Postprint: The PERK/eIF2α Axis Mediates Microglial Polarization to Promote Depression Comorbid with Breast Cancer

Authors: Fan Hongqiao, Fan Yingyi, Pei Xiaohua, Pei Xiaohua

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Abstract

Background: Breast cancer is one of the major chronic diseases that seriously threatens the health of women globally, with an increasing incidence trend. Depression is the most common psychological comorbidity in breast cancer patients and can promote breast cancer progression. PKR-like endoplasmic reticulum kinase (PERK)/eukaryotic initiation factor 2α (eIF2α) axis-mediated microglial polarization plays a key role in the pathogenesis of both depression and breast cancer; however, its mechanism in breast cancer with comorbid depression remains unclear.

Objective: To investigate the mechanism by which the PERK/eIF2α axis mediates microglial polarization to promote breast cancer with comorbid depression.

Methods: Animal experiments were conducted from May 2022 to December 2022. Thirty mice were randomly divided into blank control group (Control group), tumor-bearing group (4T1 group), model group (Model group), agonist group (CCT020312 group), and inhibitor group (ISRIB group), with 6 mice per group. Following 21 consecutive days of intervention, tumor volume was calculated; sucrose preference test and open field test were employed to evaluate depressive-like behaviors; hematoxylin-eosin (HE) staining was used to assess tumor morphology and hippocampal neuronal morphology; immunofluorescence (IF) was utilized to observe CD86/ionized calcium-binding adapter molecule 1 (Iba-1) and CD206/Iba-1 levels in hippocampal tissue; Western blot was applied to detect protein levels of key PERK/eIF2α axis factors including PERK, eIF2α, activating transcription factor 4 (ATF4), and C/EBP homologous protein (CHOP) in hippocampal tissue.

Results: The sucrose preference, total movement distance, central area entries, and central area distance in the Model group were lower than those in the Control group, while depressive-like behaviors were higher, with statistically signifi-

cant differences (P<0.05). Tumor volume in the Model group was greater than that in the 4T1 group, and tumor volume in the CCT020312 group was greater than that in the Model group, with statistically significant differences (P<0.05). The sucrose preference, total movement distance, central area entries, and central area distance in the open field test in the CCT020312 group were lower than those in the Model group, whereas these parameters in the ISRIB group were higher than those in the Model group, with statistically significant differences (P<0.05). HE staining revealed densely arranged tumor cells with a large nuclear-cytoplasmic ratio in the 4T1, Model, and CCT020312 groups, with significantly increased nuclear division in the CCT020312 group; the ISRIB group exhibited large areas of patchy necrosis and cellular debris in tumor tissues, enlarged intercellular spaces, and decreased mitotic figures. Neurons in the 4T1 group showed atrophy, while neurons in the Model and CCT020312 groups displayed varying degrees of atrophy, increased cytoplasmic concentration, nuclear hyperchromatism, and necrosis, most prominently in the CCT020312 group; the ISRIB group showed reduced cytoplasmic concentration and fewer hyperchromatic nuclei. Immunofluorescence staining demonstrated that CD86/Iba-1 and CD206/Iba-1 protein levels in the Model group were higher than those in the 4T1 group; CD86/Iba-1 protein level in the CCT020312 group was higher than that in the Model group while CD206/Iba-1 protein level was lower; CD206/Iba-1 protein level in the ISRIB group was higher than that in the Model group while CD86/Iba-1 protein level was lower, with statistically significant differences (P<0.05). Western blot analysis revealed that PERK, eIF2α, ATF4, and CHOP protein levels in the CCT020312 group were higher than those in the Model group, while these protein levels in the ISRIB group were lower than those in the Model group, with statistically significant differences (P<0.05).

Conclusion: The mechanism of breast cancer with comorbid depression may be associated with PERK/eIF2α axis-mediated imbalance of microglial polarization, which induces hippocampal neuronal inflammation.

Full Text

Mechanistic Study of PERK/eIF2α Axis-Mediated Microglial Polarization Promoting Depression in Breast Cancer

FAN Hongqiao[1,2], **FAN Yingyi**[3], **PEI Xiaohua**[3*]

[1]Department of Traditional Chinese Medicine Surgery, The First Affiliated Hospital of Hunan University of Chinese Medicine, Changsha 410007, China
[2]Department of Breast Surgery, Xiamen Hospital of Beijing University of Chinese Medicine, Xiamen 361000, China
[3]Department of Breast Surgery, The Third Affiliated Hospital of Beijing University of Chinese Medicine, Beijing 100029, China

Corresponding Author: Pei Xiaohua, Professor/Doctoral Supervisor; E-mail:

pxh_{127}@163.com

Abstract

Background: Breast cancer is a major chronic disease that seriously threatens women' s health globally, with rising incidence rates. Depression is the most common psychological comorbidity in breast cancer patients and can promote breast cancer progression. The PKR-like endoplasmic reticulum kinase (PERK)/eukaryotic initiation factor 2α (eIF2α) axis-mediated microglial polarization plays a key role in the pathogenesis of both depression and breast cancer, but its mechanism in breast cancer complicated by depression remains unclear.

Objective: To investigate the mechanism by which the PERK/eIF2α axis-mediated microglial polarization promotes depression in breast cancer.

Methods: Animal experiments were conducted from May 2022 to December 2022. Thirty mice were randomly divided into five groups (n=6 each): control group, tumor-bearing group (4T1 group), model group, agonist group (CCT020312 group), and inhibitor group (ISRIB group). Following 21 days of continuous intervention, tumor volume was calculated. Depressive-like behaviors were assessed using sucrose preference test and open field test. Hematoxylin-eosin (HE) staining evaluated tumor morphology and hippocampal neuronal morphology. Immunofluorescence (IF) examined CD86/ionized calcium-binding adapter molecule 1 (Iba-1) and CD206/Iba-1 levels in hippocampal tissue. Western blot detected protein levels of PERK, eIF2α, activating transcription factor 4 (ATF4), and C/EBP homologous protein (CHOP).

Results: The model group showed significantly lower sucrose preference, total movement distance, central zone entries, and central zone distance compared to the control group, with more pronounced depressive-like behaviors ($P<0.05$). Tumor volume in the model group was higher than in the 4T1 group, and CCT020312 group tumor volume exceeded that of the model group ($P<0.05$). The CCT020312 group exhibited further reductions in sucrose preference, total movement distance, central zone entries, and central zone distance compared to the model group, while the ISRIB group showed improvements in these parameters ($P<0.05$). HE staining revealed tightly packed tumor cells with high nuclear-to-cytoplasmic ratios in the 4T1, model, and CCT020312 groups, with the most prominent nuclear division in the CCT020312 group. The ISRIB group displayed extensive plaque-like necrosis and cellular debris with enlarged intercellular spaces and reduced mitosis. Hippocampal neurons showed atrophy in the 4T1 group, with progressive atrophy, increased cytoplasmic density, nuclear hyperchromasia, and necrosis in the model and CCT020312 groups, most severe in the CCT020312 group. The ISRIB group demonstrated reduced cytoplasmic concentration and fewer hyperchromatic nuclei. Immunofluorescence showed elevated CD86/Iba-1 and CD206/Iba-1 levels in the model group compared to the 4T1 group. The CCT020312 group had higher CD86/Iba-1 but

lower CD206/Iba-1 than the model group, while the ISRIB group showed the opposite pattern ($P<0.05$). Western blot analysis confirmed that CCT020312 group had significantly higher PERK, eIF2α, ATF4, and CHOP protein levels than the model group, whereas the ISRIB group had lower levels ($P<0.05$).

Conclusion: The mechanism of depression in breast cancer may involve PERK/eIF2α axis-mediated imbalance of microglial polarization, inducing hippocampal neuronal inflammation.

Keywords: Breast cancer complicated by depression; PERK/eIF2α axis; Microglial polarization

Introduction

The comorbidity of breast cancer and depression has attracted widespread attention. According to 2023 cancer statistics, breast cancer accounts for 31% of new cancer cases among women in the United States, and remains the most common malignant tumor among women in China [1]. Psychological stress plays an important role in tumor development. Studies have shown that depression is the most common psychological comorbidity in breast cancer patients, with a prevalence of 32% globally and up to 42.1% in Chinese breast cancer patients [2-3]. Breast cancer complicated by depression not only increases the risk of cancer onset and metastasis but also exacerbates physical symptoms, reduces survival time, and significantly diminishes quality of life [4].

The pathogenesis of depression has been extensively studied, with previous research focusing on inflammatory responses, monoamine neurotransmitters and their receptors, and the hypothalamic-pituitary-adrenal (HPA) axis [5]. Recent studies demonstrate that chronic unpredictable psychological stress damages microglial structure and function, triggering intense inflammatory responses that lead to depression and other psychiatric disorders [6]. The relationship between psychological stress and endoplasmic reticulum stress has also gained attention. The PKR-like endoplasmic reticulum kinase (PERK)/eukaryotic initiation factor 2α (eIF2α) axis is a crucial signaling pathway in endoplasmic reticulum stress. Research indicates this axis plays key roles in both depression and breast cancer pathogenesis. LI et al. [7] found that in a mouse model of depression, PERK/eIF2α axis signaling factors and M1 microglial markers were significantly upregulated, suggesting that the PERK/eIF2α axis promotes depression development by regulating M1 microglial polarization [8]. Other studies confirm that PERK/eIF2α axis activation promotes breast cancer invasion and metastasis [9]. While the PERK/eIF2α axis is implicated in both conditions, its specific mechanism in breast cancer complicated by depression, particularly its relationship with microglial polarization, remains unclear.

Microglia, as the primary immune cells in the central nervous system, play a critical role in depression pathogenesis through polarization imbalance. How-

ever, research on how the PERK/eIF2α axis regulates microglial polarization to influence breast cancer with comorbid depression is scarce. This study establishes a breast cancer with depression model to investigate the mechanism by which PERK/eIF2α axis-mediated microglial polarization imbalance promotes this comorbidity, providing new therapeutic targets.

Methods

Experimental Animals

Thirty SPF-grade female Balb/c mice weighing 18-20 g were purchased from Beijing Huafukang Bioscience Co. (License No. SCXK (Beijing) 2020-0004). All experimental procedures were approved by the Animal Ethics Committee of Xiamen University School of Medicine (Approval No. SYXK (Min) 2018-0010). Mice were housed under natural lighting with a 12-hour light/dark cycle at 21-23°C and 48-68% humidity, with free access to food and water.

Instruments and Reagents

Instruments: Gel imaging system (Tanon 4600SF, Shanghai); Cryogenic high-throughput tissue grinder (MB-48L-1, Zhejiang Meibi Instruments).

Cell Line and Reagents: 4T1 mouse breast cancer cell line (Beijing Annuolun Biotechnology, Cat# AX31L184); CD86, CD206, and Iba-1 antibodies (Abcam, Cat# ab239075, ab64693, ab5076); RIPA lysis buffer, BCA protein assay kit, Western transfer buffer, and β-actin antibody (Shanghai Siding Biotechnology, Cat# SD0005/SD0006/SD0007, SD0012, SD0026, SD0034); Corticosterone injection (CORT) (MedChemExpress, Cat# HY-B1618); PERK/eIF2α axis agonist CCT020312 (MedChemExpress, Cat# HY-119240); PERK/eIF2α inhibitor ISRIB (MedChemExpress, Cat# HY-12495).

Experimental Groups and Model Construction

After one week of acclimation, mice were randomly divided into five groups (n=6 each): control group, tumor-bearing group (4T1 group), model group, agonist group (CCT020312 group), and inhibitor group (ISRIB group). Except for the control group, the 4T1 group received subcutaneous injection of 4T1 cells (2$×10^{5}$ cells/mouse) into the second mammary fat pad. The model, CCT020312, and ISRIB groups received 4T1 cells combined with subcutaneous corticosterone injection on the dorsal skin for 28 days to establish the breast cancer with depression model.

Drug Administration

Drug intervention began one week after corticosterone administration. The CCT020312 group received intraperitoneal injection of CCT020312 (2 $mg \cdot kg^{-1} \cdot$

d^{-1}), while the ISRIB group received ISRIB (2.5 $mg \cdot kg^{-1} \cdot d^{-1}$). The 4T1 and model groups received distilled water by gavage once daily for 21 days [Figure 1: see original paper].

Behavioral Testing

Sucrose Preference Test (SPT): Mice were given free access to food and water during 48 hours of two-bottle training (one with 2% sucrose solution, one with pure water, with bottle positions exchanged after 24 hours). Sucrose consumption was measured over 8 hours (with one bottle exchange) on day 0 and day 28. Sucrose preference index (%) = (sucrose consumption)/(sucrose consumption + water consumption) × 100%.

Open Field Test (OFT): The apparatus consisted of a 40 cm × 40 cm × 40 cm arena with an overhead digital camera. Mice were placed in the center and recorded for 5 minutes. On day 28, TopScanLite 2.00 software (Clever Sys, United States) analyzed total movement distance, central zone entries, and central zone distance, and generated movement trajectory maps.

Tumor Volume Measurement

Body weight was recorded weekly. Tumor formation was defined as long diameter × short diameter reaching 3 mm × 3 mm. Tumor dimensions were measured with electronic calipers on days 1, 3, 6, 9, 12, 15, 18, and 21 post-formation. Tumor volume = long diameter × $(\text{short diameter})^2/2$.

Tissue Sample Preparation

Tumor Tissue: After blood collection, mice were euthanized by cervical dislocation. Tumors were photographed and bisected. One half was fixed in 4% paraformaldehyde for $ $24 hours for HE staining; the other half was stored in cryovials at ultra-low temperature.

Hippocampal Tissue: The brain was placed on ice with the parietal lobe upward. The hemispheres were separated along the sagittal line, and the cortex was flipped to expose the crescent-shaped hippocampus. The hippocampus was gently dissected free from the cortex.

Histological Staining

Fixed tumor tissues were rinsed overnight, dehydrated in graded ethanol, paraffin-embedded, and sectioned at 4 m thickness. Sections were deparaffinized, stained with hematoxylin-eosin, mounted, and examined under microscopy.

Immunofluorescence Staining

Hippocampal sections were deparaffinized and rehydrated. Antigen retrieval was performed using EDTA buffer (pH 8.0). Sections were blocked with BSA for 30 minutes, incubated with primary antibodies (CD86 1:200, Iba-1 1:300, CD206 1:200) overnight, then with Cy3- or FITC-conjugated secondary antibodies. Nuclei were counterstained with DAPI. Slides were mounted and photographed within 48 hours using a fluorescence microscope. Positive area was analyzed using ImageJ.

Western Blot Analysis

Twenty mg of hippocampal tissue was homogenized in 200 L lysis buffer (with 2 L protease inhibitor). Protein concentration was determined by BCA assay. Samples were separated by SDS-PAGE (120 V, 60 minutes) and transferred to membranes (400 mA, 30 minutes). After blocking with 5% skim milk, membranes were incubated overnight at 4°C with primary antibodies against PERK, eIF2α, ATF4, and CHOP (1:1000). Following TBST washes, membranes were incubated with secondary antibodies for 1 hour, washed, and visualized using ECL reagent. Band densities were analyzed using ImageJ.

Statistical Analysis

Data were analyzed using GraphPad Prism 9.0. Normally distributed data are presented as mean ± standard deviation ($\bar{x}\pm s$). Comparisons between two groups used Student' s t-test, while multiple groups used one-way ANOVA with LSD post-hoc test. For non-homogeneous variance, Welch' s and Dunnett' s tests were applied. Repeated measures ANOVA was used for multiple time-point data. Statistical significance was set at $P<0.05$ (two-tailed).

Results

Behavioral Comparisons

No significant difference in sucrose preference was observed among groups on day 0 ($P>0.05$). On day 28, the model group showed significantly lower sucrose preference compared to the control group and its own baseline ($P<0.05$). The CCT020312 group exhibited further reduced sucrose preference versus the model group, while the ISRIB group showed increased preference ($P<0.05$) .

Significant differences were found among groups in total movement distance, central zone entries, and central zone distance ($P<0.05$). The model group showed reductions in all parameters compared to controls ($P<0.05$). The CCT020312 group demonstrated further decreases versus the model group, while the ISRIB group showed improvements ($P<0.05$) , [Figure 2: see original paper].

Tumor Volume Comparisons

Significant differences in tumor volume were observed among groups on days 7, 14, 21, and 28 ($P<0.05$). The model group had larger tumors than the 4T1 group, while the ISRIB group had smaller tumors than both model and CCT020312 groups ($P<0.05$). The CCT020312 group showed increased tumor volume compared to the model group on days 7, 21, and 28 ($P<0.05$) .

Histological Analysis

Tumor Tissue: HE staining revealed tightly packed tumor cells with high nuclear-to-cytoplasmic ratios and increased mitotic figures in the 4T1, model, and CCT020312 groups, most pronounced in the CCT020312 group. The ISRIB group exhibited extensive plaque-like necrosis, cellular debris, enlarged intercellular spaces, and reduced mitosis [Figure 3: see original paper].

Hippocampal Tissue: Neuronal atrophy was observed in the 4T1 group. The model and CCT020312 groups showed progressive neuronal atrophy, increased cytoplasmic density, nuclear hyperchromasia, and necrosis, most severe in the CCT020312 group. The ISRIB group displayed reduced cytoplasmic concentration and fewer hyperchromatic nuclei [Figure 4: see original paper].

Immunofluorescence Analysis

Significant differences were found in CD86/Iba-1 and CD206/Iba-1 levels among groups ($P<0.05$). The model group showed elevated levels of both markers compared to the 4T1 group ($P<0.05$). The CCT020312 group had higher CD86/Iba-1 but lower CD206/Iba-1 than the model group, while the ISRIB group showed the opposite pattern ($P<0.05$) [Figure 5: see original paper], .

Western Blot Analysis

Significant differences were observed in hippocampal PERK, eIF2α, ATF4, and CHOP protein expression among groups ($P<0.05$). The 4T1 group showed higher expression than controls, with further elevation in the model group ($P<0.05$). The CCT020312 group exhibited the highest expression levels, while the ISRIB group showed reduced expression compared to the model group ($P<0.05$) [Figure 6: see original paper], .

Discussion

Microglia, as the principal immune cells of the central nervous system, play critical roles in neuroinflammation, neuronal protection, and repair [10]. Chronic stress can disrupt M1/M2 microglial polarization balance, increase pro-inflammatory cytokine release, impair hippocampal neurogenesis, and promote both depression and tumor progression [11]. The PERK/eIF2α axis,

a core endoplasmic reticulum stress (ERS) pathway, regulates inflammatory responses and apoptosis, though its role in breast cancer with comorbid depression remains unclear. This study investigated whether the PERK/eIF2α axis influences neuroinflammation and breast cancer progression by regulating microglial polarization.

CD86 and CD206 serve as markers for M1 and M2 microglia, respectively, while Iba-1 is a general microglial marker. Our breast cancer with depression model demonstrated reduced sucrose preference, decreased open field test activity, and accelerated tumor growth, accompanied by increased M1 markers (CD86/Iba-1) and decreased M2 markers (CD206). These findings align with previous reports [12], suggesting that M1 polarization may induce neuronal inflammation through pro-inflammatory cytokines (e.g., TNF-α, IL-1β), impairing hippocampal function and promoting tumor progression. However, the upstream regulatory mechanisms controlling microglial polarization require further investigation.

Psychological stress enhances endoplasmic reticulum stress activity [13]. The PERK/eIF2α axis is a key ERS signaling pathway. Upon ER activation, PERK dissociates from GRP78/Bip and phosphorylates eIF2α to inhibit cyclin D1 translation, reducing mRNA translation and protein synthesis to prevent ER protein accumulation [14]. Simultaneously, eIF2α selectively enhances translation of ATF4 and CHOP mRNA to improve protein folding, reduce misfolded protein accumulation, and restore ER function [13]. Studies in traumatic brain injury have shown that modulating the PERK/eIF2α/ATF4 pathway can regulate M1/M2 microglial polarization and inhibit neuroinflammation [14], but this relationship remains unexplored in breast cancer with depression.

CCT020312 is a selective PERK/eIF2α axis agonist, while ISRIB is a selective inhibitor. CCT020312 has been shown to activate microglia and promote neuroinflammation after traumatic brain injury [15]. ISRIB can reverse HPA axis hyperactivity, reduce serum corticosterone levels, decrease hippocampal glucocorticoid receptor expression, and lower FosB expression in the hypothalamic paraventricular nucleus in depression models [16]. Our findings demonstrate that activating the PERK/eIF2α axis with CCT020312 exacerbated depressive behaviors, worsened hippocampal neuronal damage, increased M1 microglia, decreased M2 microglia, and enhanced tumor growth. Conversely, ISRIB reversed these effects, suggesting that PERK/eIF2α axis activation promotes M1 polarization, aggravates neuronal inflammation and apoptosis, and accelerates breast cancer progression, while inhibition promotes M2 polarization, reduces inflammation, protects neurons, and delays cancer progression.

This study has several limitations. First, the mechanisms by which depression promotes breast cancer progression are complex; we used only the murine 4T1 cell line without human breast cancer cell lines or MMTV-PyMT transgenic mice. Second, due to technical constraints, we did not perform intrahippocampal injections of CCT020312 or ISRIB. Future studies should employ MMTV-PyMT transgenic mice, integrate multi-omics technologies to identify potential

hippocampal target genes, and utilize advanced neuroscientific techniques such as stereotaxic injection to further elucidate the mechanisms of breast cancer with depression.

In conclusion, our breast cancer with depression mouse model demonstrated M1 microglial polarization, suggesting that M1 polarization-induced inflammation may contribute to chronic stress-promoted breast cancer progression. Enhanced PERK/eIF2α signaling activity promotes M1 polarization, exacerbates depression, and accelerates breast cancer progression. These findings indicate that the mechanism of depression in breast cancer may involve PERK/eIF2α axis-mediated imbalance of microglial polarization and induction of hippocampal neuronal inflammation.

Author Contributions

FAN Hongqiao: Animal model construction, drug intervention, and index detection. FAN Yingyi: Statistical analysis. PEI Xiaohua: Final manuscript revision and overall responsibility.

Conflict of Interest

The authors declare no conflicts of interest.

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