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Original Article

TET-1 as Epigenetic Regulator of Ferroptosis in Preeclampsia Pathogenesis

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Abstract:

Background: Preeclampsia, a life-threatening gestational hypertensive syndrome, is pathogenically linked to placental oxidative stress. Emerging evidence implicates ferroptosis in disease progression, though epigenetic regulators of this process remain undefined. The role of Ten-Eleven Translocation 1 (TET-1) in modulating placental redox homeostasis requires systematic investigation.

Methods: We analyzed 126 placental tissues in a retrospective cohort. Multimodal assessments included immunohistochemical quantification of TET-1, HIF1A and SLC7A11 expression, qRT-PCR validation, oxidative stress assays, and bioinformatic interrogation of TET-1 interactomes. Multivariable logistic regression modeled clinical and molecular predictors with age, BMI, TET-1 expression and obstetric history.

Results: TET-1 expression was significantly suppressed in preeclamptic placentas versus controls (protein IHC: 142.3±18.7 vs 218.9±22.1, P<0.001; mRNA: 0.32±0.11-fold, P<0.001). Reduced TET-1 expression could predict disease risk (adjusted OR=0.172, 95%CI: 0.047–0.638; P=0.008), as did family history (OR=2.952, 95%CI:1.058–8.239; P=0.039). Mechanistically, TET-1 downregulation correlated with elevated HIF-1α methylation and SLC7A11 repression (r=0.489, P=0.0014), forming an epigenetic-ferroptotic axis. Oxidative stress markers increased significantly, with protein interaction validation confirming TET-1- HIF-1α binding.

Conclusion: We discovered TET-1-directed control of the HIF1A-SLC7A11 ferroptosis checkpoint as a potential element of preeclampsia pathogenesis. This epigenetically-gated pathway offers actionable targets for biomarker-driven risk prognostication and molecular therapy in gestational hypertensive disorders.

Keywords: Preeclampsia, TET-1, HIF-1α, SLC7A11, Ferroptosis

Introduction

Preeclampsia [1-3] is a pregnancy-specific disorder characterized by high blood pressure and proteinuria after 20 weeks of gestation. It can cause severe complications for both the mother and the fetus, such as fetal growth restriction, preterm birth, and even stillbirth. The prognosis of preeclampsia depends on its severity and the timing of diagnosis and treatment. Early detection and appropriate management can significantly improve the outcome.

One of the main causes of preeclampsia is oxidative stress [4, 5] in placental tissue. A large number of studies have demonstrated this mechanism. Ferroptosis [6] is a form of regulated cell death characterized by the accumulation of iron-dependent lipid peroxides. Recent studies [7, 8] have suggested that ferroptosis may be involved in the pathogenesis of preeclampsia. For example, some researchers have found that the expression of ferroptosis-related genes is altered in preeclamptic placentas [9, 10]. These findings indicate a potential link between preeclampsia

and ferroptosis, which warrants further investigation.

For a deeper understanding and prevention of this disease, it is crucial to explore the underlying molecular mechanisms. Some studies have investigated the relationship between gestational hypertension and ferroptosis. However, certain mechanisms remain unclear. For instance, some studies [11-15] have pointed out that although it is known that DNA methylation can influence the expression of ferroptosis genes, the specific pathways and regulatory factors are yet to be fully elucidated. Among the numerous molecular regulatory mechanisms, epigenetic studies emerged. Among them, Ten-Eleven Translocation 1 (TET-1) [16-18], as an important demethylase, is becoming the focus of research.

DNA methylation [19-21] is a process by which methyl groups are added to the DNA molecule, typically at the cytosine residues within CpG dinucleotides. This modification can alter the chromatin structure and affect the accessibility of the DNA to transcription factors and other regulatory proteins [22], thereby leading to the suppression or activation of gene expression. DNA methylation exerts a significant influence in the regulation of gene expression. TET 1 with its unique demethylation function [23] enables fine regulation of the methylation status of specific genes.

In our study of preeclampsia, we identified a striking regulatory pathway. TET 1 can regulate the reduced methylation of the HIF-1a gene [24]. As HIF-1 α (Hypoxia-Inducible Factor-1 α), the regulation of its expression and function is essential for cells to adapt to the hypoxic state. When TET 1 causes the methylation of the HIF-1a gene to be reduced, it may enhance the HIF-1 α activity and expression. Further studies showed that this change would enhance SLC7A11 expression. SLC7A11 is a molecular [25, 26] that is closely related to cellular metabolism and against oxidative stress. The improvement in its expression level contributes to the resistance to intracellular oxidative stress and ferroptosis.

Materials and Methods

Immunohistochemistry (IHC) Staining and Scoring

The placental tissue tissues were fixed, dehydrated, embedded in paraffin, and sectioned (4 μm). The slides were incubated with the following primary antibodies: SLC7A11 (HA600098, 1:200), 4-HNE (MHN-020P, 1:200).

Four categories were used to grade IHC staining: 0 represented no staining, 1+ represented light staining only apparent at high magnification, 2+ represented intermediate staining, and 3+ represented dark staining of the linear membrane visible even at low magnification. Visual evaluation was used to ascertain the proportion of cells at various staining intensities. The score was computed using the following formula: 1 × (% of 1+ cells) + 2 × (% of 2+ cells) + 3 × (% of 3+ cells).

Malondialdehyde (MDA) assay

Using an MDA assay kit (S0131S; Beyotime Biotechnology, China), the assay's lipid peroxidation levels were measured in accordance with the manufacturer's instructions.

RNA isolation and Real-Time Quantitative Polymerase Chain Reaction

Total RNA was extracted from tissues using TRIzol reagent (Invitrogen). Following reverse transcription, mRNA expression levels were quantified in triplicate via SYBR Green-based quantitative polymerase chain reaction (qPCR) (Servicebio) on a Bio-Rad CFX96 system, with β-actin serving as the normalization control. At least three independent biological replicates were analyzed. The primer sequences: TET-1 FORWARD TTGGCGAAGTGGCTCCTCTCC, REVERSE GGGCTGGTGGTTTGGCTGATG.

Reactive Oxygen Species (ROS) Level Assay

Thermo Fisher Scientific's C11-BODIPY® 581/591 (D3861) was used to detect ROS. Then, C11-BODIPY was incubated in tissues with medium for 30 minutes at 37 °C after 24 hours. FlowJo V10 was used to examine the outcomes.

Results

TET-1 expression was significantly downregulated in preeclampsia placenta tissue relative to normal placenta tissues

To investigate differential TET-1 expression in normal versus preeclamptic placental tissues, we initially performed immunohistochemistry (IHC) on randomly selected specimens (n=5 per group). Analysis revealed significantly higher TET-1 protein expression in normal placentas compared to preeclamptic samples **(Figure 1A, B)**, suggesting TET-1 suppression in preeclampsia. This finding was corroborated by qRT-PCR, demonstrating significantly reduced TET-1 mRNA levels in preeclamptic tissues **(Figure 1C)**.

Subsequently, we expanded our cohort to 126 placental samples for comprehensive IHC evaluation. Using a median IHC score of 195 as the threshold (scores ≥195 = high expression; < 195 = low expression), samples were stratified into high (n=65) and low (n=61) TET-1 expression groups. Notably, the majority of normal placentas exhibited high TET-1 expression, while the majority of preeclamptic placentas displayed low expression **(Figure 1D, E)**, indicating a robust association between TET-1 downregulation and preeclampsia.

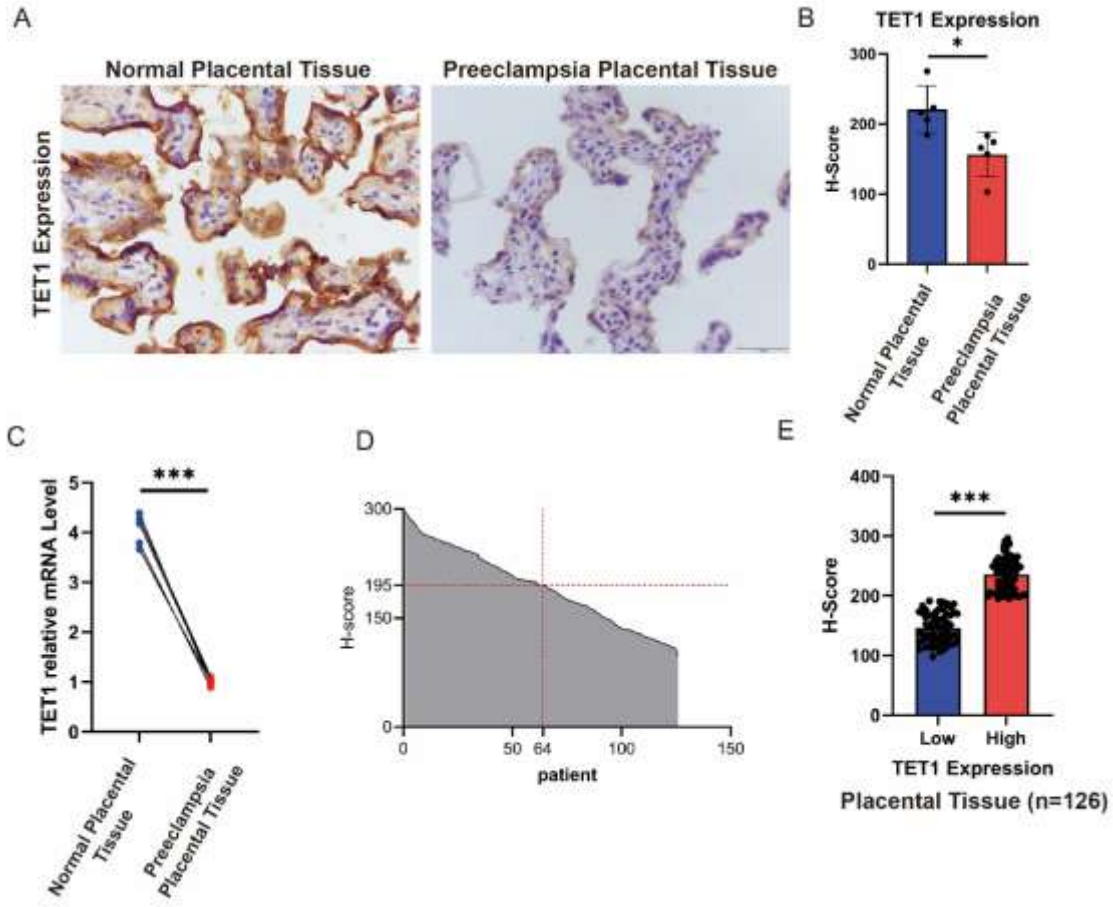

Figure 1. TET-1 expression levels vary significantly between normal and pathological placental tissues. A-B) Representative images of TET-1 IHC staining in placental tissues of patients with or without preeclampsia (n = 5). Scale bar, 50 μm, $^{*}P < 0.05$. C) Relative mRNA expression level at

TET-1 in placental tissues of patients with or without preeclampsia. $^{***}P < 0.001$. D) Distribution of TET-1 expression levels in 126 placental tissues as represented by various H-score ranges. 65 had H-score of H ≥ 195 (TET-1 high). E) TET-1 IHC expression in placental specimens (N=126). High expression: n=65; Low expression: n=61. $^{***}P < 0.001$.

Univariate and Multivariate Logistic Analyses of Factors Causing Preeclampsia

To further explore the related factors of preeclampsia, we conducted a retrospective analysis of the information of 126 patients. The clinical characteristics of the control and preeclampsia groups was showed in the **Table 1.**

Table1 Baseline Clinical Characteristics of the Control and Preeclampsia Groups

Characteristics	Preeclampsia	
	No	Yes
Age	30.06±4.742	34.79±4.853
Multiparas		
No	38	10
Yes	32	46
BMI	25.913±3.4183	29.338±3.5802
Gestational diabetes		
No	50	23
Yes	20	33
Placenta previa		
No	65	39
Yes	5	17
History of cesarean section		
No	50	26
Yes	20	30
Family history of preeclampsia		
No	41	10
Yes	29	46
Anxiety		
No	49	36
Yes	21	20
TET-1 expression levels		
Low	17	44
High	53	12

Then we performed univariate logistic regression to examine the association between relevant clinical factors and the development of preeclampsia **(Table 2).**

Table 2 Univariate Analysis of Factors Associated with Preeclampsia

Characteristics	B	S.E.	Waldχ^2	P	OR	95%CI
Age	0.195	0.042	21.275	<0.001	1.215	1.119-1.320
Multiparas (Yes)	1.698	0.423	16.078	<0.001	5.462	2.382-12.526
BMI	0.264	0.058	21.089	<0.001	1.303	1.164-1.458
Gestational diabetes (Yes)	1.277	0.379	11.347	0.001	3.587	1.706-7.542
Placenta previa (Yes)	1.735	0.548	10.035	0.002	5.667	1.937-16.574

History of cesarean section (Yes)	1.059	0.377	7.915	0.005	2.885	1.379-6.034
Family history of preeclampsia (Yes)	1.872	0.425	19.410	<0.001	6.503	2.827-14.959
Anxiety (Yes)	0.260	0.382	0.462	0.497	1.296	0.613-2.740
TET-1 expression levels (Low)	-2.436	0.429	32.304	<0.001	0.087	0.038-0.203

Our analysis revealed that factors other than anxiety were significantly associated with preeclampsia onset (***P* <0.05**). Significant variables identified in the univariate analysis were subsequently incorporated into a multivariable regression model. The result found that only TET-1expression levels (***P*=0.008**) and family history of preeclampsia (***P*=0.039**) were predictors of preeclampsia development. Moreover, elevated TET-1 expression demonstrated an inverse association with preeclampsia risk. **(Table 3)**. These results collectively suggest that diminished TET-1 expression is associated with the occurrence of preeclampsia.

Table 3 Multivariate Logistic Regression Analysis of Independent Risk Factors for Preeclampsia

Characteristics	B	S.E.	Waldχ2	P	OR	95%CI
Age	0.243	0.277	0.766	0.381	1.274	0.741-2.193
Multiparas (Yes)	0.156	0.920	0.029	0.865	1.169	0.193-7.097
BMI	-0.314	0.425	0.545	0.460	0.731	0.318-1.680
Gestational diabetes (Yes)	0.042	0.555	0.006	0.939	0.958	0.323-2.847
Placenta previa (Yes)	1.118	0.653	2.929	0.087	3.060	0.850-11.013
History of cesarean section (Yes)	-0.138	0.634	0.047	0.828	0.871	0.252-3.018
Family history of preeclampsia (Yes)	1.083	0.524	4.274	0.039	2.952	1.058-8.239
TET-1 expression levels (High)	-1.758	0.668	6.933	0.008	0.172	0.047-0.638

TET-1 and SLC7A11 Are Associated with Preeclampsia in Placenta Tissue

Given the established association between TET-1 expression and preeclampsia, subsequent investigations will focus on demonstrating the potential molecular mechanisms. As was indicated in the preceding article, preeclampsia has been linked in the literature to ferroptosis. Therefore, we must first investigate if the placental tissue, particularly the ferroptosis-associated genes, differs from normal placental tissue in preeclamptic patients. Ferroptosis genes and TET-1 were highly repressed in preeclampsia placental tissue, as seen by **Figure 2 A**, which also shows a significant difference in TET-1 and SLC7A11 expression between normal placental tissue and preeclampsia placental tissue. The expression of SLC7A11 and TET-1 was considerably different in the three additional normal placental tissues and the preeclampsia placental tissues that we collected at the same time **(Figure 2 B)**. Further data analysis revealed a significant positive correlation between TET-1 and SLC7A11 (**Figure 2C**; r = 0.4891, *p* = 0.0014, 95% CI: 0.2095 to 0.6947).This indicated a potential connection between ferroptosis and the development of preeclampsia.

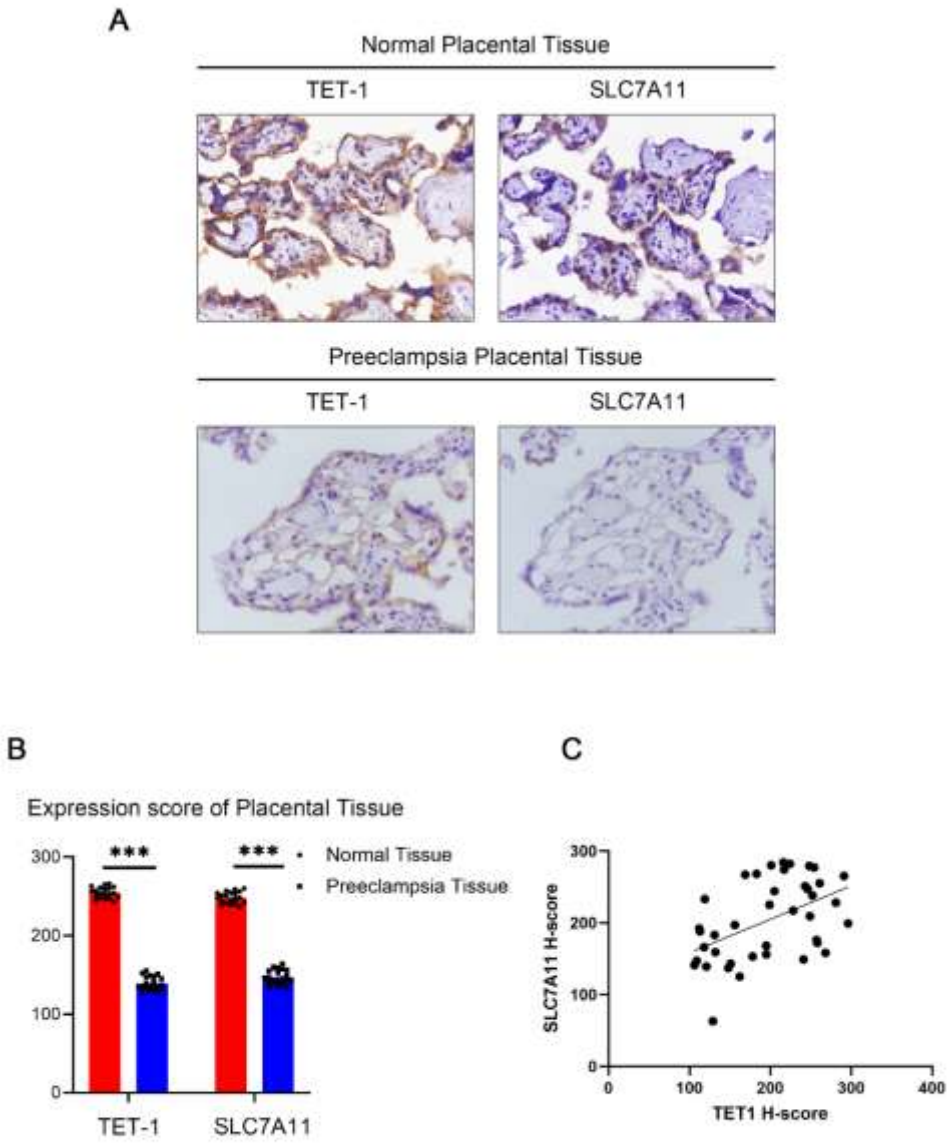

Figure 2. The expression of TET-1 and SLC7A11 in placental tissues from patients witha is inhibited. A) Representative images of TET-1 and SLC7A11 IHC staining in placental tissues of patients with or without preeclampsia. Scale bar, 50 µm. B) Expression score at SLC7A11 and TET-1 levels in placental tissues of patients with or without preeclampsia (N = 20). $^{***}P < 0.001$. C) Correlation analysis between TET-1 and SLC7A11 expression (Each group, n = 20) r = 0.4891, $p = 0.0014$, CI: 0.2095 to 0.6947.

Preeclampsia is Related with Ferroptosis by HIF-1α

To substantiate the occurrence of ferroptosis in different placental tissues, we measured the levels of Reactive Oxygen Species (ROS) and Malondialdehyde (MDA) expression within the placental tissue **(Figure3 A, B)**. We found a considerable rise in the content of ROS and MDA in preeclampsia placental tissue. To further elucidate the association between TET-1 genes and ferroptosis genes, we utilized bioinformatics tools Sting and HitPredict to forecast proteins that interact with TET-1. Our analysis identified nine

primary interactors with TET-1, such as HIF-1α, DCAF1, PSPC1, S100P, MBD3, DDB1, EPAS1, SMG7 and SIN3A. Among these, the interaction with HIF-1α was notably significant **(Figure 3C)**.

TET-1 Modulates SLC7A1 by Inhibiting the Methylation of HIF-1-α.

Upon reviewing the literature, we identified Hypoxia-inducible factor 1-alpha (HIF-1α) as a transcription factor that regulates the expression of SLC7A11. We postulate that DNA demethylation, which enhances HIF-1α's transcriptional activity and reduces its methylation, subsequently elevates the transcriptional expression of SLC7A11. Additional evidence supports the notion that preeclampsia's pathogenesis is linked to the downregulation of SLC7A11, a gene critical for counteracting oxidative stress. Subsequent experiments confirmed our hypothesis. As shown in **Figure3D and E**, there was a significant decrease in TET-1, HIF-1α, and SLC7A11 levels in placental tissue from preeclamptic patients. We propose that TET-1 promotes SLC7A11 expression and demethylates HIF-1α, thereby enhancing the body's resistance to oxidative stress. Preeclamptic patients exhibited reduced TET-1 function, increased methylation of HIF-1α, and diminished SLC7A11 function in their placentas, impairing their defense against oxidative stress.

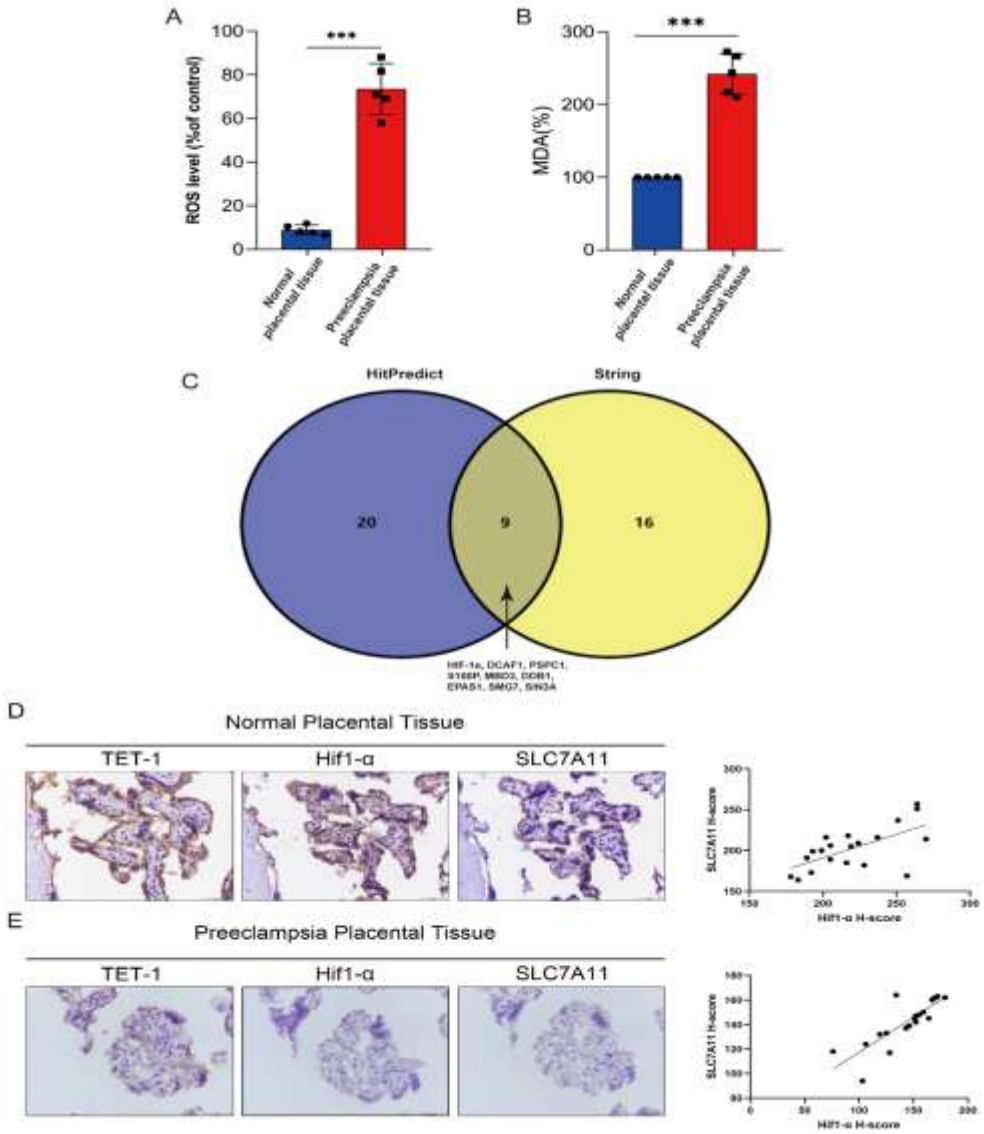

Figure 3. Preeclampsia is associated with ferroptosis by TET-1-HIF-1α-SLC7A11 Axis. A) Cellular

reactive oxygen species level was analyzed via a flow cytometer using dichlorodihydro fluorescein diacetate. $^{**}P < 0.001$; B) The level of MDA in placental tissues. $^{***}P < 0.001$; C) Venn diagram showing the common interaction protein with TET-1 in the String and the HitPredict database. D) Representative images of TET-1, HIF-1α and SLC7A11 IHC staining in placental tissues of patients without preeclampsia. Scale bar, 50 μm. Correlation analysis between TET-1 and SLC7A11 expression without preeclampsia (Each group, n = 20) r = 0.6359, $p = 0.0026$, CI: 0.2691 to 0.8416. E) Representative images of TET-1, HIF-1α and SLC7A11 IHC staining in placental tissues of patients with preeclampsia. Scale bar, 50 μm. Correlation analysis between TET-1 and SLC7A11 expression without preeclampsia (Each group, n = 20) r = 0.8248, $p < 0.0001$, CI: 0.6021 to 0.9285.

Discussion

Our study demonstrated a significant differential expression pattern of TET-1 between normal and preeclamptic placental tissues, with pronounced suppression of TET-1 in preeclampsia. This finding was robustly validated through clinical specimen analysis (n=126), establishing low TET-1 expression as a key factor associated with preeclampsia pathogenesis. Mechanistically, emerging evidence positions TET-1 as a critical regulator of DNA demethylation that functionally intersects with ferroptosis pathways. In alignment with this paradigm, we identified and experimentally confirmed a significant correlation between TET-1 and the ferroptosis marker SLC7A11 **(Figure 2C)**, substantiating the role of TET-1-mediated epigenetic regulation in preeclampsia -associated ferroptotic processes.

The current study unveils a potential mechanistic link between preeclampsia and ferroptosis, shedding new light on the pathogenesis of this pregnancy-specific syndrome. Our findings are consistent with the existing body of literature that implicates oxidative stress as a key factor in the development of preeclampsia[4, 5]. The observed repression of ferroptosis-associated genes and TET-1 in preeclamptic placental tissues suggests a disrupted cellular defense mechanism against oxidative stress, which may contribute to the etiology of the disease.

The significant difference in TET-1 and SLC7A11 expression between normal and preeclamptic placental tissues, as demonstrated in our study, underscores the importance of these molecules in the pathophysiology of preeclampsia. The repression of TET-1, a key demethylase enzyme, may lead to increased methylation and subsequent downregulation of HIF-1α, a transcription factor critical for the cellular response to hypoxia. This downregulation could impair the expression of SLC7A11, a key player in cellular metabolism and antioxidant defenses, thereby sensitizing cells to ferroptosis and oxidative stress.

The interaction between TET-1 and HIF-1α, as revealed by our bioinformatics analysis, is particularly noteworthy. This interaction may represent a critical node in the regulatory network that maintains cellular redox balance. The significant interaction with HIF-1α suggests that TET-1's demethylation activity may be essential for the proper functioning of HIF-1α, which in turn influences the expression of SLC7A11. This regulatory cascade may be disrupted in preeclampsia, leading to a compromised antioxidant response and increased susceptibility to ferroptosis.

The implications of our findings are twofold. Firstly, the differential expression of TET-1 and SLC7A11 in preeclamptic placentas may serve as a biomarker for the early diagnosis of the disease. Secondly, the identification of this epigenetic pathway offers a potential target for therapeutic intervention. Modulating the activity of TET-1 or the methylation status of HIF-1α could potentially

restore the antioxidant balance and mitigate the severity of preeclampsia.

Conclusion

In conclusion, we discovered TET-1-directed control of the HIF1A-SLC7A11 ferroptosis checkpoint as a potential element of preeclampsia pathogenesis. This epigenetically-gated pathway offers actionable targets for biomarker-driven risk prognostication and molecular therapy in gestational hypertensive disorders.

Data Availability

The data generated in this study are available within the article. Additional data or resources related to this article are available upon reasonable request from the corresponding authors.

Patient Sample Collection and Ethical Approval

The retrospective research of this study was approved by the Institutional Research Ethics Committee of the third Affiliated Hospital of Soochow University. A total 126 placental tissue samples with were collected from third Affiliated Hospital of Soochow University between January 2019 and July 2024. All samples were obtained after obtaining the tissue samples during surgery, formalin fixation and paraffin embedding were performed using standard methods. Clinical trial number: not applicable.

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Conflict of Interest: The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Informed Consent

Informed consent was obtained from all participants at The Third Affiliated Hospital of Soochow University through either the Cesarean Section or Vaginal Delivery surgical consent forms, and all placental tissues were subsequently discarded as medical waste without preservation.

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