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New Perspectives on Epigenetic Regulation in Immune Thrombocytopenia (ITP): Focusing on the Interaction Mechanism of DNA Methylation and Vitamin D

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Abstract

Immune thrombocytopenia (ITP) is an acquired autoimmune disorder characterized by increased platelet destruction and insufficient platelet production. Recent research has highlighted the central role of epigenetic regulation, particularly DNA methylation, in the pathogenesis of ITP. Concurrently, vitamin D deficiency has been confirmed to be associated with the occurrence, development, and treatment response of ITP. This review systematically elaborates on the abnormalities in DNA methylation in ITP (e.g., downregulation of DNMT3A/3B expression, S-adenosylhomocysteine (SAH) accumulation leading to hypomethylation) and their impact on T/B cell dysfunction, Treg/Th17 imbalance, and impaired megakaryocyte maturation. It delves into the mechanisms by which vitamin D directly or indirectly (e.g., by regulating DNMTs, miRNAs, histone modifications) modulates DNA methylation status through the vitamin D receptor (VDR) signaling pathway. The latest clinical evidence for drugs targeting DNA methylation (e.g., low-dose decitabine) and vitamin D supplementation therapy is critically reviewed, with a specific focus on analyzing the synergistic potential of their combined application. Based on recent studies, the theoretical framework of the "Vitamin D-DNA Methylation Axis" as a novel target for ITP diagnosis and treatment is proposed, providing a basis for developing personalized epigenetic therapeutic strategies.

Keywords

Immune Thrombocytopenia, DNA Methylation, Epigenome, Vitamin D

1. Overview of ITP and Epigenetic Background

Immune thrombocytopenia (ITP) is an autoimmune disease characterized by antibody-mediated platelet destruction and impaired megakaryocyte production, leading to a significant decrease in platelet count ($<100 \times 10^9$/L) and a substantially increased risk of bleeding. Traditional views focused on humoral immune abnormalities (e.g., anti-GPIIb/IIIa antibodies), but recent research has confirmed that cellular immune dysregulation (Treg reduction, Th17/Th1 polarization, cytotoxic T cell activation) and epigenetic dysregulation are key driving factors [1]-[3]. Epigenetics regulates gene expression without altering the DNA sequence, primarily involving three major mechanisms: DNA methylation, histone modifications, and non-coding RNAs. These mechanisms play a central role in immune loss of tolerance and megakaryocyte differentiation defects in ITP [4].

2. Core Mechanisms of DNA Methylation in ITP Pathogenesis

2.1. Molecular Basis of DNA Methylation Homeostasis Imbalance

Enzyme Expression Abnormalities: mRNA and protein expression of DNMT3A and DNMT3B, responsible for establishing DNA methylation imprints, are significantly lower in peripheral blood mononuclear cells (PBMCs) of ITP patients compared to healthy controls [5]. Although no difference exists between chronic ITP (>12 months) and newly diagnosed ITP patients, the persistently low expression of DNA methyltransferases (DNMTs) suggests their involvement in disease maintenance rather than serving as activity markers [5].

Methyl Donor Metabolic Dysregulation: Plasma S-adenosylhomocysteine (SAH) concentration is significantly elevated in ITP patients. SAH, a potent methyltransferase inhibitor, competitively binds to the enzyme active site, inhibiting DNMT activity and leading to global DNA hypomethylation [6] [7]. Increased SAH levels positively correlate with lymphocyte DNA hypomethylation and represent a key metabolic driver of epigenetic dysregulation in ITP [6].

2.2. Immune Cell Dysfunction Driven by DNA Hypomethylation

T Cell Polarization Imbalance: DNA hypomethylation promotes a pro-inflammatory environment:

Th1/Th2 Imbalance: Abnormal hypomethylation at gene loci for IFN-γ (Th1) and IL-4 (Th2) leads to a Th1 polarization bias, exacerbating inflammation [8].
Treg/Th17 Imbalance: The gene locus for forkhead box P3 (FOXP3), the key Treg transcription factor, exhibits physiological hypomethylation in Treg cells to maintain their function. However, in ITP, Treg numbers are reduced and their function is suppressed, potentially related to abnormal methylation at other regulatory sites (e.g., CTLA4) [9]. Concurrently, pro-inflammatory Th17 cells may be activated due to de-repression at gene loci like IL-17A [10].

B Cell Abnormal Activation and Autoantibody Production: DNA hypomethylation can lift the inhibition of autoreactive B cells, promoting their differentiation

into plasma cells and the production of anti-platelet autoantibodies (e.g., anti-GPIIb/IIIa, GPIb/IX) [11]. These antibodies facilitate platelet phagocytosis by macrophages via Fcγ receptors and may inhibit megakaryopoiesis.

Direct Cytotoxic Effect of Cytotoxic T Cells (CTLs): $CD8^+$ CTLs can directly lyse platelets via Fas/FasL and perforin/granzyme pathways and kill megakaryocytes in the bone marrow [12]. DNA hypomethylation may participate in regulating the expression of CTL-related effector molecules (e.g., perforin, granzyme B).

2.3. DNA Methylation Abnormalities and Impaired Megakaryocyte Maturation

Expression of key genes for megakaryocyte differentiation and maturation (e.g., TRAIL, NF-E2, GATA1, FLI1) is finely regulated by DNA methylation [13].

Bone marrow megakaryocytes in ITP patients often exhibit maturation arrest (increased small megakaryocytes) and increased apoptosis. Studies found that plasma from ITP patients can induce downregulation of tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) expression in megakaryocytes, promoting their apoptosis. Hypermethylation of the TRAIL gene promoter region may be one cause of its silencing [14].

3. Immunomodulatory and Epigenetic Regulatory Role of Vitamin D in ITP

3.1. Association between Vitamin D Deficiency and ITP

Serum levels of $1,25(OH)_2D_3$ and expression of the vitamin D receptor (VDR) are significantly reduced in active ITP patients and positively correlate with platelet count [15]. Vitamin D deficiency is considered a risk factor for ITP development and progression.

3.2. Direct Immunomodulatory Effects of Vitamin D

$1,25(OH)_2D_3$ exerts potent immunomodulatory functions by binding to VDR: Inhibits PBMC proliferation and reduces inflammatory cell infiltration.

Reverses abnormal T cell polarization: Suppresses Th1 (IFN-γ) and Th17 (IL-17) differentiation, promotes Th2 (IL-4, IL-10) responses [16].

Induces Treg differentiation and function: Promotes FOXP3 expression and enhances Treg suppressive capacity [14].

Modulates cytokine networks: Downregulates pro-inflammatory cytokines (TNF-α, IL-6, IL-17), upregulates anti-inflammatory cytokines (IL-10, TGF-β) [16].

3.3. Vitamin D-Mediated Epigenetic Regulation (Core New Advances)

Vitamin D can profoundly influence the DNA methylation landscape through the VDR signaling pathway:

Regulation of Methyltransferase Expression: Reduced expression of DNMT1

and DNMT3B was observed in $CD4^+$ T cells of mice supplemented with vitamin D (cholecalciferol) [18]. Downregulation of DNMT1 and DNMT3B was also noted in prostate cancer cells treated with calcitriol [19].

Molecular Mechanisms Regulating DNMTs: Transcriptional Regulation: VDR can directly bind to or interfere with the binding of other transcription factors (e.g., SP1) to the DNMT3B promoter region, inhibiting its transcription [19]. miRNA-Mediated: Vitamin D upregulates miR-98-5p, which targets the 3'UTR region of DNMT3B mRNA, promoting its degradation [19]. Influence on Methyl Donor Metabolism: Vitamin D can upregulate the expression of Bhmt1 (betaine-homocysteine methyltransferase) in $CD4^+$ T cells [18]. Bhmt1 catalyzes the conversion of homocysteine to methionine, which is subsequently converted to S-adenosylmethionine (SAM)—the primary methyl donor for DNA methylation. This pathway may impact the methylation cycle. Indirect Regulation Dependent on Histone Modifications: Targeting of specific genomic regions by DNMT3A/3B depends on histone marks (e.g., H3K36me3) [20]. VDR can alter local chromatin states by regulating the expression or recruiting chromatin remodeling complexes of histone-modifying enzymes (histone methyltransferases/demethylases, acetyltransferases/deacetylases), indirectly influencing the recruitment and activity of DNA methylation enzymes [21].

Targeting TET Enzymes: VDR binding sites are also found near the ten-eleven translocation (TET)2 and TET3 genes (involved in active DNA demethylation) [22], suggesting vitamin D may influence hydroxymethylation levels (5 hmC)—a key step in active demethylation—by regulating TET enzymes.

4. Targeting DNA Methylation and Vitamin D Pathways: Novel Therapeutic Strategies for ITP

4.1. Demethylating Agents: Low-Dose Decitabine (DAC)

Mechanism of Action: DAC is a DNMT inhibitor. At low doses, it primarily exerts demethylating effects, promoting gene re-expression.

Efficacy Evidence: Promoting Megakaryocyte Maturation and Platelet Release: Low-dose DAC reverses ITP plasma-induced megakaryocyte maturation arrest and apoptosis. This mechanism is associated with demethylation of key gene promoters (e.g., TRAIL), restoring their expression, and promoting megakaryocyte maturation and platelet production [14] [23]. In animal models, DAC significantly increased platelet release from the spleen and bone marrow [23]. Immunomodulation: In treating refractory ITP patients, low-dose DAC significantly reduced $CD16^+$ inflammatory monocytes and activated $CD4^+$ T cell numbers, while enhancing the suppressive function of Treg cells [24].

Clinical Outcomes: For adult ITP patients refractory or relapsed after first-line (corticosteroids, IVIG) and second-line (TPO-RAs, rituximab) therapies, low-dose DAC demonstrates good response rates (ORR approximately 60% - 80%) and sustained responses, significantly increasing platelet counts and improving bleeding symptoms [24] [25].

4.2. Vitamin D Supplementation Therapy

Corrects the vitamin D deficiency state in patients.

Increases Platelet Count: Multiple observational studies and small randomized controlled trials (RCTs) indicate that vitamin D supplementation correlates with elevated platelet counts [26].

Improves Immune Parameters: Upregulates Treg proportion and function, suppresses Th17 responses, and shifts the cytokine profile towards an anti-inflammatory direction [16] [17].

Potential as Adjunctive Therapy: Vitamin D may enhance the efficacy of other ITP treatments (e.g., corticosteroids, TPO-RAs) or reduce their required dosages [26].

4.3. Combined Demethylation and Vitamin D Therapy: Synergistic Rationale and Prospects (Core Innovation Point)

Theoretical Basis for Synergy:

1) Co-targeting Immune Dysregulation: DAC directly corrects DNA hypomethylation, restoring immune tolerance (e.g., enhancing Tregs); Vitamin D suppresses excessive inflammation (e.g., inhibiting Th1/Th17) via VDR signaling. Together, they synergistically reshape immune homeostasis.

2) Co-promoting Megakaryopoiesis: DAC promotes megakaryocyte maturation by demethylating key genes (TRAIL, etc.); Vitamin D may support megakaryocyte differentiation by modulating the bone marrow microenvironment or directly acting on megakaryocyte VDR.

3) Vitamin D Enhances DAC's Epigenetic Effect: Vitamin D, by downregulating DNMTs (e.g., DNMT1, DNMT3B) [18] [19] and potentially influencing methyl donor metabolism (upregulating Bhmt1) [18], may reduce the enzyme activity and substrate levels required to maintain abnormal methylation states. Theoretically, this could enhance the demethylation efficiency of low-dose DAC or prolong its duration of action.

4) Vitamin D May Mitigate Potential DAC Side Effects: The immunomodulatory and anti-inflammatory effects of vitamin D may help alleviate treatment-related inflammatory responses.

Core Hypothesis Needing Investigation: The central hypothesis of this review is that baseline patient $1,25(OH)_2D_3$ levels may influence the efficacy of demethylating therapy (e.g., DAC).

Hypothesis: Patients with severe vitamin D deficiency may have more severe DNA methylation dysregulation (e.g., lower DNMT expression, more pronounced hypomethylation of pro-inflammatory genes) and more impaired immune cell (especially Treg) function. In such cases, DAC monotherapy may be insufficient to fully restore immune homeostasis and megakaryocyte function. Conversely, patients with sufficient vitamin D levels may have an epigenetic background and immune baseline state more conducive to DAC efficacy.

Validation Directions: Prospective clinical studies are needed to compare treat-

ment outcomes (platelet response rate, response depth, duration) in ITP patients with high vs. low baseline $1,25(OH)_2D_3$ levels receiving DAC therapy. Dynamic monitoring before and after treatment should include: T/B cell subset changes (e.g., Treg frequency/function, Th17, activated T/B cells); Key cytokine profiles (IFN-γ, IL-4, IL-10, IL-17, TGF-β, etc.); DNA methylation status (genome-wide/specific gene loci e.g., FOXP3 TSDR, TRAIL promoter methylation levels); Megakaryocyte-related parameters (bone marrow megakaryocyte count, maturity, platelet production rate).

5. Summary and Future Perspectives

The pathogenesis of ITP results from the interplay of genetic predisposition, immune dysregulation, and epigenetic dysfunction. Abnormal DNA methylation (particularly hypomethylation driven by low DNMT3A/3B expression and SAH accumulation) is a core mechanism linking immune cell (T/B cells, Treg/Th17 imbalance) dysfunction and impaired megakaryocyte maturation. Vitamin D deficiency is not only a risk factor for ITP; its multidimensional immunomodulation (inhibiting inflammation, promoting tolerance) via VDR signaling and its regulatory effects on DNA methylating enzymes (DNMTs) and methyl metabolism reveal its crucial position within the ITP epigenetic network.

Low-dose decitabine (DAC), targeting DNA methylation, provides an effective therapeutic option for refractory ITP, with its core mechanism lying in demethylating key genes to promote megakaryocyte maturation and restore immune tolerance. Supplementing vitamin D is a rational strategy to correct deficiency and improve immune imbalance. Significant synergistic potential exists between the two in terms of mechanism: vitamin D may create a more favorable epigenetic background for DAC by downregulating DNMTs and influencing methyl metabolism, jointly promoting the reconstruction of immune homeostasis and the recovery of megakaryocyte function.

Future research should focus on: 1) Mechanistic Deep Dive: Utilizing single-cell multi-omics technologies (scRNA-seq, scATAC-seq, sc-methyl-seq) to meticulously dissect the epigenetic (especially DNA methylation) characteristics of different immune cell subsets and megakaryocyte lineages in ITP patients and their relationship with vitamin D status. 2) Combination Therapy Validation: Conducting rigorous prospective clinical trials to evaluate the efficacy and safety of DAC combined with vitamin D3 versus monotherapy in refractory ITP, with a key focus on analyzing the predictive value of baseline $1,25(OH)_2D_3$ levels for DAC efficacy. Deeply investigate the impact of combination therapy on immune cell dynamics (Treg function, T/B cell subsets, cytokines), DNA methylation patterns (specific gene loci, genome-wide), and megakaryocyte biology. 3) Precision Diagnostic and Prognostic Biomarker Development: Identifying biomarker combinations based on DNA methylation signatures (e.g., specific gene methylation profiles) and vitamin D metabolic status for early diagnosis, subtyping, prognosis assessment, and treatment response prediction in ITP. 4) Exploration of Novel Ep-

igenetic Drugs: Developing new small-molecule compounds or biologics that more specifically and safely target DNMTs, TETs, or the vitamin D metabolism/VDR signaling pathway.

6. Conclusion

Elucidating the role of the "Vitamin D-DNA Methylation Axis" in ITP will not only deepen the understanding of the disease's nature but also lay a solid foundation for developing personalized, synergistic therapeutic strategies based on epigenetic reprogramming and nutritional immunomodulation, ultimately improving the long-term prognosis and quality of life for ITP patients.

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Conflicts of Interest

The author declares no conflicts of interest regarding the publication of this paper.

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