AN OVERVIEW OF B CELL IMMUNOMODULATORY ROLE IN NORMAL PREGNANCY AND PREECLAMPSIA

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During pregnancy, the key determinant to pregnancy success is the response of the maternal immune system towards the semi-allogeneic fetus. The pregnant uterus produces numerous cytokines such as interleukin (IL)-10 and transforming growth factor-beta (TGF-β) that are of critical importance from an immune perspective due to their immunosuppressive properties. Specific B cells can have a regulatory function in addition to their humoral activity. Pre-eclampsia (PE) is a syndrome that arises in 4%–8% of pregnancies and defined as new-onset proteinuria and hypertension after 20 weeks gestation. PE is characterized by maternal endothelial dysfunction caused by circulating fetal-derived factors from the placenta. The American College of Obstetricians and Gynecologists (ACOG) 2020 described the diagnostic criteria of PE as elevated systolic blood pressure to 140 mm Hg or higher or elevated diastolic blood pressure to 90 mm Hg or higher measured at least 4 hours apart on two occasions after 20 weeks of gestation in a formerly normotensive woman. In the pathophysiology of PE, B cells are a major player. A number of studies have linked abnormal B cell numbers and functions to obstetric problems.

Keywords: *Normal pregnancy, Preeclampsia (PE), B cell subsets.*

INTRODUCTION

Role of B cells in normal pregnancy

During both pregnancy and nursing, maternal B cells are responsible for a key supply of antibody-mediated protective immunity for both mother and baby[1]. Cellular responses are supposed to be reduced during pregnancy and compensated for by enhanced humoral responses to minimize damaging responses[2&3]. The capability of B cells to produce antibodies has been used to indirectly assess their role in pregnancy. As a result, protective antibodies have been associated to a healthy pregnancy, while autoantibodies have been linked to complications during pregnancy[4].

An important study showed that pregnant women, in comparison with non-pregnant women, have substantially higher titers of asymmetric antibodies in their serum. The same group, years later, showed that women with recurrent spontaneous miscarriage have noticeably lower quantities of asymmetric antibodies in their blood than normal pregnant women[5].

B cells derived from a human term placenta and triggered *in vitro* with CD40L and a grouping of cytokines (IL-10, IL-4, and IL-19) produced a substantial number of pregnancy-protective antibodies[6]. Although it

has not been proven, various studies suggest that B2 cells are the primary B cell subset responsible for the production of pregnancy-protective asymmetric antibodies[6&7].

The link between Bregs and pregnancy success was first discovered in mice. An increase in CD5$^+$CD1d$^+$ Bregs is required for preventing immunological abortion in pregnant mice. In fact, transplanting Bregs to abort-prone mice increases Treg cells while keeping dendiritic cells immature, promoting fetal-maternal tolerance[8]. Women who received rituximab, a B cell-depleting antibody, during pregnancy had a higher rate of pregnancy loss in first-trimester[9].

Long-lived antibody-secreting cells were largely produced by memory B cells that protect the host from future pathogen challenges. Many investigations have shown that the reactivation of memory B cells and antibody-secreting cells do not perfectly overlap[10&11].

B cells
cell development and phenotypes

The functional rearrangement of the immunoglobulin (Ig) loci is critical for B-cell development in mice[12] and humans[13]. This is performed through an error-prone process involving the variable (V), diversity (D) and joining (J) gene segments of the heavy (H) chain locus, in addition to the V and J gene segments of the light (L) chain locus[14].

Among bone marrow (BM) B-cell precursors , five major B-cell maturation stages have been recognized based on the status of Ig chain genes and the expression of a diversity of cell surface and intracellular proteins: pro-B, pre-B-I, pre-B-II, immature/Transitional B cells (TrB cells), and mature/naïve B-cells[15&16].

Some cell-surface antigens associated with B cell development

Immunoglobulin is expressed poorly or not at all on the cell surface before the immature B-cell stage, but it is expressed throughout B-cell development until the plasma cell stage. As a result, examining the surface expression of numerous cell-surface markers is frequently employed to distinguish between early and late developmental stages. CD10, CD19, CD20, CD21, CD24, CD27, CD34 and CD38[19&20] are among the most important. Their expression is

frequently assessed in clinical settings to either identify specific functionality or as a target for clinical intervention[21].

B cells and their function

B cells and T cells are lymphocytes that make up the adaptive immune system, which responds to infection in a specific way. They produce antibodies as part of the humoral immunity component of the adaptive immune system. B cells also produce cytokines and are known as professional Ag-presenting cells (APCs). In addition to humoral immunity, B cells regulate a number of activities that are critical for immunological homeostasis[22].

Interleukins such as IL-4, IL-6, IL-10 and tumour necrosis factor-alpha (TNF-α) are all immunomodulatory cytokines that B cells can release. T-cell, dendritic cell (DC) and APC functions are influenced by immunomodulatory cytokines, which also govern lymphoid tissue organisation and neogenesis, wound healing, and transplanted tissue rejection, as well as tumour formation and immunity. B cells can also function as effector cells, releasing polarised cytokines that influence T-cell differentiation[23].

Regulatory B cells (Bregs) control T helper Th-1 and Th17 cell development by decreasing production of pro-inflammatory cytokines by dendritic cell indirectly[24&25]. Breg cells also express transforming growth factor-beta (TGF-β), IL-35, in addition to IL-10 as immune-regulatory cytokines. By generating TGF- β, lipopolysaccharide (LPS)-activated B cells can promote CD4+ apoptosis and anergy in CD8+ effector T cells[26&27]. In humans, Breg cells are also essential for preserving invariant natural killer (iNKT) cell homeostasis[28].

B cells and disease state

B cells have long been linked with humoral immunity, but now known to have a role in cellular immunity as well. B cells activate T cells by antigen presentation, costimulation, and cytokine production. These cells influence antimicrobial defenses and tissue inflammation as well, and function as regulatory cells that govern both cellular and humoral responses[29].

B cells are crucial for immunological responses and long-term well-being[30]. However, an evidence suggests that B cells have a role in the pathophysiology of a variety

of autoimmune illnesses, raising the possibility that they could be a therapeutic target[31]. B cells act as effector cells in autoimmune disorders because they regulate lymphoid tissue structure, aid in antigen presentation, and contribute to costimulation[32].

B cells in autoimmune disorders

Given the random nature of clonal divergence, the generation of self-reactive B cells is unpreventable; in fact, at least half of the antibodies produced by immature human B cells are self-reactive[33]. Antibodies to certain pathogens, as bacteria, may provide an initial kind of "native" immunity. The presence of these self-reactive B cells in the periphery may potentially widen the repertoire of antibodies available in the periphery for expansion, mutation, and selection in reaction to pathogens. Somatic mutations in germinal centers, which boost peripheral diversity, may also contribute to mutations that lead to the development of new autoreactive antibodies. As a result, B cells may arise that express antibodies that have some potential to bind to self-antigens[31].

During B-cell development, at least three pathways are hypothesized that lead to tolerance. These pathways include clonal deletion, receptor editing and anergy[34&35]. According to animal studies, autoimmune B cells have genetic defects that cause tolerance loss. In animals, genetic anomalies that produce intrinsic B-cell abnormalities can develop systemic lupus erythematosus (SLE)-like disorders[36]. An increased risk of autoimmune disease occurred as some human genetic predispositions appeared to have a direct effect on B cells[37&38].

Importantly, as shown in an animal model of SLE, antigen presentation by self-reactive B cells with broken tolerance can activate T cells that were previously anergic to the self-antigen[39&40]. This B-cell impact could contribute to epitope spreading, which occurs when the T-cell compartment becomes reactive to additional locations on a self antigen over time. This appears to be the case with rheumatoid arthritis, where activated T cells are assumed to be the primary mediators of the inflammatory cascade[41].

Negative effects of B cells on tumors

In tumor environment, numerous studies and clinical trials have highlighted both the positive and negative roles of B cells. Agreed that B cells are a vital constituent of the adaptive immune system, their complex functions will have a significant impact on anti-tumor response and will be extensively used for a variety of clinical applications[42]. Many malignancies are extremely infiltrated with B cells, according to several experimental and clinical trials, including breast cancer[43], prostate cancer[44] and colorectal cancer[45].

In addition to the tumor-suppressing capabilities of B cells, B cells suppress immunological responses in a variety of ways, with Bregs being the most vital one[46]. Besides, by interacting with tumor tissues and certain types of lymphocytes, such as T cells, APCs, regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs), B lymphocytes can act as inhibitory effectors[42].

Limited studies have looked into the immunosuppressive role of IL-35-secreting Bregs in tumor promotion. Zhang *et al.* discovered that IL-35 is an independent prognostic factor as well as a therapeutic target for nasopharyngeal carcinoma[47]. According to clinical trials, $CD19^+IL-10^+$ Bregs in hepatocellular carcinoma patients are much lower than in healthy controls and patients with chronic hepatitis B infection before surgery, but they dramatically increase and remain high after surgery[48]. TGF-β-secreting Bregs as well as IL-10 and IL-35-secreting Bregs have received a lot of attention[42].

Role of B cells in other diseases

A study found that in both primary interstitial disorders and secondary interstitial involvement of a primary glomerular disease, such as IgA nephropathy, CD20-positive B cells were found to comprise a considerable percentage of the interstitial infiltrate. The absence of CD10 (pre-B cells) and the presence of CD27 as a B-memory cell marker indicated that most B cells were mature[49]. A significant correlation was found between B cells and the degree of renal function[50].

Preclampsia

INTRODUCTION

Preeclampsia (PE), a pregnancy-specific illness, is characterized as hypertension and substantial proteinuria in a previously normotensive woman after the 20th week of pregnancy[51&52].

A diastolic blood pressure (DBP) of 90 mmHg or more on two occasions at least four hours apart, or a single DBP of 110 mmHg or more, is considered hypertension in pregnancy[53&54]. Significant proteinuria is defined as the presence of 300 mg of protein in 24 hour urine or 30 mg/mmol on spot protein. This correlates with 2+ or more protein in the urine in a semi-quantitative analysis[55].

PE can cause a maternal syndrome (hypertension and proteinuria with or without other multisystem abnormalities) and/or a fetal syndrome [intrauterine growth retardation (IUGR), reduced amniotic fluid, and abnormal oxygenation][56].

Incidence

It is the most prevalent medical complication of pregnancy, with an increasing global frequency that is related to severe maternal morbidity and mortality, accounting for around 50,000 fatalities yearly[57&58]. PE arises in 3.7 percent of nulliparous women and 1.3 percent of multiparous women[59]. In Egypt, The maternal mortality rate is informed to be 37 per 100,000 live births[60]. A study on the occurrence of hypertensive illnesses with pregnancy in Egypt revealed that 4.2% of women had pregnancy-induced hypertension, 3.8% had PE and eclampsia was diagnosed in 0.3% of women[61].

Etiology and risk factors

Clinicians commonly regard PE as a maternal disease with varying degrees of fetal involvement, failing to know that PE is a couple's disease with maternal and fetal manifestations[62]. According to most theories, PE is thought to be produced by a cascade of aberrant maternal inflammatory responses, endothelial cell activation/damage with a deranged hemodynamic milieu, and deranged immunity[63&64].

Multifetal gestations, a history of PE, obesity, diabetes mellitus, vascular and connective tissue disorders such as SLE and antiphospholipid antibodies, age >35 years at first pregnancy, smoking, and African American race are all risk factors for PE[65]. During the first pregnancy, the risk of developing PE is 4.1%. Among women who have had PE in all past pregnancies, the risk increases to 14.7% in the second pregnancy and 31.9% in the third pregnancy[66].

Classification of preeclampsia

The current classification of hypertension in pregnancy was proposed in 1972 by the American College of Obstetricians and Gynecologists (ACOG) Committee on Terminology. The National High Blood Pressure Education Program Working Group prepared additional modifications in 2000, resulting in a classification scheme that provides straightforward, short and clinically relevant features for each of the four categories. This system differentiates four types of pregnancy hypertension: gestational hypertension, PE/eclampsia, chronic hypertension, and chronic hypertension with superimposed PE[67]. Several changes were made far ahead in the ACOG classification of gestational hypertension and PE, with the newest being published in 2020[55].

The ACOG Executive Summary recommends that the term "mild" be dropped. The terms "PE without severe features" or "PE with severe features" are recommended. This disease is rarely stable, but can quickly develop from "mild" PE to severe PE, HELLP Syndrome, and/or eclampsia, especially before the age of 34 weeks[68].

Pathophysiology

A defective interaction between trophoblastic cells and uterine natural killer (NK) cells is currently thought to be the cause of trophoblastic invasion failure. TNF-α is also released into the circulation through the same mechanism. Maternal killer immunoglobulin like receptors and fetal Human Leukocyte Antigen-C (HLA-C) molecules are also involved in this immunologic pathway at the placental level[69].

As a result of placental pieces discharge into the circulation, a microtrauma at the level

of the placenta was formed. These fragments motivate a systemic inflammatory response, activating leucocytes and platelets, which promotes inflammation, releases free radicals and leads to vascular endothelial damage and dysfunction[70]. Hypertension, proteinuria and other systemic reactions are all symptoms of vascular endothelial dysfunction and injury[71]. Researchers found that there is a connection between defective angiogenesis, variations in local oxygen tension and immunological changes in the early placental microenvironment, all of which could play a role in the development of PE[64&72].

Some components of both innate and adaptive immune systems may have a role in the physiopathology of PE by cytokines production, modulating immune responses or displaying a changed function that could lead to the disease's symptoms[72].

The innate immune system

In a normal pregnancy, nonspecific or innate immune system leukocytes are vital because they aid implantation and participate in various activities at the feto-maternal interface[63]. Under hypoxic circumstances, activated monocytes and neutrophils are present in the fetal and placental circulation, which may contribute to increased vascular resistance and morbidity of the fetus in PE[73]. Monocytes from preeclamptic individuals secrete significant quantities of IL-1β, IL-6 and IL-8, which could be a key source of proinflammatory cytokines in PE[74].

Inflammatory cytokines released by T cells have been linked to neutrophil activation in PE. Activated neutrophils can harm arteries and interact with platelets and coagulation processes, causing vascular damage[75]. In early human pregnancy, uterine NK cells, may impede the invasion of the extravillous trophoblast[76].

Preeclamptic women's peripheral NK cells had lower amounts of intracellular vascular endothelial growth factor (VEGF) than normal pregnant women[77]. Although dendritic cells play a key role in triggering induced Treg, they do not induce iTreg cells well in PE[78].

The adaptive immune system
Role of T cells

At the fetal-maternal interface, a transition from a Th1 to a Th2 phenotype may not occur in PE. So, Th1/Th2 paradigm has been employed to describe T cell behavior in the disease. Th2 cytokines like IL-10 and IL-5 can be suppressed in PE, but Th1 cytokines like IL-1, IL-2, and IFN-γ are abundant[79]. The occurrence of inflammatory diseases could be linked with lower Treg function in PE[80]. In addition to Tregs, PE may also involve IL-17-producing CD4 T cells (Th17). The ratio of Tregs:Th17 cells showed to be lower in preeclamptic patients[81].

Role of B cells

In the pathogenesis of PE, B cells play a major role[82]. Before or during pregnancy, auto-antibody production such as anti-phospholipid antibodies, can arise after an infection. These autoantibodies can be responsible for pregnancy-related disorders. The development of PE is linked to the production of pathogenic antibodies and alterations in immunological markers[83,84].

A number of studies showed a link between abnormal B cell numbers and functions to obstetric problems[85-88]. According to a major study, preeclamptic women have functional changes in peripheral B-lymphocytes, as shown by two findings: significantly increased populations of peripheral CD27$^+$CD38$^-$ memory B-cells and CD27$^+$CD38$^+$ plasma cell pre-cursors and enhanced capacity of B cells differentiation into antibody-producing cells[88].

Treatment of preeclampsia

Induction of labor/early delivery remains the critical treatment for PE. Health outcomes associated with delivery versus expectant management of severe PE that occurred before 34 weeks are limited and inconclusive, according to trial evidence. Preventing seizures and controlling hypertension are the management goals during labor[55].

Magnesium sulfate is the drug of choice for avoiding eclamptic seizures in women with severe PE and treating eclamptic seizures in women who already have them[55]. The significance of magnesium sulphate as a first-line treatment for eclampsia and as a preventive measure against eclampsia in women with

severe PE has been emphasized by guideline groups[89-91].

Antihypertensive medication therapy is advised for pregnant women who have a verified systolic blood pressure of 160 mm Hg or a diastolic blood pressure of 110 mm Hg or both[55]. Intravenous hydralazine, intravenous labetalol and calcium channel blockers, particularly short-acting oral nifedipine, have been increasingly widespread in recent years[92].

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لمحة عامة عن الدور المناعي للخلية البائية في الحمل الطبيعي وتسمم الحمل

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خلال فترة الحمل ، المحدد الرئيسي لنجاح الحمل هو استجابة الجهاز المناعي للأم تجاه الجنين. رحم المرأة الحامل ينتج العديد من السيتوكينات مثل انترلوكين ١٠ و β-TGF وقد تم تحديدها على أنها ذات أهمية حاسمة من منظور المناعة بسبب خصائصها المثبطة للمناعة. يمكن أن يكون لخلايا بائيــة محددة وظيفة تنظيمية بالإضافة الي نشاطها الخلطي. تسمم الحمل (مقدمات الارتعاج) هي متلازمة تنشأ في ٤–٨% من حالات الحمل وتتميز ببروتينية البول وارتفاع ضغط الدم بعد ٢٠ أسبوعا من الحمـــل. تسمم الحمل (مقدمات الارتعاج) يتميز بخلل بطاني للأم الناجم عن العوامل المتنقلة المشتقة من الجنـــين من المشيمة. وفقا لهيئة أطباء النساء والتوليد الأمريكية لوحظت معايير تشخيص تسمم الحمل (مقدمات الارتعاج) على أنها ضغط دم انقباضي يبلغ ١٤٠ ملم زئبق أو أكثر أو ضغط دم انبساطي يبلغ ٩٠ ملم زئبق أو أكثر في مناسبتين يفرق بينهم على الأقل ٤ ساعات بعد ٢٠ أسبوعا من الحمل في امرأة تعاني من ضغط دم طبيعي سابقا. في الفيزيولوجيا المرضية لتسمم الحمل (مقدمات الارتعاج) ، تعد الخلايـــا البائية لاعبا رئيسيا . عدد من الدراسات ربط أعداد ووظائف الخلايا البائية غيـــر الطبيعيـــة بمشـــاكل الحمل.