inflammation appears to contribute to the growth of the tumour[52]. However, tumours generally do not elicit the classical 'calor (heat), rubor (redness), dolor (pain)' response — the hallmark of acute inflammation. Instead, most tumours elicit the more subtle chronic inflammation of macrophage-driven tissue

© 2008 Nature Publishing Group

remodelling and wound healing. Thus, it is possible that developing tumours may elicit similar suppressive mechanisms, and benefit from the same functional privilege, as natural tissue repair (checkpoint 1). Therefore, the role of inflammation in tumorigenesis may be complex. APCs from tumour microenvironments show constitutive defects in T-cell stimulation[53], implying that APCs are immature or are actively suppressive (checkpoints 2 and 3). Developing tumours might selectively recruit suppressive APCs or convert stimulatory APCs into suppressors. In either case, local APCs may then migrate to draining lymph nodes and present tumour antigens in a suppressive manner to T cells[54]. Known suppressor mechanisms in tumour-draining lymph nodes include IDO, PDL1 and/or PDL2 and T_{Reg} cells, although it is doubtless that other mechanisms exist. This concept may explain how developing tumours evade immune surveillance and why tumour antigens released after chemotherapy typically fail to provoke protective immunity[55]. Perhaps even more disconcertingly, once tumours have established local immune privilege, vaccination with tumour antigens may expand T_{Reg} cells that block the ability of vaccine-induced effector T cells to attack tumour cells in local microenvironments where tumours reside[56]. This has potentially important implications for designing effective tumour-vaccine strategies.

Tumours are also highly effective in establishing local immunosuppression that blocks the effector functions of tumour-infiltrating T cells (checkpoint 4). Factors from tumour cells and host stromal cells (for example, $CD11b^+$ macrophages, myeloid-derived suppressor cells and other cell types) might inhibit effector T-cell functions by modulating the cross-presentation of tumour antigens[57] and via active suppression[58,59]. Examples of mediators of active suppression include T_{Reg} cells, FASL, PDL1 and/or PDL2, IDO, arginase and immunosuppressive cytokines (TABLE 1). Functionally, these local mechanisms preserve the tumour as a privileged site, even if all preceding checkpoints are circumvented. This robust multilevel local suppression might explain why even cancer immunotherapies that succeed in inducing systemic immune responses are only rarely accompanied by significant clinical effects on tumours. Some chemotherapeutic agents may reduce T_{Reg}-cell numbers at tumour sites, and increase the immunogenicity of dying tumour cells[60], thus providing potential opportunities to induce effective anitumoral immune responses. However, T_{Reg} cells quickly reappear in tumour microenvironments following chemotherapy, and tumours appear to quickly re-establish the same locally privileged status that nurtured their original development. Hence, delivering chemotherapy in combination with therapies designed to transiently disrupt this local immune privilege may be more effective than either alone. Likewise, because host stromal cells can actively suppress immune responses while supporting tumour growth, targeting cytotoxic T lymphocytes to attack both the stroma and the tumour may also be a promising therapeutic approach[61].

Chronic infections. Chronic infections (BOX 1) present an immunological paradox: how do certain pathogenic microorganisms — sources of foreign antigens and TLR ligands that should stimulate immune responses — persist in immunocompetent individuals? Similar to tumours, we propose that certain pathogens have evolved effective strategies to co-opt natural regulatory mechanisms to create immune privilege.

Regarding inflammation (checkpoint 1), granulomatous inflammation is the hallmark of certain chronic infections. Granulomas are highly organized structures that consist of pathogens, infected cells and other host cells that can serve to physically 'wall off' infections. Granulomas do not eradicate the microorganism, and granulomatous inflammation can be intensely immunosuppressive. Indeed, classic granulomatous diseases such as tuberculosis and leprosy can result in

Table 1 | **Local regulatory mechanisms that suppress immunity and tissue inflammation**

Regulatory cell type	Potential regulatory mechanisms	Regulatory consequence	Refs
Tumour-associated macrophages, myeloid-derived suppressor cells	IDO, arginase (via GCN2), iNOS, anti-oxidants, glucocorticoids and prostaglandins	Inhibition of effector T-cell functions	61
		Induced metabolic stress responses	32
Immature DCs (alternatively activated DCs)	Poor co-stimulation (signal 1 not signal 2)	T-cell anergy and/or apoptosis	28
		Deviated T-cell responses	41
Regulatory DCs	IDO (via GCN2 or catabolites); negative co-stimulation	T-cell anergy and/or apoptosis	31
		(de novo) regulatory T-cell differentiation	44
		(pre-formed) regulatory T-cell activation	71
Effector T cells	CTLA4 (negative signals)	Down-regulation of effector functions	72
T_H cells	T_H2 cells and T_H3 cells	Differential help, cytokines (suppression of T_H1 cells)	21
$FOXP3^+$ regulatory T cells	IL-10, TGFβ, altered APC functions (decommissioning), (reverse signalling via CTLA4, GITR)	T-cell suppression, reduced T-cell–APC interactions	42
		Reduced inflammation	73
Invariant NKT-cells	IFNγ (IDO, iNOS)	Altered APC functions (decommissioning)	74
Regulatory B cells ($CD5^+$)	IL-10, TGFβ	Reduced inflammation; suppression of effector T cells	75
Stromal (parenchymal) cells (epithelial and/or endothelial cells)	FAS/FASL, IFNs and IDO	Cell death (apoptosis), cell-cycle arrest,	34
		Cell stress responses	61
	PDL1 and PDL2 expression	PD1-mediated T-cell exhaustion	35

APC, antigen-presenting cell; CTLA4, cytotoxic T-lymphocyte antigen 4; DC, dendritic cell; FASL, FAS ligand; FOXP3, forkhead box P3; GCN2, general control non-depressible 2; GITR, glucocorticoid-induced tumour-necrosis-factor-receptor-related protein; IDO, indolamine 2,3-dioxygenase; IL-10, interleukin-10; IFNs, interferons; iNOS, inducible nitric-oxide synthetase; PD1, programmed cell death 1; PDL1, programmed cell death 1 ligand; TGFβ, transforming growth factor-β; T_H, T helper.

© 2008 Nature Publishing Group

systemic anergy. Even when infections induce more 'acute' inflammatory responses, the nature of the inflammation might actually suppress a sterilizing host immune response. For example, acute *Leishmania major* infection elicits local IL-10 production[62,63], which limits collateral damage during the initial infection, but is also immunosuppressive and allows the pathogen to persist[64]. Further, it has been proposed that *L. major* actively recruits and expands T_{Reg} cells, which may be pathogen-specific and contribute to pathogen persistence[45,65,66]. This scenario is analogous to a recent report showing that tumours can also stimulate tumour-specific T_{Reg} cells[56]. Such scenarios may help to explain why it is difficult to provoke effective immunity in patients with established chronic infections using vaccines. As vaccines are designed to mimic key attributes of natural infection (particularly inflammation), it will be important to ensure that vaccines, whether prophylactic or therapeutic, do not inadvertently elicit the type of inflammation that suppresses host immunity to pathogens.

What factors might contribute to the local immunosuppression that protects pathogens from host immunity (checkpoint 4)? Granulomas have highly organized boundaries that contain many host cells, such as macrophages, DCs and T_{Reg} cells, which are potentially immunosuppressive. For example, many DCs that surround the granulomas caused by infection with *Listeria monocytogenes* express IDO, one implication being that these cells may suppress T-cell responses specific for pathogens[67], although IDO might also confer beneficial antimicrobial functions. Granulomas might benefit the host because they effectively cocoon infected areas and create a stable host–pathogen 'stand-off' that might be preferable to chronic, destructive inflammation. Nevertheless, areas within and around granulomas are functionally immune privileged, which might allow pathogens to persist.

What about chronic infections that do not create granulomas? Speculatively, some pathogens may persist by creating privileged microenvironments via physiologic mechanisms that do not require formation of granulomatous structures. In these cases, molecular and biochemical barriers may suffice to shield infected cells from immune destruction. In light of this, it is noteworthy that HIV activates the IDO mechanism in macrophages and DCs[68,69], a response that may render HIV-infected cells resistant to HIV-specific T cells. Whether regulatory APCs actually create single-cell sanctuaries *in vivo* is unknown — if verified, it suggests a new set of molecular targets for evicting pathogens that create immune privilege.

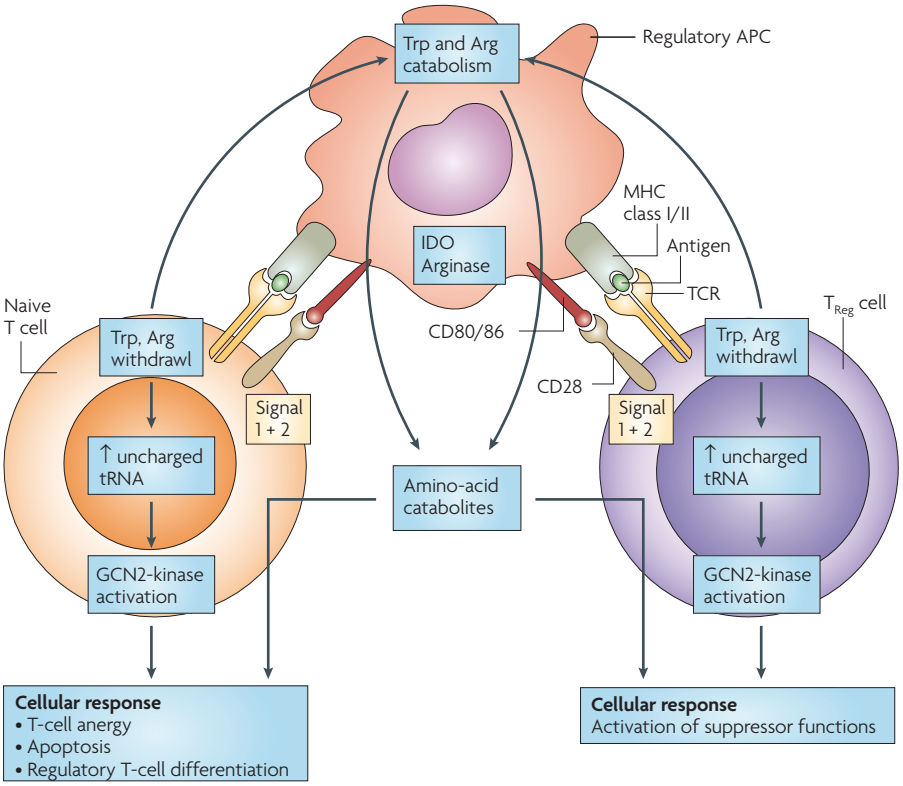

Figure 3 | **Regulatory APCs may suppress T-cell responses by inducing metabolic stress in naive and T_{Reg} cells that respond to antigen.** Antigen-presenting cells (APCs) that express indoleamine 2,3-dioxygenase (IDO) or arginase deplete tryptophan (Trp) or arginine (Arg) in T cells, increasing uncharged tRNA levels, which then activate the ribosomal stress-response kinase GCN2 (general control non-derepressible 2) in naive or forkhead box P3 (FOXP3)$^+$CD4$^+$CD25$^+$ regulatory T (T_{Reg}) cells that recognize antigen on APCs. Together with antigen-specific activation signals via the T-cell receptor (TCR) and co-stimulatory molecule CD28 (signal 1 and signal 2), induced metabolic stress responses may cause naive and T_{Reg} cells to undergo the regulatory cellular responses indicated in the text boxes. Additionally, amino-acid catabolites may alter T-cell and T_{Reg}-cell responses to antigen-specific activation[70]. APCs themselves might undergo similar stress responses, which could alter their phenotypic and functional characteristics[70].

Future prospects

Improving the success rate of immunotherapy will depend on elucidating the fundamental mechanisms by which certain sites and locations are shielded from effective immune responses. The concept of acquired immune privilege describes how local suppression that is mediated by specialized regulatory cells may have potent and dominant effects on immune functions at specific sites. This concept emphasizes the need to develop new methods to study immune responses *in situ*, in the actual tissues subjected to antigenic and inflammatory insults, rather than systemically in peripheral blood or spleen. The presence of robust local physiological barriers that suppress immune effector functions means that therapies must target mechanisms that establish and maintain local immune privilege. Obviously, global disruption of all immune privilege might lead to autoimmunity; nevertheless, it may be clinically beneficial to disrupt the pathological form of acquired local privilege that develops in cancer and certain chronic infections. Otherwise, even successful stimulation of systemic immunity against particular target antigens may not yield clinical benefits where it matters — at the privileged local sites where tumours and persistent pathogens thrive. Even worse, therapies that do not target local immune privilege may reinforce pre-existing functional suppression and tolerance making patients more, rather than less, susceptible to these chronic disease states.

Andrew L. Mellor and David H. Munn are at the Immunotherapy and Cancer Centers, Medical College of Georgia, Augusta, Georgia USA.
e-mails: amellor@mcg.edu; dmunn@mail.mcg.edu

doi: 10.1038/nri2233
Published online 7 December 2007

© 2008 Nature Publishing Group

1. Parmiani, G., De Filippo, A., Novellino, L. & Castelli, C. Unique human tumor antigens: immunobiology and use in clinical trials. *J. Immunol.* **178**, 1975–1979 (2007).
2. Simpson, E. A historical perspective on immunological privilege. *Immunol. Rev.* **213**, 12–22 (2006).
3. Caspi, R. R. Ocular autoimmunity: the price of privilege? *Immunol. Rev.* **213**, 23–35 (2006).
4. Niederkorn, J. Y. See no evil, hear no evil, do no evil: the lessons of immune privilege. *Nature Immunol.* **7**, 354–359 (2006).
5. Carson, M. J., Doose, J. M., Melchior, B., Schmid, C. D. & Ploix, C. C. CNS immune privilege: hiding in plain sight. *Immunol. Rev.* **213**, 48–65 (2006).
6. Fijak, M. & Meinhardt, A. The testis in immune privilege. *Immunol. Rev.* **213**, 66–81 (2006).
7. Medawar, P. B. Some immunological and endocrinological problems raised by evolution of viviparity in vertebrates. *Symp. Soc. Exp. Biol.* **7**, 320–328 (1953).
8. Waldmann, H. *et al.* Regulatory T cells and organ transplantation. *Semin. Immunol.* **16**, 119–126 (2004).
9. Tafuri, A., Alferink, J., Moller, P., Hammerling, G. J. & Arnold, B. T cell awareness of paternal alloantigens during pregnancy. *Science* **270**, 630–633 (1995).
10. Jiang, S. P. & Vacchio, M. S. Multiple mechanisms of peripheral T cell tolerance to the fetal "allograft". *J. Immunol.* **160**, 3086–3090 (1998).
11. Zhou, M. & Mellor, A. L. Expanded cohorts of maternal $CD8^+$ T cells specific for paternal MHC class I accumulate during pregnancy. *J. Repro. Immunol.* **40**, 47–62 (1998).
12. Munn, D. H. *et al.* Prevention of allogeneic fetal rejection by tryptophan catabolism. *Science* **281**, 1191–1193 (1998).
13. Mellor, A. L. *et al.* Prevention of T cell-driven complement activation and inflammation by tryptophan catabolism during pregnancy. *Nature Immunol.* **2**, 64–68 (2001).
14. Aluvihare, V. R., Kallikourdis, M. & Betz, A. G. Regulatory T cells mediate maternal tolerance to the fetus. *Nature Immunol.* **5**, 266–271 (2004).
15. Crispe, I. N. *et al.* Cellular and molecular mechanisms of liver tolerance. *Immunol. Rev.* **213**, 101–118 (2006).
16. Green, E. A., Choi, Y. & Flavell, R. A. Pancreatic lymph node-derived $CD4^+CD25^+$ Treg cells: highly potent regulators of diabetes that require TRANCE-RANK signals. *Immunity* **16**, 183–191 (2002).
17. Samy, E. T., Parker, L. A., Sharp, C. P. & Tung, K. S. Continuous control of autoimmune disease by antigen-dependent polyclonal $CD4^+CD25^+$ regulatory T cells in the regional lymph node. *J. Exp. Med.* **202**, 771–781 (2005).
18. Kraal, G., Samsom, J. N. & Mebius, R. E. The importance of regional lymph nodes for mucosal tolerance. *Immunol. Rev.* **213**, 119–130 (2006).
19. Loser, K. *et al.* IL-10 controls ultraviolet-induced carcinogenesis in mice. *J. Immunol.* **179**, 365–371 (2007).
20. Iweala, O. I. & Nagler, C. R. Immune privilege in the gut: the establishment and maintenance of nonresponsiveness to dietary antigens and commensal flora. *Immunol. Rev.* **213**, 82–100 (2006).
21. Matzinger, P. Friendly and dangerous signals: is the tissue in control? *Nature Immunol.* **8**, 11–3 (2007).
22. Matzinger, P. The danger model: a renewed sense of self. *Science* **296**, 301–305 (2002).
23. Medzhitov, R. & Janeway, C. A., Jr. Decoding the patterns of self and nonself by the innate immune system. *Science* **296**, 298–300 (2002).
24. Sansonetti, P. J. & Di Santo, J. P. Debugging how bacteria manipulate the immune response. *Immunity* **26**, 149–161 (2007).
25. Mellor, A. L. *et al.* Cutting edge: CpG oligonucleotides induce splenic $CD19^+$ dendritic cells to acquire potent indoleamine 2,3-dioxygenase-dependent T cell regulatory functions via IFN type 1 signaling. *J. Immunol.* **175**, 5601–5605 (2005).
26. Wingender, G. *et al.* Systemic application of CpG-rich DNA suppresses adaptive T cell immunity via induction of IDO. *Eur. J. Immunol.* **36**, 12–20 (2006).
27. Reis e Sousa, C. Dendritic cells in a mature age. *Nature Rev. Immunol.* **6**, 476–483 (2006).
28. Hackstein, H. & Thomson, A. W. Dendritic cells: emerging pharmacological targets of immunosuppressive drugs. *Nature Rev. Immunol.* **4**, 24–34 (2004).
29. Hawiger, D. *et al.* Dendritic cells induce peripheral T cell unresponsiveness under steady state conditions *in vivo*. *J. Exp. Med.* **194**, 769–779 (2001).
30. Probst, H. C., Lagnel, J., Kollias, G. & van den Broek, M. Inducible transgenic mice reveal resting dendritic cells as potent inducers of $CD8^+$ T cell tolerance. *Immunity* **18**, 713–720 (2003).
31. Mellor, A. L. & Munn, D. H. IDO expression in dendritic cells: tolerance and tryptophan catabolism. *Nature Rev. Immunol.* **4**, 762–774 (2004).
32. Bronte, V. & Zanovello, P. Regulation of immune responses by L-arginine metabolism. *Nature Rev. Immunol.* **5**, 641–654 (2005).
33. Okazaki, T. & Honjo, T. The PD-1–PD-L pathway in immunological tolerance. *Trends Immunol.* **27**, 195–201 (2006).
34. Ferguson, T. A. & Griffith, T. S. A vision of cell death: FasL and immune privilege — 10 years later. *Immunol. Rev.* **213**, 228–238 (2006).
35. Keir, M. E., Francisco, L. M. & Sharpe, A. H. PD-1 and its ligands in T-cell immunity. *Curr. Opin. Immunol.* **19**, 309–314 (2007).
36. Munn, D. H. *et al.* Expression of indoleamine 2,3-dioxygenase by plasmacytoid dendritic cells in tumor-draining lymph nodes. *J. Clin. Invest.* **114**, 280–290 (2004).
37. Munn, D. H. *et al.* GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. *Immunity* **22**, 1–10 (2005).
38. Fallarino, F. *et al.* The combined effects of tryptophan starvation and tryptophan catabolites down-regulate T cell receptor ζ-chain and induce a regulatory phenotype in naive T cells. *J. Immunol.* **176**, 6752–6761 (2006).
39. Sharma, M. D. *et al.* Plasmacytoid dendritic cells from mouse tumor-draining lymph nodes activate mature Tregs via indoleamine 2,3-dioxygenase. *J. Clin. Invest.* **117**, 1–13 (2007).
40. Rodriguez, P. C., Quiceno, D. G. & Ochoa, A. C. L-arginine availability regulates T-lymphocyte cell-cycle progression. *Blood* **109**, 1568–1573 (2007).
41. Morelli, A. E. & Thomson, A. W. Tolerogenic dendritic cells and the quest for transplant tolerance. *Nature Rev. Immunol.* **7**, 610–621 (2007).
42. Mahnke, K., Johnson, T. S., Ring, S. & Enk, A. H. Tolerogenic dendritic cells and regulatory T cells: a two-way relationship. *J. Dermatol. Sci.* **46**, 159–167 (2007).
43. Mahnke, K., Qian, Y., Knop, J. & Enk, A. H. Induction of $CD4^+$/$CD25^+$ regulatory T cells by targeting of antigens to immature dendritic cells. *Blood* **101**, 4862–4869 (2003).
44. Ochando, J. C. *et al.* Alloantigen-presenting plasmacytoid dendritic cells mediate tolerance to vascularized grafts. *Nature Immunol.* **7**, 652–662 (2006).
45. Suffia, I. J., Reckling, S. K., Piccirillo, C. A., Goldszmid, R. S. & Belkaid, Y. Infected site-restricted $Foxp3^+$ natural regulatory T cells are specific for microbial antigens. *J. Exp. Med.* **203**, 777–788 (2006).
46. Zhou, F., Rouse, B. T. & Huang, L. Induction of cytotoxic T lymphocytes *in vivo* with protein antigen entrapped in membranous vehicles. *J. Immunol.* **149**, 1599–1604 (1992).
47. Zhou, G. & Levitsky, H. I. Natural regulatory T cells and *de novo*-induced regulatory T cells contribute independently to tumor-specific tolerance. *J. Immunol.* **178**, 2155–2162 (2007).
48. Cobbold, S. P. *et al. Immune* privilege induced by regulatory T cells in transplantation tolerance. *Immunol. Rev.* **213**, 239–255 (2006).
49. Tang, Q. & Bluestone, J. A. Plasmacytoid DCs and T_{reg} cells: casual acquaintance or monogamous relationship? *Nature Immunol.* **7**, 551–553 (2006).
50. Rudensky, A. Y. & Campbell, D. J. *In vivo* sites and cellular mechanisms of T reg cell-mediated suppression. *J. Exp. Med.* **203**, 489–492 (2006).
51. Dunn, G. P., Old, L. J. & Schreiber, R. D. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity* **21**, 137–148 (2004).
52. Balkwill, F. & Mantovani, A. Inflammation and cancer: back to Virchow? *Lancet* **357**, 539–545 (2001).
53. Gabrilovich, D. Mechanisms and functional significance of tumour-induced dendritic-cell defects. *Nature Rev. Immunol.* **4**, 941–952 (2004).
54. Munn, D. H. & Mellor, A. L. Tumor draining lymph nodes as a site of tolerance induction. *Immunol. Rev.* **213**, 146–158 (2006).
55. van der Most, R. G., Currie, A., Robinson, B. W. & Lake, R. A. Cranking the immunologic engine with chemotherapy: using context to drive tumor antigen cross-presentation towards useful antitumor immunity. *Cancer Res.* **66**, 601–604 (2006).
56. Zhou, G., Drake, C. G. & Levitsky, H. I. Amplification of tumor-specific regulatory T cells following therapeutic cancer vaccines. *Blood* **107**, 628–636 (2006).
57. Nagaraj, S. *et al.* Altered recognition of antigen is a mechanism of $CD8^+$ T cell tolerance in cancer. *Nature Med.* **13**, 828–835 (2007).
58. Gajewski, T. F. *et al.* Immune resistance orchestrated by the tumor microenvironment. *Immunol. Rev.* **213**, 131–145 (2006).
59. Zou, W. Regulatory T cells, tumour immunity and immunotherapy. *Nature Rev. Immunol.* **6**, 295–307 (2006).
60. Apetoh, L. *et al.* Toll-like receptor 4-dependent contribution of the immune system to anticancer chemotherapy and radiotherapy. *Nature Med.* **13**, 1050–1059 (2007).
61. Zhang, B. *et al.* Induced sensitization of tumor stroma leads to eradication of established cancer by T cells. *J. Exp. Med.* **204**, 49–55 (2007).
62. Peters, N. & Sacks, D. Immune privilege in sites of chronic infection: *Leishmania* and regulatory T cells. *Immunol. Rev.* **213**, 159–179 (2006).
63. Trinchieri, G. Interleukin-10 production by effector T cells: Th1 cells show self control. *J. Exp. Med.* **204**, 239–243 (2007).
64. Belkaid, Y. *et al.* The role of interleukin (IL)-10 in the persistence of *Leishmania major* in the skin after healing and the therapeutic potential of anti-IL-10 receptor antibody for sterile cure. *J. Exp. Med.* **194**, 1497–1506 (2001).
65. Belkaid, Y., Piccirillo, C. A., Mendez, S., Shevach, E. M. & Sacks, D. L. $CD4^+CD25^+$ regulatory T cells control *Leishmania major* persistence and immunity. *Nature* **420**, 502–507 (2002).
66. Yurchenko, E. *et al.* CCR5-dependent homing of naturally occurring $CD4^+$ regulatory T cells to sites of *Leishmania major* infection favors pathogen persistence. *J. Exp. Med.* **203**, 2451–2460 (2006).
67. Popov, A. *et al.* Indoleamine 2,3-dioxygenase-expressing dendritic cells form suppurative granulomas following *Listeria monocytogenes* infection. *J. Clin. Invest.* **116**, 3160–3170 (2006).
68. Grant, R. S. *et al.* Induction of indoleamine 2,3-dioxygenase in primary human macrophages by human immunodeficiency virus type 1 is strain dependent. *J.Virol.* **74**, 4110–4115 (2000).
69. Boasso, A. *et al.* HIV inhibits $CD4^+$ T-cell proliferation by inducing indoleamine 2,3-dioxygenase in plasmacytoid dendritic cells. *Blood* **109**, 3351–3359 (2007).
70. Manlapat, A. M., Kahler, D. J., Chandler, P. R., Munn, D. H. & Mellor, A. L. Cell autonomous control of interferon type I expression by indoleamine 2,3-dioxygenase in regulatory $CD19^+$ dendritic cells. *Eur. J. Immunol.* **37**, 1064–1071 (2007).
71. Fallarino, F., Gizzi, S., Mosci, P., Grohmann, U. & Puccetti, P. Tryptophan catabolism in IDO^+ plasmacytoid dendritic cells. *Curr. Drug Metab.* **8**, 209–216 (2007).
72. Chambers, C. A., Kuhns, M. S., Egen, J. G. & Allison, J. P. CTLA-4-mediated inhibition in regulation of T cell responses: mechanisms and manipulation in tumor immunotherapy. *Annu. Rev. Immunol.* **19**, 565–594 (2001).
73. Miyara, M. & Sakaguchi, S. Natural regulatory T cells: mechanisms of suppression. *Trends Mol. Med.* **13**, 108–116 (2007).
74. Nowak, M. & Stein-Streilein, J. Invariant NKT cells and tolerance. *Int. Rev. Immunol.* **26**, 95–119 (2007).
75. Mizoguchi, A. & Bhan, A. K. A case for regulatory B cells. *J. Immunol.* **176**, 705–710 (2006).

DATABASES

Entrez Gene: http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=gene

FASL | IDO | IL-10 | PDL1 | PDL2 | TGFβ

FURTHER INFORMATION

Andrew Mellor's homepage: http://www.mcg.edu/itc

ALL LINKS ARE ACTIVE IN THE ONLINE PDF

© 2008 Nature Publishing Group

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.