Article

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Possible Correlation Between Serum PDCD4 Levels and Hypothalamic Inflammation in Obesity

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Background: The hypothalamic feeding circuit is highly vulnerable to obesity-inducing diets, as observed in diet-induced obesity (DIO) models. Programmed cell death factor 4 (PDCD4) is widely expressed in various tissues and organs. Depending on the context, it exhibits both pro-inflammatory and anti-inflammatory properties. This study aimed to analyze serum PDCD4 levels and investigate its correlation with hypothalamic inflammation in obesity.

Methods: A total of 195 participants were separated into two groups according to their body mass index (BMI): normal weight group (18.5 kg/m^2 $\leq$ BMI $<$ 24 kg/m^2) and obesity group (BMI $\geq$28 kg/m^2). Serum levels of the following were measured using enzyme-linked immunosorbent assay (ELISA): PDCD4, neuropeptide Y (NPY), Ionized calcium-binding adapter molecule 1 (Iba1), and NOD-like receptor thermal protein domain-associated protein 3 (NLRP3). Other biochemical indicators were analyzed. Statistical analyses were performed to evaluate the association between serum PDCD4 levels and other biochemical indicators.

Results: A significant increase in serum PDCD4 level was evident in the obesity group compared with the control group. A binary logistic regression analysis revealed a statistically significant relationship between PDCD4 and obesity ($p < 0.05$). Based on Spearman correlation analysis, a positive correlation was found between the serum PDCD4 level and BMI, and the serum PDCD4 level was positively correlated with NPY, Iba1 and NLRP3 levels ($p < 0.05$). Furthermore, serum PDCD4 level was found to be independently associated with Iba1 and NLRP3, indicating the role of PDCD4 in regulating hypothalamic inflammation in the obesity context.

Conclusion: In addition to a significant elevation in obese patients, serum PDCD4 level is independently correlated with Iba1 and NLRP3 levels, suggesting a mediating role of PDCD4 in the activation of Iba1 and NLRP3, which is crucial for facilitating peripheral-to-central inflammatory crosstalk and ultimately the occurrence of hypothalamic inflammation.

Keywords: serum PDCD4 levels; obesity; hypothalamic inflammation; neuroinflammation

Introduction

Obesity is characterized by a significant increase in body weight and an excessive accumulation of body fat, particularly triglycerides [1]. This condition induces low-grade systemic inflammation, contributing to a range of complications [2]. In addition to metabolic disturbances in peripheral organs, disruption of brain function is another major complication of obesity-related inflammation, notably occurring in regions responsible for regulating energy homeostasis and systemic metabolism [3].

Hypothalamus plays a pivotal role in energy metabolism homeostasis [4]. Research has shown that astrocytes and microglia contribute to this regulatory function [5]. At the core of this process is the melanocortin system, where a specific subset of neurons synthesizes appetite-stimulating neuropeptides, such as agouti-related peptide (AgRP) and neuropeptide Y (NPY) [6]. The neurons in the arcuate nucleus (ARC) of the medial basal hypothalamus (MBH) respond to metabolic signals, influencing food intake and energy expenditure.

Ionized calcium-binding adapter molecule 1 (Iba1), also known as allograft inflammatory factor 1 (AIF1), is a calcium-binding protein. Iba1 is highly expressed in microglia and macrophages [7], which are crucial mediators in the inflammatory response. During hypothalamic inflammation, microglia and macrophages become activated and migrate to the inflammatory site, where Iba1 expression significantly increases. Therefore, Iba1 is viewed as a marker of activated microglia and macrophages in hypothalamic inflammation [8].

NOD-like receptor thermal protein domain-associated protein 3 (NLRP3) is a member of the NOD-like receptor family. Upon sensing a danger signal, NLRP3 leads to the recruitment of pro-caspase-1 [9]. The NLRP3 inflammasome is formed when this aggregation occurs, activating caspase-1. The activated enzyme then cleaves pro-interleukin (IL)-1β and pro-IL-18 into their active forms, triggering inflammation and possibly inducing cell death [10]. The programmed cell death factor 4 (PDCD4) gene, discovered in research on apoptosis mechanisms, contains 11 exons, and its protein contains two MA-3 functional domains, two RNA-binding domains, two nuclear localization signals, a C-terminal nuclear export signal, and two phosphorylation sites [11]. PDCD4 is widely expressed in tissues and organs, and plays a role in inflammatory disease progression [12]. Findings from animal studies revealed the association of PDCD4 expression with lipid accumulation and inflammation [13], but its biological activity and mechanism remain obscure. To investigate the relationship and predictive value of serum PDCD4 levels in hypothalamic inflammation among obese patients, a cohort of 195 patients was analyzed to examine correlations between PDCD4 levels, hypothalamic neuropeptides, and metabolic indicators.

Methods

Research Subjects

From September 2022 to April 2024, 195 individuals (aged 18–65) who attended for physical examinations in the Physical Examination Center of Nantong First People's Hospital were enrolled in the study. The included participants were divided into two groups based on their body mass index (BMI): 112 individuals in the normal weight group (18.5 kg/m^2 $\leq$ BMI $<$ 24 kg/m^2), and 83 individuals in the obesity group (BMI $\geq$28 kg/m^2, used as the diagnostic criterion for obesity).

Patients with severe liver or kidney insufficiency, severe cardiovascular or cerebrovascular disease, pregnancy, malignancies, various acute or chronic infections, autoimmune system diseases and the use of immunosuppressive or obesity-affecting drugs (e.g., glucocorticoids) were excluded. This study was approved by the Clinical Research Ethics Committee of Nantong First People's Hospital, and written informed consent was obtained from every participant.

Physical Fitness Assessments and Biochemical Analyses

Physical parameters, including age, sex, height, weight, systolic blood pressure (SBP), and diastolic blood pressure (DBP), were collected and recorded for all study participants. BMI was calculated by dividing weight (kg) by the square of height (m). Biochemical indicators, such as total cholesterol (TC), triglycerides (TG), high-density lipoprotein cholesterol (HDL-C), and low-density lipoprotein cholesterol (LDL-C), were measured using standardized instruments and testing protocols in the laboratory department of Nantong First People's Hospital.

Measurement of Serum PDCD4 Concentration

Fasting venous blood was drawn, in a volume of approximately 5 mL, from each participant. The collected blood samples were immediately spun at 3000 rpm and 4 ℃ for 10 min. These serum samples were then separated, labeled, and stored at –80 ℃. Serum levels of PDCD4, NLRP3, Iba1, and NPY were determined using a human PDCD4 enzyme-linked immunosorbent assay (ELISA) kit (EH2218, Wuhan Fine Biotech Co., Ltd., Wuhan, China), a NLRP3 ELISA kit (EH4202, Wuhan Fine Biotech Co., Ltd.), an AIF1 ELISA kit (EH1425, Wuhan Fine Biotech Co., Ltd.), and a human NPY ELISA kit (YB-NPY-Hu, Shanghai Yubo Biotechnology Co., Ltd., Shanghai, China), respectively. The absorbance of the samples was detected at 450 nm using an enzyme-linked analyzer (H1M, BioTek Instruments, Inc., Winooski, VT, USA). A standard curve was generated by plotting the standard concentration (X) against the absorbance value (Y). The logistic equation was utilized to fit the standard curve and calculate the sample concentration.

Statistical Analysis

Statistical analyses were conducted using the IBM SPSS version 23.0 (IBM Corp., Armonk, NY, USA) and GraphPad Prism version 8.0 (GraphPad Software, LLC, San Diego, CA, USA). The normality of data distribution for continuous variables was evaluated using the Kolmogorov–Smirnov test; results with $p \geq 0.05$ indicate that the variable follows a normal distribution. The chi-squared test was used to evaluate the inter-group differences in categorical variables. The independent *t*-tests was employed to compare normally distributed variables between groups, with their data presented as mean $\pm$ standard deviation; whereas the Mann–Whitney *U* test was used for analysis of non-normally distributed variables, with their data expressed as median (interquartile range). Binary logistic regression analysis was utilized to evaluate the associations between obesity and related factors, with odds ratios (ORs) reported along with 95% confidence intervals. The relationships between the variables were determined using Spearman correlation analysis. Univariate regression analysis was used to determine the influence of each variable,

Table 1. General characteristics of the normal weight and obesity groups.

	Grouping		Statistic	p
	Normal weight group (n = 112)	Obesity group (n = 83)		
Gender (male)	74 (66.07%)	71 (85.54%)	$\chi^2 = 9.479$	**
Age (years)	29.44 ± 7.82	36.89 ± 11.82	$t = –4.722$	***
Height (cm)	170.46 ± 8.64	171.21 ± 8.42	$t = –0.605$	0.546
Body weight (kg)	62.50 ± 8.82	89.48 ± 11.14	$t = –18.230$	***
BMI (kg/m^2)	21.70 (2.82)	30.27 (3.68)	$z = –11.928$	***
SBP (mmHg)	120.00 ± 11.30	125.23 ± 8.90	$t = –1.365$	0.176
DBP (mmHg)	74.67 ± 6.62	78.09 ± 8.21	$t = –0.995$	0.323
WBC (×10^9/L)	6.29 ± 1.48	7.17 ± 1.62	$t = –3.563$	***
RBC (×10^{12}/L)	4.99 ± 0.46	5.25 ± 0.45	$t = –3.524$	***
Hb (g/L)	147.25 ± 12.98	155.46 ± 12.14	$t = –4.132$	***
PLT (×10^9/L)	250.86 ± 67.08	243.93 ± 59.53	$t = 0.692$	0.490

** $p < 0.01$, *** $p < 0.001$, BMI values represent the median (interquartile range).

Abbreviations: BMI, body mass index; DBP, diastolic blood pressure; Hb, hemoglobin; PLT, platelet; RBC, red blood cell; SBP, systolic blood pressure; WBC, white blood cell.

and subsequently multivariate regression analysis was conducted. In order to address the potential multicollinearity among these interrelated variables and to identify independent predictors, stepwise multiple linear regression analyses were performed. The independence of errors was evaluated using the Durbin-Watson statistic. The presence of multicollinearity was diagnosed using tolerance and Variance Inflation Factor (VIF) criteria. Receiver operating characteristic (ROC) curves were generated to assess diagnostic performance. A p-value < 0.05 was considered statistically significant.

Results

General Characteristics of Patients

Table 1 presents the general characteristics of the two patient groups. The differences in height, SBP, DBP and platelet count between the normal weight group and obesity group were not statistically significant ($p > 0.05$). However, white blood cell (WBC) count, red blood cell (RBC) count, and hemoglobin (Hb) levels were higher in the obesity group than in the normal weight group ($p < 0.05$) (Table 1).

Biochemical Characteristics of Patients

Table 2 summarizes the biochemical characteristics of the two groups of patients. There were no statistically significant differences in total bilirubin, total protein, and creatinine between the normal weight group and the obesity group ($p > 0.05$). Compared with the normal weight group, the obesity group exhibited significantly increased levels of alanine aminotransferase (ALT), aspartate aminotransferase (AST), and glutamyl transpeptidase (GGT) ($p < 0.05$). Additionally, the obesity group exhibited higher levels of triglycerides, total cholesterol, and LDL-C ($p < 0.05$), but lower HDL-C levels ($p < 0.05$) compared to the normal weight group. Notably, compared with the normal weight group, the obesity group showed significantly elevated serum levels of PDCD4 (Table 2).

Correlation Between Obesity and Various Biochemical Parameters

To further investigate the risk variables associated with obesity, binary logistic regression analysis was conducted, with obesity status designated as the dependent variable. The biochemical characteristics that attained statistical significance, as shown in Table 2, were considered for multivariate logistic regression analysis. Variables exhibiting model overfitting or multicollinearity were excluded based on collinearity analysis. Multivariate logistic regression analysis revealed that PDCD4 and blood urea nitrogen (BUN) are independently associated with obesity ($p < 0.05$). ALT, AST, GGT, NPY, Uric Acid (UA) and TG were not found to be statistically significant in the multivariate logistic regression analysis ($p > 0.05$, Table 3). The area under the ROC curve (AUC) for serum PDCD4 was 0.81 (95% CI: 0.7441–0.8719, $p < 0.001$), indicating high diagnostic accuracy (sensitivity: 90.9%; specificity: 63.3%) (Fig. 1). These results demonstrate the high diagnostic value of serum PDCD4 for obesity.

Correlation Between Serum PDCD4 Level and Various Parameters

Our results show that serum PDCD4 level was positively correlated with BMI, Iba1, NLRP3, NPY and LDLC ($p < 0.05$ and $|r| > 0.3$, Table 4). No statistical significance was observed for other parameters ($p > 0.05$ or $|r| \leq 0.3$, Table 4).

Table 2. Biochemical characteristics of the normal weight and obesity groups.

	Grouping		Statistic	*p*
	Normal weight group (n = 112)	Obesity group (n = 83)		
PDCD4 (pg/mL)	1413.14 (484.74)[a]	3842.45 (3751.23)[a]	*z* = –7.94	***
NPY (pg/mL)	100.47 (131.04)[a]	214.94 (204.26)[a]	*z* = –5.769	***
ALT (U/L)	17 (12.3)[a]	34.5 (27.0)[a]	*z* = –7.370	***
AST (U/L)	19 (7.0)[a]	21 (9.8)[a]	*z* = –4.124	***
GGT (U/L)	16 (11.0)[a]	34.5 (39.3)[a]	*z* = –7.323	***
TBIL (μmol/L)	10.4 (5.8)[a]	10.55 (6.2)[a]	*z* = –0.376	0.335
TP (g/L)	74.51 ± 3.92	74.43 ± 9.06	*t* = 0.071	0.943
BUN (mmol/L)	4.81 ± 1.32	5.24 ± 1.19	*t* = –2.152	*
CR (μmol/L)	74.25 ± 13.31	75.97 ± 13.74	*t* = –0.801	0.424
UA (μmol/L)	317.99 ± 74.88	404.63 ± 86.12	*t* = –6.655	***
TG (mmol/L)	1.05 (0.48)[a]	2.25 (3.12)[a]	*z* = –5.620	***
TC (mmol/L)	4.12 ± 0.75	4.88 ± 1.04	*t* = –4.013	***
HDL-C (mmol/L)	1.36 ± 0.33	1.14 ± 0.27	*t* = 3.396	**
LDL-C (mmol/L)	2.24 ± 0.60	3.08 ± 0.84	*t* = –5.410	***

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. a: median (interquartile range).

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; CR, creatinine; GGT, glutamyl transpeptidase; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; NPY, neuropeptide Y; PDCD4, programmed cell death factor 4; TBIL, total bilirubin; TC, total cholesterol; TG, triglyceride; TP, total Protein; UA, Uric Acid.

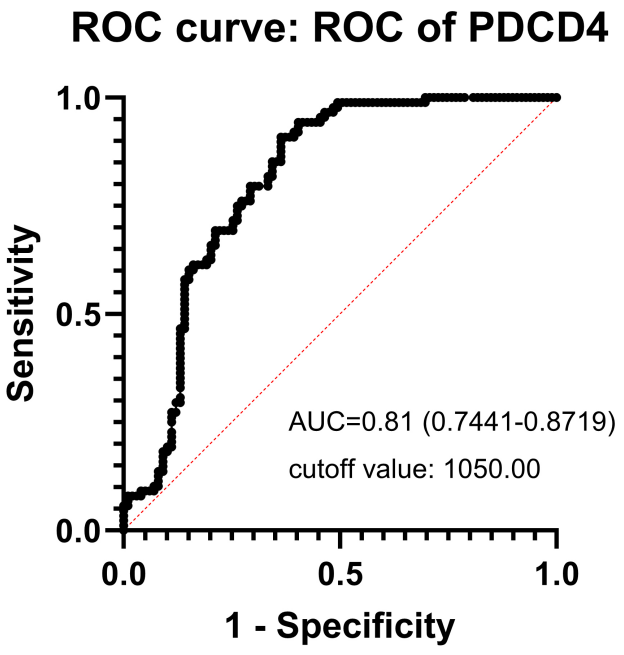

Fig. 1. ROC curve of serum PDCD4 in the study population. Abbreviations: AUC, area under the curve; ROC, receiver operating characteristic.

Table 3. Multivariate logistic regression analysis with obesity as the dependent variable.

Parameters	OR	95% CI	*p*
ALT	1.280	0.936–1.751	0.123
AST	0.803	0.421–1.533	0.506
GGT	1.098	0.992–1.215	0.072
PDCD4	1.004	1.000–1.008	*
NPY	1.047	0.990–1.107	0.108
BUN	8.821	1.175–16.467	*
UA	0.986	0.945–1.028	0.507
TG	16.501	2.049–30.953	0.065
HDL-C	0.073	0.001–7.954	0.274

* $p < 0.05$.

OR, odds ratio; 95% CI, 95% confidence interval.

Correlation Between Serum Iba1 Level and PDCD4 and NLRP3

During hypothalamic inflammation, microglia and macrophages become activated, migrate to the inflammatory site, and exhibit significantly increased expression of Iba1. Thus, Iba1 can serve as a marker of activated microglia and macrophages in hypothalamic inflammation. NLRP3 plays a crucial role in the modulation of inflammation and immunoregulation. The activation of NLRP3 protein has been associated with the pathogenesis of multiple inflammatory diseases, and NLRP3 inflammasome plays a role in obesity-associated inflammation. The NLRP3 holds significance in the early identification of high - risk septic patients, particularly those suffering from septic shock. Moreover, elevated levels of NRLP3 may lead to suboptimal outcomes in septic prediction. Our Spearman correlation analysis showed that Iba1 exhibited positive correlation with PDCD4, NLRP3 and TG ($p < 0.05$ and $|r| > 0.3$) (Table 5). To address the issue of multicollinearity among the numerous associated variables, stepwise multiple linear regression models were used to identify predictors of ele-

Table 4. Analysis of the correlation of PDCD4 level with other parameters in the study population.

Parameters	PDCD4	
	r	*p*
BMI	0.651	**
Iba1	0.419	***
NLRP3	0.686	***
NPY	0.419	**
ALT	0.233	**
AST	0.188	*
GGT	0.137	0.101
TBIL	0.159	0.08
TC	0.240	*
TG	0.220	*
TP	–0.022	0.877
CR	0.056	0.507
BUN	0.132	0.186
UA	0.201	*
HDL-C	–0.120	0.456
LDL-C	0.340	**
WBC	0.243	**
RBC	0.128	0.103
Hb	0.204	*
PLT	0.016	0.344

* $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. NLRP3, NOD-like receptor thermal protein domain-associated protein 3; Iba1, ionized calcium-binding adapter molecule 1.

Table 5. Correlation analysis between Iba1 level and other parameters in the study population.

Parameters	Iba1	
	r	*p*
BMI	0.226	**
Age	0.211	*
PDCD4	0.334	**
NLRP3	0.380	**
NPY	0.244	*
TG	0.334	**
LDL-C	0.258	*

* $p < 0.05$, ** $p < 0.01$.

vated levels of Iba1 and NLRP3. In the regression analysis, the Durbin–Watson (D–W) statistic was 2.065 in Table 6 and 2.069 in Table 7, indicating no significant autocorrelation among variables and suggesting that the models were appropriately specified. According to the results of stepwise multiple linear regression models analysis, Iba1 and NLRP3 were positively correlated with PDCD4 (Tables 6,7, respectively), suggesting that serum PDCD4 is strongly associated with Iba1 and NLRP3.

Discussion

Obesity represents a complex and multifactorial disorder characterized by the excessive accumulation of body fat, which is detrimental to the well-being and health. While it has been conventionally ascribed to an imbalance between energy intake and consumption, obesity is now recognized as a multifaceted chronic condition, akin to the aging process. Pathological adipocyte enlargement disrupts nutritional signaling and contributes to a range of metabolic irregularities, including oxidative stress, mitochondrial dysfunction, immune dysregulation, and chronic low-grade inflammation [14–16]. Obesity is linked to numerous diseases, influenced by the interplay of genetic, nutritional, and metabolic factors. These include disruptions in glucose metabolism and systemic inflammation, mediated by pro-inflammatory cytokines secreted by various cell types that also regulate adipose tissue metabolism. Importantly, obesity-induced inflammation extends beyond peripheral tissues to the central nervous system [17]. Neuroinflammation, an immune response in the nervous system, is frequently hailed as a protective mechanism that promotes the repair and regeneration of neurons [18,19]. However, chronic neuroinflammation causes brain dysfunction and injury, which is a key feature of central nervous system diseases [20]. Thus, understanding the shared molecular pathways associated with neuroinflammation and neuronal apoptosis is crucial for advancing knowledge of the pathogenesis of neurological disorders and identifying potential therapeutic targets.

PDCD4 is recognized as capable of inducing apoptosis [21]. It is evolutionarily conserved and expressed in normal tissues and organs [22]. Given its critical role in regulating apoptosis, the expression patterns and potential functionalities of PDCD4 within the nervous system have garnered escalating research attention. Research has shown that stress elevates PDCD4 expression in the mouse hippocampus [23]. Similar increases have been observed in various models, including rat spinal cord injury [24], chronic sciatic nerve injury-induced neuropathic pain [25], hippocampal neuronal oxygen-glucose deprivation/reoxygenation injury [26], and mouse retinal ischemia-reperfusion-induced neuronal damage [27]. Additionally, evidence suggests that exposure to ethanol elevates PDCD4 expression in rat primary cortical neurons. This observation indicates the presence of a possible association of PDCD4 with fetal alcohol syndrome [28]. Despite substantial evidence linking PDCD4 to inflammatory diseases, its precise biological function remains unclear due to conflicting experimental data. Some studies suggest PDCD4 acts as a pro-inflammatory cytokine. For example, PDCD4 deficiency has been shown to reduce JNK phosphorylation, nuclear factor kappa B (NF-κB) activation [29] and interleukin (IL)-6 production in mouse macrophages and protect PDCD4-deficient mice from death induced by lipopolysaccharide (LPS). High lev-

Table 6. Stepwise multiple linear regression with Iba1 as the dependent variable.

Parameters	B	SE	Beta	*t*	*p*	VIF
(Constant)	−95.664	245.908		−0.389	0.700	
Age	3.246	2.444	0.219	1.328	0.195	1.307
BMI	1.702	8.004	0.054	0.213	0.833	3.117
PDCD4	0.049	0.020	0.463	2.490	*	1.667
NPY	0.159	0.296	0.117	0.539	0.594	2.278
TG	18.389	19.487	0.187	0.944	0.354	1.891
TC	38.246	72.958	0.239	0.524	0.604	9.984
LDL-C	−82.216	86.982	−0.437	−0.353	0.353	10.291
NLRP3	87.905	36.588	0.532	2.403	*	2.365

* $p < 0.05$.

VIF, variance inflation factor.

Table 7. Stepwise multiple linear regression model with NLRP3 serving as the dependent variable.

Parameters	B	SE	Beta	*t*	*p*	VIF
(Constant)	−0.396	0.466		−0.851	0.398	
Age	0.005	0.007	0.062	0.723	0.472	1.342
BMI	0.092	0.022	0.466	4.209	***	2.278
PDCD4	<0.001	<0.001	0.391	4.198	***	1.606
Iba1	0.001	0.001	0.123	1.514	0.135	1.233
NPY	<0.001	0.001	−0.054	−0.605	0.547	1.490
GGT	0.002	0.002	0.036	0.440	0.662	1.236

*** $p < 0.001$.

els of PDCD4 have been shown to cause cell death and augment pro-inflammatory cytokine production, exacerbating damage to porcine intestinal epithelial cells caused by toxins [30]. Conversely, other evidence indicates that PDCD4 may have anti-inflammatory effects. For instance, PDCD4 deficiency in mice accelerates activation of the IL-6/STAT3 pathway, exacerbating colitis and promoting colorectal cancer [31]. In models of acute liver injury triggered by either LPS or d-galactosamine, PDCD4-deficient mice exhibited more severe hepatocyte necrosis and apoptosis, inflammatory cell infiltration, cytokine release, and intrahepatic hemorrhage compared to wild-type mice [32]. These findings reveal that PDCD4 may play a complex and context-dependent role in inflammatory processes and neuronal damage, but further investigation into its precise mechanisms is warranted.

In this study, we found that serum PDCD4 levels were significantly higher in obese patients than in healthy individuals. Moreover, serum PDCD4 level was positively correlated with Iba1 and NLRP3, suggesting a potential link between PDCD4 and obesity-associated neuroinflammation. NLRP3 plays an essential role in systemic inflammatory responses. Upon activation, NLRP3 inflammasome promotes caspase-1–mediated maturation and release of IL-1β and IL-18 [33–35], thereby amplifying the inflammatory cascade. Recent studies reported that NLRP3 not only participates in instigating peripheral inflammation but also plays a role in inducing neuroinflammation, particularly in the hypothalamus [36,37]. Importantly, PDCD4 has been reported to promote microglial inflammation by activating the NLRP3 pathway [38]. Besides its role in obesity, NLRP3 has been implicated in the early identification of high-risk septic patients, particularly those with septic shock [39,40]. In our study, serum levels of Iba1, PDCD4, and NLRP3 were positively correlated, further supporting their involvement in hypothalamic microglial activation [41].

NLRP3 inflammasome activation has been identified as a vital mechanism underlying hypothalamic microglial activation, contributing to the onset and progressive development of hypothalamic inflammation [42]. Based on these findings, we hypothesize that obesity-induced upregulation of PDCD4 promotes the release of peripheral inflammatory cytokines by activating the NLRP3 inflammasome. These inflammatory mediators may cross the blood-brain barrier or activate vagus nerve signaling, leading to hypothalamic microglial activation. This neuroinflammatory process may disrupt feeding center function and energy homeostasis, ultimately contributing to obesity-related metabolic dysregulation.

Several limitations of the present study should be acknowledged. First, in this cross-sectional survey, it was not possible to establish a causal relationship between elevated serum PDCD4 level and hypothalamic inflammation in obesity. Second, our study was conducted in a single province, which may limit the generalizability of the findings. Thus, larger, multicenter studies with more participants are needed to confirm the association between el-

evated serum PDCD4 levels and hypothalamic inflammation in obese individuals. Third, the current analysis relied on a single blood measurement, which may not capture the changes in PDCD4 level over time. To address this shortcoming, longitudinal assessments at different stages of obesity could offer deeper insights into the dynamic role of PDCD4 in the development of obesity and hypothalamic inflammation. Another limitation of this study that deserves our attention is the imbalanced gender ratio of the obesity group and the normal weight group, with fewer women in the obesity group than in the normal weight group. This can be explained by the higher prevalence of male obesity compared to female obesity in the region where this study was conducted [43]. It is important to note that there are marked differences between men and women in terms of body fat distribution, hormone levels, basal metabolic rate, and susceptibility to obesity-related complications, such as cardiovascular disease and type 2 diabetes. Such a gender distribution imbalance in our sample might impact the findings of this study. Therefore, future research should utilize gender-balanced samples, with a particular emphasis on expanding the sample size of obese female patients, in order to comprehensively investigate the distinct manifestations and mechanisms of obesity across genders.

Conclusion

This study is the first to identify a synergistic increase in serum PDCD4, NLRP3, and Iba1 levels in obese individuals and to highlight their interrelationship. Our findings suggest that PDCD4 may activate the NLRP3 inflammasome, facilitating peripheral-to-central inflammatory crosstalk, triggering hypothalamic microglial activation, and ultimately contributing to hypothalamic inflammation. This study provides a novel insight into the molecular mechanisms underlying obesity-related neuroinflammation and highlights potential targets for future therapeutic interventions.

Availability of Data and Materials

The data used to support the fundings of this study are available from the corresponding authors upon request.

Author Contributions

Conceptualization, DMZ and FZ; methodology, JJL, FZ and DMZ; investigation, JJL, QNG and DHS; resources, DMZ, ZHG and FZ; data curation, JJL, DHS and ZHG; writing—original draft preparation, JJL; writing—drafting and critical revision, FZ, DHS, ZHG and DMZ; writing—review and editing, FZ, JJL and QNG; visualization, JJL; supervision, FZ and DMZ; funding acquisition, QNG, FZ and DMZ. All authors have read and agreed to the published version of the manuscript. All authors agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

This study was performed in line with the principles of the Declaration of Helsinki and was approved by the ethics committee of the Nantong First People's Hospital (Ethics Code: 2024KT196). Informed consent was obtained from all participants included in this study. Participants agreed to the publication of their data by signing an informed consent form.

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Conflict of Interest

The authors declare no conflict of interest.

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