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The T helper type 17/regulatory T cell paradigm in pregnancy

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Summary

T helper type 17 (Th17) and regulatory T (Treg) cells are active players in the establishment of tolerance and defence. These attributes of the immune system enmesh to guarantee the right level of protection. The healthy immune system, on the one hand, recognizes and eliminates dangerous non-self pathogens and, on the other hand, protects the healthy self. However, there are circumstances where this fine balance is disrupted. In fact, in situations such as in pregnancy, the foreign fetal antigens challenge the maternal immune system and Treg cells will dominate Th17 cells to guarantee fetal survival. In other situations such as autoimmunity, where the Th17 responses are often overwhelming, the immune system shifts towards an inflammatory profile and attacks the healthy tissue from the self. Interestingly, autoimmune patients have meliorating symptoms during pregnancy. This connects with the antagonist role of Th17 and Treg cells, and their specific profiles during these two immune challenging situations. In this review, we put into perspective the Th17/Treg ratio during pregnancy and autoimmunity, as well as in pregnant women with autoimmune conditions. We further review existing systems biology approaches that study specific mechanisms of these immune cells using mathematical modelling and we point out possible future directions of investigation. Understanding what maintains or disrupts the balance between these two opponent yet reciprocal cells in healthy physiological settings, sheds light into the development of innovative pharmacological approaches to fight pregnancy loss and autoimmunity.

Keywords: autoimmunity; defence; mathematical modelling; pregnancy; systems biology; T helper type 17/regulatory T cell ratio; tolerance.

Introduction

T helper 17 (Th17) and regulatory T (Treg) cells are part of the complex machinery that constitutes the immune system. The healthy immune system not only recognizes and fights infection but also regulates undesired immune responses against tissue self antigens or harmless non-self organisms. This requires a fine balance established within the network of molecules and cells that provide an immune response. However, there are circumstances that require a 're-tuning' of this balance. In fact, in situations such as pregnancy, the immune system faces a dilemma: it has to protect the mother against infection and, at the same time, to accept the semi-allogeneic fetus.[1] This embodies active regulation of inflammatory immune processes occurring during pregnancy to guarantee specific tolerance towards the foreign fetal antigens. The referred regulation process includes a network of various immune cell populations and molecules that are responsible for the immune balance in pregnancy (reviewed in ref. 2). As an example, Th17 and Treg cells form complex and dynamic networks to maintain homeostasis. These cells

Abbreviations: CNS, conserved non-coding sequence; DC, dendritic cell; FOXP3, forkhead box protein 3; IL, interleukin; MS, multiple sclerosis; PE, pre-eclampsia; PlGF, placental growth factor; PTB, preterm birth; pTreg cells, peripheral regulatory T cells; RA, rheumatoid arthritis; RPL, recurrent pregnancy loss; sFlt-1, soluble fms-like tyrosine kinase receptor-1; SLE, systemic lupus erythematodes; TGF-β, transforming growth factor-β; Th17 cells, T helper 17 cells; Treg cells, regulatory T cells; URPL, unexpected recurrent pregnancy loss

interact with many other types of cells to orchestrate the desired immune response. In this review, we focus on the interactions between Th17 and Treg cells in two specific situations, namely pregnancy and autoimmunity.

Origin and characteristics of Th17 and Treg cells

T cells are lymphocytes that mature in the thymus[3] and have specific receptors, namely the T-cell receptors.[4] These cells are part of the adaptive immune response.[5] In particular, Th cells, also known as $CD4^+$ T cells, are activated by antigen-presenting cells and proceed to clonal expansion and cytokine secretion.[6] The cytokine profile secreted at this stage will determine the cell differentiation into any of the several subsets of Th cells and so define the type of immune response.[7] These subsets include (but not only) the Th1, Th2, Treg and Th17 cells,[8,9] as illustrated in Fig. 1.

Regulatory T cells are classified as $CD4^+$ T cells expressing the transcription factor Forkhead box protein 3 (FOXP3)[10] and generate in the thymus (referred as tTreg cells) and in the periphery (referred as pTreg cells).[11] These immune cells express specific anti-inflammatory cytokines such as interleukin-10 (IL-10) and transforming growth factor-β (TGF-β), which dampen an excessive effector immune response.[12] This effector response arises from the fight against bacterial and pathogenic infections, which is partly mediated by Th17 cells (reviewed in ref. 13). Th17 cells are also a lineage of $CD4^+$ T cells and are characterized by expressing the transcription factor retinoic acid receptor-related orphan receptors and the cytokine IL-17,[14] among others. However, Th17 and Treg cells present a certain level of plasticity, meaning that distinct milieus account for distinct cell fate.[15] In particular, the Th17 cells have different fates in different inflammatory frameworks[16,17] and, interestingly, Th17 cells that present plasticity towards Th1 have higher survival rate and less senescence than Th1 cells.[18] Moreover, under some circumstances, Treg cells are able to transdifferentiate into Th17 cells[19] and vice versa.[20] Notwithstanding, diminishing the Treg and/or augmenting the Th17 dynamic profiles in humans can: (i) antecede gestational problems, such as preterm birth (PTB),[21] pre-eclampsia (PE)[22] or recurrent pregnancy loss (RPL)[23] and (ii) ensue the onset of autoimmune diseases, such as multiple sclerosis (MS)[24] and rheumatoid arthritis (RA).[25]

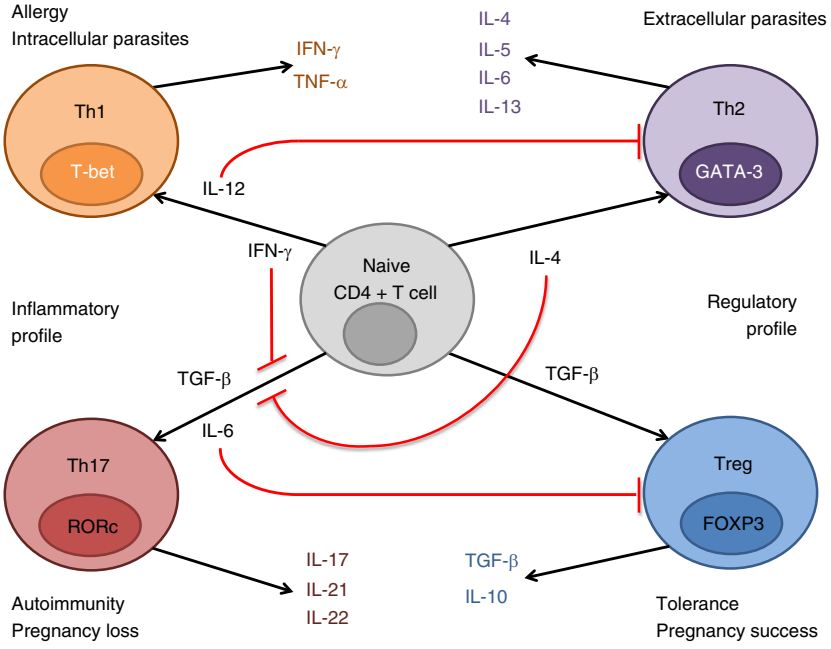

Figure 1. Illustrative scheme of naive T cell differentiation into T helper type 1 (Th1), Th2, Th17 or regulatory T (Treg) cells, depending on the cytokine profile. Interleukin-12 (IL-12) and interferon-γ (IFN-γ) stimulated naive T cells differentiate to Th1 cells. These cells express IFN-γ and tumour necrosis factor-α (TNF-α), and are responsible for intracellular parasite clearance and allergy conditions. IL-4 stimulated naive T cells induce a Th2 response. Th2 cells express IL-4, IL-5, IL-6 and IL-13, and are responsible for clearance of extracellular parasites. Transforming growth factor-β (TGF-β) stimulated naive T cells induce a Treg response. Treg cells express TGF-β and IL-10 and are responsible for tolerance and pregnancy success. These three cell types express one cytokine responsible for its induction, in a positive feedback mechanism. TGF-β and IL-6 stimulated naive T cells induce a Th17 response. Th17 cells express IL-17, IL-21 and IL-22 and are responsible for autoimmunity and pregnancy loss. Th17 cells do not present a positive feedback mechanism, but IFN-γ or IL-4 can inhibit the differentiation from naive T cells to Th17. Moreover, IL-6 and IL-12 inhibit Treg and Th2 cells, respectively.

Role of Th17/Treg balance in pregnancy

At the onset of pregnancy, the semen also modulates the maternal immune response to promote a fetus-friendly environment, so contributing to a healthy gestation.[26,27] This immune-modulatory stimulus will signal to the maternal immune response,[28] activating a network of cells [human and murine macrophages and dendritic cells (DCs), as well as murine granulocytes,[29] $CD4^+$ $CD25^+$ Treg cells,[30] human lymphocytes[31] and $FOXP3^-$ Treg cells[32]] and molecules (human TGF-β_1 and IL-10,[32] IL-8 and IL-2 receptor,[33] among others) that will dampen the inflammatory immune response of the mother and allow the growth and development of the semi-allogeneic fetus.[32] However, this immune tolerance towards the fetus must not compromise the capacity to fight infections and diseases. This tightly regulated mechanism between tolerance and defence encompasses specific kinetic profiles for Treg cells present at the feto–maternal interface.[34] These profiles will determine the pregnancy fate. Specifically, the fine balance between Treg and Th17 cells mediates maternal tolerance to the fetus.[35,36] In fact, in humans, specific Treg subsets such as $CD4^+$ $CD25^{bright}$ and $CD4^+$ $CD25^+$ Treg cells increase in the first trimester of pregnancy.[37,38] This last Treg subset peaks in the second trimester and decreases until reaching a low level, measured post-partum.[38] In the last stage of pregnancy, fetal Treg cells decrease to allow labour initiation.[39] Controversially, other Treg subtypes, such as $CD4^{dim}$ $CD25^{high}$ $Foxp3^+$ Treg cells have been reported in humans to start decreasing already in the second trimester.[40] In addition, only sustained and not transient $Foxp3^+$ Treg cell expression allows the efficient suppression of the maternal effector immune response towards the fetus.[41] Later in pregnancy, the hormonal and cytokine setting at the feto–maternal interface is thought to recruit the immune cells necessary to establish a favourable environment for the human[42,43] and murine[44] pregnancy to proceed. Specifically, murine DCs have the ability to signal not only the production of Treg cells but also of IL-17-producing cells, effectively protecting against specific invading pathogens and, meanwhile, allowing a successful pregnancy.[45] However, this shift in the immune response during pregnancy has a systemic impact. In fact, the human microbiota communities might oscillate when there is a change in the immune response, such as in the case of pregnancy.[46]

In evolutionary terms, mammals have developed mechanisms of maternal tolerance towards the fetus. To shed light on this phenomenon, Samstein and colleagues studied specific evolutionary traits involved in pTreg cell differentiation during pregnancy.[11] This study hypothesizes that a conserved non-coding sequence (CNS1), enhancer of pTreg but not essential for thymus Treg cell generation, plays an important role in feto–maternal tolerance. The authors showed, in a murine model, that pTreg cells recognize paternal antigens and suppress a maternal effector T-cell response. CNS1-deficient mice are unable to induce pTreg cells, therefore maternal effector T cells can enter the placenta, so inducing spontaneous abortions. Interestingly, and according to the same study, CNS1 is present in the genome of specific placental mammals, but not in specific non-placental mammals or non-mammals. Hence, the authors suggest that CNS1 is an essential factor for pTreg expression in placental mammals.

Next, we review the role of the tandem Th17/Treg in specific pregnancy complications, namely PTB, PE and (unexpected) RPL.

Preterm birth

Preterm birth is defined as birth before 37 weeks of gestation[47] and is a global problem that, in 2010, affected 11·1% of all live births.[48] It ensues short- and long-term complications; it is a risk factor in > 50% of neonatal deaths[48] and is reported to be responsible for 35% of effective neonatal death.[49] Long-term complications such as metabolic bone disease of prematurity[50] or respiratory complications[51] are associated with PTB.

At the cellular level, Treg cells are involved in murine fetal acceptance[28,52] and Koucky *et al.*[21] report that, in humans, low levels of circulating Treg cells, together with short cervical length, correlate with PTB. Moreover, IL-6 is elevated in such situations, in humans and mice.[53] This suggests that the Th17/Treg balance differs between term and PTB. Accepted strategies to diminish the risk of PTB, encompass the vaginal administration of the hormone progesterone.[54] Interestingly, Areia *et al.*[55] show that in healthy pregnant women, Treg cells express the receptor for progesterone, the membrane progesterone receptor α, suggesting that the protective effect of progesterone on PTB situations might act by activating Treg cell proliferation.

Pre-eclampsia

Pre-eclampsia is a hypertensive disorder that manifests during pregnancy. It affects 2–8% of all pregnancies[56] and is involved in 40% of births before the 35th week.[57] PE manifests during the second half of pregnancy, through high blood pressure and high proteinuria levels;[58] however, an impaired trophoblast invasion during the early stage of pregnancy has been proposed to cause PE.[57] As a consequence, the blood supply to the fetus diminishes.[59] To increase PE diagnosis accuracy, Maynard *et al.*[60] proposed that excessive placental soluble fms-like tyrosine kinase receptor-1 (sFlt-1) and placental growth factor (PlGF) correlate with PE condition. Stepan *et al.*[61] suggested an algorithm to test if a woman is prone to PE based on measured sFlt-1/PlGF ratios. Women with an abnormal sFlt-1/PlGF ratio can have an increased risk of

PE. Interestingly, the inflammatory immune response observed in PE patients is, in fact, an exacerbation of the normal inflammatory response preceding birth. Indeed, several studies suggest that the immune system plays an important role at the onset of PE. Vargas-Rojas *et al.* tested the T-cell composition in umbilical cord blood from healthy and pre-eclamptic pregnant women. The authors observed a shift towards inflammation in the Th1/Th2 and Th17/Treg balances, where the Th1 and Th17 populations remained constant, but the Th2 and Treg populations decreased.[22] In contrast, other authors point out that maternal cytotoxic T lymphocytes increase in patients with PE.[62,63] Perez-Sepulveda *et al.* suggest that, in PE patients, immature DCs undergo maturation and initiate a pro-inflammatory response, whereas in a normal pregnancy, DC maturation is blocked, so rendering an immune response dominated by Treg and Th2 cells.[57] Besides T cells, decidual natural killer cells play a critical role in the pathogenesis of PE. This unique immune cell population contributes to the remodelling of the spiral arteries and a failure in this process was associated with PE development. Hiby *et al.*[59] found that the interaction between maternal killer immunoglobulin receptors expressed by natural killer cells and MHC molecules expressed on trophoblasts determines placental development. The same research group revealed that specific combinations of HLA-C and activating killer immunoglobulin receptors not only increase the risk for PE but also augment the risk for other pregnancy complications.[64] In addition, reduced numbers of $CD56^{++}$ $CD16^{-}$ non-activated natural killer cells and diminished Treg cell frequencies were detected in the cord blood of babies from women with PE, underlining the importance of both immune cell populations for successful pregnancy outcome.[65]

In short, women with PE have normal levels of Th17 populations, but decreased levels of Treg populations so altering the Th17/Treg ratio.

(Unexplained) recurrent pregnancy loss

Recurrent pregnancy loss is defined as the loss of three or more consecutive pregnancies before the 20th week of pregnancy.[66] RPL affects couples in 1%,[67] 60% of which remain to be explained.[68] Uterus anatomic abnormalities, parental chromosomal incompatibility or poor blood supply can associate with an elevated rate of miscarriage. However, there are situations of RPL where no epidemiological or pathological diagnosis associates with miscarriage.[69] These are referred to as unexplained RPL (URPL). Some authors suggest that the condition of URPL can be due to maternal immune rejection of the fetus.[70] In fact, URPL incidence increases when Th17 populations increase and Treg populations decrease,[23] which suggests overwhelming pro-inflammatory responses towards the fetus. Moreover, elevated presence of IL-6 correlates with higher abortion levels in humans and mice.[71]

Other authors tested if ovarian ageing increases the rate of URPL, but the results indicate that the former does not affect the levels of the latter.[72]

In conclusion, the Th17/Treg ratio during a healthy pregnancy shifts in favour of the Treg cells. However, in specific pregnancy disorders (PTB: decrease of Treg levels; PE: increase of Th17 levels; URPL: increase of Th17 levels and a decrease of Treg levels), the balance between the Th17/Treg is disturbed and inflammatory immune responses are insufficiently regulated.

Role of Th17/Treg balance in autoimmune disorders

When mechanisms underlying tolerance induction fail, autoreactive immune cells survive, are activated and attack self tissue structures. These undesired immune responses can be directed towards specific organs or multiple organ systems and will result in a phenomenon called autoimmunity. Autoimmune disorders are often characterized by Th1 or Th2 dominance. However, other Th subsets like Th17 and Treg cells were suggested to be critically involved in disease severity and progression. More precisely, the ratio between Th17 and Treg cells seems to be fundamental for disease outcome. Here we will discuss the participation of both, Th17 and Treg cells, in some of the most common autoimmune diseases with a specific focus on their balance.

Systemic lupus erythematodes

Systemic lupus erythematodes (SLE) is a severe chronic autoimmune disorder affecting multiple organ systems. The disease is characterized by elevated levels of autoantibodies, an activation of complement factors and abnormal Th responses. Reportedly, patients with SLE suffer from a dysregulated balance of Th1 and Th2 responses and there is accumulating evidence that an altered Th17/Treg ratio contributes to disease activity and its progression. It has been shown that patients with SLE have significantly diminished Treg levels[73,74] and an impaired Treg cell suppressive activity,[74,75] when compared with healthy controls. This leads to stronger T effector cell responses defined by increased proliferation rates and elevated cytokine levels[74] as well as to augmented autoantibody levels,[76] all processes resulting in an increase of disease severity. The potential of Treg cells to positively influence disease activity was confirmed in a study by Scalapino *et al.* The authors showed that adoptive transfer of *in vitro* expanded Treg cells ameliorated disease progression in a murine lupus-prone model.[77] Along with a reduced number of Treg cells, elevated Th17 levels have

been reported in the same patient pool. Thereby augmented Th17 numbers positively correlated with disease activity.[78–84] Underlying the significance of an imbalance in the ratio between both Th subsets, Ma *et al.*[85] observed that Th17 or Treg cells alone were not correlated to SLE development; however, their ratio was significantly altered in SLE patients and this strongly correlated with disease severity. Hence, it can be assumed that, in this specific situation, the diminution in the Treg pool - accompanied by an increase in the number of Th17 cells - follows Treg cell differentiation into Th17 cells.

Rheumatoid arthritis

Rheumatoid arthritis is a chronic autoimmune disorder affecting the synovial joints of the body. It was identified as a disease with a Th1-dominant profile; however, disease pathology seems additionally to be influenced by an altered Th17/Treg balance. Patients suffering from RA display increased Th17 and reduced Treg levels.[25,86] Moreover, they produce more pro-inflammatory cytokines that are involved in the differentiation and maintenance of pathogenic Th17 cells.[87] Komatsu *et al.*[19] observed that under arthritic conditions Treg cells lose their Foxp3 expression and undergo transdifferentiation into Th17 cells; a mechanism that seems to be IL-6 dependent. Pathogenic Th17 cells then accumulate in inflamed joints and contribute to the progression of the disease.[19] Interestingly, treatment strategies tested in rodent models resulting in a shift of the Th17/Treg ratio in favour of immune suppression improved disease activity in the joints.[88–90] In addition to the significant influence of surrounding cytokines on Treg to Th17 cell differentiation, DCs may impact Th17/Treg cell ratio. It has been proposed that monocyte-derived DCs from patients with RA produce high levels of IL-6 and IL-23, so favouring Th17 cell generation. Furthermore, the same DCs had an impaired ability to induce Treg cells.[91] Molecules implicated in Th17/Treg plasticity in RA may belong to the signal transducer and activator of transcription pathway, as suggested by different studies.[92,93] In contrast to most studies, Ju *et al.* found no alterations in Th17 and Treg levels when compared with healthy controls.[92] For that reason, more research is needed to finally confirm a significant contribution of Th17 cells for disease aggravation and of Treg cells for disease amelioration.

Multiple sclerosis

Multiple sclerosis is an inflammatory, demyelinating disease of the central nervous system. The disorder was reported to be associated with a reduced number and functionality of Treg cells,[94] although studies differ in their findings regarding various Treg subsets. For instance, Fletcher *et al.*[24] showed that patients with MS revealed a normal frequency of the $CD4^+$ $CD25^+$ $CD127^{low}$ $Foxp3^+$ Treg subset, but had a deficit in the relative frequency and the suppressive function of the $CD4^+$ $CD25^+$ $CD127^{low}$ $Foxp3^+$ $CD39^+$ Treg subset. The impaired ability of Treg cells obtained from patients with MS in suppressing T effector cells seems to be associated with an enhanced IL-6 receptor expression, as well as IL-6 production.[95] Moreover, Th17 cell populations are augmented in MS[96] and they express higher basal levels of activation markers and other markers involved in cell adhesion to the endothelium.[97] Nyirenda *et al.*[98] suggested that infections leading to an activation of the TLR2 on the surface of Treg cells may promote a shift into a more Th17-like phenotype. Interestingly, the Th17/Treg balance fluctuates during disease and is responsible for disease activity and progression.[99] Although relapses are associated with increased Th17 numbers, elevated levels of Treg cells can be observed during the remitting phases. Thereby, fluctuations in the numbers of both Th populations seem to be influenced by microRNA clusters,[100,101] suggesting miRNAs as targets for MS treatment. Additionally, vitamin A supplementation was proposed to up-regulate Treg markers and may therefore be suitable to reduce disease activity in patients with MS.[102] Other therapeutic interventions shown to reduce IL-17 and IL-23 levels,[103] decrease peripheral and central Th17 responses and enhance Treg frequency and IL-10 production[104] are promising in MS therapy.

In conclusion, autoimmune disorders are often characterized by a disturbed Th17/Treg balance that results in increased levels of pathogenic Th17 cells associated with reduced Treg numbers and activity. Hence, therapies altering the Th17/Treg ratio in favour of the Treg cells may have a great benefit for the patients. Figure 2 qualitatively illustrates how the Th17/Treg ratio can differ

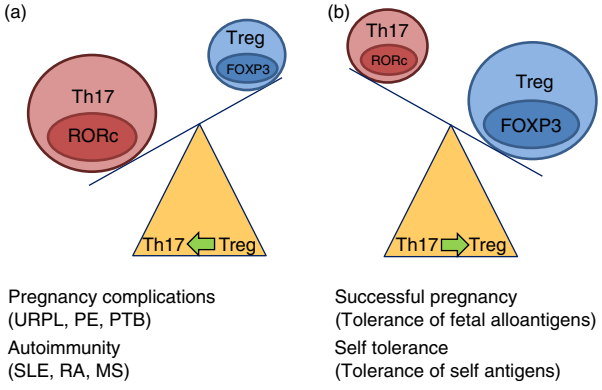

Figure 2. Illustrative description of the T helper type 17 (Th17)/regulatory T (Treg) balance in (a) pregnancy complications and autoimmunity and (b) a healthy pregnancy and self tolerance. Abbreviations: MS, multiple sclerosis, PE, pre-eclampsia, PTB, preterm birth; RA, rheumatoid arthritis; SLE, systemic lupus erythemsatosus; URPL, unexpected recurrent pregnancy loss.

between a healthy pregnancy or self tolerance situations and conditions of autoimmunity and pregnancy complications.

Influence of Th17 and Treg cells on autoimmune disease activity during pregnancy

Many women suffering from autoimmune diseases experience alterations in their disease activity when they become pregnant. In addition, autoreactive immune responses may interfere with fetal well-being in pregnant autoimmune patients. Strong hormonal and immunological changes take place during pregnancy. Autoimmune diseases dominated by inflammatory immune responses such as RA and MS reportedly improve during late pregnancy. As discussed above, patients with MS or RA suffer from a disturbed Th17/Treg ratio with increased Th17 levels and diminished Treg cell numbers, which have been implicated in disease activity and progression. Normal pregnancy is characterized by an increased Treg/Th17 ratio and this may positively influence disease outcome. Indeed, two studies suggested an association between the number of Treg cells and an improvement of RA disease activity in pregnancy.[105,106] Another study investigated fluctuations of Th17 and Treg cells in patients with MS during pregnancy. Based on their results the authors concluded that disease amelioration in patients with MS during their third trimester could not be related to a decrease in the number of circulating Th17 cells or to an increase in Treg cell levels.[107] In contrast, Sánchez-Ramón *et al.*[108] proposed an association between pregnancy-induced Treg cell expansion and MS amelioration. However, Treg cells from pregnant women with MS seem to have an impaired suppressive capacity when compared with Treg cells from healthy pregnant women.[94] Hence, although there is accumulating evidence of a disturbed Th17/Treg balance in RA and MS, it remains to be clarified whether pregnancy-induced changes in the Th17/Treg ratio may be responsible for disease amelioration.

Systems biology approaches to understand the Th17/Treg balance

Systems biology is a scientific approach to tackle medical questions using mathematical modelling.

Mathematical models have been successfully used to answer a broad spectrum of medical questions. In the specific field of immunology, the pair Th17/Treg has been modelled by Hong *et al.*,[109] by combining different experimental published observations in a mathematical model that shows how polarized signals can control the different T-cell phenotypes.

Busse *et al.*[110] studied the spatiotemporal dynamics of IL-2 using mathematical modelling and experiments to show that this cytokine switches between two functions, working as a digital toggle switch in T-cell proliferation and as an analogue amplifier for the IL-2 uptake capacity of Treg cells.

Naldi *et al.*[111] proposed a logical model of the regulatory network and signalling pathways involved in Th cell differentiation, which paves the way to explore novel *in silico* approaches to a better understanding of Th cell differentiation. Other authors also investigated the differentiation of Th cells by analysing the dynamic properties of the molecular network controlling the differentiation of Th cells to Th1, Th2, Th17 or Treg cells.[112]

However, to the best of our knowledge, mathematical modelling has not yet been applied to understand the Th17/Treg balance in pregnancy and in autoimmunity. This sophisticated immune process can be antagonistic, and a deeper understanding of the mechanisms leading to the polarization to Treg or Th17 will pave the way to new biopharmaceutical approaches that fight disorders of the immune system leading to pregnancy loss or autoimmunity.[113]

The investigation of the dynamic profiles of the Th17/Treg ratio in a natural, physiological condition such as pregnancy can help our understanding of how to recover homeostasis in the setting of autoimmune diseases.

It is therefore paramount to understand how the immune balance is established and what disrupts it, using an innovative methodology that combines mathematical modelling with experimental data.

Discussion

Pregnancy and autoimmunity are challenging situations for the immune system. Treg and Th17 cells play a dominant role in both, although with opposing profiles. In fact, Treg activation ensures pregnancy success and lower Treg numbers are associated with higher risk of pregnancy loss. In parallel, Th17 cells are important players in the development and progression of autoimmune diseases such as collagen-induced arthritis and its antagonist partner, Treg cells, dampen the strength of this inflammatory response and hence diminish the symptoms of autoimmunity.[114]

Strikingly, the immune cellular phenotype that regulates inflammation during pregnancy, also hinders the development of autoimmunity, such as RA or MS.[115]

The role of Treg cells in pregnancy has been extensively studied[34,44,116,117] and reviewed.[28,118,119] Treg numbers increase during pregnancy and decrease in the case of spontaneous abortion.[37,120] In fact, abrogation of the protective effect of Treg cells culminates in pregnancy loss in a gestational murine model.[121] Moreover, higher levels of inflammatory markers, such as IL-6 or TGF-β, have been measured in many women suffering from PTB[115] and higher levels of Th17 cells have been measured in women with RPL compared with normal

pregnancy situations.[23] Complementing this, the symptoms of autoimmune diseases such as MS and RA diminish during a normal pregnancy, which is explained by the immune regulatory mechanisms that dampen an overwhelming inflammatory immune response against the semi-allogeneic fetus. It is therefore fundamental to understand the regulatory mechanisms ensuing during pregnancy, and this will pave the way to develop new medical and pharmaceutical strategies to fight autoimmune diseases.

Within this review, we put into perspective the role of Th17/Treg balance in pregnancy and autoimmunity. We further review this paradigm in autoimmunity during pregnancy and we inspect the literature that includes mathematical modelling approaches to understanding specific aspects of the Th17 and/or Treg cell profiles.

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Disclosures

The authors declare that there are no conflicts of interest.

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