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Research Article

Human endogenous retrovirus W family envelope protein (ERVWE1) regulates macroautophagy activation and micromitophagy inhibition via NOXA1 in schizophrenia

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ABSTRACT

The human endogenous retrovirus type W envelope glycoprotein (ERVWE1), located at chromosome 7q21–22, has been implicated in the pathophysiology of schizophrenia. Our previous studies have shown elevated ERVWE1 expression in schizophrenia patients. Growing evidence suggests that autophagy dysfunction contributes to schizophrenia, yet the relationship between ERVWE1 and autophagy remains unclear. In this study, bioinformatics analysis of the human prefrontal cortex RNA microarray dataset (GSE53987) revealed that differentially expressed genes were predominantly enriched in autophagy-related pathways. Clinical data further demonstrated that serum levels of microtubule-associated protein 1 light chain 3β (LC3B), a key marker of macroautophagy, were significantly elevated in schizophrenia patients compared to controls, and positively correlated with ERVWE1 expression. Cellular and molecular experiments suggested that ERVWE1 promoted macroautophagy by increasing the LC3B II/I ratio, enhancing autophagosome formation, and reducing sequestosome 1 (SQSTM1) expression via upregulation of NADPH oxidase activator 1 (NOXA1). Concurrently, NOXA1 downregulated the expression of key micromitophagy-related genes, including PTEN-induced kinase 1 (PINK1), Parkin RBR E3 ubiquitin-protein ligase (Parkin), and the pyruvate dehydrogenase E1 subunit α 1 (PDHA1). As a result, ERVWE1, via NOXA1, inhibited micromitophagy by suppressing the expression of PINK1, Parkin, and PDHA1, thereby leading to impaired production of mitochondrial-derived vesicles (MDVs). Mechanistically, ERVWE1 enhanced NOXA1 transcription by upregulating upstream transcription factor 2 (USF2). In conclusion, ERVWE1 promotes macroautophagy and inhibits micromitophagy through USF2-NOXA1 axis, providing novel mechanistic insight into the role autophagy dysregulation in schizophrenia. These findings suggest that targeting autophagy pathways may offer novel therapeutic strategies for schizophrenia treatment.

INTRODUCTION

Approximately 8% of the nucleotide sequences in the human genome resemble infectious retroviruses and are remnants of retroviral infections that occurred millions of years ago in human germline cells. These sequences are known as human endogenous retroviruses (HERVs) (Da et al., 2024; Hayward, 2017; Jakobsson and Vincendeau, 2022). Initially considered "junk DNA" due to mutations and recombination-induced deletions, which prevent the normal assembly of viral particles and horizontal transmission, HERVs are now recognized as important

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contributors to various biological processes (Jakobsson and Vincendeau, 2022). HERVs consist of four main genes: *gag* (viral structural proteins), *pro* (proteases), *pol* (reverse transcriptase and integrase), and *env* (viral surface envelope proteins) (Jakobsson and Vincendeau, 2022). Additionally, long terminal repeats (LTR) at the 5′ and 3′ ends of the HERV genome contain regulatory regions essential for viral transcription (Grandi and Tramontano, 2018a). HERVs are named based on the cellular transfer RNA (tRNA) that binds to their viral primer binding site (PBS) to initiate reverse transcription. For example, HERV-W corresponds to the tRNA for tryptophan, HERV-K for lysine, and HERV-L for leucine (Grandi and Tramontano, 2018a; Vargiu et al., 2016). HERVs are classified into several families, including class I (Gamma-retrovirus), II (Beta-retrovirus), and III (Spuma-retrovirus), based on sequence similarity (Grandi et al., 2016; Wang et al., 2018a).

Most HERVs have lost their ability to express functional viral proteins due to evolutionary mutations and epigenetic suppression by the host (Grandi and Tramontano, 2018b). However, a small number of activated HERVs can encode functional retroviral proteins, participating in processes like stem cell pluripotency (Macfarlan et al., 2012), embryonic development (Garcia-Montojo et al., 2020), gene regulation (Frost et al., 2023), and immune responses during viral infections (Balestrieri et al., 2019; Da et al., 2024; Durnaoglu et al., 2021; Stricker et al., 2023). Reactivation of HERVs can be triggered by various factors, including external environmental factors like drugs (Liu et al., 2013), radiation (Lee et al., 2012), and viral infections (Illescas-Montes et al., 2019; Liu et al., 2017), and internal factors such as aging (Nevalainen et al., 2018), cytokines (Cipriani et al., 2022), as well as epigenetic modifications (Garcia-Montojo et al., 2018). Reactivated HERVs have been implicated in the development of several diseases, including cancers (Jansz and Faulkner, 2021; Rivas et al., 2022), autoimmune diseases (Kremer et al., 2019), and neuropsychiatric disorders (Duarte et al., 2024; Huang et al., 2006; Karlsson et al., 2001; Wang et al., 2018a). Recent studies have also demonstrated that reactivated HERVs including HERV-W can modulate both innate and adaptive immune responses, highlighting their potential roles in pathogenesis and clinical applications (Yu et al., 2024).

HERV-W, a class I transposable elements, is one of the oldest groups of HERVs families. ERVWE1, also known as HERV-W env, ERVW-1, or syncytin-1, is a HERV-W-derived envelope protein (Wang et al., 2018a). Under normal physiological conditions, ERVWE1 mediates trophoblast fusion and plays a crucial role in maintaining maternal immune tolerance during pregnancy (Mi et al., 2000; Tolosa et al., 2012). Recent studies suggest that ERVWE1 is implicated in a variety of diseases, including autoimmune disorders (Jakobsson and Vincendeau, 2022; Posso-Osorio et al., 2021), cancers (Grandi and Tramontano, 2018a; Jakobsson and Vincendeau, 2022; Yu et al., 2014; Zhou et al., 2021), and neuropsychiatric disorders (Aftab et al., 2016; Jakobsson and Vincendeau, 2022; Karlsson et al., 2001; Wang et al., 2018a). Our previous work have demonstrated that ERVWE1 is abnormally overexpressed in the serum of patients with schizophrenia (Jia et al., 2025; Li et al., 2023b; Li et al., 2024; Wang et al., 2018b; Wu et al., 2023a,b; Xia et al., 2021; Xue et al., 2023; Yan et al., 2022; Yao et al., 2023; Zhang et al., 2024), suggesting that it may contribute to the development of schizophrenia.

Schizophrenia is a chronic and debilitating mental illness that affects approximately 1% of the global population (Jauhar et al., 2022) and is associated with dysfunction in brain regions involved in cognition and behavior (Adraoui et al., 2023; Chen et al., 2021). Despite extensive research, the precise causes and mechanisms of schizophrenia remain unclear. However, growing evidence indicates that autophagy plays a critical role in the pathophysiology of schizophrenia (Bjornson et al., 2024; Schneider et al., 2016; Tan et al., 2024). Autophagy in mammalian cells can be classified into three main types based on the way intracellular substrates are transported to lysosomes: macroautophagy, microautophagy, and chaperone-mediated autophagy (CMA) (Nie et al., 2021). Macroautophagy, often referred to simply as autophagy, is the primary intracellular degradation system where autophagic cargo is transported to lysosomes for degradation (Mizushima and Komatsu, 2011). Key genes in macroautophagy, such as sequestosome 1 (SQSTM1), microtubule-associated protein 1 light chain 3β (LC3B), and beclin1 (Lee et al., 2020; Sun et al., 2023), are closely associated with the pathophysiology of schizophrenia (Merenlender-Wagner et al., 2015). Our previous research has showed that ERVWE1 promotes the expression of brain-derived neurotrophic factor (BDNF) (Huang et al., 2011; Qin et al., 2016), and elevated BDNF levels are linked to enhanced autophagy, potentially contributing to cognitive deficits in brain disorders (Tomoda et al., 2022). In contrast to macroautophagy, microautophagy involves the direct uptake of autophagic cargo by lysosomes or late endosomes via membrane protrusions and invaginations, where it is subsequently degraded (Kuchitsu and Taguchi, 2024). A specific form of microautophagy, micromitophagy, is characterised by the formation of mitochondrial-derived vesicles (MDVs) (Wang et al., 2023). Micromitophagy is independent of classical autophagic structures such as LC3 and autophagy-related gene 5 (Atg5) (Lemasters, 2014). In MDVs-mediated micromitophagy, phosphatase and tensin homolog (PTEN)-induced kinase 1 (PINK1) and parkin RBR E3 ubiquitin-protein ligase (Parkin) are involved in the budding of MDVs from mitochondria (McLelland et al., 2014), and in the presence of specific protein receptors, MDVs fuses with endolysosomes to complete mitochondrial degradation (McLelland et al., 2016). Reactive oxygen species (ROS), often induced by oxidative stress, play a significant role in autophagy regulation (Li et al., 2015). ROS overproduction is closely linked to nicotinamide adenine dinucleotide phosphate (NADPH) oxidase (NOX) activation, with NOXA1, a member of the NOX family, being a key regulator of ROS production (Chocry and Leloup, 2020). NOXA1 works in concert with NOX organizer 1 (NOXO1) to modulate ROS generation through NOX1 (Ambasta et al., 2006; Kim et al., 2007). Previous studies from our group have shown that oxidative stress contributes to the pathological changes observed in schizophrenia (Zhang et al., 2024). However, the relationship between ERVWE1, NOXA1, autophagy, and neuropsychiatric disorders, particularly schizophrenia remains unexplored.

In this study, we conducted bioinformatics analysis to assess the differential expression of autophagy-related genes in the brains of schizophrenia patients and healthy controls. Clinical data revealed significantly elevated serum levels of LC3B protein in schizophrenia patients, which correlated positively with ERVWE1 expression. Cytological experiments further demonstrated that ERVWE1 activated macroautophagy by upregulating NOXA1, promoting the formation of autophagosomes. Additionally, ERVWE1 inhibited PINK1-Parkin-mediated micromitophagy via NOXA1. Moreover, ERVWE1 was found to enhance NOXA1 promoter activity and expression through transcription factors upstream transcription factor 2 (USF2). In conclusion, our findings suggest that ERVWE1 activates macroautophagy and inhibits micromitophagy through NOXA1 upregulation via USF2, providing novel insights into the role of ERVWE1 in schizophrenia pathogenesis and offering potential diagnostic biomarkers and therapeutic targets for schizophrenia treatment.

RESULTS

Elevated LC3B levels in schizophrenia and its correlation with ERVWE1

Biomarkers in serum have shown promise for diagnosing and assessing disease progression. However, reliable biological markers for schizophrenia remain elusive (Hu et al., 2022; Sabherwal et al., 2016). Thus, screening for dependable biomarkers is crucial for schizophrenia diagnosis. The biomarker selection process generally involves three stages: screening, validation, and confirmation, with bioinformatics prediction emerging as a reliable method for screening biomarkers (Qiu et al., 2023). We initially analyzed the GSE53987 microarray dataset (Lanz et al., 2019), which identified 4584 genes upregulated and 3705 downregulated genes ($\log2\ (FC)| > 1$, $P < 0.05$) (Fig. 1A). KEGG pathway enrichment analysis revealed a significant enrichment

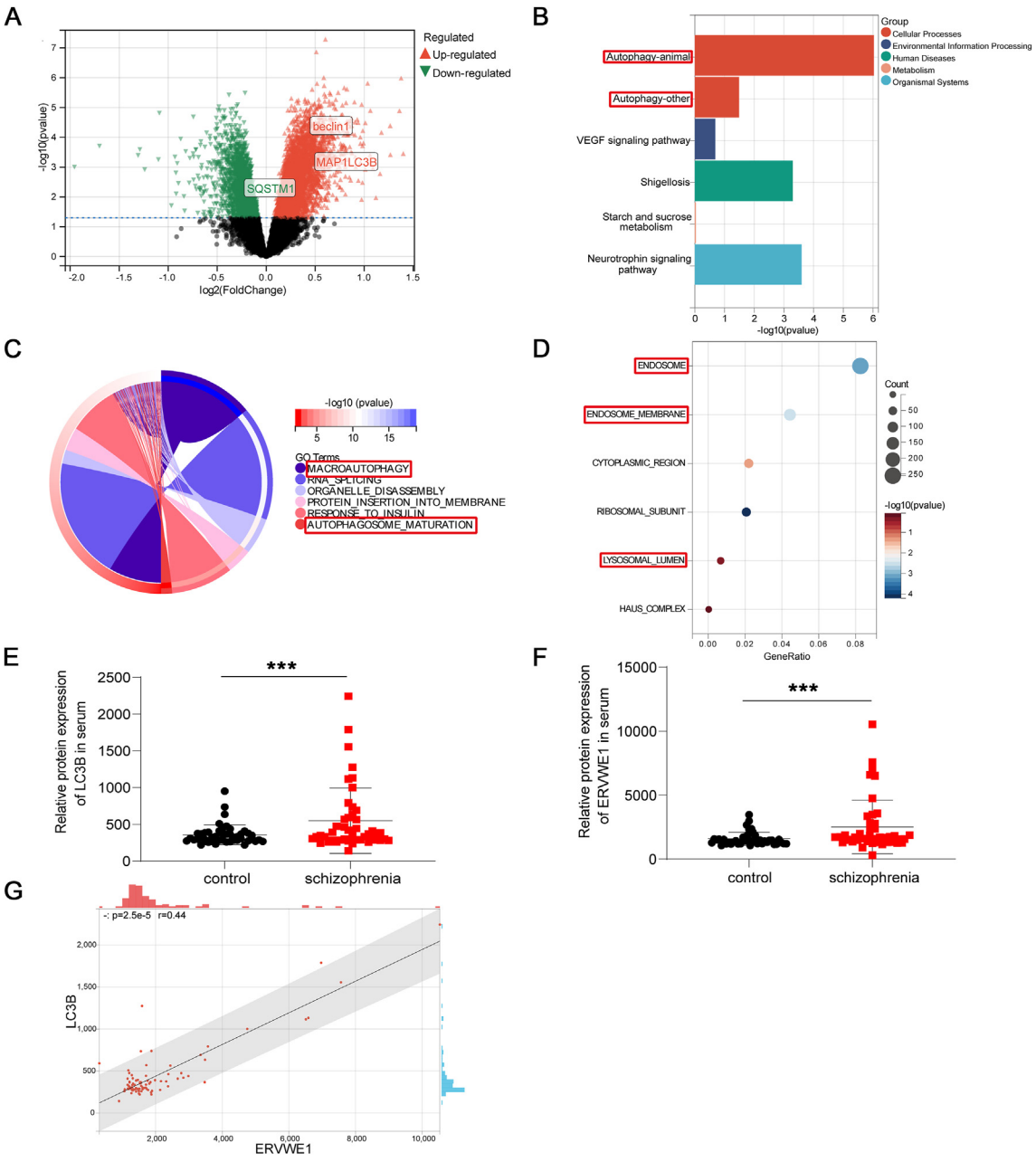

Fig. 1. Expression of macroautophagy-related gene LC3B in schizophrenia and correlation between ERVWE1 and LC3B. **A** Volcano plot and expression profiling of differentially expressed genes (DEGs) associated with macroautophagy. Dataset GSE53987 was analyzed using R software. **B** KEGG pathway enrichment analysis of DEGs. **C** GO biological processes enrichment analysis of DEGs. **D** GO cellular component enrichment analysis of DEGs. **E** Serum LC3B measured by ELISA in schizophrenia patients (n = 45) and healthy controls (n = 45). **F** Serum ERVWE1 measured by ELISA in schizophrenia patients (n = 45) and healthy controls (n = 45). **G** Spearman's correlation analysis showing a positive association between LC3B and ERVWE1 expression levels in schizophrenia (P = 2.5e-5, r = 0.44). X-axis: ERVWE1 concentration; Y-axis: LC3B concentration. Statistical analysis: Wilcoxon signed-rank test and Spearman's rank correlation analysis. ***$P < 0.001$.

of DEGs in macroautophagy-associated pathways (Fig. 1B). Numerous studies have linked autophagy to schizophrenia (Merenlender-Wagner et al., 2015), and some autophagy-related proteins hold potential as biological markers for the disorder (Sabherwal et al., 2016). GO biological processes enrichment analysis indicated that DEGs were predominantly involved in macroautophagy and autophagosome maturation (Fig. 1C). GO cellular components of DEGs showed that DEGs were mainly associated with macroautophagy-related components such as the endosome, endosome membrane, and lysosomal lumen (Fig. 1D).

Given the elevated expression of LC3B, a macroautophagy-related gene, observed in Fig. 1A, we analyzed serum samples from 45 patients with schizophrenia and 45 healthy controls. The results revealed that serum levels of LC3B were approximately 40% higher in schizophrenia patients compared to controls (Fig. 1E). Additionally, ERVWE1 levels were about 50% higher in patients with schizophrenia (Fig. 1F), which aligns with our previous studies (Jia et al., 2025; Li et al., 2023b; Li et al., 2024; Wang et al., 2018b; Wu et al., 2023a,b; Xia et al., 2021; Xue et al., 2023; Yan et al., 2022; Yao et al., 2023; Zhang et al., 2024). Correlation analyses revealed a significant positive relationship between serum levels of ERVWE1 and LC3B in schizophrenia patients (Fig. 1G). These findings suggest that ERVWE1 is positively correlated with LC3B expression and may serve as a potential blood biomarker, as well as a possible contributing factor in the pathophysiology of schizophrenia.

ERVWE1 activates macroautophagy

While clinical data showed higher LC3B levels in schizophrenia patients, LC3B expression alone is insufficient to assess autophagy. Previous studies indicate that a comprehensive assessment of LC3B, beclin1, and SQSTM1 expression, along with autophagosome formation, is necessary to confirm autophagy (Klionsky et al., 2021; Levy et al., 2017). To further explore the relationship between ERVWE1 and macroautophagy-related genes, we transfected ERVWE1 into SH-SY5Y cells, a human neuroblastoma cell line widely used in neuropsychiatric research (Jahn et al., 2017). Successful transfection was confirmed by RT-qPCR and Western blotting analysis (Supplementary Fig. S1A and S1B). We found that ERVWE1 upregulated LC3B mRNA levels while decreasing SQSTM1 levels (Fig. 2A and B). In addition, we observed an increase in the LC3B II to LC3B I ratio in SH-SY5Y cells transfected with ERVWE1, with a subsequent increase in beclin1 protein expression (Fig. 2C). We also detected the degradation of SQSTM1 over time, with the most pronounced degradation at 48 h post-transfection (Fig. 2D). The quantification of LC3B-positive puncta, considered the gold standard for measuring autophagosome formation (Runwal et al., 2019), showed that ERVWE1 increased the number of LC3B-positive puncta compared to controls. Cells transfected with the pcDNA3.1 vector alone exhibited diffuse LC3B distribution, while cells transfected with ERVWE1 displayed distinct LC3B-positive puncta (Fig. 2E and F). These results indicate that ERVWE1 promotes autophagosome formation and activates macroautophagy by increasing LC3B-positive puncta and promoting SQSTM1 degradation.

ERVWE1 activates macroautophagy by upregulating NOXA1 expression

Oxidative stress-induced overaccumulation of ROS can disrupt cellular homeostasis and promote autophagy (Li et al., 2015). NOX enzymes, which transport electrons across the plasma membrane to generate superoxide, are key producers (Bedard and Krause, 2007). The overexpression of NOX is associated with neurodegenerative disorders and neurotoxicity, contributing to the progression of neuropsychiatric diseases (Kaur et al., 2023). Our bioinformatics analysis of the GSE202537 dataset revealed that NOXA1 was differentially expressed in schizophrenia patients (Fig. 3A). To investigate the role of NOXA1 in macroautophagy, we constructed a NOXA1 overexpression vector and transfected it into SH-SY5Y cells. NOXA1 expression was confirmed by RT-qPCR and Western blotting analysis (Supplementary Fig. S1C and S1D). We found that NOXA1 significantly increased LC3B mRNA levels (Fig. 3B), and decreased SQSTM1 mRNA levels (Fig. 3C). Western blotting analysis further revealed an increase in the LC3B II to LC3B I ratio (Fig. 3D), while SQSTM1 levels decreased over time, with the most significant reduction at 48 h (Fig. 3E). Confocal microscopy of SH-SY5Y cells transfected with pcDNA3.1-NOXA1 revealed a marked increase in LC3B-positive puncta, compared to controls, indicating enhanced autophagosome formation (Fig. 3F and G). These results suggest that NOXA1 activates macroautophagy by upregulating macroautophagy-related genes and promoting autophagosome formation.

We have previously shown that ERVWE1 downregulates GSH expression (Zhang et al., 2024), a known ROS scavenger (Ursini and

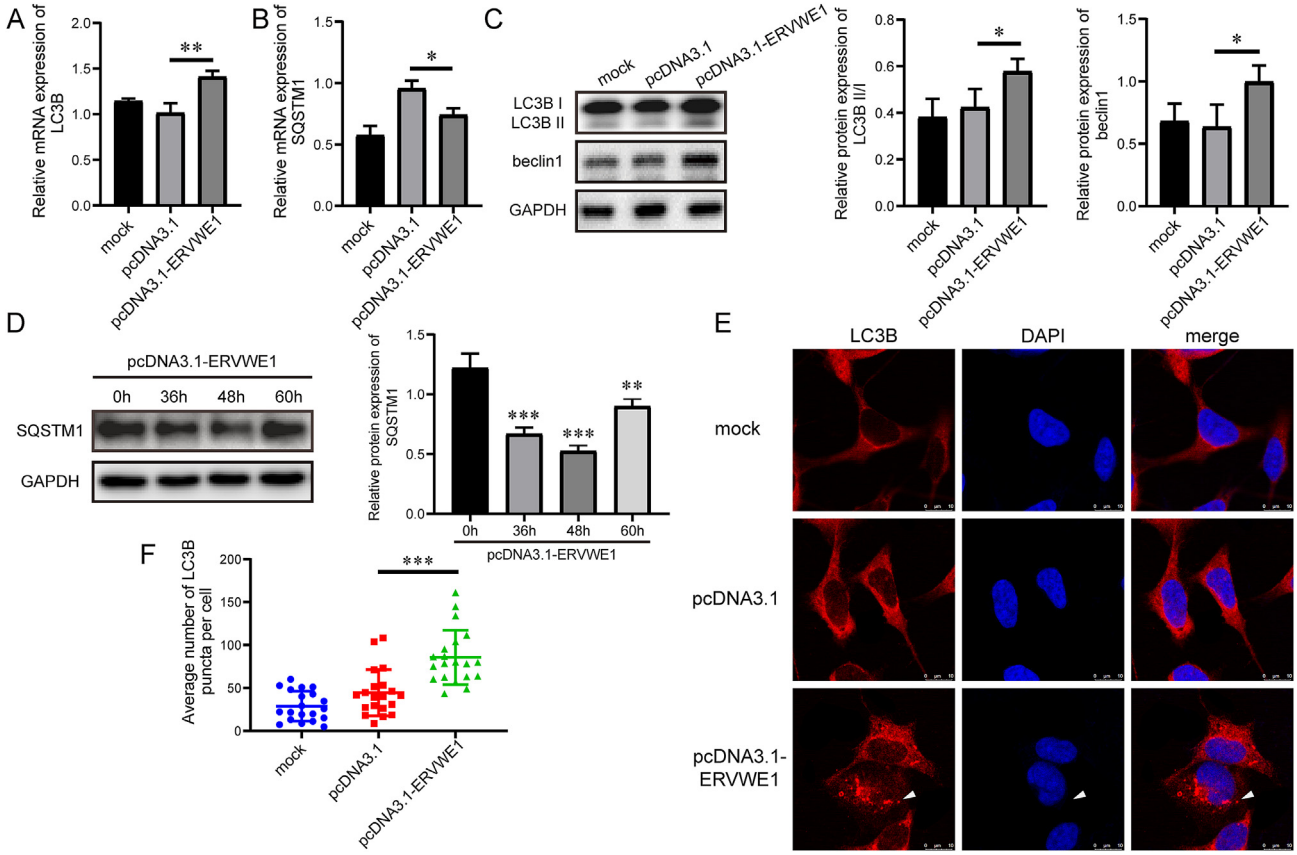

Fig. 2. ERVWE1 regulates macroautophagy-related genes and activates macroautophagy. **A, B** RT-qPCR analysis of LC3B and SQSTM1 mRNA expression levels in SH-SY5Y cells transfected with ERVWE1. **C** Western blotting analysis showing changes in LC3B II/I ratio and the beclin1 protein levels in ERVWE1-transfected SH-SY5Y cells. **D** Western blotting analysis of time-dependent changes in SQSTM1 protein levels in ERVWE1-transfected SH-SY5Y cells. **E** Immunofluorescence staining of LC3B (red) in SH-SY5Y cells transfected with ERVWE1. (Scale bar = 10 μm). **F** Quantification of LC3B-positive puncta per cell (n = 20) using Image J software. Data are presented as mean ± SD. Statistical analysis: one-way ANOVA and Student's *t*-test. All experiments were performed in triplicate. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

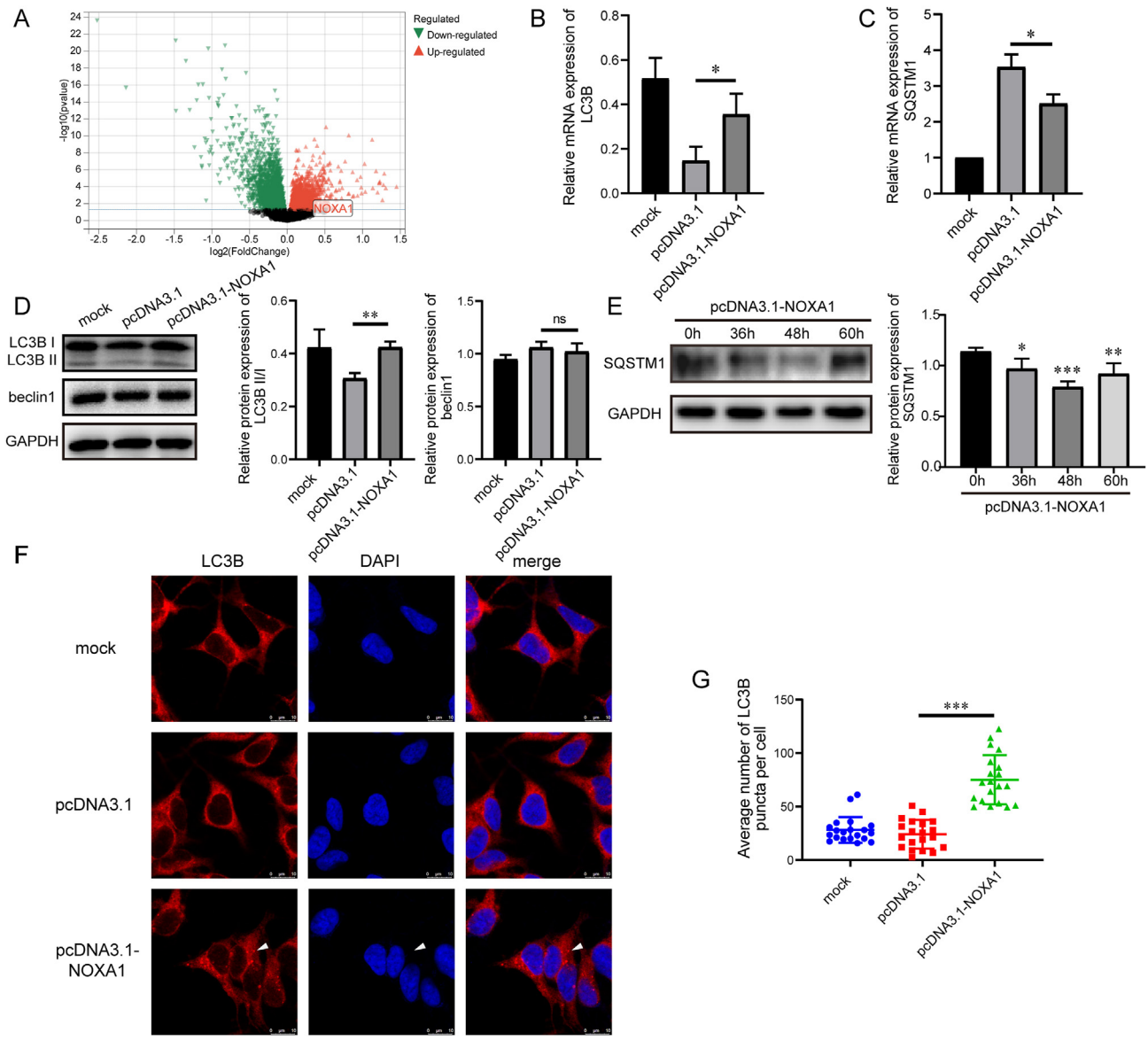

Fig. 3. NOXA1 regulates macroautophagy-related genes and activate macroautophagy. **A** Volcano plot and expression of DEGs in schizophrenia dataset GSE202537, analyzed using R software. **B, C** RT-qPCR analysis of LC3B (**B**) and SQSTM1 (**C**) mRNA expression levels in SH-SY5Y cells transfected with NOXA1. **D** Western blotting analysis showing changes in LC3B II/I ratio and beclin1 protein levels in NOXA1-transfected SH-SY5Y cells. **E** Western blotting analysis of time-dependent changes in SQSTM1 protein levels in NOXA1-transfected SH-SY5Y cells. **F** Immunofluorescence staining of LC3B (red) in NOXA1-transfected SH-SY5Y cells. (Scale bar = 10 μm). **G** Quantification of LC3B-positive puncta per cell (n = 20) using Image J software. Data are presented as mean ± SD. Statistical analysis: one-way ANOVA and Student's *t*-test. All experiments were performed in triplicate. ns: $P > 0.05$, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$.

Maiorino, 2020). Given the ROS-promoting role of NOX, we explored the relationship between ERVWE1 and NOXA1. We found that ERVWE1 significantly upregulated both the mRNA (Fig. 4A) and protein levels (Fig. 4B) of NOXA1 in SH-SY5Y cells. To determine the role of NOXA1 in ERVWE1-mediated macroautophagy activation, we knocked down NOXA1 expression and co-transfected it with ERVWE1 in SH-SY5Y cells (Supplementary Fig. S1E, S1F, and S1G). NOXA1 knockdown significantly reduced LC3B mRNA expression, while increased SQSTM1 mRNA expression (Fig. 4C and D). Western blotting confirmed that NOXA1 knockdown reversed the ERVWE1-induced increase in the LC3B II to LC3B I ratio and the decrease in SQSTM1 levels (Fig. 4E). Confocal microscopy further showed that NOXA1 knockdown reduced the number of LC3B-positive puncta and caused their transition from aggregation to a diffuse distribution (Fig. 4F and G). These results suggest that ERVWE1 activates macroautophagy by upregulating NOXA1.

Bioinformatics analysis reveals suppressed micromitophagy in schizophrenia

Mitochondrial dysfunction is a common feature of neurodegenerative and neuropsychiatric disorders, including schizophrenia (Palikaras and Tavernarakis, 2020). In mammalian cells, PDHA1-positive TOM20--negative MDVs play a role in mitochondrial homeostasis when mitochondria are damaged (Wang et al., 2023). Bioinformatics analysis of the GSE53987 dataset predicted upregulation of the mitochondrial outer membrane protein TOM20 in schizophrenia (Fig. 5A). However, micromitophagy-related genes, including PINK1 and Parkin, were significantly downregulated in schizophrenia patients (Fig. 5B and C). Furthermore, we observed reduced PDHA1 expression (Fig. 5D), which is necessary for the aggregation of PINK1 and recruitment of Parkin to the outer mitochondrial membrane (McLelland et al., 2014). These findings suggest that micromitophagy is inhibited in schizophrenia patients. KEGG

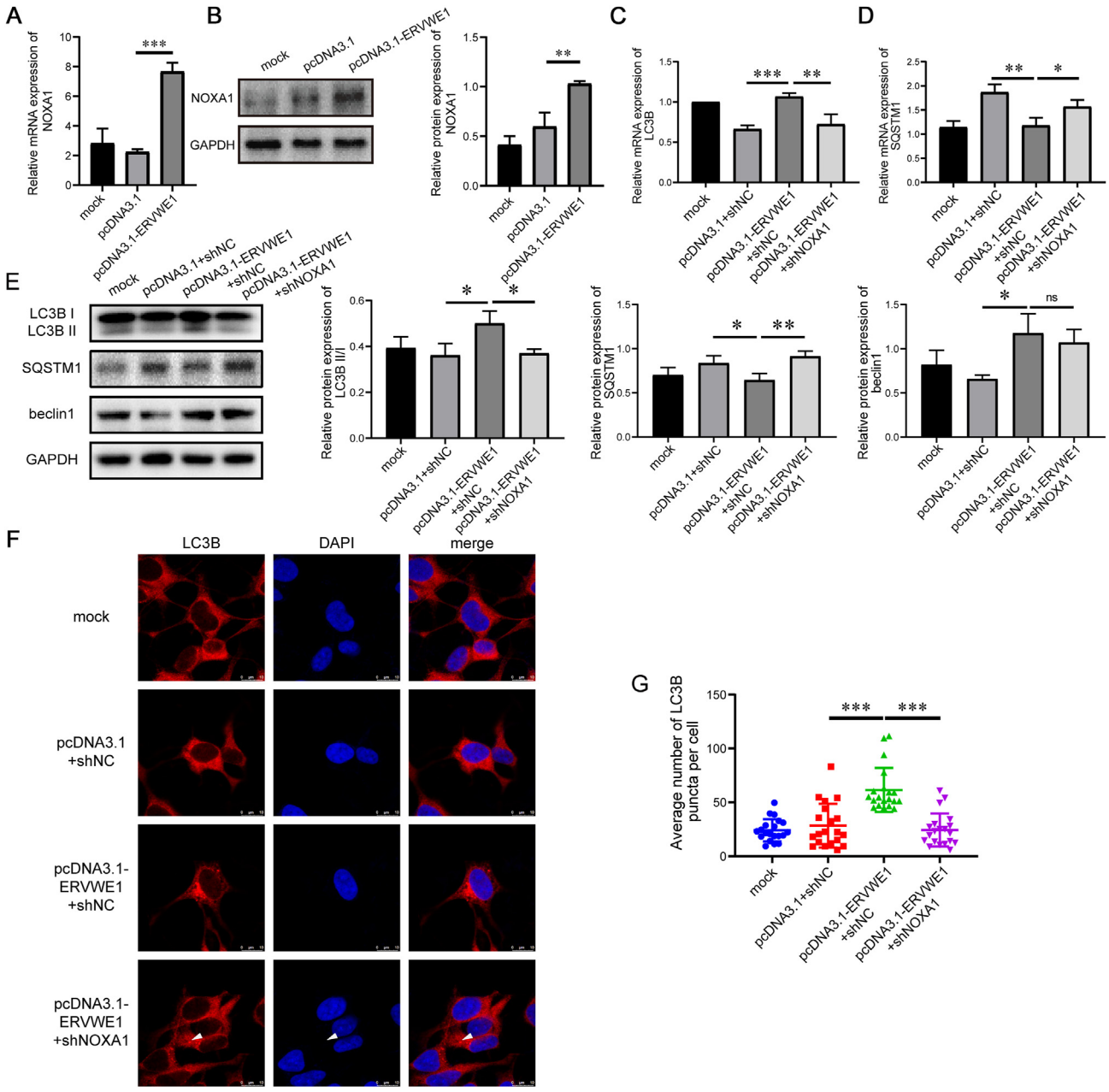

Fig. 4. NOXA1 is involved in ERVWE1-induced activation of macroautophagy in SH-SY5Y cells. **A** RT-qPCR analysis of NOXA1 mRNA expression levels in SH-SY5Y cells transfected with ERVWE1. **B** Western blotting analysis confirming NOXA1 protein expression in ERVWE1-transfected SH-SY5Y cells. **C, D** RT-qPCR analysis LC3B (**C**) and SQSTM1 (**D**) mRNA expression levels in SH-SY5Y cells co-transfected with ERVWE1 and shNOXA1. **E** Western blotting analysis showing changes in LC3B II/I ratio, SQSTM1, and beclin1 protein levels in SH-SY5Y cells co-transfected with ERVWE1 and shNOXA1. **F** Immunofluorescence staining of LC3B (red) in SH-SY5Y cells co-transfected with ERVWE1 and shNOXA1. (Scale bar = 10 μm). **G** Quantification of LC3B-positive puncta per cell (n = 20) using Image J software. Data are presented as mean ± SD. Statistical analysis: one-way ANOVA and Student's *t*-test. All experiments were performed in triplicate. ns: $P > 0.05$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

pathway and GO biological process enrichment analyses revealed that DEGs were significantly enriched in mitophagy and related pathways (Fig. 5E and F). GO cellular component enrichment analysis indicated that DEGs were associated with mitochondria and mitochondrial components (Fig. 5G), suggesting that mitophagy may be suppressed in schizophrenia.

ERVWE1 inhibits PINK1 and parkin-mediated micromitophagy via NOXA1

Previous studies have shown that ERVWE1 can induce mitochondrial fragmentation damage (Li et al., 2024), which may affect micromitophagy (Lemasters, 2014). We further investigated the role of ERVWE1 in micromitophagy. To explore this, we transfected ERVWE1 into SH-SY5Y cells and examined the mRNA levels of micromitophagy-related genes. We found that ERVWE1 significantly reduced the expression of PINK1 (Fig. 6A) and Parkin (Fig. 6B), while increasing the expression of TOM20 (Fig. 6C) and PDHA1 (Fig. 6D). Western blotting analysis of total protein levels confirmed these changes (Fig. 6E). Additionally, mitochondrial protein analysis revealed down-regulation of PINK1, Parkin, and PDHA1, as well as an upregulation of TOM20 (Fig. 6F), further indicating that ERVWE1 inhibits micromitophagy. To assess this more directly, we used confocal microscopy to visualize PDHA1-positive TOM20-negative MDVs. The results clearly demonstrated a significant reduction in the number of PDHA1-positive

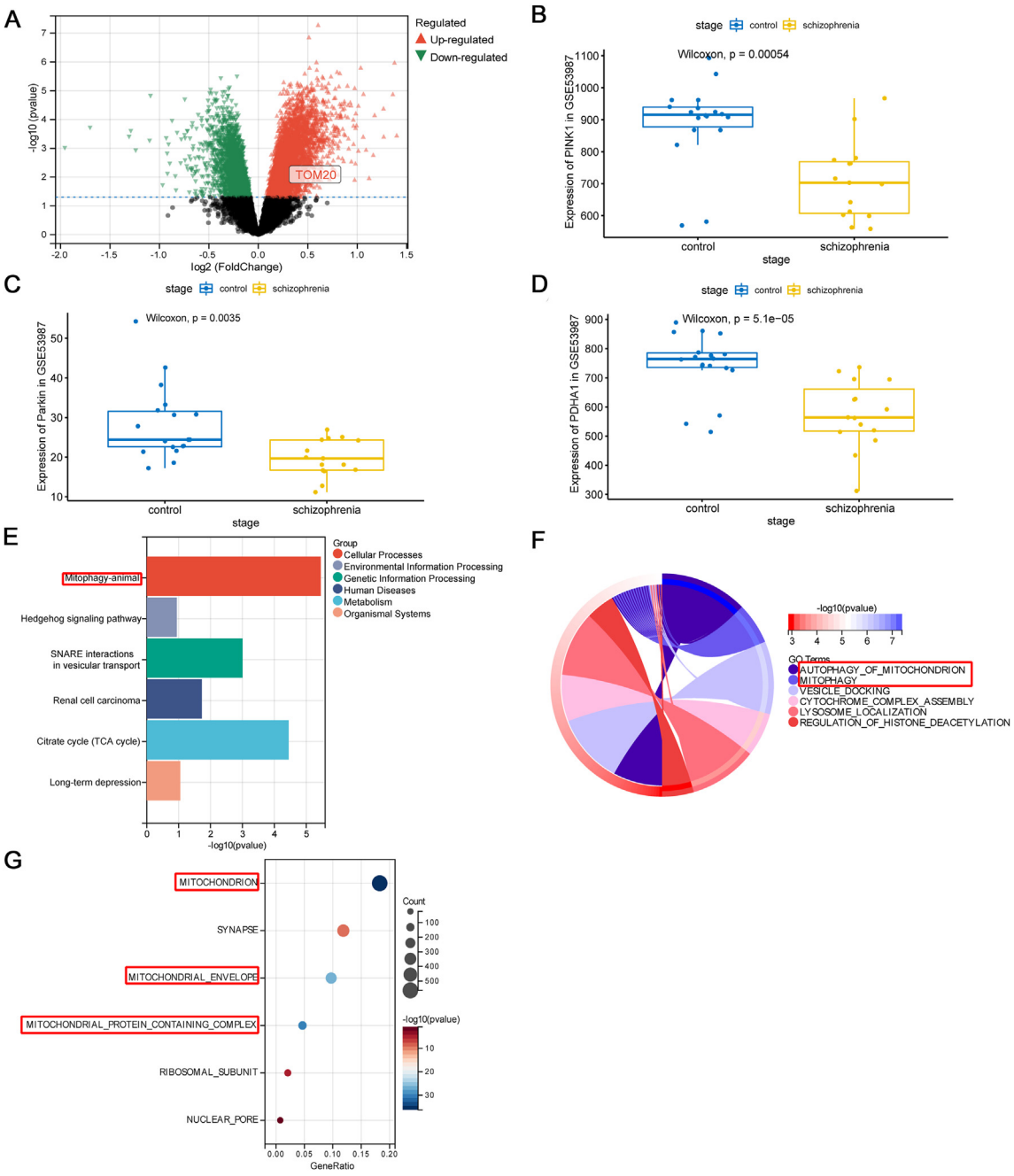

Fig. 5. Bioinformatic analysis of micromitophagy-related genes and pathway enrichment in schizophrenia dataset GSE53987. **A** Volcano plot and expression profiling of differentially expressed micromitophagy-related genes in GSE53987, analyzed using R software. **B–D** Comparison of mRNA levels of PINK1 (**B**), Parkin (**C**), and PDHA1 (**D**) between schizophrenia patients and healthy controls in GSE53987. **E** KEGG pathway enrichment analysis of DEGs in GSE53987. **F** GO bioprocess enrichment analysis of DEGs. **G** GO cellular component enrichment analysis of DEGs. Statistical analysis: Wilcoxon signed-rank test.

MDVs in ERVWE1-transfected cells. These vesicles were clearly distinguished by red fluorescence, in contrast to the TOM20-positive MDVs, which were labeled with green fluorescence (Fig. 6G). A zoomed-in image further illustrated this difference. The number of PDHA1-positive TOM20-negative MDVs was quantified using Image J software, and the calculations revealed a decrease ratio of MDVs to cell numbers (Fig. 6H). These findings support our conclusion that ERVWE1 inhibits micromitophagy.

Given the ERVWE1-induced mitochondrial damage (Li et al., 2024) and activation of NOXA1, we next explored whether NOXA1 mediated the inhibition of micromitophagy. In SH-SY5Y cells overexpressing NOXA1, we observed a significant reduction in the mRNA levels of PINK1, Parkin, and PDHA1 (Fig. 7A, B, and C), which was accompanied by a corresponding decrease in their protein levels, as confirmed by Western blotting (Fig. 7D). These results suggest that NOXA1 may suppress micromitophagy by modulating the PINK1-Parkin pathway. To validate these observations, we examined SH-SY5Y cells transfected with either the pcDNA3.1 vector or pcDNA3.1-NOXA1 using confocal microscopy. NOXA1-overexpressing cells exhibited a marked reduction in the number of PDHA1-positive MDVs, labeled with red fluorescence. In contrast, control cells displayed a significantly higher number of these vesicles (Fig. 7E). Magnified images of the MDVs confirmed this reduction. Quantification of PDHA1-positive TOM20-negative MDVs using Image J software revealed a significant decrease in the ratio of MDVs to cell numbers in NOXA1-overexpressing cells (Fig. 7F). These results provide strong evidence that NOXA1 contributes to the inhibition of

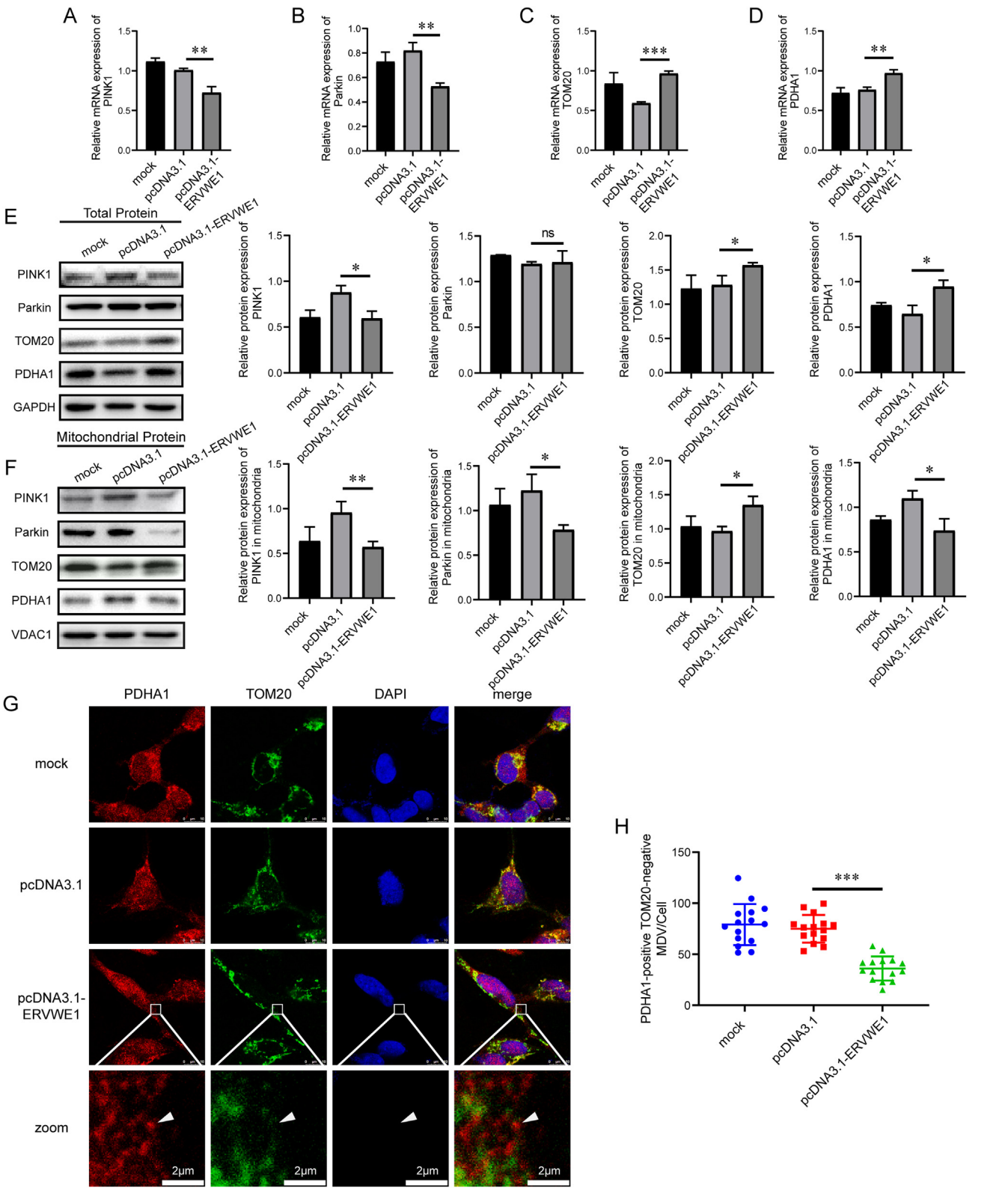

Fig. 6. ERVWE1 inhibits micromitophagy and decreases the number of mitochondrial-derived vesicles (MDVs). **A–D** RT-qPCR analysis of PINK1 (**A**), Parkin (**B**), TOM20 (**C**), and PDHA1 (**D**) mRNA expression levels in ERVWE1-transfected SH-SY5Y cells. **E** Western blotting analysis of PINK1, Parkin, TOM20, and PDHA1 protein levels in total cell lysates from ERVWE1-transfected SH-SY5Y cells. **F** Western blotting analysis of PINK1, Parkin, TOM20, and PDHA1 protein levels in mitochondrial fractions from ERVWE1-transfected SH-SY5Y cells. **G** Immunofluorescence staining of PDHA1 (red) and TOM20 (green) in SH-SY5Y cells transfected with ERVWE1. (Scale bar = 10 μm). **H** Quantification of the ratio of PDHA1-positive TOM20-negative MDVs to cell number (n = 15) using Image J software. Data are presented as mean ± SD. Statistical analysis: Student's *t*-test. All experiments were performed in triplicate. ns: $P > 0.05$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

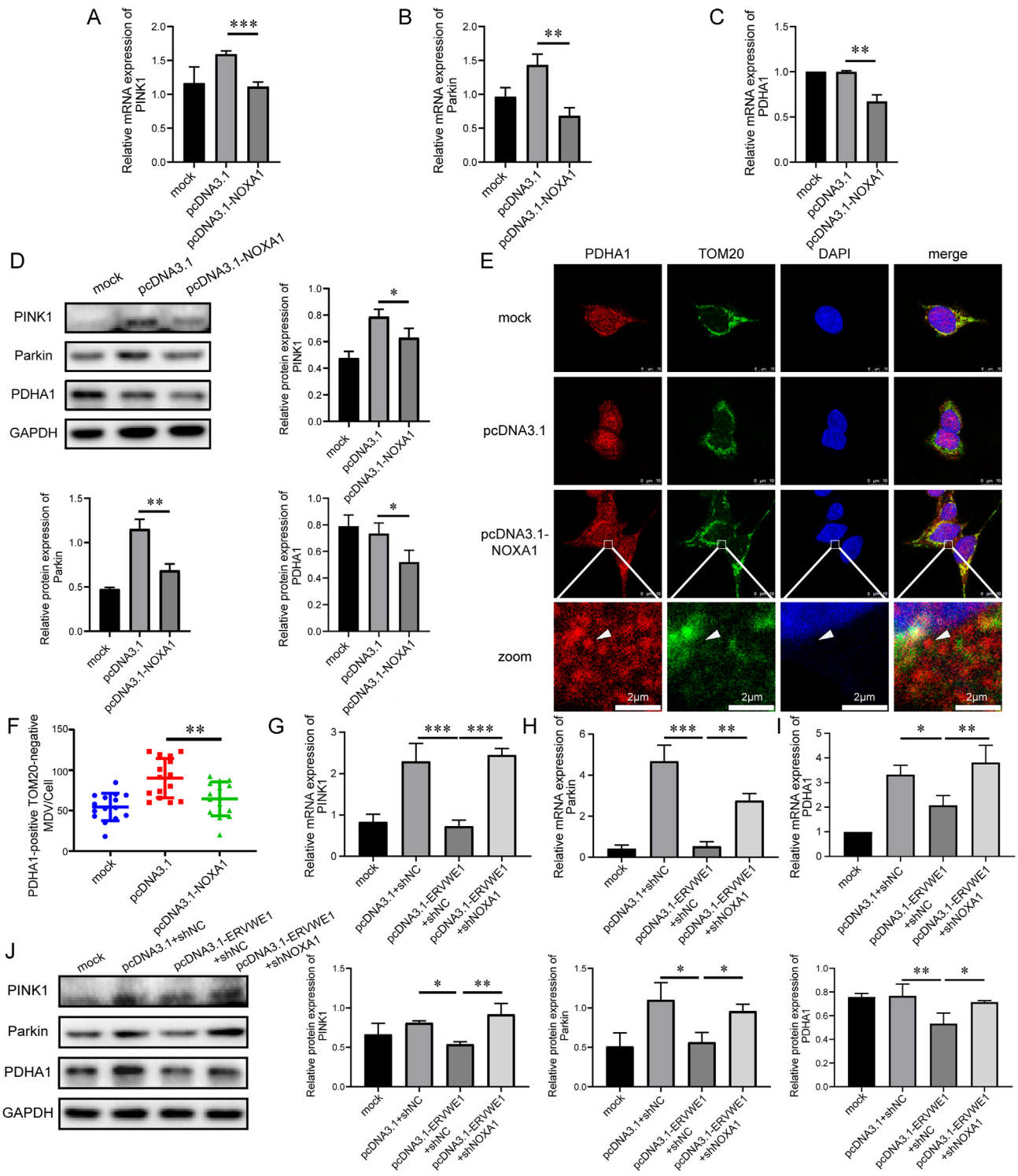

Fig. 7. ERVWE1 inhibits micromitophagy via the PINK1-Parkin pathway mediated by NOXA1. **A, B, and C** RT-qPCR analysis of PINK1 (**A**), Parkin (**B**), and PDHA1 (**C**) mRNA expression levels in NOXA1-transfected SH-SY5Y cells. **D** Western blotting analysis of PINK1, Parkin, and PDHA1 protein expression in NOXA1-transfected SH-SY5Y cells. **E** Immunofluorescence staining of PDHA1 (red) and TOM20 (green) in SH-SY5Y cells transfected with NOXA1. (Scale bar = 10 μm). **F** Quantification of PDHA1-positive TOM20-negative MDVs per cell (n = 15) using Image J software. **G, H, and I** RT-qPCR analysis of PINK1 (**G**), Parkin (**H**) and PDHA1 (**I**) mRNA expression levels in SH-SY5Y cells co-transfected with ERVWE1 and shNOXA1. **J** Western blotting analysis of PINK1, Parkin, and PDHA1 protein expression in SH-SY5Y cells co-transfected with ERVWE1 and shNOXA1. Data are presented as mean ± SD. Statistical analysis: one-way ANOVA and Student's *t*-test. All experiments were performed in triplicate. $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

micromitophagy, likely by interfering with the PINK1-Parkin signaling pathway.

Considering that ERVWE1 induces the expression of NOXA1 and impairs mitochondrial function, we further next investigated the interaction between ERVWE1 and NOXA1 in micromitophagy regulation. We knocked down NOXA1 expression of in SH-SY5Y cells and co-transfected with ERVWE1. The results showed that silencing NOXA1 significantly reversed the ERVWE1-induced inhibition of micromitophagy. Specifically, we

observed that the mRNA expression of PINK1, Parkin, and PDHA1 was significantly increased in NOXA1-knockdown cells transfected with ERVWE1 (Fig. 7G, H, and I). Western blotting confirmed this reversal, showing that down-regulation of NOXA1 restored PINK1, Parkin, and PDHA1 protein levels, which are critical for the formation of PDHA1-positive TOM20-negative MDVs (Fig. 7J). These findings suggest ERVWE1 inhibits micromitophagy by upregulating NOXA1 expression.

ERVWE1 promotes NOXA1 expression through upregulation of transcription factor USF2

We further explored the mechanism by which ERVWE1 promotes NOXA1 expression. Using transcription factor prediction tools such as PROMO (Farre et al., 2003), human TFDB (Hu et al., 2019), and HOCOMOCO (Kulakovskiy et al., 2018), we identified two potential transcription factors that could regulate NOXA1 expression: MYC-associated zinc finger protein (MAZ) and USF2 (Fig. 8A). Among these, we found that USF2 was the only transcription factor that could significantly increase NOXA1 mRNA levels in response to ERVWE1 (Fig. 8B), which was confirmed by subsequent analysis of USF2 protein levels (Fig. 8C). The mRNA levels of MAZ did not show significant changes (Fig. 8D), ruling out its involvement in ERVWE1-mediated NOXA1 upregulation. We next constructed a USF2 vector and transfected it into SH-SY5Y cells (Supplementary Fig. S2A and S2B). Quantitative PCR analysis confirmed that USF2 upregulated NOXA1 expression at mRNA level (Fig. 8E), and Western blotting further validated this increase at the protein levels (Fig. 8F). These results suggest that USF2 is a transcription factor that regulates NOXA1 expression. To determine whether USF2 mediates ERVWE1-induced NOXA1 upregulation, we knocked down USF2 expression in SH-SY5Y cells and co-transfected the cells with ERVWE1 (Supplementary Fig. S2C, S2D, and S2E). Silencing USF2 significantly reduced both the mRNA (Fig. 8G) and protein expression (Fig. 8H) levels of NOXA1 induced by ERVWE1. These results indicate that ERVWE1 upregulates NOXA1 expression through the activation of USF2.

Transcriptional regulation often involves long-range interactions between enhancers and promoters (Rodriguez et al., 2019). To investigate the direct role of USF2 in activating NOXA1 expression, we isolated genomic DNA fragments from the NOXA1 promoter region (ranging from −2000 to +50) and ligated them into the pGL3-basic luciferase reporter vector. The luciferase assay demonstrated that USF2 significantly activated NOXA1 promoter activity (Fig. 8I). Further experiments using five truncated promoter constructs (Fig. 8J and K) identified a critical region between −592 and −376 that was essential for USF2-mediated NOXA1 transcriptional regulation (Fig. 8L). These results suggest that ERVWE1 activates NOXA1 expression by promoting the expression of the transcription factor USF2, which in turn upregulates NOXA1 expression through its promoter region.

In summary, our findings indicate that in schizophrenia, ERVWE1 promotes NOXA1 expression through USF2, leading to the activation of macroautophagy and the inhibition of micromitophagy. ERVWE1-induced NOXA1 upregulation appears to be a key regulatory mechanism for these processes in SH-SY5Y cells, and these findings may have implications for understanding the molecular pathophysiology of schizophrenia.

DISCUSSION

Schizophrenia is a multifactorial disorder with complex etiology, involving genetic, environmental, and viral factors. In recent years, studies have implicated HERVs, particularly the HERV-W family, in the pathogenesis of schizophrenia (Huang et al., 2006; Karlsson et al., 2001; Li et al., 2019). One of the key proteins in this family, ERVWE1, has been shown to be overexpressed in patients with recent-onset schizophrenia, suggesting its potential role in the molecular and cellular mechanisms underlying the disease (Karlsson et al., 2001; Perron et al., 2008). ERVWE1 is involved in several key processes that may impact neuronal function in schizophrenia. First, ERVWE1 has been shown to influence the expression of schizophrenia-related genes, such as BDNF and DRD2, through various signaling pathways including the activation of GSK3β, CREB, and the PP2A/AKT1/GSK3 pathway (Huang et al., 2011; Qin et al., 2016; Yan et al., 2022). These changes could lead to altered neuronal signaling and contribute to the cognitive and behavioral deficits observed in schizophrenia (Sudhof, 2017). Second, ERVWE1 impacts ion channels activation. For example, it induces Ca^{2+} influx through activation of TRPC3 channels (Chen et al., 2019) and activates potassium channels (SK2, SK3) via CREB phosphorylation (Li et al., 2013) or decreasing 5-HT4R (Wu et al., 2023b). ERVWE1 also enhances sodium inward flow via DRD2 (Yan et al., 2022), which could further disturb neurotransmitter balance in the brain. These effects may underlie the dopaminergic dysregulation observed in schizophrenia, which is linked to psychotic symptoms (Grace, 2016). Third, ERVWE1 influences mitochondrial morphology and function. It has been shown to trigger mitochondrial fragmentation via the circ_0001810/miR-1197/AK2 signaling pathway (Li et al., 2024) and impair mitochondrial dysfunction by inhibiting the activity of complex I via the CPEB1/NDUFV21P1/NDUFV2 signaling pathway (Xia et al., 2021). Mitochondrial dysfunction is a well-established feature of many neuropsychiatric disorders, including schizophrenia, and may contribute to the neurodegenerative aspects of the disease (Ni and Chung, 2020). Fourth, ERVWE1 is involved in activating unfolded protein responses (UPR) in the endoplasmic reticulum, further exacerbating cellular stress. ERVWE1 inhibits GANAB expression, increasing XBP1 expression and splicing, and activating ATF6-mediated UPR (Xue et al., 2023), all of which can lead to neuronal dysfunction and death. Fifth, ERVWE1 has been shown to impair neuronal morphology. For instance, it reduces hippocampal neuron density and disrupts dendritic spine morphology by inhibiting the Wnt/JNK non-classical pathway (Yao et al., 2023). Additionally, ERVWE1 affects synaptic plasticity in 5-HT neurons by reducing m^6A modification of HTR1B mRNA (Wu et al., 2023a). Sixth, ERVWE1 triggers neuronal death including apoptosis, pyroptosis, and ferroptosis. It induces IFN-β-mediated neuronal apoptosis (Li et al., 2023b), as well as neuron pyroptosis through the NLRP3-CASP1-GSDMD pathway (Jia et al., 2025). Furthermore, ERVWE1 promotes ferroptosis by downregulating the expression of GPX4 and SLC3A2 (Zhang et al., 2024). Seventh, ERVWE1 induces abnormal neuronal function. It mediates dopaminergic neurons hyperfunction by regulating dopamine synthesis, reuptake, and transport (Yan et al., 2022). Finally, ERVWE1 triggers neuroinflammation. Specifically, it enhances nitric oxide production and promotes microglia migration by regulating the inducible nitric oxide synthase expression (Xiao et al., 2017). ERVWE1 also activates C-reactive protein (CRP) through the Toll-like receptor 3 (TLR3) signaling cascade in glial cells (Wang et al., 2018b) and stimulates cytotoxic T lymphocyte responses (Tu et al., 2017). Additionally, ERVWE1 increases the production of TNF-α and IL-10 by inhibiting MyD88 (Wang et al., 2021b). A recently published meta-analysis confirms that, in addition to the above molecular mechanisms proposed, ERVWE1 blood concentrations may be abnormally increased in some schizophrenia patients. Furthermore, ERVWE1 has been shown to induce schizophrenia-like behavioral phenotypes in animal models, and these neurobehavioral abnormalities can be significantly ameliorated by intervention with specific neutralizing antibody (Soleimani et al., 2024). These findings provide important theoretical support for the development of immune-targeted therapies for schizophrenia. In conclusion, ERVWE1 represents a significant risk factor in the pathogenesis of schizophrenia. In this paper, we demonstrated that LC3B, a macroautophagy-related gene, was upregulated in first-episode schizophrenia and was closely associated with ERVWE1. Further investigation revealed that ERVWE1 activated macroautophagy and inhibited micromitophagy in schizophrenia patients through the USF2-NOXA1 pathway, suggesting a critical role for ERVWE1 in autophagy dysregulation and neuronal damage in schizophrenia.

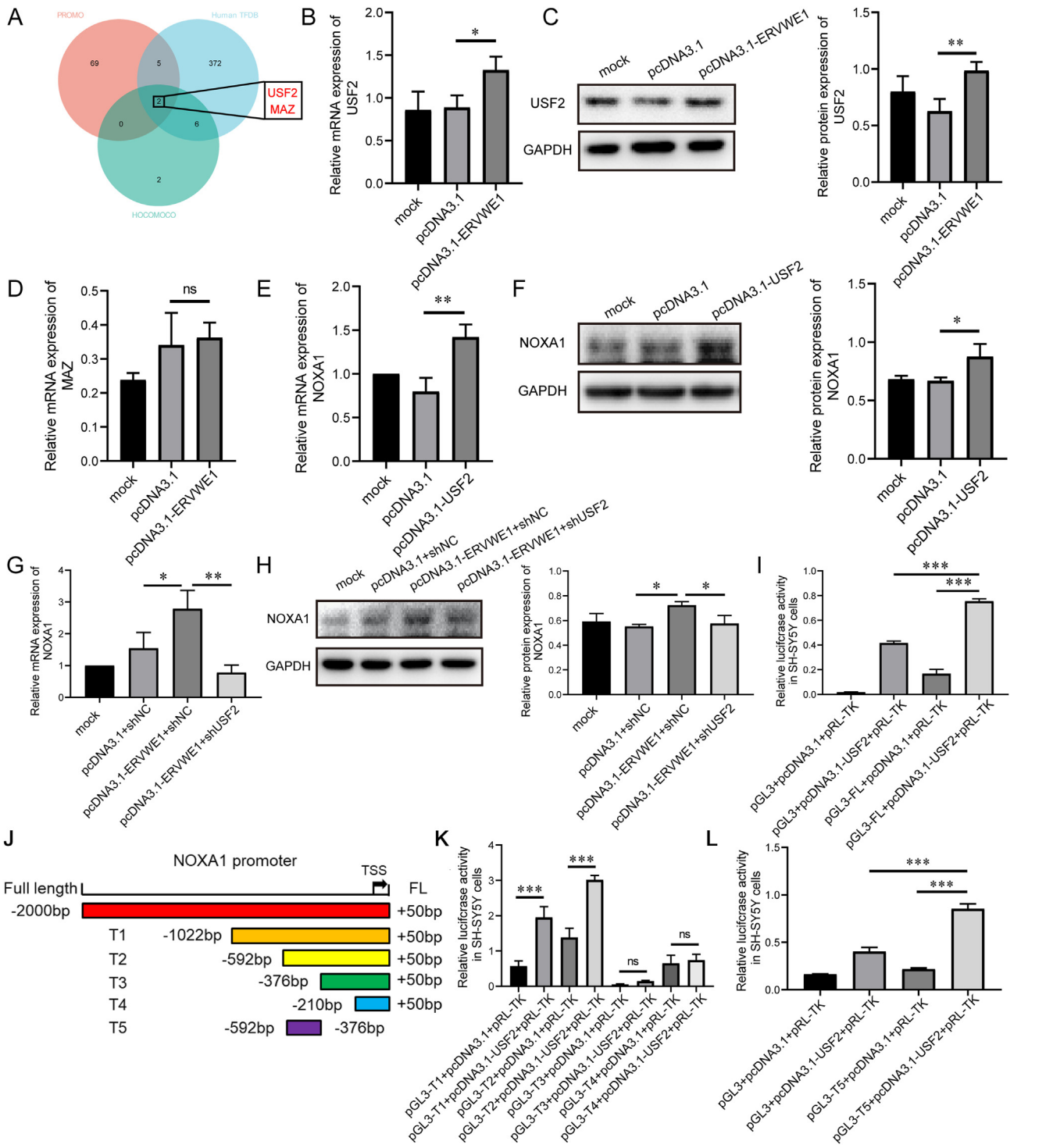

Fig. 8. ERVWE1 upregulates NOXA1 expression through the transcription factor USF2. **A** Bioinformatic predictions identify USF2 and MAZ as potential transcriptional regulators of NOXA1. **B** RT-qPCR analysis of USF2 mRNA expression levels in ERVWE1-transfected SH-SY5Y cells. **C** Western blotting analysis of USF2 protein expression in ERVWE1-transfected SH-SY5Y cells. **D** RT-qPCR analysis of MAZ mRNA expression levels in ERVWE1-transfected SH-SY5Y cells. **E, F** RT-qPCR and Western blotting analyses of NOXA1 expression levels in USF2-transfected SH-SY5Y cells. **G, H** RT-qPCR and Western blotting analyses of NOXA1 expression levels in SH-SY5Y cells co-transfected with ERVWE1 and shUSF2. **I** Luciferase assay demonstrating activation of the NOXA1 full-length promoter by USF2 in SH-SY5Y cells co-transfected with pGL3-NOXA1 and pcDNA3.1-USF2. **J** Schematic representation of truncated pGL3-NOXA1 promoter plasmids. **K** Luciferase assay showing the activity of different-length NOXA1 promoter in SH-SY5Y cells co-transfected with pcDNA3.1-USF2. **L** Luciferase assay showing activity of the truncated NOXA1-T5 promoter co-transfected with pcDNA3.1-USF2 in SH-SY5Y cells. Data are presented as mean ± SD. Statistical analysis: one-way ANOVA and Student's *t*-test. All experiments were performed in triplicate. ns: $P > 0.05$, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

Schizophrenia diagnosis remains largely reliant on subjective psychiatric assessment, patient history, and physical examination (Owen et al., 2016), with no definitive objective biomarkers currently available (He et al., 2018). Therefore, identifying reliable biomarkers and developing efficient early detection methods for schizophrenia is crucial. GEO databases have emerged as vital resources for studying disease mechanisms, offering important tools for identifying potential biomarkers and drug targets for schizophrenia (Kumarasinghe et al., 2012). To investigate whether schizophrenia is associated with altered gene expression in specific brain regions, researchers have compared gene expression profiles in multiple brain regions of postmortem patients. This analysis revealed differential expression of macroautophagy-related genes in the brains of patients with schizophrenia, particularly in brodmann area 22 (BA22) of the superior temporal cortex, a region that has been hypothesized to be involved in the pathogenesis of schizophrenia (Horesh et al., 2011). In this study, we utilized the GSE53987 schizophrenia-related dataset from the GEO database and performed enrichment and bioinformatics analyses. Our examination of DEGs revealed that macroautophagy-related genes, including LC3B and beclin1, were upregulated in schizophrenia, while SQSTM1 was downregulated. Enrichment and cluster analyses further indicated that many of these DEGs were involved in the macroautophagy pathway, suggesting that macroautophagy-related genes may play a significant role in the progression of schizophrenia. Our clinical analysis showed that LC3B expression was upregulated in schizophrenia patients and positively correlated with ERVWE1 expression. Several studies have linked LC3B, an autophagy marker, to various neuropsychiatric disorders, proposing that it may serve as a biological marker for schizophrenia. Taken together, these findings support the hypothesis that LC3B could serve as both a biomarker and a risk factor for schizophrenia.

Our clinical results further showed that ERVWE1, a key factor associated with viral infections, was strongly correlated with LC3B expression in schizophrenia patients. Immunoblotting for LC3B has become a reliable method for monitoring autophagy and autophagic processes, including autophagic cell death (Tanida et al., 2008). Previous research has demonstrated that viral infection affects macroautophagy. For instance, the 2AB protein of Senecavirus A inhibits selective autophagy and type I interferon production by degrading LC3 (Sun et al., 2022a). Similarly, recombinant Newcastle disease virus (rL-RVG)-induced autophagy is linked to gastric adenocarcinoma cell death (Bu et al., 2015). In line with these studies, we found that ERVWE1 activated macroautophagy, consistent with earlier research (Bar-Yosef et al., 2019). A study based on autopsy samples demonstrated that autophagy-related protein RB1CC1 was significant up-regulation in the dentate gyrus of schizophrenia patients, suggesting that RB1CC1-mediated autophagy abnormalities may contribute to hippocampal neurogenesis disorders in schizophrenia (Lappas et al., 2025). Furthermore, autophagy activation has been observed in the phencyclidine (PCP) model of schizophrenia (Jevtic et al., 2016), supporting the notion that autophagy may represent a critical therapeutic target in neuropsychiatric disorders, including schizophrenia and Alzheimer's disease (Sragovich et al., 2017). Interestingly, a recent genetic study has identified 995 single nucleotide polymorphisms (SNPs) in 19 autophagy-related genes associated with schizophrenia, suggesting that autophagy may be down-regulated in schizophrenia patients (Su et al., 2024b). While autophagy normally aids in the removal of damaged organelles and cellular debris to reduce cellular stress and promote neuronal repair, excessive autophagy can be detrimental, potentially leading to neuronal damage (Ajoolabady et al., 2021). Previous studies from our group demonstrate that ERVWE1 induces neuronal apoptosis (Li et al., 2023b), as well as triggers neuronal dysfunction and morphological abnormalities (Wu et al., 2023a; Yao et al., 2023). These findings suggest that overactivation of macroautophagy by ERVWE1 may contribute to neuronal damage and dysfunction in schizophrenia, potentially exacerbating symptoms by affecting dopaminergic pathways.

NOX family members have been implicated in various neuropsychiatric disorders, reflecting their role in oxidative stress and neuronal damage. Serum levels of NOX1 and raftlin were found to be significantly elevated in schizophrenia patients and positive correlated with symptom severity, implying that NOX1 could serve as a potential biomarker for schizophrenia (Hursitoglu et al., 2022). Moreover, rutin treatment was shown to ameliorate ketamine-induced schizophrenia-like behavior in mice by reducing NOX2 expression and oxidative stress (Oshodi et al., 2021). In other psychiatric disorders, ALI-induced upregulation of neutrophil NOX-2/ROS has been linked to depression-like symptoms in mice (Nadeem et al., 2017b). TLRs and NOX-2-derived ROS contribute significantly to the pathogenesis of autism spectrum disorders (Nadeem et al., 2017a). In individuals with bipolar disorder, both NOX2 and microglia markers are reduced in the brain (Seredenina et al., 2017). In contrast, our bioinformatics also revealed increased expression of NOXA1, a key component of the NOX complex, in schizophrenia patients. NOX-generated ROS plays an essential role in the progression of various central nervous system (CNS) disorders, including schizophrenia (Sorce et al., 2012). For instance, NOX4 has been implicated in oxidative stress in peripheral blood lymphocytes of schizophrenia patients (Ershova et al., 2022), and NOX2 inhibition by clozapine metabolites leads to microglia inactivation, providing neuroprotection in neuropsychiatric disorders, particularly schizophrenia (Frick et al., 2013). Given that ROS can regulate autophagy, NOX appears to link oxidative stress and autophagic processes. For example, alamandine mitigates liver fibrosis by modulating NOX4-dependent ROS-induced autophagy (Huang et al., 2020), and *Vibrio vulnificus* promotes ROS production and autophagic cell death through the lipid raft-dependent c-Src/NOX signaling pathway (Song et al., 2016). Our findings revealed that NOXA1, an essential cytoplasmic subunit for NOX1 activation, could induce macroautophagy. NOX-induced autophagy is closely related to neuronal damage. For example, NOX2 activation increases autophagic activity in spinal cord neurons and contributes to morphine tolerance (Xiao et al., 2021). Moreover, NOX-generated oxidative stress plays a key role in inducing autophagy in the hippocampus during seizures triggered by pentylenetetrazol (PTZ) (Zhu et al., 2016). In models of neuroinflammation, NOX also cooperates with autophagy to drive pro-inflammatory responses in microglia and dopaminergic neuronal death (Lopez-Lopez et al., 2021). This suggests that NOXA1 may play a crucial role in schizophrenia pathogenesis by driving neuronal damage through autophagic processes.

Viral infections are also known to impact NOXA1 expression. The human immunodeficiency virus (HIV) protein Tat, for example, increases the expression of NOX1 and its coactivator NOXA1 (Kovacs et al., 2021). In patients with hepatitis C virus (HCV)-associated chronic hepatitis C (CHC), long-term losartan treatment downregulates *NOX* genes, including *NOXA1* (Colmenero et al., 2009). Interestingly, our study identified that ERVWE1 increased NOXA1 expression. Animal model of α-virus infection, such as those involving α-viruses, have shown up-regulation of NOX subunits in the CNS (Blakely et al., 2016). Additionally, activation of microglia by encephalomyocarditis virus (EMCV) induces ROS production through NOX2 (Ano et al., 2012), further suggesting the involvement of viral factors in NOXA1 regulation. These observations support the hypothesis that ERVWE1 may contribute to the pathogenesis of schizophrenia by upregulating NOXA1 and triggering neuronal damage through autophagy.

Previous studies have shown that NOXA1 induces macroautophagy. Our results showed that ERVWE1 elevated NOXA1 expression and down-regulation of NOXA1 reversed the macroautophagy activation induced by ERVWE1. In particular, NOX proteins have been implicated in inducing neuronal damage through autophagy. For example, apocynin has been demonstrated to alleviate neuronal damage in a rat model of traumatic brain injury by reducing NOX2 expression, inhibiting neuronal autophagy, and modulating the TLR4/NF-kappaB signaling pathway (Feng et al., 2017). Additionally, NOX plays a critical role in neuronal damage associated with viral infections. The binding of the HIV viral envelope glycoprotein gp120 to chemokine co-receptors CCR5 or CXCR4

leads to optic rod formation and synaptic dysfunction, processes that are dependent on NOX signaling (Smith et al., 2021). In a similar context, NOX2 contributes to oxidative stress in microglial cells infected with myocarditis encephalopathica virus, causing oxidative damage to neurons (Ano et al., 2010). Elevated NOX activity has been linked to CNS degeneration, both of which are implicated in neuropsychiatric disorders, including schizophrenia (Kaur et al., 2023). These findings suggest a possible mechanism by which ERVWE1 contributes to the pathogenesis of schizophrenia. Specifically, ERVWE1 may activate macroautophagy via the up-regulation of NOXA1, resulting in neuronal damage. Moreover, while ERVWE1-induced changes in beclin1 are also observed, these alterations likely occur through pathways independent of NOXA1. Together, our results offer new insights into the complex interactions between NOX, viral infection, and autophagy in the context of neuropsychiatric diseases, particularly schizophrenia.

In this study, we also explored the role of microautophagy, another autophagic pathway distinct from macroautophagy. Microautophagy, particularly micromitophagy, has been implicated in the selective degradation of damaged mitochondria (Lemasters, 2014). In yeast, microautophagy predominates over macroautophagy, whereas in mammalian cells, macroautophagy is the dominant pathway for mitochondrial quality control (Wang et al., 2023). Our bioinformatics analyses of schizophrenia-related datasets revealed a connection between mitochondrial autophagy (mitophagy) and the disease. Differential analyses indicated that multiple genes associated with mitophagy, including micromitophagy, are differentially expressed in schizophrenia, which is consistent with previous studies (Ni and Chung, 2020). An integrative analysis combining single-cell transcriptomic data and machine learning revealed significant dysregulation of micromitophagy-related molecules in schizophrenia (Yang et al., 2024). In addition, morphological abnormalities, including a reduction in mitochondrial number in astrocytes, have been observed in schizophrenia patients, possibly reflecting impaired mitochondrial autophagy (Bernstein et al., 2025; Kolomeets and Uranova, 2010). Mitochondrial dysfunction is a hallmark of many neurodegenerative and psychiatric disorders, including Alzheimer's, Parkinson's, and schizophrenia, and is closely linked to synaptic abnormalities (Palikaras and Tavernarakis, 2020). Our results suggest that micromitophagy may be involved in schizophrenia pathophysiology, possibly influenced by viral infections that induce mitochondrial autophagy.

Furthermore, viral infection has been shown to disrupt mitochondrial autophagy. For instance, influenza A virus protein PB1–F2 impairs immune responses by inducing mitochondrial autophagy-associated molecules like PINK1 and Parkin (Wang et al., 2021a). Similarly, the Newcastle disease virus reprograms cellular metabolism by degrading SIRT3 via a PINK1-PRKN-dependent pathway (Gong et al., 2022). Interestingly, our experimental data suggested that ERVWE1 inhibited micromitophagy, potentially exacerbating mitochondrial damage in schizophrenia. Recent studies have highlighted that dysfunctional mitochondrial autophagy, coupled with mitochondrial damage, is implicated in neuropsychiatric disorders (Liu et al., 2022). For example, urolithin A, a mitochondrial autophagy inducer, can reverse mitochondrial dysfunction and alleviate neuropsychiatric symptoms such as those seen in depression (Chen et al., 2023). This reinforces the idea that micromitophagy is a key process in maintaining mitochondrial health and preventing neurodegeneration.

Members of the NOX family are involved in diverse cellular processes, including the regulation of mitophagy and mitochondrial function (Su et al., 2023). Among these processes, PINK1 and Parkin play critical roles in mediating mitophagy by controlling the generation of PDHA1-positive TOM20-negative MDVs (Todkar et al., 2021). Notably, NOX4 has been shown to drive mitochondrial ROS production, which activates mitochondrial autophagy via the nuclear factor erythroid 2-related factor 2 (Nrf2)/PINK1 pathway to support hepatocellular carcinoma cell survival following incomplete radiofrequency ablation (Peng et al., 2023). Furthermore, PINK1/Parkin-mediated mitochondrial autophagy can reduce plasma advanced oxidation protein products (AOPP) levels and inhibit NOX-dependent ROS production (Li et al., 2023a; Zhu et al., 2018). HIF-1 signaling, by promoting PDK1 expression, inhibits PDH activity under hypoxic conditions, thereby limiting mitochondrial ROS production and preserving ATP levels to protect against oxidative damage and apoptosis (Kim et al., 2006). Although these studies provide important insights into macroautophagy and oxidative stress responses, the specific contribution of NOX family members to PINK1/Parkin-mediated micromitophagy remains poorly understood. Our findings fill this gap by demonstrating that NOXA1 inhibited micromitophagy through down-regulating the expression of PINK1, Parkin, and PDHA1. This impairment of mitochondrial autophagy likely exacerbates mitochondrial dysfunction, a process increasingly recognized as a critical contributor to neuropsychiatric disorders. For instance, mutations in ubiquilin 2 (UBQLN2), a protein involved in Parkin-mediated mitochondrial autophagy, are associated with ALS/FTD, where it promotes neuronal survival by facilitating mitochondrial outer membrane rupture after injury (Ma et al., 2023). Similarly, therapeutic interventions such as baicalin, which restores PDK2-PDH axis function and attenuates mitochondrial oxidative stress, have shown neuroprotective effects (Liu et al., 2024). Additionally, paeoniflorin has been shown to alleviate mitochondrial damage and reverse depression-like behaviors by enhancing mitophagy and inhibiting the activation of NLRP3 inflammasomes (Su et al., 2024a). Similarly, biomarkers related to mitochondrial autophagy, such as exosomal miR137-COX6A2 and gamma synchrony, are associated with psychopathology and neurocognitive deficits in schizophrenia (Khadimallah et al., 2022). Taken together, these findings suggest that NOXA1 may contribute to the pathogenesis of schizophrenia by inhibiting PINK1-Parkin-mediated micromitophagy and thereby exacerbating mitochondrial damage.

Further investigation confirmed that silencing NOXA1 reversed the ERVWE1-and NOXA1-induced downregulation of PINK1, Parkin, and PDHA1. NOX, through its regulation of autophagy and mitochondrial damage, plays a crucial role in neuropsychiatric conditions. For example, allicin has been shown to reduce the expression of NOX2 and NOX4, inhibit ROS production and oxidative stress, and improve mitochondrial function, thereby mitigating depressive behaviors induced by a high-fat diet (Gao et al., 2019). Moreover, NOX is involved in mitochondrial damage induced by viral infection. In the case of SARS-CoV-2, the virus increases NOX and ROS production, disrupts autophagy, and causes mitochondrial dysfunction (Anwar et al., 2022). Excessive NOX production is a well-established contributor to oxidative stress and mitochondrial damage in neuropsychiatric disorders (Kaur et al., 2023). These findings support the notion that ERVWE1, through regulation of NOXA1, may contribute to schizophrenia pathogenesis by inhibiting PINK1-Parkin-mediated micromitophagy, leading to mitochondrial damage and further exacerbating disease progression.

Transcription factors are key regulatory proteins that influence gene expression by binding to specific DNA sequences (Smith and Matthews, 2016). Several transcription factors, such as FOXO1, have been shown to modulate NOX expression and contribute to oxidative stress. For instance, activation of FOXO1 in cardiomyocytes upregulates Krüppel--like factor 5 (KLF5), which in turn stimulates NOX4 expression, leading to oxidative stress and diabetic cardiomyopathy (Kyriazis et al., 2021). Similarly, angiotensin II (Ang II) affects NOX2 through the transcription factor octamer-binding transcription factor 1 protein (Oct-1), promoting superoxide anion production and endothelin-1 expression in endothelial cells (Kamhieh-Milz et al., 2023). However, little is known about the regulation of NOXA1 expression by transcription factors. In this study, we identified two potential transcription factors, USF2 and MAZ, that may regulate NOXA1 expression, based on bioinformatics predictions using PROMO (Farre et al., 2003), human TFDB (Hu et al., 2019), and HOCOMOCO (Kulakovskiy et al., 2018). Our findings suggest that ERVWE1 enhances the expression of USF2, which in turn upregulates NOXA1 expression. Transcription factors also play critical roles in

virus-host interactions, with previous studies demonstrating how certain host transcription factors regulate viral replication. For example, ZFP36L2 effectively inhibits the replication of flavivirus by binding to viral RNA and further degrading it (Lin et al., 2025), and IRF-3 mediates apoptosis in response to Sendai virus infection (Heylbroeck et al., 2000). These findings suggest that the transcription factor USF2 may also be involved in the regulation of NOXA1 by ERVWE1, contributing to the pathogenesis of schizophrenia.

To explore the mechanism by which USF2 regulates NOXA1, we performed luciferase reporter assays, which demonstrated that USF2 enhances NOXA1 promoter activity. Specifically, regions −592 to −376 of the NOXA1 promoter were identified as essential for USF2-induced NOXA1 expression. Furthermore, USF2 mediated the regulation of NOXA1 promoter activity by ERVWE1. Previous research has shown that USF2 activates the platelet-responsive protein 1 (THBS1), which triggers the transforming growth factor-β (TGF-β)/SMAD family member 3 (Smad3) signaling pathway, contributing to cellular pyrolysis and exacerbating sepsis-induced acute kidney injury, thus promoting oxidative stress (Sun et al., 2022b). Our study provides the first evidence that USF2 is a key transcription factor involved in the regulation of NOXA1 expression and this pathway may be altered by ERVWE1 in the context of schizophrenia.

CONCLUSIONS

Our clinical data indicate that plasma LC3B levels are significantly elevated in individuals with schizophrenia compared to healthy controls, with a positive correlation observed between LC3B and ERVWE1 expression. *In vitro* experiments further demonstrated that ERVWE1 upregulates NOXA1 expression, leading to the promotion of autophagosome formation and activation of macroautophagy. Additionally, we found that ERVWE1 inhibited micromitophagy by increasing NOXA1 expression, which in turn decreases the expression of key micromitophagy-related genes, PINK1 and Parkin, and reduces the production of PDHA1-positive TOM20-negative MDVs. Moreover, our findings revealed that ERVWE1 enhanced NOXA1 promoter activity via the transcription factor USF2, thereby further amplifying NOXA1 expression (Fig. 9). Taken together, these results suggest that ERVWE1 induce neuronal damage and mitochondrial dysfunction in schizophrenia through modulation of the autophagy pathway, specifically by disrupting both macroautophagy and micromitophagy. This provides a novel insight into the molecular mechanisms underlying schizophrenia pathogenesis. These findings offer potential new directions for therapeutic interventions targeting the autophagy and mitochondrial pathways in neuropsychiatric disorders, particularly schizophrenia.

MATERIALS AND METHODS

Blood samples

Blood samples were collected from 45 schizophrenia patients and 45 healthy controls at Renmin Hospital, Wuhan University. All schizophrenia patients met the diagnostic criteria for recent-onset schizophrenia-related psychoses as defined by the Diagnostic and Statistical Manual of Mental Disorders, 5th edition. These patients were diagnosed with schizophrenia for the first time and had no history of acute infectious. Healthy controls had no psychiatric illnesses. There were no significant differences between the patient and control groups in terms of median age, education level, body mass index, smoking status, or gender distribution. Serum samples were obtained by centrifugation at 1000×*g* for 10 min and stored at −80 °C until further analysis. Detailed information on participants can be found in Supplementary Table S1.

Cell culture and transfection

The human neuroblastoma cell line SH-SY5Y was obtained from the American Type Culture Collection (ATCC, USA). Cells were maintained in a 1:1 mixture of Minimum Essential Media (2225320; Gibco, USA) and F12 Medium (2209586; Gibco, USA), supplemented with 10% fetal bovine serum, 1% sodium pyruvate and 100 U/mL penicillin-streptomycin. Cells were cultured at 37 °C in 5% CO_2. Transfections were performed using Lipofectamine™ 2000 Transfection Reagent (11668030; Invitrogen, USA) according to the manufacturer's instructions.

Plasmids' construction

The plasmid pcDNA3.1-ERVWE1 was constructed in our laboratory (Zhang et al., 2024). The genes for human NOXA1 (NM_001256067.2) and USF2 (NM_003367.4) were amplified according to sequences inform the National Center for Biotechnology Information (NCBI) database and cloned into pcDNA3.1 plasmid to generate pcDNA3.1-NOXA1 and pcDNA3.1-USF2, respectively.

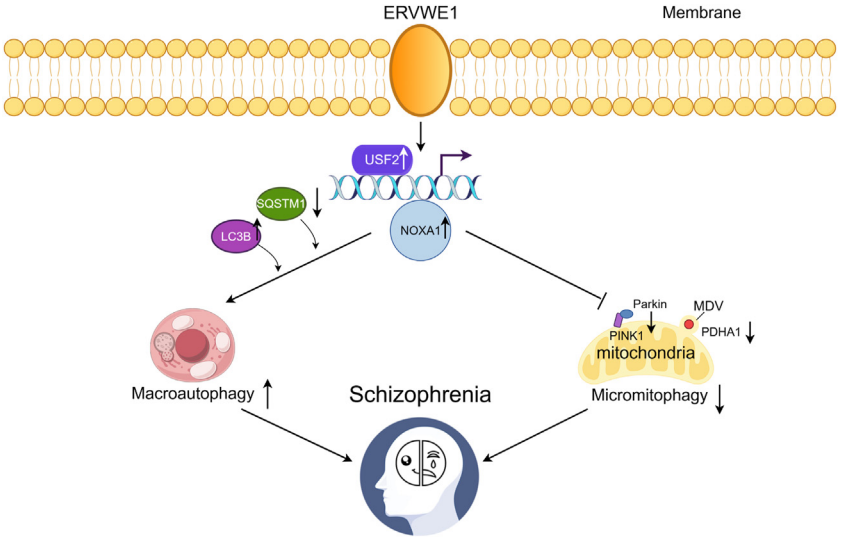

Fig. 9. Hypothetical model of ERVWE1-mediated neuronal and mitochondrial damage via macroautophagy in schizophrenia. ERVWE1 increases NOXA1 expression via the transcription factor USF2, leading to enhanced macroautophagy and inhibited micromitophagy. This dysregulation of autophagy contributes to mitochondrial and neuronal damage, potentially playing a role in the pathogenesis of schizophrenia. The figure was created by Figdraw.

Short hairpin RNA (shRNA) targeting NOXA1, USF2, and a negative control (shNC) were inserted into the pSilencer 2.1-U6 neo shRNA expression vector (AM5764; Ambion Inc., USA) using BamHI and HindIII restriction enzymes.

Promoter regions of human NOXA1 (−2000 to +50, −1022 to +50, −592 to +50, −376 to +50, −210 to +50, and −592 to −376) were cloned into the pGL3-basic luciferase reporter vector, which contains a firefly luciferase gene. All primers were designed using Premier 5.0 software and are listed in Supplementary Table S2. All constructs were confirmed by sequencing (Sangon Biotech, China).

Bioinformatics

We retrieved the human hippocampus and striatal gene expression profile from GSE53987 (Lanz et al., 2019) and GSE202537 (Ketchesin et al., 2023) in the GPL570 and GPL18573 platform, respectively, for schizophrenia and controls. Datasets were obtained from the Gene Expression Omnibus (GEO) database. Differentially expressed genes (DEGs) were visualized using volcano plots and heatmaps generated via Sanger box online tool (Shen et al., 2022). Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) enrichment analysis were performed using Sanger box ($P < 0.05$). The expression levels of PINK1, Parkin, and pyruvate dehydrogenase E1 subunit α 1 (PDHA1) in patients versus were analyzed using the Wilcoxon test and visualized using the ggplot2 (R package).

ELISA

Human ERVWE1 (LB111222B; Liberi Bio, China) and LC3B (LB10281B; Liberi Bio, China) serum levels were measured using commercially available ELISA kits following the manufacturer's instructions. Standard curves were plotted, and absorbance was measured at 450 nm using a Multiskan FC plate reader.

Real-time quantitative PCR

Total RNA was extracted from cultured cells using TRIzol reagents (15596018; Invitrogen, USA). Reverse transcription was performed on 1 μg of RNA using ReverTra Ace (FSK-101; TOYOBO, Japan). Real-time Quantitative Polymerase Chain Reaction (q-PCR) was carried out on an iCycler system (Bio-Rad, USA) ® using SYBR Select Master Mix (2992239AX; Aidlab Biotechnologies Co. Ltd., China). Glyceraldehyde-3-phosphate dehydrogenase (GAPDH) was used as an internal control. mRNA expression levels were quantified using the $2^{-\Delta\Delta Ct}$ method. Primer sequences are listed in Supplementary Table S2.

Mitochondrial isolation

Mitochondrial were isolated using a mitochondrial extraction kit (SM0020; Solarbio, China) following the manufacturer's instructions. Cells were resuspended in precooled lysis buffer, transferred to a small-volume glass homogenizer, and homogenized 40 times in an ice bath. The cell suspension was centrifuged at 1000×*g* for 5 min at 4 °C, and the supernatant was then centrifuged at 12,000×*g* for 10 min at 4 °C. The mitochondrial pellet was resuspended in storage buffer, and protein concentrations were measured using a BCA protein assay kit (23250; Thermo Fisher Scientific, USA).

Luciferase activity assay

The luciferase activity was measured using the Dual-Luciferase Reporter Assay Kit (DL101; Vazyme, China) according to the manufacturer's protocol. SH-SY5Y cells were seeded in 24-well plate and co-transfected with plasmids for 24 h at 37 °C and 5% CO_2. Luciferase activity was measured, with the Renilla luciferase reporter plasmid (pRL-TK) serving as an internal control.

Western blotting analysis

After 48 h of transfection, SH-SY5Y cells were lysed in M-PER™ mammalian protein extraction reagent (UC282138; Thermo Fisher Scientific, USA) supplemented with protease and phosphatase inhibitors (P8340; Sigma, Germany). Protein concentrations were determined using the BCA protein Assay kit (23250; Thermo, USA). Samples were loaded onto a 12% SDS-PAGE gel and transferred to a PVDF membrane (ISEQ00010; Millipore, USA). Membranes were incubated overnight at 4 °C with primary antibodies. Primary antibody species are listed in Supplementary Table S3. The membranes were subsequently incubated with secondary antibodies Goat anti-Mouse IgG-HRP (1:10,000; AS003; Abclonal, China) or Goat anti-Rabbit IgG-HRP (1:10,000; AS014; Abclonal, China) and visualized using ECL chemiluminescence (SW2030; Biosharp, China) via an automatic chemiluminescence system (5200; Tanon, China).

Confocal microscopy

SH-SY5Y cells were seeded in confocal dish, fixed in 4% paraformaldehyde, and permeabilized with 0.2% Triton X-100 in PBS (pH 7.4). After blocking with bovine serum albumin (BSA) in PBS for 1 h, cells were incubated overnight at 4 °C with primary antibodies. Primary antibody species are listed in Supplementary Table S3. Following a 1 h incubation with fluorescence-conjugated secondary antibodies, the nucleus was stained with DAPI (C0060; Solarbio, China) for 15 min at 37 °C. PDHA1-positive translocase of the outer mitochondrial membrane complex subunit 20 (TOM20)-negative MDVs were detected and counted as previously described (Todkar et al., 2021). Immunofluorescence signals were captured using a confocal laser scanning microscope (TCS SP8; Leica Microsystems, Germany) equipped with an HCX PLAPO 63*/1.40 oil objective len. The images were processed and analyzed in two-dimensional planes using green (FITC, excitation spectrum: 488 nm), red (Cy3, excitation spectrum: 552 nm), and blue (DAPI, spectrum excitation: 405 nm) channels. The experiment was repeated three times. Image J software was used for data analysis and quantification.

Statistical analysis

All data are presented as mean ± standard deviation (SD). For the clinical results, we used median and Wilcoxon signed-rank test from at least three independent experiments. The correlation between ERVWE1 and LC3B expression was assessed using Spearman rank correlation. Statistical analyses were performed using GraphPad Prism 5 and IBM SPSS software Statistics 20. One-way ANOVA and Student's *t*-test were used where appropriate, with a *P*-value of < 0.05 considered statistically significant.

DATA AVAILABILITY

All the data generated during the current study are included in the manuscript.

ETHICS STATEMENT

The blood sample collection in this study has been approved by the Institutional Review Board of the School of medicine of Wuhan University (No. 20070718). Informed consents have been obtained from the legal guardians before drawing blood.

AUTHOR CONTRIBUTIONS

Jiahang Zhang: investigation, data curation, methodology, and writing-original draft. Huiling Wang: resources and formal analysis. Xing Xue: software. Xiulin Wu and Wenshi Li: formal analysis and supervision. Zhao Lv: methodology. Yaru Su: data curation. Mengqi Zhang, Kexin

Zhao, Xu Zhang, Chen Jia: formal analysis. Fan Zhu: conceptualization, project administration, and writing-review & editing.

CONFLICT OF INTEREST

The authors declare that they have no conflict of interest.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.virs.2025.05.007.

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