Immunomodulation by the Female Sex Hormones

F.M. Menzies[§,1] and F.L. Henriquez[*,2]

[1]*Strathclyde Institute of Pharmacy and Biomedical Sciences, University of Strathclyde, 27 Taylor Street, Glasgow G4 0NR, UK*

[2]*School of Science and Engineering, University of the West of Scotland, Paisley PA1 2BE, UK*

Abstract: Pregnancy is a highly regulated process, requiring strict control of the immune system in order to prevent rejection of the semiallogenic foetus. One aspect of pregnancy immunology that has been of great interest is the influence of female sex and pregnancy associated hormones, such as progesterone and oestrogen, on cells of the immune system.

This review evaluates studies investigating the ability of these hormones to modulate the function of cells of both the innate and adaptive arms of the immune system and mechanisms by which immunity to infection can be altered due to increased levels of progesterone and oestrogen. Finally, the influence of pregnancy on the most common autoimmune diseases, on toxoplasmosis and on malaria is reviewed.

1. INTRODUCTION

Pregnancy is a complex process in which cells and molecules of the maternal immune system interact in such a way as to prevent the rejection of the semiallogenic foetus. Development and modulation of pregnancy is controlled by the presence and levels of various sex and pregnancy associated hormones, such as oestrogens and progesterones. In addition, the cytokine environment is important for a successful pregnancy, with studies showing a Th1 environment to be associated with abortion and a Th2 environment allowing the successful continuation of pregnancy [1].

The elevated levels of oestrogen and progesterone observed during pregnancy possess a number of modulatory functions on cells of the immune system, including macrophages, natural killer (NK) cells, dendritic cells (DCs), T cells and B cells. The endometrium is one of the most important organs during pregnancy [2] and presents an immunologically competent environment, with 30% of cells being of the immune system [3]. Within the uterus of non-pregnant women, NK cells, macrophages, T cells and B cells are abundant [2-4] and inhibit the implantation and the development of the embryo. However, during pregnancy, the activity of these cells against the foetus is specifically suppressed by oestrogen and progesterone, allowing successful embryo implantation [5-9].

*Address correspondence to this author at the School of Engineering and Science, University of the West of Scotland , 1 High Street , Paisley , PA1 2BE , Scotland, UK; Tel: 0044 141 848 3119 ;
E-mail: fiona.henriquez@uws.ac.uk

[§]Current Address: Department of Reproductive and Maternal Medicine, Faculty of Medicine, University of Glasgow, Glasgow Royal Infirmary, 10 Alexandra Parade, Glasgow G31 2ER, UK

2. EFFECT OF SEX HORMONES ON IMMUNE CELL FUNCTION

2.1. Innate Immunity

Macrophages

Macrophages are known as Hofbauer cells in the human foetal chorionic villus of the placental unit [10]. Their distribution throughout uterine tissue depends on oestrogen and progesterone levels throughout the oestrous cycle [11]. They are present at the foetal-placental interface, in particular, around the spiral arteries, where they act to support the process of trophoblast invasion of the endometrium by phagocytosing apoptotic cells [12]. It has been suggested that macrophages within the decidua of the first trimester display characteristics of the alternatively activated phenotype as opposed to the classically activated phenotype [13]. However, *in vitro* studies have observed that the influence of 17β-oestradiol on macrophage function is varied, based on which cell line, species, or hormone concentration is used.

17β-oestradiol administration to RAW 264.7 cells for 4 hours prior to LPS administration prevents the induction of the morphological changes typically seen with LPS alone [14]. In addition 17β-oestradiol can modulate the ability of macrophages to produce various cytokines, for example, the downregulation of IL-1β, IL-6 and TNF-α by murine splenic macrophages [15, 16]. Studies with LPS-treated rat peritoneal macrophages have shown that 17β-oestradiol influences TNF-α production by these in a concentration-dependent manner [17], whereas 17β-oestradiol has no effect on TNF-α production by cells of the murine J774A.1 line [18].

Macrophage function is also subject to modulation by progesterone. It has been shown in both rat and murine macrophages that progesterone reduces LPS and IFN-γ stimulated nitrite production in a dose-dependent manner

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[19, 20]. Jones *et al*. (2008) [21] further describe the ability of progesterone to down modulate nitrite production by murine bone marrow derived (BMD) macrophages through binding to the glucocorticoid receptor (GluR) rather than the progesterone receptor (PR). By comparison, IL-12 production by macrophages can be modulated by progesterone through either the glucocorticoid or progesterone receptor [21].

These experimental systems using macrophage cell lines and LPS can only be used to speculate the role that the female sex hormones have on macrophages found within the female reproductive tract or at the foetal-maternal interface. From these results, however, it can be assumed that oestrogens and progesterone will act to down modulate the inflammatory functions of these cells, as this would prove detrimental to the successful continuation of pregnancy.

Dendritic Cells

Within the uterus, DCs protect the host against pathogens without endangering the developing foetus by uptake of the apoptotic particles of the invading trophoblast [22]. CD83+ CD25+ DCs are present within the human decidua, as shown by both immunocytochemistry [23] and by flow cytometry [24]. Juretic *et al*. (2004) [25] have reviewed the role of DCs at the maternal-foetal interface and provide a model whereby stimulation of immature DCs in a Th2-bias environment (such as during pregnancy) will promote tolerogenic function, and stimulation in a Th1 bias environment will result in the maturation of DCs with a high capacity for antigen presentation. Since the Th2 environment associated with pregnancy is thought to be related to the high levels of progesterone and oestrogen present within the female reproductive tract, a great deal of focus has recently centred on the influence of these hormones on DCs.

Initial studies on the immunomodulation of DCs by oestrogens were carried out through use of toremifine and tamoxifen [26, 27]. These antioestrogens inhibit the differentiation of monocytes into DCs, suggesting that oestrogens are important in the development of DCs from their precursors. This was confirmed in studies by Paharkova-Vatchkova *et al*. (2004) [28], who showed that 17β-oestradiol promotes the differentiation of DCs from murine bone marrow precursors, rather than increasing the proliferation of existing DCs. Furthermore, in recent studies it is demonstrated that DC differentiation is regulated by the oestrogen receptor-α (ER-α) [29].

17β-oestradiol has the ability to modulate cytokine production by DCs. However, there is a lack of consistency between studies, as it appears to be biphasic in its functions, dependent upon which concentration is used [30-33]. For example, production of the proinflammatory cytokine IL-6 by immature peripheral blood mononuclear cell (PBMC)-derived human DCs is only affected by 17β-oestradiol at concentrations above 1mg/ml where a dose-dependent increase in IL-6 production is observed [34].

IL-10 is an anti-inflammatory cytokine and although some studies have shown that 17β-oestradiol has no effect on IL-10 production by immature PMBC-derived DCs [34], others have found that 17β-oestradiol can cause a significant increase in IL-10 production in human PBMC-derived DCs up to a concentration of 10ng/ml [31], a level which corresponds to pregnancy.

The ability of 17β-oestradiol to modulate IL-12 production by immature and mature DCs is below the range of detection [31, 34]. Similarly, levels of the proinflammatory cytokine TNF-α, either released by immature DCs or found intracellularly, are unaffected by 17β-oestradiol [31, 33, 34]. The effect of progesterone on cytokine production reveals that in murine BMD-DCs, IL-6 and IL-12 production is unaffected, however, IL-10 and TNF-α is increased [31]. Since TNF-α is a Th1 proinflammatory cytokine, it is generally regarded as dangerous to the developing foetus. However, *in vivo*, progesterone will not be found in isolation and therefore if TNF-α levels are looked at in response to both progesterone and oestrogen at a range of concentrations, then it can be seen that TNF-α remains at basal levels [31].

Natural Killer Cells

Studies in murine models have found that uterine natural killer (uNK) cells are crucial for successful implantation and are found on the mesometrial side of the pregnant uterus [35]. During the first trimester of pregnancy in humans, uNK cells reach peak numbers, making up 70% of all lymphocytes present, however by full-term pregnancy, no uNK cells are detectable [36]. NK cells are a well-known source of IFNγ and studies in IFN-$\gamma^{-/-}$ mice and RAG-$2^{-/-}\gamma_c^{-/-}$ mice demonstrate that IFN-γ production by murine uNK cells is important for vascular remodelling, maintenance of the deciduas within the second trimester and regulation of the uNK cell population [37-40]. Decidual NK (dNK) cells have the potential to produce not only Th1-associated cytokines (NK1), but also Th2-associated cytokines (NK2) given an appropriate stimulus, and immunoregulatory cytokines such as TGF-β (NK3) and IL-10 (Nkr1) [41], which would contribute to the provision of a suitable environment for successful pregnancy. Decreased numbers of Nkr1 and NK3 cells have been associated with the phenomenon of spontaneous abortion [41]. Furthermore, in humans, the non-classical MHC class I molecule HLA-G is expressed in the placenta and can inhibit trafficking of maternal NK cells across the placenta [42], thereby protecting the foetal cells from rejection [39].

NK cell activity differs throughout the human menstrual cycle, with higher levels of activity observed in those women in the follicular phase of the cycle than the luteal phase [43]. This suggests that NK cells are influenced by oestrogen and progesterone. As illustrated in Fig. (**1**), NK cell activity can also be modulated by the release of Progesterone-Induced Blocking Factor (PIBF), a 34-kDa protein produced by decidual lymphocytes upon exposure to progesterone. Despite being necessary during pregnancy at the foetal-maternal interface, uNK cells still possess high concentrations of perforin, a molecule that mediates NK cell cytotoxicity. PIBF has been found to downmodulate the cytotoxic activity of NK cells [44-46] through inhibition of arachidonic acid release from lymphocytes, which subsequently reduces prostaglandin production and IL-12 release [47]. IL-12, in conjunction with IFN-γ, normally promotes NK cell activity. In this setting, lowered NK cell activity contributes to the successful continuation of pregnancy.

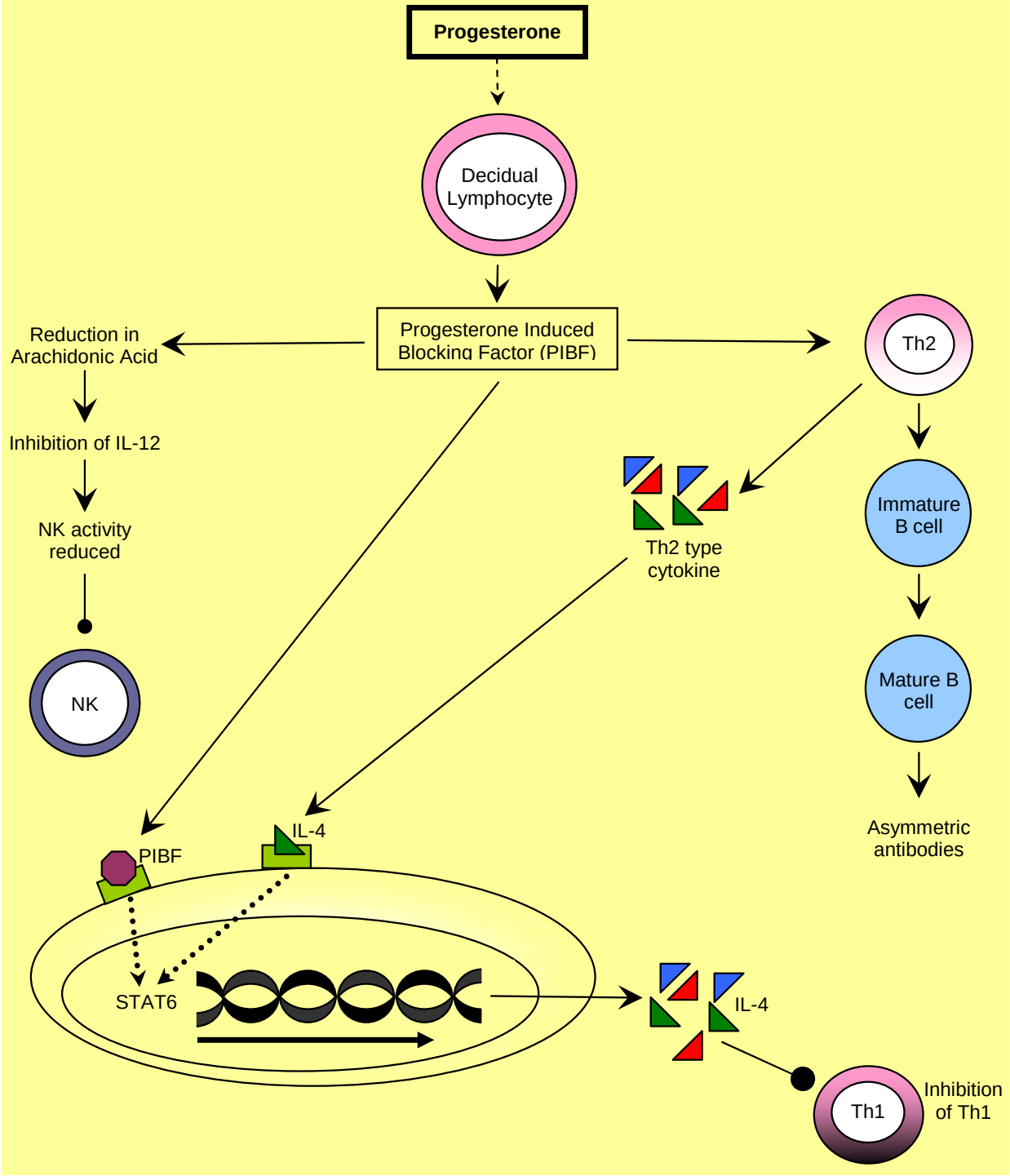

Fig. (1). Examples of effects of Progesterone Induced Blocking Factor (PIBF) on cells of the immune system. Progesterone induces production of PIBF from deciudal lymphocytes, which can act to potentiate the Th2 environment associated with pregnancy. PIBF reduces NK cell cytotoxicity, stimulates production of asymmetric antibodies, and increases IL-4 production by a STAT6 dependent mechanism. In doing so, Th1 responses are inhibited [44-46].

2.2. T Cells

It has been observed that during pregnancy there is a general substantial improvement in the symptoms of Th1-associated autoimmune diseases such as multiple sclerosis, rheumatoid arthritis (RA) and thyroiditis. For example, only patients with rheumatoid arthritis negative for autoantibodies improve during pregnancy [48]. This has been widely attributed to a bias towards a Th2 cytokine environment [49].

The cytokine profile is important for the maintenance of pregnancy. Murine studies have found that IFN-γ is only detectable during the first and second trimesters of successful pregnancy, whereas the Th2 cytokines IL-4, IL-5

and IL-10 are constitutively secreted by the foetal-placental unit until term [50]. Makhseed *et al*. (2001) [1] describe a strong Th1 bias in abortion-prone women and recurrent aborters, in comparison with women who have normal pregnancies.

Examination of the effects of pregnancy hormones on T cell populations have identified potential explanations to the shift towards to Th2 environment. *In vitro* studies illustrate that progesterone can influence the functional differentiation into Th1 and Th2 subsets by enhancing IL-4 and IL-10 producing T cells and reducing the ability of T cells to secrete IFN-γ [51].

Another potential mechanism for the modulation of Th1/Th2 balance is *via* the action of PIBF (Fig. **1**). This molecule contributes to the reduction in cell-mediated responses that could be detrimental during pregnancy. In addition to the prevention of NK cell activity [44-46], PIBF has been shown to skew the immune environment to a Th2 phenotype through increasing the production of IL-3, IL-4 and IL-10 from both CD4+ and CD8+ T cells *in vitro* [52] and *in vivo* [53]. Kozma *et al*. (2006) [54] have suggested the existence of a novel IL-4R, comprised of the IL-4Rα chain in association with a GPI-anchored PIBF receptor, which subsequently activates STAT6 upon binding of PIBF. This mechanism occurs through protein kinase C (PKC) phosphorylation without any adjustments in intracellular Ca^{2+} levels [55].

As reviewed by Pernis (2007) [56], oestrogens can also modulate various aspects of CD4+ T helper cell development and function. Oestrogens can influence the Th1/Th2 balance by depressing Th1 and favouring Th2 responses [30]. Consequently, females exhibit higher Th2 immunity than males, and therefore produce higher levels of IL-4, IL-5, IL-6 and IL-10 [57]. Contrary to this, a study by Fox *et al.* (1991) [58] has shown that 17β-oestradiol directly stimulates the IFN-γ promoter, which would suggest a role for oestrogens in the development of a Th1 response. Furthermore, studies show that 17β-oestradiol has the capability to induce the development of IFN-γ producing cells [59]. The contradictory Th1 and Th2 inducing ability of the oestrogens could be due to the concentration present, as suggested by Beagley and Gockel (2003) [30]; as low concentrations may favour IFN-γ production and higher concentrations may favour IL-10 production by the same cells. Therefore 17β-oestradiol is biphasic in its actions, with low doses facilitating induction of immune responses and higher doses, such as those present during pregnancy, suppressing immune activation.

As well as acting to influence mature T cells through alteration of cytokine production, both progesterone and oestrogen influence T cell development. Moreover, progesterone can inhibit T cell lymphopoiesis at the pre-T cell (CD3- CD44+ CD25+) stage in a progesterone-receptor (PR) dependent mechanism during pregnancy, by a process also described as necessary for normal fertility [60]. In contrast, during a subsequent study by Rijhsinghani *et al*. (1996) [61], it was found that progesterone had no ability to block T cell development, with oestrogen instead having an effect on T cell development. As well as reducing thymus size and cellularity, oestrogen reduced the numbers of both the CD4+ and CD8+ T cell populations [61].

In addition to the alteration of Th1 and Th2 cell behaviour in the presence of female sex hormones, tolerance of the semiallogenic foetus is also achieved through the actions of the CD4+CD25+ regulatory T cells (Tregs) population. These cells have been implicated in the control of autoimmune diseases and in doing so can act to potentiate self-tolerance. This concept has been applied in many studies, both human and murine, to understand the role of these cells in maintenance of maternal tolerance of the foetus [reviewed 62, 63]. Human Tregs have been classified into $CD4+CD25^{low}$ and $CD4+CD25^{high}$ populations, with the former having no immunoregulatory functions and the latter having a strong potential for regulation [62]. $CD4+CD25^{high}$ Tregs constitute 2-6% of CD4+ T cells in humans [62]. In mice, Tregs are simply described as CD4+CD25+, and constitute approximately 10% of CD4+ T cells. The existence and role of these cells in the maintenance of pregnancy has been elucidated by the identification of the essential transcription factor Foxp3 as a marker for the cell type [64, 65]. Pregnancy is associated with an increase in the number of Tregs in the blood, most prevalent during the second trimester [66] and in the decidua [67]. Aluvihure *et al*. (2004) [68] showed that the maternal population of CD4+CD25+ Tregs in mice is systemically expanded, rather than in the thymus, during pregnancy and this is independent of alloantigen. A subsequent study has since shown data to support that the expansion of CD4+CD25+ Tregs is driven by foetal alloantigen [69]. The conflicts in these results are possibly due to differences in the time periods examined.

One method by which Tregs are thought to mediate maternal tolerance of the foetus is through induction of the enzyme indoleamine 2,3-dioxygenase (IDO), expressed by a variety of cells including macrophages [70] and DCs [71]. This enzyme acts to deplete essential amino acid tryptophan and in doing so, prevents T cell attack of the developing foetus [72, reviewed by 73, 74]. IDO expression is upregulated in DCs and both peripheral and blood monocytes through Treg expression of CTLA-4 [75] possibly after exposure to foetal antigen.

The direct effects of the female sex and pregnancy-associated hormones on Tregs is presently an understudied area. Most of the work carried out in this area has focused on the ability of oestrogen to potentiate the ability of Tregs to suppress immune function. Interestingly, it has been found that oestrogen increases the proportion of CD4+ T cells that are CD25+ as well as increases Foxp3 expression and enhances Treg suppression [76-78]. It remains to be seen what the effect of progesterone, in the presence or absence of oestrogen, has on the expansion and function of the Treg population and what signalling mechanisms are involved.

2.3. B Cells and Antibodies

During pregnancy, humoral immunity predominates with an overall increase in total antibody production, however generation of new B cells is reduced. It has been shown that oestrogen causes a selective reduction in pre-B cells and IL-7-responsive cells in the bone marrow [79], with subsequent studies demonstrating that oestrogen influences B lymphopoiesis by altering early, critical events [80]. It has been strongly suggested that the down regulation of B cell lymphopoiesis is due to the expression of Bcl2 [81]. This

antiapoptotic molecule is regulated by progesterone, which interacts directly with its promoter [82].

Asymmetric antibodies are IgG molecules that possess a mannose-rich oligosaccharide in one arm of the Fab region [83]. The altered structure of these molecules therefore renders them ineffective at activating the effector functions typically associated with antibodies such as opsonisation for phagocytosis and complement fixation. It was first suggested by Malan Borel *et al.* (1991) [84] that these molecules function to protect the foetus by acting as blocking antibodies. It has since been recognised that higher levels of asymmetric antibodies exist in healthy pregnant women than in recurrent aborters [85]. This action has been attributed to the ability of progesterone to induce PIBF (Fig. **1**). Asymmetric antibodes play a protective role during pregnancy by inactivating the effector mechanisms, which could attack the semiallogenic foetus [86, 87].

3. SIGNALLING OF THE FEMALE SEX HORMONES

In order for oestrogen and progesterone to exert their immunomodulatory functions, they must first bind to receptors. The receptors involved and signalling pathways induced upon hormone release is complex and not yet fully understood.

3.1. Oestrogen Receptors

Oestrogen receptors exist in two isoforms, ER-α and ER-β, which are the products of two genes on different chromosomes. Oestrogen is able to function *via* genomic or non-genomic mechanisms [88, 89]. The genomic mechanism refers to the binding of oestrogen to nuclear (intracellular) receptors, which are ligand dependent transcription factors capable of regulating gene expression in a number of ways including direct DNA binding of homodimers / heterodimers of ER-α and ER-β, or by binding to other transcription factors [90]. ERs modulate gene expression through transcription activation functions, AF-1 and AF-2, which bind coactivators or corepressors. As well as binding nuclear receptors, oestrogen can rapidly modulate cells by binding to membrane ERs [91], although oestrogen itself does not increase the expression of membrane ER-α [92].

The presence of ERs on immune cells has been of great interest in recent times. By carrying out quantitative RT-PCR, Phiel *et al.* (2005) [93] have shown that CD4+ T cells express a greater level of ER-α mRNA than ER-β mRNA, with CD8+ T cells expressing a similar, but low, level of mRNA for both ER-α and ER-β. In addition it was shown that B cells express a higher level of ER-β mRNA than ER-α mRNA. At the protein level, it was found that both CD4+ and CD8+ T cells possess 17β-oestradiol binding sites [94], B cells express nuclear ERs but not membrane ERs [95] and macrophages also express nuclear ERs [96, 97].

3.2. Progesterone Receptors

Progesterone has the ability to exert its functions through both the Progesterone receptor (PR) and the Glucocorticoid Receptor (GluR) [98]. The PR is an intracellular receptor that is a member of the nuclear receptor superfamily [99, 100] and exists in two distinct isoforms, PR-A and PR-B, both of which are transcribed from a single gene, but regulated *via* distinct promoters [101-103]. The PR can be expressed constitutively, for example, in mice the PR is found in the smooth muscle cells of the uterus, uterine blood vessels and urinary bladder, to name a few [104]. However, PR expression can be upregulated by oestrogen, despite neither isoforms containing an oestrogen response element (ERE). Interestingly, Flötotto *et al.* (2004) [105] found that PR-B expression is stimulated by only ER-α by an AF-1 dependent mechanism.

The PR can also mediate its biologic functions through either genomic or non-genomic mechanisms [106]. Classical genomic signalling involves the binding of progesterone to the receptor, inducing a conformational change in its structure, leading to the separation of a multi-protein chaperone complex. In doing so, receptors can form homodimers which are able to bind the progesterone response elements (PREs) within the promoter regions of target genes to modulate gene expression [100]. Recently, a great deal of effort has been made to understand the non-genomic signalling mechanisms that mediate the rapid, membrane-initiated effects of progesterone [107] due to the potential for therapeutic modulation.

The presence of a classical progesterone receptor on immune cells is an area of much controversy. Immunohistological studies that neither PRs nor ERs were present on lymphocytes, macrophages or uterine NK cells [108]. In contrast, subsequent studies have demonstrated the existence of PRs and ERs in macrophages and NK cells by quantitative RT-PCR and immunohistochemistry [97, 109]. In addition, membrane PRs are also present in human T cells [110].

4. PREGNANCY AND AUTOIMMUNE DISEASE

Generally during pregnancy there is a substantial improvement in the symptoms.

of Th1-associated autoimmune disease. However, some autoimmuneconditions can cause risks and complications for both the pregnant woman and the foetus [111]. For example, in Graves' disease anti-thyroid autoantibodies can result in miscarriages, premature births and intrauterine growth retardation for the foetus. The expectant mother can develop high blood pressure and heart complications [111]. Hashimoto's thyroiditis is characterised by T cell autoreactivity against thyroid antigens, thus causing hypothyroidism and a decrease in the IQ of children born to mothers suffering from the disease [112].

Hashimoto's thyroiditis fluctuates during pregnancy. The autoimmune component ameliorates during the second half of gestation but is aggravated post-partum [113]. This may be due to the shift in T cell responses. In marked contrast, in the case of type 1 diabetes (IDDM) sufferers, symptoms are not alleviated during pregnancy and patients must be carefully monitored as IDDM can be induced by both Th1 and Th2 events [114]. In clinical studies of patients affected by inflammatory bowel disease, the outcome of pregnancy is normal, although there is an increased risk of premature delivery or low birth weight [115]. Stillbirth, congenital abnormalities and preterm labour are often associated with inflammatory activity at conception, whereas absence of inflammation leads to a normal outcome [116, 117]. As a result patients are advised to conceive during remission. However, Crohn's disease is exacerbated in the last trimester

and post-partum, and this is thought to be due to the decrease of endogenous corticosteroids after delivery [118]. In other inflammatory bowel conditions, such as ulcerative colitis, pregnancy appears to increase disease activity during the first trimester [119]. Usually, ulcerative colitis is also associated with low birth weight and preterm labour but there is evidence to illustrate that infants born to mothers with this condition may experience neurological sequelae [120].

In Systemic Lupus Erythematosus (SLE) an association between activedisease at conception and danger to the foetus has been reported [121]. There has been much debate as to whether SLE is ameliorated or exacerbated during pregnancy, with studies providing evidence for both cases [122]. However, if flares of SLE occur, they are no more severe during pregnancy than before [123]. Recent studies highlight the increased danger to both mother and foetus of lupus nephritis at the time of conception. This is due to increased episodes of hypertension and a higher risk of preeclampsia [122]. In addition, the transplacental passage of antiphospholipid antibodies can result in neonatal lupus syndromes, with ensuing t higher risk of congenital heart problems and transient cutaneous lupus for the foetus [124]. The exacerbation of SLE is attributed to the presence of oestrogens, which favour humoral immunity, and prolactin, which has an effect on the T and B lymphocyte population [125, 126]. Since pregnancy in general results in a suppression of cell-mediated responses, humoral immunity is preserved and thus the production of autoantibodies is not affected. The symptoms of Rheumatoid Arthritis (RA) are generally alleviated during pregnancy. RA is characterised by a severe inflammation and destruction of the joints and by extraarticular manifestations, including vasculitis. These symptoms improve dramatically during early pregnancy and the patient can go into complete remission towards the end of gestation. Such amelioration is likely to be caused multiple factors including the major shift from a Th1 to a Th2/Treg environment, the presence of α-2 pregnancy-associated globulin (PAG) [122] and increase in sex hormones and serum cortisol, which suppress proinflammatory cytokines and favour IL-10 through the action of PIBF [53]. Exacerbation of RA can be seen in these patients 3-4 months postpartum, and prolactin may have a role in these flares [127, 128].

5. PREGNANCY AND INFECTION

During pregnancy many diseases are more severe and danger to the foetus and transplacental transmission may occur. Pregnant females in general are more susceptible to infection than non-pregnant females. Increase disease susceptibility and severity during pregnancy has been documented for a variety of diseases, including bacterial (Leprosy, Listeriosis) [129-131], viral (HIV, Influenza, Measles) [132-134] and parasitic (Malaria, Toxoplasmosis) [135, 136]. It is the change in immune function during pregnancy that alters susceptibility and severity to these infections. For example, some studies have suggested a greater susceptibility to HIV in the presence of elevated

Table 1. Immunological Response to Parasite Infections During Pregnancy

Parasite	Host	Response to Infection	Effect of Infection During Pregnancy	References
Leishmania major	C57BL/6 mouse	Th1 response: ↑ IFN-γ & IL-12	If there are ↑ levels of IFN-γ induced by parasite this leads to implantation failure and resorption ↓ IFNγ, ↑ IL-4, IL-5, IL-10, IgG1	[154] [155]
Neospora caninum	BALB/c mouse	Th1 response: ↑ IFNγ, IL-12	↑ IL-4, ↓ IFNγ, IL-12, TNFα	[156-158]
	Cattle	Th1 response: ↑ IFN-g production by NK cells	Th1 response to control parasite multiplication leads to destruction of placental tissues. Infiltration of CD4+ T cells, γδ T cells & NK cells ↑ IL-1β, IL-8, TNFα ↓ IL-6, TGFβ by placental macrophages leading to inflammatory response in placenta	[159, 160]
Plasmodium falciparum	Human	↑ TNFα, IFNγ	Infiltration of immune cells	[161, 162]
Toxocara canis	Dog	↑ CD4+ & CD8+ T cells, ↑ in IL-4, IL-5 & IgE production	↑ susceptibility: ↑ in IL-10 production during pregnancy, decrease in IFN-γ production	[163]
	C57BL6/J mouse	Th2 response: eosinophilia, i↑ in IgE production, ↑ in CD4+ and CD8+ T cells	↑ susceptibility: ↑ in CD4+ T cells in early infection, ↓ in CD8+ T cells in late infection	[164]
Trypanosoma cruzi	Human	↑ IFN-γ	↑ susceptibility: ↓ in IFN-γ leading to increased parasitaemia ↓ in activation of CD4+ T cells and monocytes	[165]
	BALB/c mouse	↑ IFN-γ and TNF-α	↑ susceptibility: Parasite invasion of deciduas resulting in foetal growth retardation and death	[166]
Toxoplasma gondii	BALB/c	↑ IFNγ, IL-12, CD8+ T cell activity	↓ CD4+ T cells, CD8+ T cells Congenital transmission to foetus as parasite multiplication is not controlled	[167]

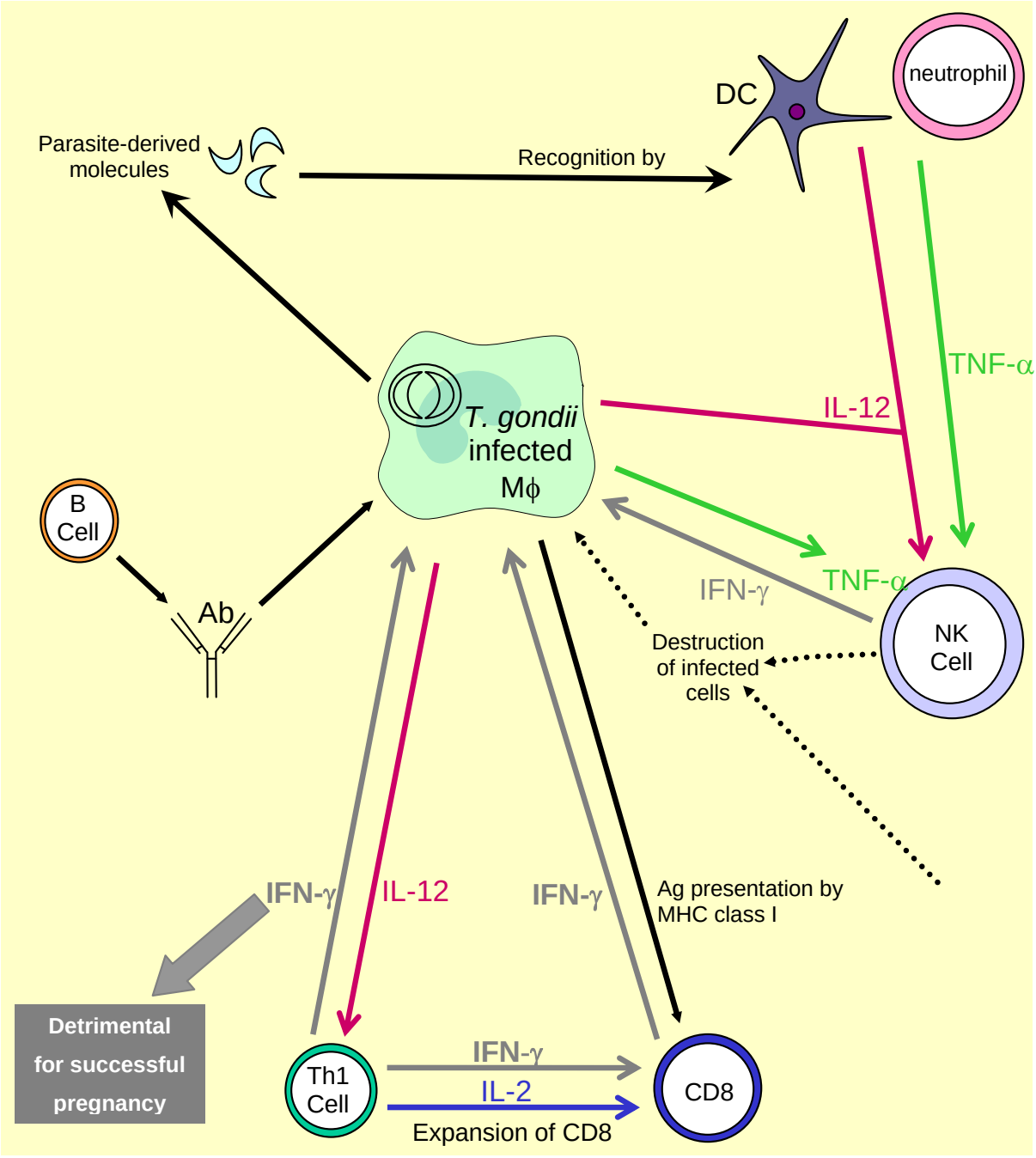

Fig. (2). Summary of protective type 1 immune response elicited by *T. gondii* infection. Upon infection of a host cell, such as the macrophage, IL-12 is released which induces the expansion of CD4+ Th1 cells as well as the effector mechanisms of NK cells. IFN-γ release from Th1 cells, CD8+ T cells, NK cells further promotes the effector mechanisms of macrophages such as tryptophan degradation and NO release. Humoral immunity is involved by release of antibodies which can induce complement or opsonise tachyzoites to prevent further parasite dissemination. Release of parasite derived molecules such as cyclophilin, HSP70 and profilin induce the release of cytokines including IL-12 and TNF-α from DCs and neutrophils. [Ab=antibody, Ag = antigen].

concentrations of progesterone [137, 138]. An increase in progesterone levels can decrease vaginal epithelium thickness [139] and sex steroids can increase the expression of co-receptors CXCR4, CD4 and CCR5 important in viral invasion of the host cells expression [140]. In addition, severity of disease during pregnancy is also associated with physiological changes, such as increased heart rate, stroke volume, oxygen consumption and lung capacity [141]. Many studies, focusing on infections during pregnancy, have utilised parasitic model infections to understand the alteration of immune function during pregnancy and the danger to the foetus.

5.1. Parasites and Pregnancy

A fine balance exists between host and parasite to ensure survival of both. The cytokine environment is often key in this process, and pregnancy can often lead to changes in the way this balance is maintained. Pregnancy is generally

regarded as a Th2 phenomenon, due to the influence that the female sex hormones have on immune cells. Alteration of the cytokine environment as the immune system responds to the presence of infection often leads to detrimental consequences for both mother and foetus. On the other hand, adjustments of the cytokine profile induced by pregnancy can change the ability of an individual to control a parasite infection. A number of studies have been carried out to consider the effect that parasites have on the mother and foetus during pregnancy and also to consider the effect that pregnancy has on the ability to control parasite numbers, some of which have been summarised in Table **1**.

One parasite, which has been extensively studied for its effects on immunity during pregnancy, is the protozoan *Toxoplasma gondii*. Female mice are more susceptible than males to *T. gondii* infection [142], and this has been attributed to the effect of the female sex hormones [15]. In addition, this parasite can be congenitally transmitted if the mother is infected for the first time during pregnancy, with the trimester at which infection occurs determining whether the foetus is aborted or survives to term, but possessing foetal abnormalities [143]. As summarised in Fig. (**2**), infection with *T. gondii* is characterised by induction of a Th1 type immune response, with production of IFN-γ and CD8+ T cell activity being crucial for control of the parasite [144-147]. IFN-γ production, as part of a Th1 immune response, is associated with abortion and so the immune response to the parasite can have detrimental consequences for the foetus. On the other hand, the Th2 environment conducive to pregnancy favours the multiplication and maintenance of the parasite. Moreover, *T. gondii*-infected IFN-γ deficient pregnant mice are less likely to abort the foetus, but exhibit high numbers of parasite within the uterus and placenta [148].

Malaria infections have presented the world with a great epidemiological problem in recent times. Four species (*Plasmodium falciparum, P. malariae, P. ovale* and *P. vivax*) cause malaria in humans, with *P. falciparum* infection being especially problematic during pregnancy. The prevalence of maternal malaria infection in Africa is approximated at 25% [149] and congenital transmission to the foetus estimated at 33% [136], therefore understanding the immune response to malaria infection is important with regard to transmission of infection and possible chemotherapeutics during pregnancy. As with *T. gondii* infection, malaria induces a strong Th1 type response in the mother, resulting in implantation failure and abortion of the foetus [150]. Much of the pathology is due to the ability of the parasite to reside within red blood cells in the placenta, mediated by binding of the parasite to chondriotin sulphate A and hyalaronic acid receptors on placental endothelial cells [151].

A recent study has considered the effects of the female sex hormones on *P. chabaudi* infection in C57BL/6 mice and found that administration of oestrogen alone or in combination with progesterone reduced infection-induced weight loss without actually effecting levels of parasitaemia [152]. This data suggested that oestrogens exhibit a protective effect for the mother by increasing levels of IFN-γ and IL-10, however this study did not consider pregnancy outcomes. The stress hormone cortisol has been found to be increased in *P. falciparum*-infected pregnant women compared with non-infected pregnant women [153]**.** At the time of delivery, cortisol concentrations were approximately 2.5 times higher than in non-pregnant women. It could be suggested that the parasite induces additional cortisol production as a means of dampening immune cell function.

6. CONCLUDING REMARKS

The female sex and pregnancy associated hormones have a wide range of effects on the cells of the immune system to allow the successful continuation of pregnancy by preventing rejection of the foetus. The modulation of the action of these cells often has implications for other aspects of immunity, such as altering the ability to deal with infection or autoimmune diseases. Much remains to be learned about the way in which cells and molecules can interact and be influenced.

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