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Review

Natural killer T cells in Preeclampsia: An updated review

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ABSTRACT

Preeclampsia (PE), as a pregnancy-specific syndrome, has become one of the main causes of maternal and fetal mortality worldwide and is known as a major risk factor for preterm birth. PE is typically characterized by hypertension, significant proteinuria, and an excessive maternal systemic inflammatory response. Recent evidences provide support for the notion that Natural killer T (NKT) cells (a small, but significant immunoregulatory T cell subset of human peripheral blood lymphocytes) play pivotal roles in pregnancy. NKT cells with unique transcriptional and cytokine profiles exist in different peripheral tissues acting as mediators between the innate and adaptive immune systems. NKT cells secrete Interleukin-4 (IL-4) and Interferon-γ (IFN-γ) which might regulate the balance between Type 1 T helper (Th1) and Type 2 T helper (Th2) responses. During pregnancy, maternal immunity is biased towards type II cytokine production to inhibit the function of type I cytokines that could be harmful for the developing fetus. This shift to type II cytokines does not occur in preeclamptic patients. In this review, we discuss the numbers, phenotype, changes, and the functional activity of Natural killer T (NKT) cells during normal pregnancy and preeclampsia.

1. Introduction

As a specific disorder, preeclampsia (PE) occurs in the second half of pregnancy [1].The complications and their associated pathologies inherent in PE are known to be as the major causes of maternal and fetal morbidity as well as mortality across the globe [2–4]. For instance, PE is thought to be responsible for preterm birth, intrauterine growth restriction, and prenatal death in the fetus as well as in eclampsia and hemolysis and elevated liver enzymes and low platelet count(HELLP) syndrome in the mother [5].

Approximately 40% of premature births are reported to be delivered before 35 weeks of gestation [2]. Furthermore, preeclampsia is claimed to be the causative factor for nearly 12–25 percent of fetal growth restriction and 15–20 percent of preterm birth cases [6].Within the recent years, the rate of maternal morbidity and mortality associated with preeclampsia has shown a considerable decrease in developed countries [5]. However, there has been reported an increase in later-life death related to cardiovascular diseases, which is independent of other risk factors [2,4]. Moreover, preeclampsia is prevalent in women who experience their first pregnancy or carry twins [7]. High blood pressure (≥ 140 mm Hg systolic or ≥ 90 mmHg diastolic on ≥ 2 occasions at least 6 h apart) [8], proteinuria [9], (at least 300 mg per 24 h) [5], and dysfunction of different organs [10] are hallmark characteristics of this clinical syndrome.

There are also some risk factors associated with preeclampsia which include nulliparity, multifetal gestations, previous history of preeclampsia, obesity, diabetes mellitus, vascular and connective tissue disorders such as systemic lupus erythematosus and antiphospholipid antibodies syndrome, age > 35 years at first pregnancy, smoking, and African-American race [11]. Recently, it has been found that immune abnormalities make significant contributions to the pathogenesis of preeclampsia [12].

The findings have suggested that innate immunity play a more important role than adaptive immunity in the emergence of preeclampsia, especially increase of circulating monocytes, neutrophils and natural killer (NK) cells [13]. Also, it is of interest to note that there is an exacerbated maternal inflammatory response in patients with preeclampsia [14]. These responses may be attributed to the dominance of Th1 cells [15].

Natural killer T (NKT) cells are recognized as a distinct subset of

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peripheral leukocytes [3]. Once activated, NKT cells secrete cytokines and boost the immune response which is triggered by a variety of interactions between NKT cells and other cell types including conventional $CD4^+$ T and $CD8^+$ T cells, dendritic cells (DCs), Natural killer (NK) cells, B cells, T regulatory (Treg) cells, macrophages and neutrophils [16]. These cells impact on large variety of immunological responses which include autoimmunity [17], antimicrobial host responses [18], resistance to tumors and transplantation immunity [19]. that are also increasingly activated in PE [3].

Some studies have provided supporting evidence for the possible significant role of NKT cells in pregnancy and preeclampsia. Consistent with this, it has been reported that treatment of pregnant mice with *α-Galactosylceramide* (α-GalCer) leads to the occurrence of abortion which might be attributed to the release of Interferon gamma (IFN-γ) by NKT cells [20,21]. Also, there are some convincing data highlighting a strong link between NKT cells and priming Type 2 T helper (Th2) immune responses [22]. Furthermore, it has been demonstrated that both NK cells and proliferating cells, which are crucial to the progression and success of pregnancy, are regulated by NKT cells [23]. Based on these facts which imply the importance of NKT cells in the emergence of preeclampsia, the current review aims to investigate the roles that NKT cells play in the pathogenesis of this condition.

2. Natural killer T subsets

NKT cells, which were first described in the late 1980s as innate-like lymphocytes [24] are known to be a new lymphocyte lineage [25]. These cells are characterized by the presence of Natural *killer cells* (NK cells) receptors with an invariant α-chain, NKT cells express αβTCR [26].

NKT cells are representative of a group of T lineage cells of thymic origin which have a variety of features. These features can be used to describe how NKT cells are different from 'conventional T cells' [26,27]. NKT cells recognize lipid antigens (mainly glycolipids) in the context of CD1d, a non-polymorphic major histocompatibility complex (MHC) class I-like molecule [27]. CD1d is expressed by hematopoietic cells [28] and on the surface of villous or extravillous trophoblasts [29] to interact with NKT cells in the deciduas [30]. The amion and the placenta are riched for sphingoglycolipids, many of which are gangliosides-containing sialic acid [31] that perhaps presented in the context of CD1d and recognized by NKT cells [32]. So it is vital to explain the roles of NKT cells-restricted CD1 that reside at the feto-maternal interface during pregnancy [33].

NKT cells are used to name some subsets of T lymphocytes, which are distinct in their phenotype, functional capacities and tissue distribution. There are two distinct types of NKT cell subpopulations [34] known as Type I and Type II lymphocytes [35].

NKT cells develop in the thymus, at least for the invariant NKT (iNKT) cells (Type I) cell lineage. There are numerous lines of convincing evidence highlighting that these cells undergo positive and negative selections [28].

Type I iNKT cells comprise a small, but significant immunoregulatory T-cell subset [29].

These cells express canonical TCRα chains which consist of certain gene segments, Vα14-Jα18 in mouse and Vα24-Jα18 in human. Furthermore, they preferentially pair with specific TCRβ chains including Vβ8, Vβ7, or Vβ2 in mouse and Vβ11 in human [24].

The majority of decidual NKT cells as well as other tissues such as bone marrow and liver and peripheral blood in human express Vβ11 [36]. iNKT cells are capable of recognizing a spectrum of bacteria-derived lipids. In addition, iNKT cells can also recognize endogenous lipids [37]. This property provides them with the ability to mature DCs and B cells in a CD40-dependent manner [38]. iNKT cells are able to quickly release both Th1-type and Th2-type cytokines (IFN-γ, TNF-α, IL-10 and IL-4) [39] in response to α-Galactosylceramide (α-GalCer). α-GalCer is also thought to have the capacity for inducing a distinct lineage of iNKT cells known as NKT10 cells [40].

Type II variant NKT cells (VNKT) [28] are defined as CD1d-dependent T lymphocytes that do not express the invariant TCR-α chain and cannot recognize the lipid antigen α-GalCer [41]. VNKT cells are able to express a more diverse range of T-cell receptors (TCRs), and often play roles conflicting or cross-regulatory with iNKT cells [28]. VNKT cells are also more abundant in human than mouse [42].

Here, we focus on Type I NKT cells [43]. iNKT cells can be subdivided into NKT1, NKT2, NKT17, NKTFH, NKT10 regulatory and Foxp3+ iNKT cells [26,44].

The maturation of these cells in mouse consists of several distinct stages on the expression of CD24, CD44 and NK1.1 molecules. The most immature stage of iNKT cells is defined as stage 0 ($CD24^{high}CD44^{low}NK1.1^-$) which is followed first by stage 1 ($CD24^{low}CD44^{low}NK1.1^-$) and then by stage 2 ($CD24^{low}CD44^{high}NK1.1$).

Mature iNKT cells (Stage 3) are subdivided into at least three distinct populations, including NKT1 ($CD4^{+/-}$ $NK1.1^+$), NKT2 ($CD4^+$ $NK1.1^-$), and NKT17 ($CD4^-$ $NK1.1^-$) [45,46].

NKT1 and NKT2 mainly reside in non-lymphoid organs, while NKT17 cells are found in the peripheral lymph nodes (Fig. 1) [26].

NKT1,when activated, express high levels of T-bet and produce IFN-γ [47]. These cells have also been demonstrated to express IL-15Rα (CD122) and loss of IL-15 also resulted in loss of NKT1 cells [48]. However, loss of T-bet or functional IL-15 has been found to enhance the number of NKT2 and NKT17 cells [47,49]. Recent findings have suggested that the transcription factor inhibitor of DNA binding 2(ID2) is highly upregulated in the NKT1 sublineage [50].

NKT2 cells, which are similar to Th2 cells, are characterized based on the cell surface expression of CD4 and interleukin-17 receptor B (IL-17RB) [51]. Moreover, these cells are able to produce interleukin-4 (IL-4) and interleukin-13 (IL-13).

IL-17RB has been shown to be expressed also by NKT17 cells [49]. A new subset of CD4, NK1.1 NKT cells, has been identified which are characterized by their ability to produce very high amounts of IL-17 (NKT-17) early after being activated without the need for polarization [52–54].

NKT-17 cells express retinoic-acid-receptor-related orphan receptor (ROR) γt and Interleukin-23 receptor (IL-23R) [55].

Natural killer T follicular helper (NKTFH) cells trigger specific antibody responses and germinal center reactions (GCs). NKTFH cells containing $CD4^+$,$CD44^{high}$,programmed cell death protein 1($PD\text{-}1^+$), C-X-C chemokine receptor type 5,$(CXCR5)^+$, B-cell lymphoma 6 protein ($Bcl6^+$) and the capacity for IL-21 secretion display high similarities to TFH cells. New findings highlight the significant role of NKTFH cells during antibody responses to protein [56,57], lipid, and carbohydrate antigens [58]. Recently, invariant NKT(iNKT) cells have been found to adopt the phenotype of TFH cells and to be localized within GCs. This finding is consistent with their ability to provide help for cognate B cells. The same procedure is required to differentiate iNKTFH and TFH cells [56] except for the fact that IL-21 is not needed for iNKTFH cell formation, even though it is crucial to their cognate functions [59].

NKT10 regulatory cells have a new surface phenotype and are able to produce a different cytokine pattern such as production of IL-10, a cytokine which mediates immune suppression. This capacity of NKT10 regulatory cells has served as a basis for suggesting the name "induced NKT10 cells". In addition, FOXP3 is required for the proper functioning of regulatory T cells (Tregs) [60]. Moreover, the expression of this transcription factor can be induced in iNKT cells [61,62]. However, NKT10 cells do not induce FOXP3 [63]. NKT10 cells possess some properties of regulatory T cells including the increased expression of cytotoxic T-lymphocyte associated protein 4 (CTLA4), neuropilin1(Nrp-1), and folate receptor 4 (FR4) [64]. Understanding the function of NKT10 subset may lead to obtaining deep insights into the anti-inflammatory role of iNKT cells in a variety of disease settings. It has been revealed that high expression levels of IL-10 mRNA are related to the