

Reproductive Immunology: Current Status and Future Directions (Part I)

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Abstract Extensive research work over the past couple of decades has indicated a series of intricate relations between immune and reproductive systems. A range of reproductive immunology topics including the roles of adoptive and innate immunity in infertility and pregnancy, the immune system's role in induction of labor and preterm delivery, and immuno-modulatory effects of the female sex hormones will be discussed in this and the next issue of the Journal. The implications of this research on the development of novel therapeutic approaches are also addressed.

Keywords Reproduction · Infertility · Immunity · aPL antibody · Complement · NK cells · Tissue factor (TF)

Over the past couple of decades a wealth of data has been accumulated on the interactions between the immune and reproductive systems. Abundant data link immune disturbances to reproductive abnormalities such as infertility, premature ovarian failure, recurrent abortions, fetal death, eclampsia, and preterm labor [1]. In addition, there is an interplay between reproductive hormones and immune responses as evidenced by the mainly immunosuppressive effects of male sex hormones and the largely immunostimulatory effects of female sex hormones [2]. Furthermore, it is well known that females have more reactive immune systems than males. The

greater reactivity of the female immune system induces rapid immune responses and prompt protection from infections but also increases the incidence of autoimmunity [3]. Since the majority of autoimmune diseases display preponderance for women with child-bearing potential, the autoimmune and reproductive interface is of critical significance. The relationship is reciprocal with autoimmunity having an impact on female fertility and/or pregnancy outcomes and pregnancy influencing autoimmune disease activity [1]. This issue of the *Clinical Reviews in Allergy and Immunology* is dedicated to reproductive immunology. It provides a comprehensive overview of an array of topics including the roles of antiphospholipid antibody (aPL), NK cells, Toll-like receptors (TRLs), and complement and tissue factor (TF) in infertility and adverse pregnancy outcomes. The contents of the volume are obviously not meant to be complete but rather to touch on several critical issues. Each paper within the issue is however meant to be a comprehensive review of a specific subject. The papers discuss the important issue of immune tolerance and rather than talk about this problem within each paper, we note a myriad of references which highlight basic and clinical examples in both mouse models and humans [4–27]. A persuasive theme in nearly all the papers is the role of inflammation. This is obviously a common theme throughout autoimmunity and, once again, to reflect the comprehensive nature of these reviews, we note numerous manuscripts which are indicative of the common threads between inflammation and reproductive processes in a variety of immune disorders in both pre-clinical models and humans [28–57]. The reviews presented in this volume clearly show that great progress has been made in our understanding of immune tolerance, inflammation, and immuno-reproductive interconnections, but also underscore the need for further studies before any of this research can be actualized into novel therapies.

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In this special issue of the Journal, Cervera and Balasch review the causes of recurrent pregnancy losses in patients with autoimmune disease focusing on the aPL antibody. Murine studies show that aPL antibodies induce pregnancy loss since the injection of serum from mice with high aPL titers to naïve mice causes fetal resorption [58] and injections of human aPL antibodies to wild-type mice induce an antiphospholipid-like syndrome [59]. However, murine data cannot straightforwardly explain the pathophysiology of human antiphospholipid syndrome (APS; see below). In humans, the presence of aPL has not been shown to directly affect fertility or pregnancy outcomes. Therefore, Cervera and Balasch rightfully note that the observed association of aPL with recurrent miscarriages in patients with APS and systemic lupus erythematosus (SLE) suggests a link, but does not conclusively prove causality [60]. The proposed mechanisms of aPL-mediated recurrent spontaneous abortions include prothrombotic mechanisms, interference with embryonic implantation, impairment of the production of chorionic gonadotropin, cytokine dysbalance including decreased IL-3 and increased TNF- α , and complement activation.

The role of complement in pregnancy failure has been well-described in experiments with complement-deficient mice [61] and it is reviewed here in detail by Tincani and her colleagues. The authors indicate that a significant increase of complement activation is associated with a variety of pathologic pregnancy outcomes including preeclampsia, recurrent spontaneous abortions, intrauterine growth retardation, and APS. In murine models of APS, the role of complement activation in pregnancy loss has been supported by the massive accumulation of C3 in the placenta and the lack of fetal resorption in C3-deficient mice. Murine data also suggest that aPL and complement activation via C3a, C5a, and MAC may collaborate in triggering inflammatory events that lead to placental thrombosis, hypoxia, and neutrophil infiltration [62]. Girardi's review goes a step further and focuses on the TF, an inflammatory molecule and a major initiator of the coagulation cascade [63]. There is increasing evidence that alterations of the TF pathway lead toward hypercoagulability in patients with aPL antibodies and dysfunction of this major pathway of blood coagulation seems to be a mechanism involved in the development of APS [64]. Girardi's research demonstrates that TF contributes to a C5a-induced oxidative burst in neutrophils leading to trophoblast injury and fetal death in murine APS [65]. Although the studies with APS mouse models connect complement activation and TF with adverse pregnancy outcomes, the murine data do not seem directly translatable to humans since there are several important differences between human and murine APS: histological analysis of human placentas from women with APS shows only a

small degree of inflammation, complement activation detected in human APS placentas is commonly not related to the pregnancy outcome, and the increased expression of TF in APS patients has not been conclusively linked to adverse pregnancy outcomes. Thus, as suggested by Tincani et al., further research is necessary to determine whether complement activation and the inflammatory processes observed in murine APS models are actually occurring in human APS.

In addition to the complement cascade, other innate immune factors can serve as potential modulators of the reproductive processes. In this issue of the Journal, two additional aspects of innate immunity are discussed in the context of reproduction: NK cells and TLR receptors. NK cells have been implicated in immunologic infertility and pregnancy loss [66]. The characteristics and functions of peripheral and uterine NK cells (pNK and uNK, respectively) are delineated in De Carolis' and Konova's reviews. These reviews indicate that pNK cells, in addition to their cytotoxic functions, act as regulators of adoptive immunity by providing stimulatory signals to T cells and dendritic cells and also point out that these cells have higher cytolytic and cytotoxic activity than uNK cells. The role of NK cells in pregnancy is reviewed in detail by De Carolis and her colleagues [67]. NK cells, accumulating in the human deciduae in the first trimester of pregnancy, play a role in immunosurveillance and angiogenesis at the fetal-maternal interface, but in certain circumstances, NK cells can exert harmful effects on pregnancy outcomes and lead to recurrent miscarriages. The latter case seems to be linked to the increased numbers and killing activity of NK cells. De Carolis et al. also discuss the complex interplay between NK cells and aPL in immunologic infertility and recurrent early abortions in patients with APS. The notion that increased NK cell levels play a role in recurrent miscarriages has led to attempts to reduce their numbers with IVIg or immunization with paternal leucocytes [68, 69]. Konova's review centers on the role of NK cells in autoimmune thyroid disease associated with pregnancy loss. Since the initial report in 1990 showed that thyroid autoantibody-positive women miscarried at double the rate compared with autoantibody-negative women [70], reproductive abnormalities in the context of thyroid autoimmunity have been a topic of extensive research. Strong evidence has been accumulated over the past two decades associating thyroid autoimmunity with unexplained infertility and low IVF success rate [71, 72]. Konova describes autoimmune thyroid disorders and altered NK cell functions as two distinct risk factors, which independently could cause adverse pregnancy outcomes [73, 74]. However, it seems that these risk factors can also cooperate with each other as observed in patients with Grave's disease and Hashimoto thyroiditis (GD and HT, respectively). Patients

with GD and HT display decreased NK cell activity caused by functional alterations that are not directly related to thyroid hormone serum levels. This observation has led to speculation that auto-reactive T cells, thyroid specific autoantibodies, and lymphocytic infiltration of the thyroid are the reasons for depressed NK cell functions and, thus, there is a direct link between the NK cell dysfunction and the pathophysiology of thyroid autoimmunity itself. The multiple roles of NK cells in normal pregnancy discussed above suggest that the functional defects involving NK maturation and/or activation observed in patients with autoimmune thyroid disease could affect their reproductive outcomes [75].

Also, Toll-like receptors (TLRs) have been implicated in reproductive processes. TLRs take a part not only in the maintenance of innate immune responses in the reproductive system, but they are also involved in pregnancy [76] and initiation of labor [77]. Riley and Nelson review the role of TLRs in placental dysfunction and pregnancy loss [78]. TLRs trigger an inflammatory response during the trophoblast invasion in early gestation and in the villous trophoblasts of late pregnancy during the onset of labor. Activation of TLRs on the trophoblast affects immune cell recruitment, cytokine secretion, and decidual responses to invading pathogens. Reley and Nelson's review discusses the mechanisms by which the TLR signal transduction at several maternal–fetal interfaces may contribute to a variety of pregnancy pathologies including intrauterine growth restriction, pre-eclampsia, and preterm labor.

Despite the intense investigative efforts over several decades, labor and preterm delivery (PTD) have remained poorly understood. A number of researchers have speculated that there is a link between PTD and either subclinical infections or autoimmunity. Those in favor of the former explanation point out that ascending vaginal flora can lead to chorioamnionitis. They argue the resultant release of endo and exotoxins from the pathogens induces the production of cytokines, prostaglandins, and metalloproteinases eventually leading to PTD [79, 80]. Other researches have postulated an association between thyroid autoimmune diseases and PDT [70]. In this issue of the Journal, Gleicher extensively reviews the immune mechanisms that underlie both labor and PTD and questions whether the origins of PDT are organ specific or autoimmunity specific. He describes multiple connections between PDT and a variety of autoimmune diseases such as SLE, rheumatoid arthritis (RA) antiphospholipid syndrome, autoimmune thyroiditis, etc [81]. The review supports the hypothesis that immune factors involved in normal tolerance of the fetal–maternal semi-allograft have the potential ability to provoke labor and that labor, occurring at term or prematurely, is induced by an immunologic placental–fetal signal. This signal has been thought to be related to

increased fetal–maternal cell traffic which can perturb NK cell tolerance and long-term engraftment resulting in a graft vs. host (GVH)-like activation of the maternal immune system. The hypothesis of maternal GVH response described here seems a plausible approach for explaining the still unanswered question regarding the physiology and pathophysiology of both labor and PTD, respectively.

Currently, we are unable to significantly impact immune disturbances that lead to reproductive disorders. This is mainly due to a poor understanding of the mechanisms underlying the immune–reproductive interactions. Elucidating these mechanisms could lead to early identification of patients at risk and to the development of therapies that target specific cell types, cell subsets, receptors, or signaling pathways. Therapeutic approaches directed toward pathogenic autoantibodies, complement, TF, NK cells, or TLRs show promise, but the data are still insufficient to recommend any novel treatments. The main reason for this deficiency is that results from animal studies cannot be directly translated to humans. Blocking of complement system and inhibition of TF with anti-TF antibodies or statins had shown therapeutic effects in mice with APS and rescued the pregnancies in aPL-treated mice [62, 65], respectively, indicating that these might be useful therapeutic options for patients with APS. Targeting TLRs or NK cells in patients with recurrent spontaneous abortions or in autoimmune thyroiditis-associated infertility [67, 78, 82] are also plausible novel treatment methodologies. However, well-designed clinical trials are essential to confirming the efficacy of any of these therapeutic approaches in patients. Obviously, more research is needed to better understand and modify immune system functions at the cellular and molecular levels in order to prevent adverse reproductive outcomes.

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