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FOXP3 and Regulatory T Cells in Preeclampsia: Immune Dysregulation, Mechanistic Insights, and Clinical Implications

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Abstract: Preeclampsia remains a major obstetric complication characterized by high maternal and fetal morbidity and mortality. Emerging evidence suggests that the failure to establish maternal-fetal immunotolerance is a primary driver of the disease. Regulatory T cells (Tregs), governed by the master transcription factor FOXP3, play a pivotal role in maintaining this immunological equilibrium.This review explores how diminished FOXP3 expression and Treg dysfunction trigger a hyper-inflammatory environment that impairs trophoblast invasion and prevents the physiological remodeling of spiral arteries. Unlike conventional reviews, this paper highlights the critical role of epigenetic modifications, such as FOXP3 promoter hypermethylation, in the loss of Treg functional stability and their subsequent plasticity toward pro-inflammatory phenotypes.Furthermore, we propose a novel diagnostic framework integrating FOXP3 expression with angiogenic markers (sFlt-1/PlGF) as an early predictive tool. The

review concludes by discussing promising therapeutic avenues, including low-dose Interleukin-2 (IL-2) immunotherapy and "immune reset" strategies, paving the way for precision medicine and personalized interventions in obstetric care.

Keywords: Preeclampsia; FOXP3; Regulatory T cells; Epigenetics; Immunotolerance; Biomarkers.

Introduction

Preeclampsia is a severe pregnancy disorder that usually appears in the third trimester, after week 20 of pregnancy. Key features: the relationship between blood pressure increase and the presence of proteinuria, and hypertensive disorders in the presence or absence of signs of organ dysfunction (1). The condition creates a risk to both the mother and the fetus because it can impact multiple bodily systems. Fetal growth restriction, premature labor, placental abruption, abnormal liver enzymes, low platelet count (HELLP syndrome), and eclampsia are among the many consequences associated with this illness. Therefore, early treatment of this illness might lessen problems for both the mother and the child(2). Maternal-fetal immune tolerance is critical to maintaining a successful pregnancy and employs unique regulatory mechanisms that depend on trophoblast expression signatures, immune regulatory cytokines, and regulatory lymphocytes. A key regulator here has been the release and regulation of factors such as sCD83 that are implicated in the creation of an anti-inflammatory microenvironment conducive to tolerance induction(3). Decidual regulatory T cells (Tregs), especially those expressing CCR8, are among the most important cellular factors that modulate immunity in the tolerance process and are essential for maintaining mother and fetus immune homeostasis. These cells ensure normal trophoblast invasion and prevent disorders during pregnancy like miscarriage and preeclampsia(4). Regulatory T cells, especially FOXP3+ cells, play vital roles in maintaining maternal-fetal immune tolerance against paternal antigens. By mechanisms of immune suppression, including CTLA-4 activation, IL-10/TGF-β production, as well as the inhibition of effector T cell proliferation, Tregs regulate immune responses at the maternal-fetal interface. Normal pregnancy is linked to a striking increase in antigen-specific Tregs, which maintain immune homeostasis in the decidual tissues. An impairment in the FOXP3 regulatory circuit raises the predisposition to inflammatory challenges, potentially leading to pregnancy complications, including preeclampsia, preterm birth, as well as preterm premature rupture of membranes(5).

Preeclampsia

Preeclampsia can be defined as a condition involving blood pressure elevation and protein excretion beyond the 20th week of gestation. Abnormal placentation and placental dysfunction, associated with inadequate uterine perfusion, have been revealed as the main causes of preeclampsia(6). The main reason for maternal mortality is pregnancy-induced hypertensive disorders (HDP). Maternal death due to hypertensive disorders is related to all forms of hypertensive disorders, as eclampsia and preeclampsia are found to be the main causes of death(7).

The hypertensive disorders of pregnancy have a classification in the international guidelines, and in relation to preeclampsia, these are recommended to be made if hypertension is associated with a

loss of maternal organ function (including the kidneys and liver) or uteroplacental dysfunction. This approach to diagnosis helps improve the ability to assess the risks associated with the condition(8).

Clinically, various studies have been utilizing timing phenotypes based on preeclampsia onset as either early-onset preeclampsia prior to 34 weeks of gestational age and late-onset preeclampsia at or after 34 weeks of gestational age. Notably, these two phenotypes often include heterogeneous cases in placental lesions, maternal risk factors, and pregnancy outcomes. Early-onset preeclampsia has been more typically associated with adverse placentation and placental lesions in severe cases, including in newborns, whereas late-onset preeclampsia has often been correlated with maternal rather than placental lesions(9)

Epidemiology and Risk Factors

Preeclampsia remains a challenge in the global obstetric environment and has a prevalence range varying between 2% and 8% according to the demographic and setting in which one seeks treatment. The effects range beyond the time of childbirth because the survivors demonstrate higher susceptibility to heart and neurological disorders in their subsequent life(10). Major clinical risk factors that appear in all or most recommendations include previous preeclampsia, chronic hypertension, pregestational diabetes mellitus, renal disease, autoimmune conditions, multifetal gestation, and obesity or increased BMI. Risk stratification remains critical because this process determines preventive measures, such as aspirin therapy for those who are at high risk(8).

Evidence related to the assessment of the risk factors portrayed in the clinical practice guidelines shows disparity in the assessment of the risks post-evaluation but shows strong associations with the presence of chronic hypertension, previous preeclampsia, diabetes mellitus, and increased maternal adiposity. This disparity likely explains the differences in the observed prevalence rates reflected across the articles. There exists a need to specify the criteria for review articles(11).

Pathogenesis

The pathogenesis of preeclampsia is thought to occur in two stages (**Figure 1**) although the fact that its exact cause is unknown. The placenta serves as where the first stage starts, and the second stage is marked by an abnormal maternal endothelial response that causes edema, proteinuria, and hypertension (12).

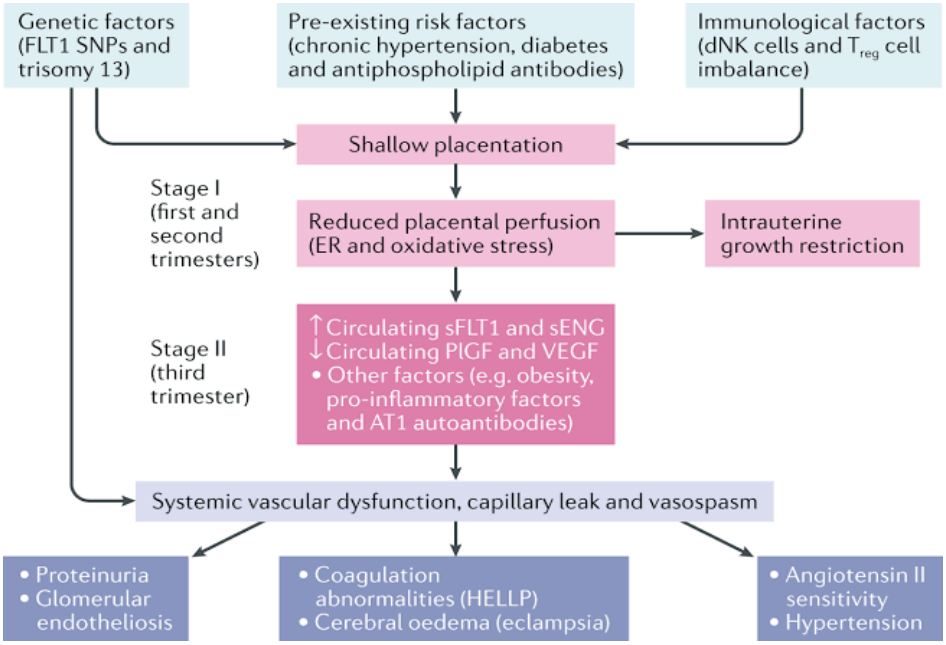

Figure 1: Pathophysiological Mechanisms and Clinical Progression of Pre-eclampsia.": The figure specifically highlights the transition from Stage I (placental origins) to Stage II (maternal systemic disease)

The two-stage model of preeclampsia development is depicted in (**Figure 1**). Shallow placentation in Stage I (first and second trimesters) is caused by immunological factors like imbalanced natural killer (dNK) cells and regulatory T cell (Treg) imbalance, pre-existing risk factors like diabetes, chronic hypertension, and antiphospholipid antibodies, and genetic factors like trisomy 13 and FMS-like tyrosine kinase 1 single nucleotide polymorphisms (FLT1 SNPs). This causes stress in the placenta and decreased placental blood flow, which may occasionally result in intrauterine growth restriction. decreased placental growth factor (PIGF) and the vascular endothelial growth factor (VEGF), increased levels of soluble FMS-like tyrosine Kinase 1 (sFLT) and soluble endoglin (SENG), and the impact of additional variables like obesity, inflammation, angiotensin II type 1 (AT1) autoantibodies, hemolysis, elevated liver enzymes, low platelet count (HELLP syndrome), cerebral edema (eclampsia), elevated angiotensin II sensitivity, and hypertension are all consequences of placental issues in Stage II (third trimester)(13). The placenta is known to have a crucial role in the pathogenesis of preeclampsia. This is known because preeclampsia can only develop during pregnancy, it resolves at the time of placental delivery, and it can develop in the absence of a live fetus as with molar pregnancies. The spiral arteries that branch off the uterine artery provide the placental tissues with blood. The growth of the placenta is a carefully coordinated process that is necessary for proper fetal growth(14). During pregnancy, there is spiral artery remodeling at different levels, which begins at the time of implantation. This results in the transformation of low-flow and high-resistance spiral arteries to high-flow and low-resistance arteries that ensure proper placental growth (**Figure 2**). In preeclampsia, there is defective spiral artery remodeling. It is considered crucial in the pathogenesis of preeclampsia(15).

The maternal spiral arteries have been invaded by cytotrophoblasts, which change them from high-flow, weakly resistant vessels during a healthy pregnancy (top) to defective remodeling during preeclampsia (bottom)(16). The spiral arteries are partly invaded by cytotrophoblasts in preeclampsia. This is mostly limited to the spiral arteries' decidual portions; the myometrial sections are not affected. The spiral arteries continue to be small, high-resistance arteries as a result of incomplete physiological changes. Increased oxidative stress and placental under perfusion are to blame for this. This means that as pregnancy progresses and the fetus's need for oxygen and nourishment increases, the uteroplacental vascular alterations become impaired, resulting in growth limitation and preeclampsia symptoms. There is insufficient explanation for the immunological, environmental, and genetic factors linked to the development of faulty vascular alterations during pregnancy, despite the aforementioned beliefs(17). (**Figure 2**)

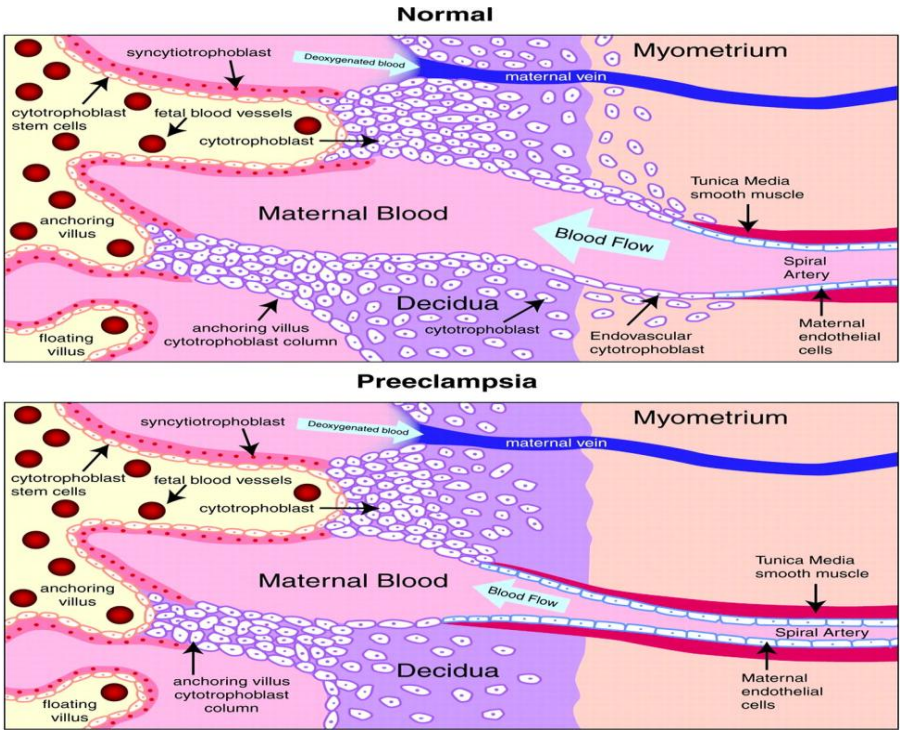

Figure 2: the physiological differences in placental development between a healthy pregnancy and one affected by preeclampsia. : **Normal Pregnancy (Top Panel)** In a healthy pregnancy, fetal cells called **cytotrophoblasts** invade the maternal uterine wall (the decidua and the inner third of the myometrium): **Spiral Artery Remodeling:** The cytotrophoblasts replace the maternal endothelial lining of the spiral arteries and destroy the thick muscular wall (**Tunica Media**). Preeclampsia (Bottom Panel) :Preeclampsia is often characterized by "shallow placentation," where this remodeling process fails. Failed Invasion: The cytotrophoblasts do not invade deeply into the myometrium. They fail to adequately replace the maternal endothelial cells. Narrow Vessels: The Tunica Media (smooth muscle) remains thick and intact. This keeps the spiral arteries narrow and reactive.

The second stage of preeclampsia development can be distinguished from a normal pregnancy by a pro-inflammatory state and enhanced maternal endothelial activation(18). Through trophoblast breakdown, oxidative stress, and the release of bioactive substances into mother's blood, placental hypoxia sets off a series of systemic pathogenic mechanisms in preeclampsia. Because of iron overload and decreased glutathione peroxidase 4 (GPx4) activity, hypoxic circumstances upset the redox equilibrium and induce lipid peroxidation and ferroptosis in placental cells(19).This results in alterations to syncytiotrophoblast structure caused by the disruption of syncytiotrophoblast microparticle (STBM) structure, leading to their release along with soluble factors such as soluble endoglin (sENG) and soluble fms-like tyrosine kinase-1 (sFLT-1) into the maternal bloodstream. These factors induce immune cells in the maternal bloodstream to produce pro-inflammatory cytokines such as TNF-α and IL-6. These soluble factors inhibit angiogenesis through blockade of vascular endothelial growth factor (VEGF) and transformation growth factor-β (TGF-β) (20) **figure 3**.

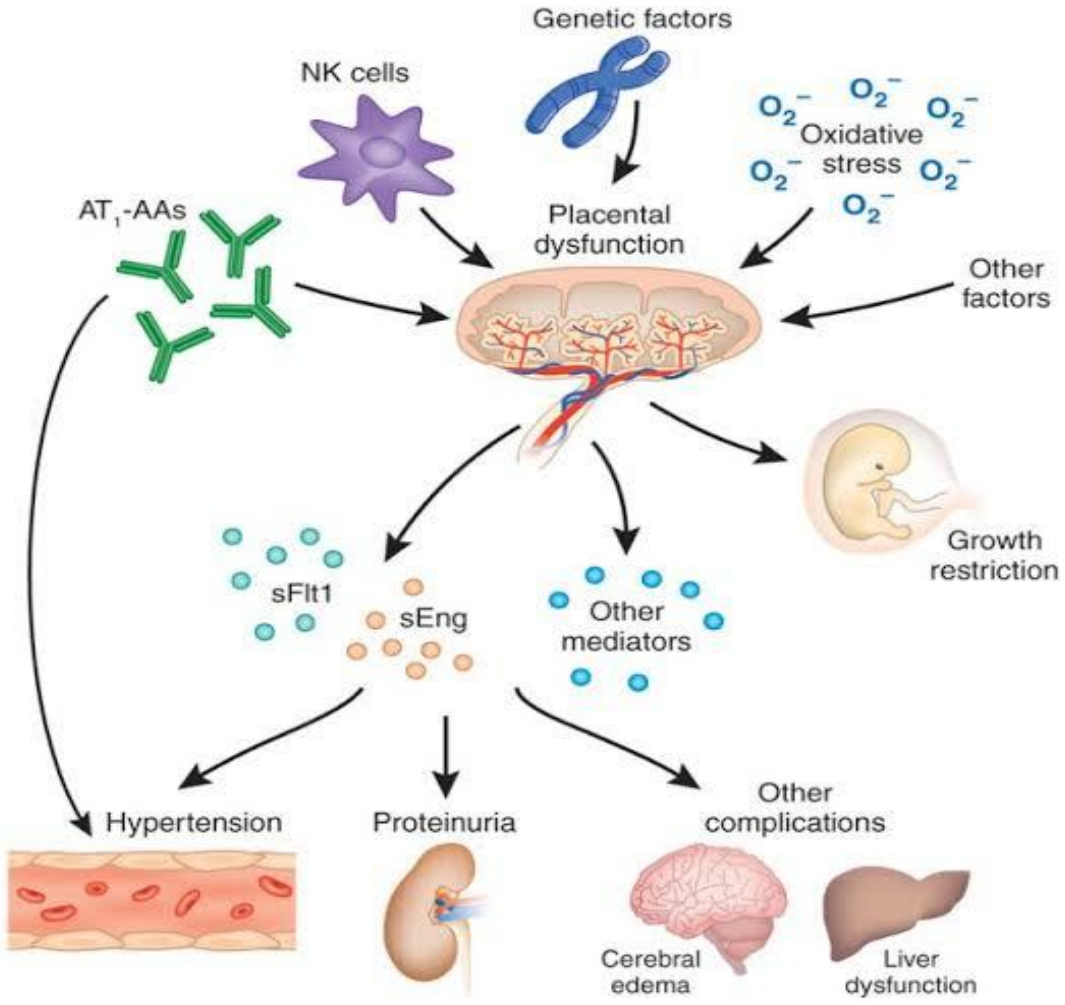

Figure 3: the pathophysiology of Preeclampsia, The process is generally divided into two stages: Placental Dysfunction (the cause) and the Systemic Syndrome (the symptoms).

Preeclampsia pathogenesis: Placental dysfunction is caused by oxidative stress, immune cell failure, NK cells, and genetic factors. Autoantibodies that target angiotensin II receptors (AT1-AAs), soluble endoglin (sENG), soluble fimbs- comparable tyrosine kinase-1 (sFLT-1), and other mediators are released in greater quantities as a result. Maternal hypertension, proteinuria, fetal development restriction, and problems such liver dysfunction and cerebral edema are the outcomes(21).

Regulatory T Cells

Regulatory T cells (Tregs) represent a professional subpopulation of $CD4^+$ T cells that play a crucial role in maintaining immune homeostasis and preventing excessive immune responses(22). Tregs mediate these immunosuppressive effects through contact-dependent mechanisms, cytokine-mediated inhibition, including interleukin-10 (IL-10) and transforming growth factor beta (TGF-β), and metabolic disruption of effector T cells(23). From their point of origin, regulatory T cells can be classified into two categories: thymic-derived regulatory T cells and peripherally induced regulatory T cells. The role played by thymic-derived regulatory T cells is primarily for maintaining central tolerance since their point of origin is the thymus together with the development process for T cells(24, 25).

Function-wise, regulatory T cells (Tregs) restrain autoimmunity, control inflammation, and modulate the immune response to self and foreign antigens. Such regulatory function is crucial, for instance, during an infection, transplant, and pregnancy, where the regulation of the degree of activation of the immune response is needed(26). Regarding pregnancy, regulatory T cells or Tregs assist in achieving maternal immune tolerance by regulating anti-fetal immune responses, thus aiding fetal survival and a healthy gestation period(27).

FOXP3

FOXP3 is well identified to be the main regulator of the development and function of regulatory T cells, or Tregs. FOXP3 is part of the fork head/winged-helix transcription factors, which are crucial for the definition of the Treg lineage phenotype itself(28). Constant expression of FOXP3 keeps regulatory T cells distinct from activated effector T cells, as it is required for maintaining the identity of regulatory T cells(29). FOXP3 promotes a transcriptional network mainly involved in repressing pro-inflammatory signals while inducing the expression of key molecules for the suppressive function, including CTLA-4 and CD25, thus allowing Tregs to suppress effector responses(30).The stability of FOXP3 expression is maintained by a characteristic epigenetic profile, including the hypomethylated status of the regulatory T cell-specific demethylated region (TSDR), which supports the suppressive function and reduces the risk of differentiation into effector cells(29). Both the presence of regulatory T cells (Tregs) and enhanced suppressive circuits happen under specific conditions within an immune system(31). Because of the critical role it plays, the deregulation of FOXP3 gene expression has been known to affect the regulation of Treg cells and has been related to many immunological disorders due to its crucial role in regulating the immune system(32).

Role of FOXP3 in Normal Pregnancy

A successful spontaneous pregnancy requires immune tolerance of the semi-allogenic fetus as well as protection against microorganisms. One of the fundamental mechanisms that mediate such immune homeostasis is the expansion and functional differentiation of regulatory T cells (Tregs), which belong to a lineage whose identity is controlled by the transcription factor FOXP3(33).

FOXP3 plays a role in the regulation of the regulatory T cell (Treg) phenotype, controlling the expression of genes involved in the immune suppressive function, and plays a crucial role in immune regulation under inflammatory conditions. Under normal pregnancies, the numbers of

FOXP3+ CD4+ Tregs increase systemically, importantly, there is an accumulation of these cells at the maternal-fetal interfaces, which help to suppress excessive activation of effector T cells against placenta and fetus antigens(34). The decidua is not immunologically inert, since implantation and early placental development confer a state of controlled inflammation. FOXP3+ regulatory T cells (Tregs) help in ensuring that the state of inflammation post-implantation remains a physiological as opposed to a pathological process by dampening a pro-Th1/Th17 response while inducing a tolerogenic microenvironment that promotes trophoblast invasion and placentation(35). One of the very important roles of FOXP3+ regulatory T cells (Tregs) during pregnancy is their contribution to uterine/decidual vascular remodeling, which is essential for optimal perfusion of the placenta. The depletion of FOXP3+ Tregs has been shown to interfere with spiral artery remodeling during early pregnancy studies, suggesting that Tregs, as well as the gene expression program mediated by FOXP3, play an important role in creating an optimal placental bed(36).

FOXP3 and Preeclampsia

Regulatory T cells, especially FOXP3+ cells, play vital roles in maintaining maternal-fetal immune tolerance against paternal antigens. By mechanisms of immune suppression, including CTLA-4 activation, IL-10/TGF-β production, as well as the inhibition of effector T cell proliferation, Tregs regulate immune responses at the maternal-fetal interface. Normal pregnancy is linked to a striking increase in antigen-specific Tregs, which maintain immune homeostasis in the decidual tissues. An impairment in the FOXP3 regulatory circuit raises the predisposition to inflammatory challenges, potentially leading to pregnancy complications, including preeclampsia, preterm birth, as well as preterm premature rupture of membranes(5). Evidence from numerous research studies has confirmed the reduced frequency as well as the suppressive functions of $FOXP3^+$ Tregs following pregnancies complicated by preeclampsia. In pregnancies complicated by PE, compared to those not complicated, reduced levels of FOXP3 gene expression were observed in the periphery, as well as within the placental tissue and the decidua. Moreover, the suppressor functions were diminished. The reduced levels of Tregs have contributed to a state of reduced immune tolerance, as well as a favorable immune microenvironment, primarily driven by effector T cells as well as NK cells. These findings indicate a possible pathogenesis of PE(37). The histological studies, along with molecular studies, have identified a substantial decrease in $FOXP3^+$ cells in the placentas of women affected by preeclampsia, especially within the basal region of the placental decidua, which experiences direct contact between maternal immune cells and the trophoblasts. The decrease in $FOXP3^+$ cells is coupled with an enhanced entry of activated macrophages, effector, T cells, associated primarily with uncontrolled local inflammation. A lack of Tregs results in excessive cytokine production, trophoblasts' poor invasiveness, as well as shallow spiral artery remodeling, identified as a set of criteria underlying the development of PE(38). Among the pioneering studies investigating this condition, it has been observed that the level of $FOXP3^+$ Tregs significantly diminished in women with preeclampsia compared to those without the condition. In fact, it has been noted that the reduced level of $FOXP3^+$ Tregs is not only quantitatively low but also functionally correlated to high levels of systemic inflammation. The study, to a large extent, formed a basis for further research, suggesting a distinct immunological feature of Tregs in women with PE(39).

It has recently been observed that another feature of pre-eclampsia is the transformation from a tolerogenic to an inflammatory immune environment, from T-reg cells to Th17 cells. The ratio of T-reg/Th17 cells has been observed to be lower in pre-eclampsia, along with higher levels of the cytokine IL-17 in pre-eclampsia, thereby increasing oxidative stress, thereby establishing a relation between FOXP3 deficiency and maternal inflammation(40).Molecular studies validate a reduction in FOXP3 gene message levels within preeclamptic tissues. This decrease is associated with a dysregulated level of immune tolerance mediators, namely IDO, HLA-G, and TGF-β. It can be speculated from these transcriptional differences that not only would a lack of FOXP3 attenuate Tregs' suppressive functions, it would affect the immune environment associated with a properly

formed placenta(41).

Dysregulation Mechanisms

The epigenetic regulatory mechanisms, like DNA methylation, histone modifications, and ncRNAs, carefully control the immune tolerance process in the maternal-fetal interface. If there's an imbalance in this process, it affects the trophoblastic invasiveness, so the placenta suffers from conditions like PE and RPL. The imbalance in epigenetics has also been identified as a key cause of the failure of the process of implantation(42). Dysmorphic DNA methylation contributes to imprinting, immune, and trophoblastic dysfunction resulting in recurring pregnancy loss. Dysregulated maternal, paternal, and placental tissues interfere with the process of implantation, as well as angiogenic defects in the body. DNA Methylation can be considered a potential biomarker for RPL based upon this process(43).MicroRNAs (miRNAs) are an important post-transcriptional regulatory process in pregnancy, having a profound impact on placental development as well as immune homeostasis between the mother and the fetus. In the case of preeclampsia, Kasimanickam et al.identified a particular miRNA profile, which was enriched in targets related to angiogenesis, oxidative stress, and the immune response. Moreover, the in-silico analysis indicated that the deregulated miRNAs targeted key pathways, which include VEGF signaling, pro-inflammatory cytokines, as well as NK/T-cell regulatory genes(44). miR-152 inhibits the HLA-G/KIR2DL4 pathway by functioning as a direct suppressor of HLA-G expression in trophoblasts, thereby reducing the trophoblasts' anti-inflammatory response to decidual NK cells. The reduced expression of HLA-G, an anti-inflammatory factor, increases the decrease in NK-cell viability, promotes the inflammatory NK phenotype, and, in the end, inhibits trophoblastic invasion(45).This immune imbalance can by the epigenetic suppression of FOXP3, in particular through hypermethylation of the FOXP3 promoter, which can impair the stability of FOXP3+ regulatory T cells and limit the inhibitory function of excessive maternal immune activation. The role of this process in autoimmune disorders has been proven, but it can also be applied in the context of pregnancy, where the lack of proper FOXP3 expression can limit maternal-fetal tolerance. The use of this process in the development of inflammatory pregnancy conditions such as preeclampsia(46). The fate, expression, and formation of NK cell memory are regulated by chromatin remodeling, DNA methylation, and histone modification. These regulatory mechanisms decide the NK cell response based upon tolerant or inflammatory mediators. In the case of pregnancy, any anomalies in these mechanisms might provoke detrimental activation in NK cells(47).

KIR gene variation occurs through duplication and promoter variation, resulting in greatly individualized NK cell repertoires. Another regulatory factor involves the epigenetics of gene silencing, which also contributes to the NK trophoblast interactions, as it has been reported in the context of placental diseases like PE(48).

FOXP3 as a Biomarker

FOXP3 is a lineage-defining transcription factor for regulatory T cells; as such, reduced FOXP3 expression at both mRNA and protein levels generally suggests compromised immune tolerance, which is a pivotal part of immunopathology for preeclampsia (PE)(49). Among clinical trials, preeclampsia (PE) has been repeatedly connected with impairments of various magnitudes related to regulatory T cells (Tregs) on a quantitative and qualitative basis. There is systematic evidence confirming a correlation of decreased numbers of Tregs with a higher probability of PE development, which explains the interest in readouts focusing on FOXP3(5).Firstly, in regards to a viewpoint of severity, tissue-level data have clinical implications since preeclampsia is an effect of placental pathology. Various investigations of the placenta or the decidual have shown lower preeclampsia values of FOXP3+ cells than in healthy women, suggesting the hypothesis for a FOXP3-related local maternal-fetal immuno-regulatory failure(50). One of the workplace implications is related to risk stratification, in that FOXP3/Tregs can add to the usual measures of angiogenic factors (sFlt-1/PlGF) in defining an "immune axis" that would better define

inflammatory profiles, especially in the diverse presentation of preeclampsia(33). But, as a marker, FOXP3 has some limitations: (1) it can be expressed differently depending on the gestational age, (2) data from PB may not necessarily reflect the situation within the decidua and the placenta, and (3) depending on the test (FACS, qPCR, or IHC, for instance), the expressions are not exactly the same(51).

Therefore, presently, the most justifiable clinical use would not be based solely on FOXP3, but FOXP3 and characteristics of Treg must be combined in multi-parameter analyses, which must include clinical risk parameters, angiogenic markers, and immune phenotyping/omics, wherein FOXP3 has incremental value in a composite model and not be utilized solely as a classifier(52).

Therapeutic Perspectives

On a conceptual level, if pregnancy exposure (PE) leads to insufficient induction or maintenance of fetal antigen-specific tolerance, a potential strategy involves the restoration of regulatory T cell (Treg) function, and, by inference, the control of FOXP3-mediated programs. Pregnancy, of course, imposes a substantially stringent standard of safety beyond the norm(53).Arguably, the strongest “therapy logic” existing within the pregnancy arena to date is based on the mechanistic and translational analysis, showing that the role of regulatory T cells (Tregs) is involved in implantation, Spiral Artery remodeling, and the development of the placenta. Therefore, the pre-clinical intervention before the onset of preeclampsia is more likely than the rescue approach(54). Among the techniques that have been discussed in general immunology concepts intended to enhance the levels of regulatory T cells (Tregs), IL-2 has been prominent owing to its ability to specifically expand and activate these cells at a low dose. Significantly, it is an immunomodulatory platform in non-pregnant women and not a treatment for preeclampsia(55). Recent events illustrate that it is the dose of interleukin-2 (IL-2), criteria for patient selection, and parameters of immune monitoring that contribute to immune response selectivity to regulatory T cells (Tregs), which has particular significance in pregnancy because unselective immune activation may, theoretically, worsen inflammation(56).A more detailed investigation into human immunology reveals the possible reorganization of the status and function of regulatory T cells (Tregs) by interleukin-2 (IL-2), and therefore the viability of the "Treg-directed immune reset approach" as a platform on that basis. It is important to note that the utility of the above evidence is largely conceptual and cannot be applied well to the treatment of Preeclampsia (PE) presently(57). Also rapidly emerging in the area of immunology is the “next-generation” approach for regulatory T cells (Tregs). This includes techniques such as adoptive transfer and engineered Tregs. Unfortunately, as innovative and exciting as these techniques may be in immunology and medicine in general, their applications in obstetric practice are purely speculative at this point and include several questions as to safety and specificity for both fetal and maternal compartments(58).

Research Gaps and Future Directions

Despite great progress in understanding immune dysregulation in preeclampsia, it remains essential to know much more concerning FOXP3-positive regulatory T cells and their role in this disorder. Most studies undertaken to date are observational and describe immune abnormalities arising post-onset of clinical symptoms and do little to illuminate whether abnormalities of FOXP3 play a causative role in pathogenesis or whether they represent immune abnormalities consequent to inflammatory injury(53). There remains little to no available literature on the evaluation of the dynamics in relation to FOXP3 profiling from early gestation to postpartum. Without access to intra-trimester information, it could be difficult to determine immunological differences between early and late cases of preeclampsia(33). Another question unanswered is the tissue specificity. Even if an analysis of the level of FOXP3 in the peripheral blood cells is often used due to its easier accessibility, the immune microenvironment of the decidual and placental tissue is, in fact, different(50). A large degree of methodological heterogeneity is a barrier. The use of different analytical techniques (qPCR, flow cytometry, immunohistochemistry), gating,

normalization techniques, and reportage make it difficult to combine results(51). On a mechanistic background, FOXP3 stability and function, including epigenetic changes, post-translational modifications, and metabolism, are not sufficiently studied during pregnancy. These aspects could underlie why FOXP3 cells lose their suppressive function despite their normal numbers at certain times(5). Future studies might focus more on the value of an integration approach involving transcriptomics, epigenetics, proteomics, and immune-phenotyping. Such approaches might clarify the potential interaction of FOXP3 mutations with angiogenic factors (sFlt-1/PlGF) that can classify preeclampsia into different endotypes(52). There is a great need for well-designed prospective cohort studies using standardized sampling and common assays. These studies should include diverse groups because geographic and ethnic differences need to be addressed when considering immune tolerance strategies(59). As far as intervention is concerned, the use of immunomodulation involving regulatory T-cells is in the experimental stages. Notwithstanding evidence available in animal studies supporting this intervention, issues of safety, timing, and specificity stand in the way of implementing it(54). Future studies will focus on the predictive aspect of risk, using FOXP3/Treg expression as add-on biomarkers. Prior to applying any ethical rationale for FOXP3 pathway modulation targets in obstetrics, full-scale, staged research will be needed as preconditions for human intervention studies(57).

Results and Discussion

Evidence suggests that preeclampsia (PE) is associated with a marked imbalance of immune tolerance in mother and fetus that is primarily caused by the suppression of FOXP3 expression and the dysfunction of regulatory T cells (Tregs). Numerous studies have demonstrated significant decreases in FOXP3 mRNA and protein expression in the peripheral blood mononuclear cells of women with preeclampsia as compared to those in pregnant women with normal blood pressure, which point to an immune system dysfunction rather than a placenta-related condition(60).Placental and decidual analyses further strengthen these findings, showing a marked reduction in FOXP3+ regulatory T cell accumulation at the maternal-fetal interface, particularly in the decidua basalis. As Tregs play an important role in preventing overactivation of the maternal immune system and promoting trophoblast invasion, it has been hypothesized that this reduction contributes directly to dysfunctional spiral artery remodeling and placentation, which are hallmark pathological changes observed in women who have developed preeclampsia. Interestingly, these alterations seem to be more pronounced in early-onset, severe cases of preeclampsia, thereby further supporting the idea that an immune disturbance contributes to this pathological state(33). Decreased expression of FOXP3 at the functional expression level has been strongly associated with decreased suppression ability of regulatory T cells (Tregs), causing an imbalanced shift towards the Th17-dominant response with a pro-inflammatory phenotype. Various studies have shown an increase in Th17/Treg ratios, as well as increased levels of IL-17, TNF-α, and IL-6, in preeclamptic pregnancies. This immune disparity triggers endothelial activation, oxidative stress, and systemic inflammation, which cumulatively lead to hypertension, proteinuria, and systemic manifestations of preeclampsia(61). There is new evidence at the molecular level regarding the epigenetic theories proposed to contribute to FOXP3 dysfunction in preeclampsia. The abnormal DNA methylation profile for FOXP3 and FOXP3 microRNAs has been observed in preeclampsia. This could potentially be responsible for decreased Treg cell stability and functionality. A mechanistic interlink has been established among environmental, genetic, and inflammation events in contributing to the pathophysiology of preeclampsia(62). Despite the concordance, there is some variation across the studies. This is most likely due to the differences in gestational age sampled, the severity of the disease, whether the samples were blood or placenta, or the methods used. However, when viewed together, the current body of literature fully underscores the importance of the dysfunction of regulatory T cells (Tregs) mediated by FOXP3 in the immunopathogenesis of preeclampsia(54). Current studies raise a fundamental question about whether reduced FOXP3 expression is the primary driver of angiogenic transformation failure or a secondary consequence of the hyperinflammatory environment. However, evidence linking Tregs

depletion and impaired spiral arterial remodeling in very early stages suggests that FOXP3 dysfunction precedes the clinical onset of symptoms. Therefore, we must move from descriptive studies to longitudinal studies starting from the embryo implantation stage to pinpoint the precise moment when the immune pathway shifts from tolerance to inflammation.

Conclusion

Strong evidence exists supporting the hypothesis that the dysregulation of FOXP3 gene expression and the dysfunction of regulatory T cells play a fundamental immunological role in the pathogenesis of preeclampsia. The dysfunction of FOXP3 leads to a defective maternal-fetal immune tolerant system with a sustained pro-inflammatory environment, causing abnormalities in placentation and the clinical manifestations of the disease. These immune disturbances can be clearly noted in early-onset cases of preeclampsia, thus bringing into focus the role of FOXP3-mediated immune homeostasis. The importance of immune homeostasis during pregnancy cannot be underestimated. The relevance of immune stability has been reiterated in the development of preeclampsia. Even if a lot of progress has been reached in the discovery of the pathways involved in the function of FOXP3, the challenge of interpretation has been the variability in methods used and the fact that most of the data are from cross-sectional studies. In conclusion, FOXP3 is a key node of an immunoregulatory system in preeclampsia that has relevant implications for disease classification and the design of therapeutic interventions. Better insight into FOXP3-based immune system networks might provide a rational basis for more refined methods of predictive as well as corrective interventions in this disease.

References

1. Narkhede AM, Karnad DRJIjoccmp-r, official publication of Indian Society of Critical Care Medicine. Preeclampsia and related problems. 2021;25(Suppl 3):S261.
2. Overton E, Tobes D, Lee AJBp, anaesthesiology rC. Preeclampsia diagnosis and management. 2022;36(1):107-21.
3. Krupa P, Wein H, Zemmrich LS, Zygmunt M, Muzzio DOJFiI. Pregnancy-related factors induce immune tolerance through regulation of sCD83 release. 2024;15:1452879.
4. Li Z, Si P, Meng T, Zhao X, Zhu C, Zhang D, et al. CCR8+ decidual regulatory T cells maintain maternal-fetal immune tolerance during early pregnancy. 2025;10(106):eado2463.
5. Green S, Politis M, Rallis KS, Saenz de Villaverde Cortabarria A, Efthymiou A, Mureanu N, et al. Regulatory T cells in pregnancy adverse outcomes: A systematic review and meta-analysis. 2021;12:737862.
6. Aisagbonhi O, Morris GPJFiG. Human leukocyte antigens in pregnancy and preeclampsia. 2022;13:884275.
7. Moodley J, Soma-Pillay P, Buchmann E, Pattinson RC. Hypertensive disorders in pregnancy: 2019 National guideline. 2019.
8. Magee LA, Brown MA, Hall DR, Gupte S, Hennessy A, Karumanchi SA, et al. The 2021 International Society for the Study of Hypertension in Pregnancy classification, diagnosis & management recommendations for international practice. 2022;27:148-69.
9. Kariori M, Katsi V, Tsioufis CJIJoMS. Late vs. Early Preeclampsia. 2025;26(22):11091.
10. Roberts JMJBp, obstetrics rC, gynaecology. Preeclampsia epidemiology (ies) and pathophysiology (ies). 2024;94:102480.
11. Elawad T, Scott G, Bone JN, Elwell H, Lopez CE, Filippi V, et al. Risk factors for pre-eclampsia in clinical practice guidelines: Comparison with the evidence. 2024;131(1):46-62.
12. Redman CW, Staff AC, Roberts JMJAjoo, gynecology. Syncytiotrophoblast stress in preeclampsia: the convergence point for multiple pathways. 2022;226(2):S907-S27.

13. Phipps EA, Thadhani R, Benzing T, Karumanchi SAJNRN. Pre-eclampsia: pathogenesis, novel diagnostics and therapies. 2019;15(5):275-89.

14. Hoffman MKJBAIJoO, Gynaecology. The great obstetrical syndromes and the placenta. 2023;130:8-15.

15. Wei X-W, Zhang Y-C, Wu F, Tian F-J, Lin YJFiI. The role of extravillous trophoblasts and uterine NK cells in vascular remodeling during pregnancy. 2022;13:951482.

16. Powe CE, Levine RJ, Karumanchi SAJC. Preeclampsia, a disease of the maternal endothelium: the role of antiangiogenic factors and implications for later cardiovascular disease. 2011;123(24):2856-69.

17. Staff AC, Fjeldstad HE, Fosheim IK, Moe K, Turowski G, Johnsen GM, et al. Failure of physiological transformation and spiral artery atherosis: their roles in preeclampsia. 2022;226(2):S895-S906.

18. Fodor P, White B, Khan RJM. Inflammation—The role of ATP in pre-eclampsia. 2020;27(1):e12585.

19. Park C, Alahari S, Ausman J, Liu R, Nguyen F, Sallais J, et al. Placental hypoxia-induced ferroptosis drives vascular damage in preeclampsia. 2025;136(4):361-78.

20. Aplin JD, Myers JE, Timms K, Westwood MJNRE. Tracking placental development in health and disease. 2020;16(9):479-94.

21. Parikh SM, Karumanchi SAJNm. Putting pressure on pre-eclampsia. 2008;14(8):810-2.

22. Sakaguchi S, Yamaguchi T, Nomura T, Ono MJc. Regulatory T cells and immune tolerance. 2008;133(5):775-87.

23. Josefowicz SZ, Lu L-F, Rudensky AYJAroi. Regulatory T cells: mechanisms of differentiation and function. 2012;30(1):531-64.

24. Basse C. T cells caracterization in thymoma: Université Paris Cité; 2024.

25. Wang C, Liao M-J, Wu Y, Lin H, Ye Z-Z, Ma W-Z, et al. Pharmacological mechanisms of traditional Chinese medicine metabolites in regulating Treg cells: an integrative pathway review. 2025;16:1527421.

26. Shevach EMJAii. Biological functions of regulatory T cells. 2011;112:137-76.

27. Somerset DA, Zheng Y, Kilby MD, Sansom DM, Drayson MTJI. Normal human pregnancy is associated with an elevation in the immune suppressive CD25+ CD4+ regulatory T-cell subset. 2004;112(1):38-43.

28. Grover P, Goel PN, Greene MIJFii. Regulatory T cells: regulation of identity and function. 2021;12:750542.

29. Malviya V, Yshii L, Junius S, Garg AD, Humblet-Baron S, Schlenner SMJI, et al. Regulatory T-cell stability and functional plasticity in health and disease. 2023;101(2):112-29.

30. Bending D, Ono MJC, Immunology E. From stability to dynamics: understanding molecular mechanisms of regulatory T cells through Foxp3 transcriptional dynamics. 2019;197(1):14-23.

31. Arneth BJC. Molecular Mechanisms of Immune Regulation: A Review. 2025;14(4):283.

32. Ichiyama K, Long J, Kobayashi Y, Horita Y, Kinoshita T, Nakamura Y, et al. Transcription factor Ikzf1 associates with Foxp3 to repress gene expression in Treg cells and limit autoimmunity and anti-tumor immunity. 2024;57(9):2043-60. e10.

33. Peng X, Chinwe Oluchi-Amaka I, Kwak-Kim J, Yang XJFiI. A comprehensive review of the roles of T-cell immunity in preeclampsia. 2025;16:1476123.

34. Saito SJMP, Practice. Reconsideration of the role of regulatory T cells during pregnancy: differential characteristics of regulatory T cells between the maternal-fetal Interface and peripheral sites and between early and late pregnancy. 2022;31(5):403-14.

35. Krop J, Heidt S, Claas FH, Eikmans MJFii. Regulatory T cells in pregnancy: it is not all about FoxP3. 2020;11:1182.

36. Hosking SL, Moldenhauer LM, Tran HM, Chan HY, Groome HM, Lovell EA, et al. Treg cells promote decidual vascular remodeling and modulate uterine NK cells in pregnant mice. 2024;10(2):e169836.

37. Headen K, Jakaite V, Mesaric VA, Scotta C, Lombardi G, Nicolaides KH, et al. The role of regulatory T cells and their therapeutic potential in hypertensive disease of pregnancy: a literature review. 2024;25(9):4884.

38. Ersoy Canillioglu Y, Senturk GE, Sahin H, Sahin S, Seval-Celik YJJoH, Cytochemistry. The distribution of Foxp3 and CD68 in Preeclamptic and Healthy Placentas: a histomorphological evaluation. 2023;71(4):211-25.

39. Toldi G, Švec P, Vásárhelyi B, Meszaros G, Rigó J, Tulassay T, et al. Decreased number of FoxP3+ regulatory T cells in preeclampsia. 2008;87(11):1229-33.

40. Braga A, Neves E, Guimarães J, Braga J, Vasconcelos CJJoRI. Th17/Treg ratio: a prospective study in a group of pregnant women with preeclampsia and fetal growth restriction. 2023;159:104122.

41. Chen J, Zhao L, Wang D, Xu Y, Gao H, Tan W, et al. Contribution of regulatory T cells to immune tolerance and association of microRNA-210 and Foxp3 in preeclampsia. 2019;19(2):1150-8.

42. Ma X, Chen X, Mu X, Cao M, Zhang YJFiI. Epigenetics of maternal-fetal interface immune microenvironment and placental related pregnancy complications. 2025;16:1549839.

43. Zhou Q, Xiong Y, Qu B, Bao A, Zhang YJFii. DNA methylation and recurrent pregnancy loss: a mysterious compass? 2021;12:738962.

44. Kasimanickam R, Kasimanickam VJCIiMB. MicroRNAs in the Pathogenesis of Preeclampsia—A Case-Control In Silico Analysis. 2024;46(4):3438-59.

45. Yang Y, Liu S, Zhu XM, Chen YY, Zhao J, Yuan YF, et al. Mechanism of microRNA-152 Regulating Decidual Natural Killer Cell Viability and Affecting Trophoblast Cell Invasiveness via the HLA-G/KIR2DL4 Axis. 2025;41(5):e70019.

46. Fakour P, Shirizadeh A, Tahamoli-Roudsari A, Solgi GJEoI. Epigenetic regulation of FOXP3 gene expression in relation to impaired function of regulatory T cells in systemic lupus erythematosus. 2024;4(5):640-57.

47. Hermans L, O'Sullivan TEJIr. No time to die: Epigenetic regulation of natural killer cell survival. 2024;323(1):61-79.

48. Bruijnesteijn J, De Groot NG, Bontrop REJFiI. The genetic mechanisms driving diversification of the KIR gene cluster in primates. 2020;11:582804.

49. Campbell N, Robbins M, Nembaware H, Deer E, Cornelius D, LaMarca BJIJoMS. Immune Cells in Preeclampsia. 2025;27(1):74.

50. Meister S, Hahn L, Beyer S, Mannewitz M, Perleberg C, Schnell K, et al. Regulatory T cell apoptosis during preeclampsia may be prevented by Gal-2. 2022;23(3):1880.

51. Tomaszewicz M, Stefańska K, Dębska-Zielkowska J, Zamkowska D, Piekarska K, Tymoniuk B, et al. PD1+ T Regulatory Cells Are Not Sufficient to Protect from Gestational Hypertension. 2025;26(7):2860.

52. Zhao Q, Li J, Diao Z, Zhang X, Feng S, Hou G, et al. Early prediction of preeclampsia from clinical, multi-omics and laboratory data using random forest model. 2025;25(1):531.

53. Saito S, Tsuda S, Nakashima AJJoRI. T cell immunity and the etiology and pathogenesis of preeclampsia. 2023;159:104125.

54. Robertson SA, Green ES, Care AS, Moldenhauer LM, Prins JR, Hull ML, et al. Therapeutic potential of regulatory T cells in preeclampsia—opportunities and challenges. 2019;10:478.

55. Lykhopiy V, Malviya V, Humblet-Baron S, Schlenner SMJG, Immunity. IL-2 immunotherapy for targeting regulatory T cells in autoimmunity. 2023;24(5):248-62.

56. Zhang R, Zhao Y, Chen X, Zhuang Z, Li X, Shen EJIRoI. Low-dose IL-2 therapy in autoimmune diseases: An update review. 2024;43(3):113-37.

57. Raeber ME, Caspar DP, Zurbuchen Y, Guo N, Schmid J, Michler J, et al. Interleukin-2 immunotherapy reveals human regulatory T cell subsets with distinct functional and tissue-homing characteristics. 2024;57(9):2232-50. e10.

58. Hassan M, Elzallat M, Mohammed DM, Balata M, El-Maadawy WHJII. Exploiting regulatory T cells (Tregs): Cutting-edge therapy for autoimmune diseases. 2025;155:114624.

59. Deer E, LaMarca B, Reckelhoff JF, Shawky NM, Edwards KJIJoMS. The Role of Mitochondrial Dysfunction and Oxidative Stress in Women's Reproductive Disorders: Implications for Polycystic Ovary Syndrome and Preeclampsia. 2025;26(13):6439.

60. Kwiatek M, Kwaśniewski W, Gęca T, Grywalska E, Rahnama-Hezavah M, Mertowski S, et al. Dysregulation of Treg/Th17 Balance and Intracellular Expression of IL-21 and IL-22 in the Pathogenesis of Gestational Hypertension. 2025;14(20):7288.

61. Eghbal-Fard S, Yousefi M, Heydarlou H, Ahmadi M, Taghavi S, Movasaghpour A, et al. The imbalance of Th17/Treg axis involved in the pathogenesis of preeclampsia. 2019;234(4):5106-16.

62. Yuan Y, Yuan H, Yang G, Yun H, Zhao M, Liu Z, et al. IFN-α confers epigenetic regulation of HBV cccDNA minichromosome by modulating GCN5-mediated succinylation of histone H3K79 to clear HBV cccDNA. 2020;12(1):135.