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REVIEW

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Tolerance, suppression and the fetal allograft

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Abstract In solid organ transplantation the recipient immune system recognises foreign alloantigens expressed by the graft. This results in an immune attack of the transplanted organ leading to rejection, which can be prevented only by therapeutic immunosuppression. During pregnancy the fetus should also be rejected by the maternal immune system, since it expresses antigens derived from the father. Whilst the immune system retains the ability to respond to foreign antigen, tolerance mechanisms ensure that inappropriate responses against self-antigen are prevented. Maternal immune aggression directed against the fetus is partly inhibited by peripheral tolerance mechanisms that act locally to deplete cells capable of attacking the fetus. Other local mechanisms inhibit the pathways that cause tissue damage after immune activation. Recent studies in mice and humans indicate that the maternal immune system undergoes a more systemic change that promotes materno-fetal tolerance. Naturally occurring regulatory T cells, which are commonly associated with maintaining tolerance to self-antigens, can also suppress maternal allo-responses targeted against the fetus. We review the mechanisms that mediate materno-fetal tolerance, with particular emphasis on changes in regulatory T cell function during pregnancy and discuss their implications.

Keywords Tolerance · Suppression · Fetal allograft · Organ transplantation · Maternal immune system

Abbreviations *CTLA:* Cytotoxic T lymphocyte associated antigen · *GITR:* Glucocorticoid-induced tumour necrosis factor receptor family related · *HLA:* Human leukocyte antigen · *IDO:* Indoleamine 2,3-dioxygenase · *IL:* Interleukin · *IPEX:* Immune dysregulation, poly-endocrinopathy, enteropathy, X-chromosome linked · *NK:* Natural killer · *TGF:* Transforming growth factor

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Introduction

The immune system has evolved in order to combat the vast array of potential pathogens to which it is exposed and, in higher vertebrates, consists of an innate and an adaptive component. The innate immune system recog-

nises molecular patterns inherent in pathogenic organisms [1], as well as the cellular stress or tissue damage that results from microbial attack [2], to initiate responses. This recognition of 'danger' by the innate immune system appears to be necessary for appropriate activation of the adaptive immune system [3, 4, 5]. A fundamental aspect of the adaptive immune system is the generation of a vast array of immune receptors by a process of random gene rearrangements, with each T or B lymphocyte expressing a unique receptor [6]. This has the potential to generate a repertoire of $1–2\times10^8$ T cells in mice and 1×10^{12} T cells in humans, capable of neutralising the majority of pathogens that are encountered. Inherent to the mechanism creating diversity in the adaptive immune system is the ability to generate lymphocytes bearing receptors that recognise self-antigen [7] and tolerance mechanisms are necessary in order to prevent these cells from causing autoimmunity.

The pioneering experiments of Owen, Billingham, Brent, Medawar and Hasek established the concept of immunological tolerance [8], first described in dizygotic cattle twins and neonatal skin transplants in mice. Although tolerance is normally defined in terms of the prevention of responses against self-antigens, these early experiments actually studied tolerance induction to foreign antigen. Historically, the immunological paradox of pregnancy, whereby the maternal immune system tolerates the presence of a fetus expressing paternal antigens, has always been linked with this early work on immunological tolerance [9]. Some of the mechanisms that mediate tolerance to self-antigens also appear to contribute to the ability of the maternal immune system to tolerate the fetus and are discussed below.

This review focuses on the means of inducing immune tolerance, the emergence of T cell suppression in mediating peripheral tolerance, the mechanisms mediating materno-fetal tolerance and the role played by regulatory T cells in mouse and human pregnancy.

Central and peripheral tolerance

Breakdown in tolerance generally results from a failure of T cell regulation [10]. Autoreactivity is controlled either during T cell development in the thymus (central tolerance) or after their maturation and exit from the thymus (peripheral tolerance) [10]. Having undergone T cell receptor gene rearrangement, $CD4^+$ T lymphocytes in the thymus (thymocytes) are selected for their ability to bind self-MHC class II expressed on the surface of thymic epithelial cells (positive selection). As a consequence mature $CD4^+$ T cells are normally activated by antigen-presenting cells expressing processed antigenic peptide displayed on the same MHC class II in the periphery. $CD4^+$ T thymocytes binding with high affinity to MHC class II/auto-antigen complexes and therefore capable of causing autoimmunity, undergo apoptosis (negative selection) [10]. Therefore in order for central tolerance to be effective, the thymus must be capable of expressing tissue specific autoantigens. Autoimmune regulator, a transcription factor expressed by thymic epithelial cells, ensures the expression of these antigens and promotes negative selection of auto-reactive T cells [7, 11]. Despite these mechanisms, some autoreactive cells do emigrate from the thymus into the periphery and are readily detectable in healthy individuals.

A number of peripheral tolerance mechanisms counter the potential of these autoreactive cells to cause autoimmune disease and these generally lead to immunological ignorance, deletion or suppression [10]. Some tissues, such as the testes and the eye, promote immunological ignorance by preventing access to cells of the immune system by virtue of an anatomical barrier and thus constitute 'immune privileged' sites. Some tissues express members of the tumour necrosis factor family and cause death of cells expressing the appropriate tumour necrosis factor receptor family member [12]. For example, activated lymphocytes express the death receptor Fas (CD95) and tissues which express Fas ligand (FasL/CD95L), such as the eye and testes, promote apoptosis of these cells (deletion). Historically, the fetus has also been regarded as an immune privileged site, although the evidence discussed below argues for this concept to be re-evaluated.

More recently it has become clear that mechanisms which promote T cell suppression are central to the induction of peripheral tolerance [12]. It is now evident that in both mice and humans a significant proportion of the peripheral T lymphocyte population consists of regulatory T cells which are capable of suppressing the activation of 'effector' $CD4^+$ and $CD8^+$ lymphocytes [13]. The importance of the central and peripheral tolerance mechanisms described above is highlighted by the fact that their failure leads to severe systemic autoimmune syndromes in humans. Mutations in the autoimmune regulator (*AIRE*) gene cause autoimmune poly-endocrine syndrome type 1 [7, 11] due to a failure of negative selection and therefore central tolerance. Defective regulatory T cell function is associated with autoimmune poly-endocrine syndrome type 2 [14]. It is noteworthy that a complete lack of regulatory T cells causes the most devastating of these autoimmune syndromes. This is characterised by immune dysregulation, poly-endocrinopathy and enteropathy and is X-chromosome linked (IPEX syndrome).

History of suppressor T cells

The fall from grace of suppressor T cells, leading ultimately to the emergence of regulatory T cells, had its origins in the lack of suitable molecular markers for these cells. However, the initial observations have proved to be robust and reproducible, making it all the more remarkable that T cell suppression became a byword for failed scientific endeavour, for such an extended period.

In 1970 Gershon and colleagues [15, 16, 17] as well as other groups [18, 19] recognised a role for thymocytes in acquiring tolerance to alloantigens. The central observation was that administration of thymocytes to recipient

mice can lead to an inhibition of the mouse immune response to sheep red blood cells. These initial findings led to a series of studies of 'suppressor T cells', which were thought to regulate antibody responses to various alloantigens [20, 21, 22, 23, 24, 25, 26, 27]. Unfortunately, the anti-sera that were available permitted only relatively crude characterisation of distinct cell populations, and depletion studies using the same anti-sera were also inevitably imprecise. The results from these experiments led erroneously to the conclusion that the suppressor T cell population resided in the $Ly2^+3^+$ (CD8α and CD8β, respectively) T cell pool. However, it was not possible to distinguish these cells from $Ly2^+3^+$ cytotoxic T cells [28, 29, 30, 31, 32], and ultimately it became clear that the major role of $CD8^+$ T cells is in the cytotoxic T cell response. Other scientific cul-de-sacs emerged contemporaneously to undermine suppressor T cell biology. Numerous reports proposed that soluble 'suppressor factors', extracted from suppressor T cells, were responsible for mediating the observed immuno-regulatory effects [33, 34, 35, 36]. The factors were thought to be heterodimers of two chains, one responsible for antigen binding and one possessing MHC gene products [37]. Using anti-sera it was determined that suppressor T cells expressed a putative MHC gene termed I-J [38, 39]. However, when the region encoding the suppressor T cell genetic determinant I-J was sequenced, it was found not to contain a functional gene [40, 41, 42].

'Suppressor circuits' involving multiple levels of inducer, acceptor and effector suppressor T cells and even contra-suppressor cells [43] were invoked [44, 45, 46], although these were never satisfactorily characterised. Further, some suppressor T cell lines were shown not to possess functional T cell receptors [47, 48].

Ultimately the credibility of suppressor T cell theories suffered a terminal blow as a result of these setbacks. However, due primarily to the work of Sakaguchi and colleagues [49, 50] suppressor cells resurfaced as regulatory T cells a decade later; in 1982 they showed that neonatal thymectomy in mice causes autoimmunity, which can be rescued by adoptive transfer of $Lyt1^+$ ($CD5^+$) T cells from adult mice. Adoptive transfer of cells from mice that have undergone neonatal thymectomy to mice lacking their own T cells (*nu/nu* mice) causes similar disease, which is also rescued by cells obtained from adult mice [51]. These experiments highlight the fact that the neonatal thymus generates naturally occurring regulatory T cells, which were subsequently characterised to be $CD4^+CD25^+$ T cells [52, 53] (Fig. 1). Powrie and colleagues [54, 55, 56] demonstrated that $CD4^+CD45RB^{lo}$ cells play an important role in the prevention of autoimmunity. It has since been shown that this is due to the population of $CD4^+CD25^+$ regulatory T cells contained within. Thornton et al. [57, 58] identified the specificity requirements of the $CD4^+CD25^+$ regulatory T cells. Despite inconsistencies in the markers that were used to identify regulatory T cells, by this time there was little doubt that the thymus generates a substantial T cell population whose main function is to suppress inappropriate immune responses.

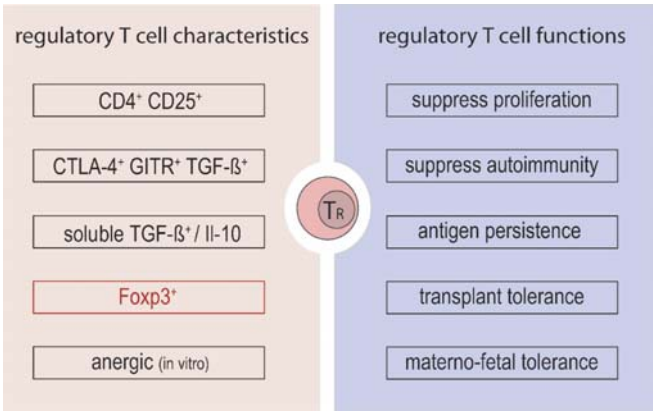

Fig. 1 Markers and functions of naturally occurring regulatory T cells. *Left* Characteristics of regulatory T cells are shown. Foxp3 (*red*) is is the only marker not shared by activated lymphocytes and other T cells capable of regulatory function. *Right* Summary of in vitro and in vivo functions attributed to regulatory T cells

Characteristics of regulatory T cells

Subsequent studies have further characterised regulatory T cells and improved our understanding of where and how they function. In addition to CD4 and CD25, naturally occurring regulatory T cells also express glucocorticoid-induced tumour necrosis factor receptor family-related (GITR) gene, cytotoxic T lymphocyte associated antigen (CTLA) 4 and transforming growth factor (TGF) β on their cell surface [13] (Fig. 1). They also produce soluble TGF-β and interleukin (IL) 10, both of which are thought to contribute to suppressor activity [13]. During normal immune responses regulatory T cell function may be suppressed by stimulation of GITR, which appears to inhibit regulatory T cell activity in vitro [59]. Furthermore, treatment with a non-depleting anti-GITR antibody in vivo leads to organ specific autoimmune disease [59]. It is important to note, however, that none of these markers are unique to regulatory T cells and are often expressed by activated effector T cells.

The important question of the antigen specificity of regulatory T cells has been studied primarily in mice expressing a T cell receptor transgene with defined antigenic specificity, as well as the cognate antigen, in the thymus. These studies indicate that naturally occurring regulatory T cells are selected in the thymus for self-antigen/MHC expressed by thymic epithelial cells [60, 61]. This occurs at affinities which would lead to deletion and therefore negative selection in non-regulatory T cells [61]. Whilst these results suggest that regulatory T cells recognise self-antigen, cross-reactivity with peptide epitopes derived from exogenous antigens remains possible.

Another characteristic, but not unique feature of regulatory T cells is that they are anergic. They do not pro-

liferate in response to T cell receptor triggering in vitro, unless additionally stimulated with IL-2 [13].

Regulatory T cell function

The suppressor activity of regulatory T cells appears to be mediated predominantly through CTLA-4, TGF-β and IL-10, either alone or in combination, depending on the experimental model used [13]. This may reflect either heterogeneity within the population of regulatory T cells or an ability of this population to differentially utilise suppressor mechanisms depending on the context.

Regulatory T cells can be activated in an antigen-specific manner but subsequently suppress responses to unrelated antigens, a phenomenon referred to as 'linked suppression' [62]. The specificity of the suppression is likely to be achieved by the temporal and spatial proximity of the various cells involved [63]. In this study regulatory T cells with the most potent capacity for preventing diabetes accumulated preferentially in the pancreatic lymph nodes and islets rather than other lymph nodes or spleen. This suggests that the regulatory T cell pool is spatially organised, with cells either being recruited to, or retained at, the site where they encounter their target self-antigen.

Regulatory T cells are capable of inhibiting the activation or function of dendritic cells, naive $CD4^+$ T cells, $CD8^+$ T cells [13] and B cells [64] in vitro (Fig. 1). Studies on regulatory T cell function in vivo have centred on CD25-antibody mediated depletion and adoptive transfer of lymphocytes into lymphopenic (*nu−/nu−* or *rag−/−*) hosts after depletion of $CD25^+$ T cells (or depletion of cells using other surrogate markers for regulatory T cells) [13, 65]. In the absence of regulatory T cells mice developed a multitude of organ specific autoimmune diseases, which could be rescued by transfer of purified regulatory T cells. However, the animal models used in these experiments resulted in some scepticism that regulatory T cells are capable of directly suppressing systemic autoimmune disease. For example, homeostatic expansion of lymphocytes occurs when small numbers of cells are transferred into lymphopenic hosts, and regulatory T cells have been shown to influence this antigen-driven process [66, 67, 68]. Under these experimental circumstances the emergence of autoimmune disease after regulatory T cell depletion could result from unchecked, auto-antigen driven expansion of effector lymphocytes. This has led some to conclude that the emergence of autoimmune disease in adoptive transfer studies is an artefact of the experimental model rather than due to the loss of function of regulatory T cells [67, 68].

The description of a unique lineage marker for regulatory T cells led to the unequivocal demonstration that these cells are necessary for the maintenance of tolerance to self-antigen. The forkhead transcription factor Foxp3 appears to be expressed exclusively by regulatory T cells and forced expression in naive $CD4^+CD25^-$ T cells confers an attenuated regulatory T cell phenotype in vitro [69, 70, 71]. The genetic proof that regulatory T cells are necessary for the maintenance of peripheral tolerance comes from a mutant mouse strain (scurfy) and a human syndrome (IPEX syndrome), both of which are caused by mutations in Foxp3. In both mice and humans the lack of Foxp3 expression leads to an absence of regulatory T cells, overwhelming autoimmunity and early fatality [69, 70, 71]. Foxp3 is thought to function by binding to DNA through a putative forkhead DNA-binding motif and repressing transcriptional activation from some promoters in T cells.

As well as suppressing autoimmune responses, other functions have been attributed to regulatory T cells. It is unclear, however, whether the cells mediating these functions are naturally occurring, $Foxp3^+$ regulatory T cells in all instances. For example, regulatory T cells have been implicated in mediating tolerance to organ transplants [62]. In addition, they can deleteriously promote chronic infections and tumour recurrence [72, 73] (Fig. 1). Interestingly, in the case of chronic infections regulatory T cells appear to inhibit pathogen clearance in murine cutaneous leishmaniasis and thereby promote better memory responses [72].

Other cells with regulatory or suppressor capability have been described including murine and human $CD4^+$ Tr1 cells, which are generated by stimulation with IL-10 and antigen [74]. In addition, under some experimental conditions, $CD8^+$ T cells, $\gamma\delta$T cells, natural killer (NK) cells [74] and B cells [75] have been shown to possess immunosuppressive capability.

The immunological paradox of pregnancy

Why the maternal immune system tolerates the presence of a fetus expressing alloantigens derived from the father has intrigued immunologists for a long time. Medawar proposed three mechanisms that may confer immune protection to the fetus [9]. It has become evident that two of these, the segregation of the fetal and maternal circulations and the immunological immaturity of fetal tissue, do not pertain during pregnancy. Fetal cells are readily detectable in maternal circulation and fetal tissue expresses MHC class I and class II and is antigenically mature [76]. Research has therefore focused on the third hypothesis, that the maternal immune system somehow ignores potentially immunogenic fetal tissue. As the fetus has historically been considered an immune privileged site, the main focus of research has been on mechanisms promoting fetal evasion that act at the materno-fetal interface.

It is also noteworthy that although Medawar hypothesised that the maternal immune system ignores the fetus, recent research indicates that the maternal immune system is not only aware of fetal alloantigens but it also responds to them [77, 78].

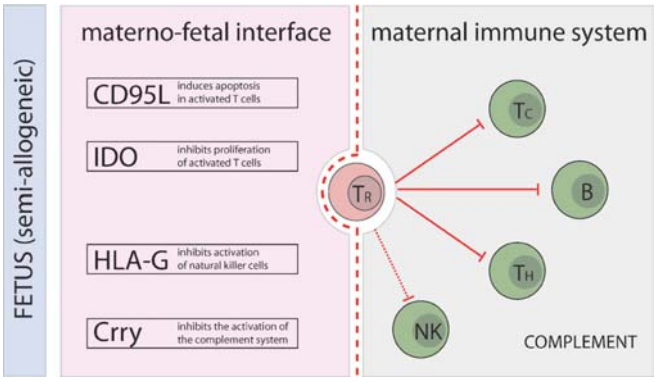

Fig. 2 Mechanisms mediating materno-fetal tolerance. *Left* Summary of locally acting mechanisms that inhibit anti-fetal immune aggression or damage pathways. *Right* Regulatory T cells (*centre*) are capable of interacting with local mechanisms (for example, the induction of IDO) as well as inhibiting allo-reactive immune cells systemically

Fetal immune evasion mechanisms

Studies on materno-fetal tolerance have highlighted fetal evasion mechanisms that can be broadly divided into those that lead to local deletion of activated maternal lymphocytes or those inhibiting effector pathways that lead to fetal tissue damage (summarised in Fig. 2). Although a number of elegant studies have demonstrated mechanisms that contribute to tolerance induction in the maternal immune system, no clear picture has emerged as to their interplay with each other.

Some tissue macrophages express the tryptophan catabolising enzyme indoleamine 2,3-dioxygenase (IDO) in response to interferon-γ [79]. This results in the rapid depletion of tryptophan and inhibition of T cell proliferation. IDO is also synthesised and secreted by the syncytiotrophoblast, the specialised fetal tissue which invades the uterus [80]. Inhibition of IDO function has been shown to lead to complement deposition at the materno-fetal interface and immunological rejection of allogeneic fetuses [80, 81]. This presumably occurs as a consequence of the survival of maternal, anti-fetal effector lymphocytes.

Activation of the complement cascade, by tissue damage or maternal lymphocytes recognising fetal alloantigen, can also be inhibited by the expression of the complement regulator protein Crry in mice. Lack of this protein leads to complement deposition at the materno-fetal interface and gestational failure in mice, which is rescued by a lack of the C3 component of complement [82]. Surprisingly, C3 appears to act both as the inducer and effector mechanism of maternal immune aggression in this model [83]. Other components of the innate immune system that are potentially capable of mediating anti-fetal immune responses are also inhibited at the materno-fetal interface. The dominant mononuclear cells infiltrating the uterus are NK cells, and these are usually inhibited by the expression of self-MHC class I on the surface of their potential target cells. Trophoblast tissue barely expresses any polymorphic human leukocyte antigens (HLA) A, B and C, making it a potential target for anti-fetal immune aggression by NK cells. This is inhibited by expression of non-polymorphic HLA, such as HLA-G, by trophoblast tissue [84]. HLA-G can bind to inhibitory receptors on NK cells to prevent killing of target cells [76].

In addition to inhibiting the proliferation of aggressive maternal lymphocytes, trophoblast tissue also appears to be able to directly kill these cells. It expresses Fas ligand (CD95L) and causes apoptosis of activated maternal lymphocytes expressing Fas (CD95) [85]. In homozygous matings of *gld* mice, a mutant strain lacking functional FasL, pregnancy is associated with extensive leukocytic infiltrates and necrosis at the decidual-placental interface leading to resorption and small litters [86].

Finally, in humans, leukaemia inhibitory factor secreted by the endometrium during implantation, appears to promote materno-fetal tolerance, since reduced levels are associated with pregnancy loss [87].

Some of these fetal evasion mechanisms are known to interact with each other. For example, the IDO-mediated inhibition of maternal lymphocytic responses against the fetus also leads to the inhibition of complement mediated inflammation at the materno-fetal interface. However, little consensus has emerged as to why a variety of mechanisms are used to ensure protection of the fetus from maternal immune aggression, and how these interact with each other. This partly reflects the fact that premature termination of pregnancy is not always the result of maternal immune aggression but can be the consequence of defective placental implantation. Some of the mechanisms described above may affect the structure and function of the placenta and the implantation site rather than maternal immune tolerance. In addition, abnormal immune responses can lead to a failure of gestation without directly affecting maternal tolerance. For example, forced immune activation by anti-CD40 antibody treatment causes pregnancy failure in mice by disrupting the pituitary-gonadal hormonal axis and reducing progesterone synthesis [88].

What has become clear is that whilst the mechanisms described above act locally to delete maternal lymphocytes capable of mediating anti-fetal immune aggression, allo-reactive cells persist throughout gestation in the maternal immune system [78]. Tafuri et al. [77] demonstrated that relatively non-immunogenic paternal tumour cells survived for the duration of pregnancy, indicating the existence of a state of specific maternal tolerance to paternal alloantigens. However, more immunogenic paternal skin grafts were rejected, suggesting that maternal cells capable of rejecting paternal alloantigens endure systemically.

Further, a variety of autoimmune diseases improve during gestation in mice and humans, with a higher risk of relapse after delivery [89, 90]. This indicates that the maternal immune system not only tolerates paternal alloantigens but also suppresses some autoimmune responses during gestation. This is not readily explained by

Table 1 The role of regulatory T cells in pregnancy. The findings relating to regulatory T cell function in mouse pregnancy are summarised on the left with a comparison of the findings relating to human pregnancy summarised on the right

Mouse	Human
1st and 2nd trimester systemic and decidual expansion of $CD4^+CD25^+$ T cells	
Increased Foxp3 expression in the uterus	
Expansion of $CD4^+CD25^+$ T cells is alloantigen independent	
$CD4^+CD25^+$ T cells suppress effector T cell allo-response in vitro	
Absence of $CD4^+CD25^+$ T cells in vivo leads to fetal rejection and failure of pregnancy	
	Reduced systemic and decidual $CD4^+CD25^+$ T cells in spontaneous abortions in vivo

locally acting mechanisms, which specifically delete maternal allo-reactive cells. These findings argue for a systemic change in the maternal immune system that induces immuno-suppression towards the fetus and promotes peripheral tolerance to auto-antigens, without leading to a generalised immuno-deficiency state.

Regulatory T cells mediate maternal tolerance to the fetus

Recent research shows that regulatory T cells are necessary for the maternal immune system to tolerate paternal alloantigens expressed by the fetus [78] (Fig. 2). In mice the proportion of $CD4^+CD25^+$ cells in the spleen, draining lymph nodes and blood increases during pregnancy, irrespective of whether the mating is between genetically identical (syngeneic) or genetically different (allogeneic) parents. This finding argues that expansion of $CD4^+CD25^+$ cells is driven by pregnancy itself, rather than exposure of the maternal immune system to paternal alloantigens.

Since a small increase in $CD4^+CD25^+$ cells can be detected as early as 2 days after successful mating, the expansion of the $CD4^+CD25^+$ cell pool appears to commence around the time of implantation. In vitro this population of cells has dominant regulatory function since maternal lymphocyte proliferation invariably increased upon depletion of $CD25^+$ cells when stimulated with syngeneic and allogeneic paternal cells.

These $CD4^+CD25^+$ T cells appear to be either preferentially recruited or locally expanded at the materno-fetal interface. A remarkably high proportion (up to 30%) of $CD4^+$ lymphocytes in the uterus of pregnant mice are $CD25^+$. This influx of regulatory T cells is reflected in a significant increase in uterine Foxp3 expression.

Crucially, absence of $CD25^+$ cells leads to a failure of gestation in allogeneically but not syngeneically mated mice. Therefore regulatory T cells are necessary for materno-fetal tolerance only when the fetus expresses paternally derived alloantigens that are distinct from maternal antigens. In the case of syngeneic pregnancy, the lack of sufficient antigenic differences between fetus and mother ensure that T cell responses are minimal and therefore regulatory T cell mediated suppression is redundant. Clearly, in out-bred mouse populations and in humans, materno-fetal antigenic differences are the norm. Whilst the failure of pregnancy often appears to occur early in gestation, immunological rejection of the fetus can be observed as late as mid-gestation. This suggests that regulatory T cells play a role in the early post-implantation phase, in addition to their function in later pregnancy. The fact that syngeneic pregnancy proceeds normally despite the absence of regulatory T cells argues that during gestation, these cells do not suppress allo-responses against minor male-type histocompatibility antigens.

In support of the findings in mice, three recent studies indicate that regulatory T cells play a similar role during human pregnancy [91, 92, 93] (Table 1). They also demonstrate an increase in systemic and decidual $CD4^+CD25^+$ T cells during the first and second trimesters. The expanded population of $CD4^+CD25^+$ T cells have all the characteristics of naturally occurring regulatory T cells. They express CTLA-4, GITR, OX40 and Foxp3, as well as suppressing the proliferation of $CD4^+$ T cells in vitro. Interestingly, one of these studies also shows that the proportion of decidual regulatory T cells is significantly lower in tissue obtained from cases of spontaneous abortion than in cases of induced abortion [91]. Although these studies do not prove that regulatory T cells mediate materno-fetal tolerance in humans, they strongly suggest that these cells play a similar role in humans to that demonstrated in mice. A comparison of the roles played by regulatory T cells in mouse and human pregnancy is summarised in Table 1. A failure of immunological tolerance has been postulated in pre-eclampsia, infertility and spontaneous abortion syndromes and the findings in mice and humans suggest that regulatory T cell function may be compromised in all of these conditions.

Despite the systemic change in the maternal immune system described above, regulatory T cells may function in the draining lymph nodes or at the materno-fetal interface, to directly inhibit allo-reactive immune responses. Furthermore, they may influence some of the local immune evasion mechanisms outlined above.

For example, regulatory T cells are capable of suppressing innate immune pathology and can inhibit natural killer cell activation in a cytokine dependent manner [94]

(Fig. 2). In addition, regulatory T cells can induce tryptophan catabolism in dendritic cells via CTLA-4 dependent and independent mechanisms, indicating that they may be capable of inducing IDO activity in the syncytiotrophoblast [95] (Fig. 2). However, mice in which the gene for IDO has been deleted have normal pregnancy outcome, suggesting that IDO independent mechanisms are sufficient to ensure materno-fetal tolerance [96].

Implications of pregnancy-induced regulatory T cell expansion

In the light of recent data, the finding of Tafuri and colleagues [77] that paternally derived tumour cells are tolerated for the duration of pregnancy may at least in part be explained by the increase in systemic regulatory T cell function. Since regulatory T cells appear to be activated by self-antigen/MHC and suppress autoimmune and semi-allogeneic responses, they would not normally suppress responses to exogenous antigens. Therefore enhanced maternal regulatory T cell function would not necessarily lead to an immuno-compromised state, as most suppressive activity would be directed towards paternal alloantigens. Given the phenomenon of linked suppression, however, it is conceivable that under some circumstances beneficial immune responses are also suppressed during pregnancy.

Increased maternal regulatory T cell function may also underlie the gestational amelioration of some autoimmune diseases, which occurs in both mice and humans. The post-partum relapse in collagen-induced arthritis (in mice), rheumatoid arthritis and multiple sclerosis (both in humans) is well described [90] and may result from return of regulatory T cell function to pre-gestational levels. The recent demonstration of reduced regulatory T cell function in patients with multiple sclerosis supports such a role for enhanced gestational regulatory T cell function [97].

It is tempting to speculate that expansion of the regulatory T cell pool during pregnancy is driven by the hormonal changes prevailing throughout gestation. In this respect, oestrogen and progesterone are known to exert a variety of influences on the immune system [90]. Determining the mechanisms that lead to enhanced regulatory T cell function during pregnancy may have implications for therapeutic intervention in organ transplantation and autoimmune diseases. In addition, it may lead to treatments for some pre-eclamptic, infertility and spontaneous abortion syndromes.

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