Impaired CD8⁺ Mucosal-Associated Invariant T Cells and Myeloid-Derived Suppressor Cells Promote The Development of Polycystic Ovary Syndrome

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Research Article

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Abstract

Background: Immune dysfunction is one of the mechanisms to promote polycystic ovary syndrome (PCOS). Various immune cells have been reported to be involved in the development of PCOS. Meanwhile, the disturbance of metabolism is closely related to PCOS. This study is to explore the effect of mucosal-associated invariant T cells and myeloid-derived suppressor cells on the pathogenesis and the metabolic dysfunction of PCOS patients.

Methods: 68 PCOS patients and 20 controls were recruited in this study and we collected the peripheral blood of participants' during their follicular phase. The frequencies of MAIT cells and MDSCs were determined by flow cytometry after being stained with different monoclonal antibodies. And the concentrations of cytokines were determined by ELISA.

Results: Compared to control group, the frequency of MDSCs, CD8⁺MAIT cells and CD38⁺CD8⁺MAIT cells were significantly decreased of PCOS patients with normal metabolism, however, proportion of CD4⁺MAIT cells exhibited a noticeable increase. PCOS patients with abnormal weight showed a lower level and activation of CD8⁺MAIT cells. On the contrary, they displayed an enrichment of CD4⁺MAIT cells. PCOS patients with glucose metabolic disorder displayed a remarkable dysregulation of MDSCs and Mo-MDSCs. MDSCs were positively correlated with MAIT cells. Negative correlations between the frequency of CD8⁺MAIT cells, CD38⁺CD8⁺MAIT cells and body mass index were revealed. CD4⁺MAIT cell was positively correlated with BMI. Mo-MDSCs were found to be negatively related to the levels of 2hour plasma glucose and HOMA-IR index.

Conclusion: The MAIT cells subpopulations and MDSCs played distinct roles in the etiology and metabolic disorders of PCOS.

1. Introduction

Polycystic ovary syndrome (PCOS), which is one of the most prevalent endocrine diseases during reproductive age in female [1]. Approximately 8–13% women are affected by PCOS worldwide [2]. Patients with PCOS usually show typical clinical symptoms, including menstrual irregularity (oligomenorrhea or amenorrhea), hirsutism, acne and infertility. Nowadays, the metabolic dysfunction in PCOS have been paid close attention by physicians and researchers, because PCOS patients frequently diagnosed with diabetes/insulin resistance, obesity and other long-term health problem [3–5]. The causes of PCOS have been studied for decades, however, the pathogenesis of PCOS still remains unclear. Recently, researches have focused on the association between immune disorders and PCOS, such as dysfunction of macrophages, dendritic cells and T regulatory cells (Tregs) [6–11].

MAIT (Mucosal-associated invariant T) cells, one kind of unconventional T lymphocytes, which are characterized by a semi-invariant T cell receptor (TCR). A restricted α chain (Va7.2-Ja33 in humans and Va19-Ja33 in mice) and one of the several β chains make up the TCR, which has been revolutionaries

conserved [12–14]. In human, MAIT cells have been defined as CD3⁺CD161⁺Vα7.2⁺ cells. According to expression of CD4 and CD8, MAIT cells group into three groups: CD8⁺MAIT cells and CD4⁻/CD8⁻ (double negative, DN) MAIT cells and CD4⁺MAIT cells [15]. It has been reported that MAIT cells are relatively rich in peripheral blood (PB), liver, and other tissues [16]. Besides, recent studies have demonstrated that MAIT cells were involved in tumor, autoimmune diseases and other diseases [17–19].

Alteration of MAIT cells' frequency and function in metabolic dysfunction, such as diabetes/insulin resistance and obesity, have been demonstrated. Carolan et al. showed a dysfunction in MAIT cells in circulation of obesity adults [20]. Magalhaes and his colleagues reported abnormalities of circulating MAIT cells from T2D and obese patients [21, 22]. These results revealed a close association between MAIT cells and disorders of metabolism. PCOS is considered to be related to metabolic irregularity, we hypothesize that MAIT cells are related to PCOS.

MDSCs (Myeloid-derived suppressor cells) have also been considered to have a vital role in the immunopathogenesis in many types of diseases [23, 24]. MDSCs represent an intrinsic part of the myeloid-cell lineage and are revealed to have a strong immunosuppressive function. There are two subsets of MDSCs: monocytic MDSC (Mo-MDSC), and polymorphonuclear MDSC (PMN-MDSC) [25]. Published reports have demonstrated that MAIT cells have potency of inducing MDSCs [26]. At present, there are no studies that explore the role of MAIT cells as well as MDSCs and the association between them in PCOS. The purpose of this study was to investigate the roles of MAIT cells as well as MDSCs in the pathogenesis and metabolic disorders in PCOS patients.

2. Materials And Methods

2.1. Patient selection

In this study, we recruited 68 patients diagnosed with PCOS and 20 age-matched women without PCOS as the control group from July 2019 to January 2020 in the First Affiliated Hospital of Anhui Medical University. The diagnostic criteria of PCOS were chosen according to the Rotterdam European Society for Human Reproduction. The control group consisted of patients who received in vitro fertilization /intracytoplasmic sperm injection because of fallopian tube factors or male factors. All patients in the control group had normal weight and glucose metabolism. All participants without pharmacological intervention including all kinds of hormone medicines, immunotherapies and other medicines (for example, Metformin, Atorvastatin) in six months. PCOS patients who had autoimmune disorder were also excluded. Extra exclusion criteria include (1) age > 35 years or age < 22 years; (2) suffering from acute infection or a state of inflammation; (3) other endocrine diseases, such as Cushing's Syndrome and thyroid diseases. All participants volunteered to enroll in this study and signed a written consent inform. The process was approved by The Ethics Review Board of the First Affiliated Hospital of Anhui Medical University (No. PJ2020-12-38). Clinical and biochemical characteristics of all participants were summarized in Table 1.

Table 1
Characteristics of PCOS patients vs controls

	PCOS patients	Controls	P-value
Age, (year)	28.10 ± 9.11	30.78 ± 4.02	0.2300
BMI, (kg/m ²)	26.26 ± 4.291	21.34 ± 1.33	< 0.0001
FSH, (IU/L)	6.46 ± 1.70	8.04 ± 2.04	0.0013
LH, (IU/L)	12.43 ± 9.60	6.15 ± 2.18	0.0075
LH/FSH	2.28 ± 3.04	0.77 ± 0.26	0.0402
E2, (pmol/L)	139.1 ± 76.27	164.5 ± 84.91	0.2240
T(nmol/L)	6.95 ± 14.42	1.25 ± 0.67	0.0987
PRL, (ng/ml)	22.31 ± 49.28	16.42 ± 11.42	0.6172
FPG, (mmol/L)	5.62 ± 1.23	5.14 ± 0.45	0.1143
2h PG, (mmol/L)	6.92 ± 2.00	6.78 ± 0.53	0.7712
FINS, (pmol/L)	16.70 ± 14.0	9.42 ± 3.45	0.0325
2h INS, (pmol/L)	52.40 ± 40.50	31.62 ± 10.67	0.0346
HOMA-IR	4.35 ± 3.81	2.16 ± 0.80	0.0182

2.2. Sample collection

We collected peripheral blood from each participant in the morning during their menstrual day 2–3. According to the Biocoll (Biochrom, Berlin, Germany) protocol, we obtained the peripheral blood mononuclear cells with density gradient centrifugation. And we also collected plasma. The peripheral blood mononuclear cells and plasma cryopreserved in the cryopreservation medium at –80°C.

2.3. Flow cytometry analysis

Cells were treated with FcR Blocking Reagent (Biolegend, Germany) before stained with human anti-bodies. MAIT cells and MDSCs stained with conjugated antibodies. The conjugated antibodies and cell staining procedure were same with our previous study [27]. According to manufacturer's instructions, compensation control and cell acquisition was performed by FACSVerse and FACSuite software. Flow cytometry results were analyzed by FlowJo software (Tree Star, Ashland, OR).

2.4. ELISA assay in serum

According to the manufacturer's protocol and procedure in our previous study, TGF, IL-6,10,12, 18, 17, and IFN-γ from plasma were analyzed by ELISA kit (Multisciences Biotech, Hangzhou, China) [27].

2.5. Statistical analysis

We analyzed statistics by using GraphPad Prism software (GraphPad Software, San Diego, CA, USA). Statistical analyses of the differences between means in two groups were performed using unpaired, two-tailed t-test. We performed Spearman analysis to find the correlation. Correlation coefficients were presented as r . P -value < 0.05 was considered significantly different.

3. Results

3.1. Alteration of MDSCs, MAIT cells in PCOS patients with normal metabolism

Figure 1 showed the gating strategy of MAIT cells (Fig. 1A) and MDSCs (Fig. 1B) in peripheral blood. MAIT cells were divided into DN, CD8⁺ and CD4⁺ three subpopulations. Finally, CD38⁺ cells were isolated. CD38 was considered as a marker of MAIT cells activation [28]. MDSCs were divided into two groups via flow cytometry, consisting of Mo-MDSCs and PMN-MDSCs. Comparing with controls, PCOS patients with normal metabolism showed a significant decrease of CD8⁺ MAIT cells frequencies (Fig. 2A, $P < 0.01$). The expression of CD38 in CD8⁺MAIT cells was prominently decreased in PCOS patients with normal metabolism (Fig. 2B, $P < 0.05$). However, there was an accumulation of CD4⁺MAIT cells (Fig. 2C, $P < 0.05$). The percentages of MDSCs were distinctly decreased of PCOS patients with normal metabolism (Fig. 2D, $P < 0.01$). A positive correlation was clarified between the percentage of MAIT cells and MDSCs (Fig. 2E, $r = 0.6067$, $P < 0.0001$). However, no statistical changes were detected in cytokines between PCOS patients with normal metabolism and controls.

3.2. The levels of MAIT cells of PCOS patients with abnormal weight and correlations between these cells and BMI

There were 45 patients without glucose metabolic dysfunction in PCOS group. According to BMI, these patients were divided into two subgroups, the normal weight subgroup (NW) ($18 < \text{BMI} \leq 24$) and the abnormal weight subgroup (AW) (the $\text{BMI} > 24$). There were 23 patients in NW group and 22 patients in AW group. Peripheral blood CD8⁺MAIT cells (Fig. 3A, $P < 0.05$) and CD38⁺CD8⁺MAIT cells (Fig. 3B, $P < 0.05$) both significantly reduced in AW group compared with those from NW group. While CD4⁺MAIT cells obviously displayed an enhancement in AW group (Fig. 3C, $P < 0.001$). The frequency of CD8⁺MAIT cells (Fig. 3D, $r = -0.2623$, $P = 0.0307$) and CD38⁺CD8⁺MAIT cells (Fig. 3E, $r = -0.2708$, $P = 0.0255$) negatively correlated with BMI. The frequency of CD4⁺MAIT cells positively correlated with BMI (Fig. 3F, $r = 0.3730$, $P = 0.0017$).

3.3. Attenuation of MDSCs from PCOS patients with glucose metabolic disorder

32 patients with normal weight were divided into two groups, normal glucose (NG) subgroup and abnormal glucose (AG) subgroup. PCOS patients with a fasting glucose level less than 6.1mmol/L and a 2hour glucose level less than 7.8mmol/L were assigned to the NG group. The remaining patients were

divided into the AG group. There were 23 patients in the NG group and 9 patients in the AG group. Compared with NG group, AG group have decreased levels of MDSC (Fig. 4A, $P < 0.05$). And AG group have lower levels of Mo-MDSC, as compared to that from NG group (Fig. 4B, $P < 0.05$). Negative correlation between Mo-MDSC and the level of 2-hour plasma glucose (Fig. 4C, $r = -0.2453$, $P = 0.0438$) as well as HOMA-IR index (Fig. 4D, $r = -0.2427$, $P = 0.0461$) were also found. For the frequencies of MAIT cells and PMN-MDSCs population, no significant differences between subgroups were found.

4. Discussion

In our study, the association between cytokines, MAIT cells and MDSCs were explored in PCOS patients. In the last decades, abundant evidences have indicated that immune responses play an important role in PCOS, including the immunological activities of different T-cells, macrophages and associated inflammatory factors [6–11]. However, till now there is no study that showed investigation of MAIT cells and MDSCs in PCOS patients. In this study, we revealed that the disorders of circulatory MAIT cells as well as MDSCs might be an immunological pathogenesis for PCOS and was associated with metabolic dysfunction.

It has been reported that the abnormality of Th17 cells percentage was associated with PCOS [29]. Due to the same secretion of IL-17, MAIT cells have been reported to have a similar function of Th17 cells [30]. In this study, a decreased frequency of CD8⁺MAIT cells in PCOS patients was revealed. Moreover, CD38⁺CD8⁺MAIT cells, known as activated MAIT cells, were also reduced. MAIT cells are divided into three subgroups, CD8⁺MAIT cells, CD4⁺MAIT cells, and CD8⁻CD4⁻MAIT cells [15]. Our results indicated that the impaired frequency and function of CD8⁺MAIT cells might have a close link with PCOS. Early studies have suggested that CD8⁺MAIT cells played a protective role in some diseases [31, 32]. Consistent with previous studies, our study also revealed the protective role of CD8⁺MAIT cells in PCOS. Nonetheless, CD4⁺MAIT cells displayed an expansion in PCOS. It has been known that the functional roles and frequencies of MAIT cells differ between different subsets and different diseases [33, 34]. In this study, our results also support the distinct roles of CD8⁺MAIT and CD4⁺MAIT cells. Recently, PCOS was also recognized as a chronic inflammatory disease [35, 36]. Therefore, our findings would suggest that the protective role of CD8⁺MAIT cells in PCOS are weakened, which is similar to the results from other chronic inflammatory diseases.

Two of the major problems from patients with PCOS are overweight and obesity. In our study, we found that with the increase of BMI, the frequencies of CD8⁺MAIT cells and CD38⁺CD8⁺MAIT cells decreased. Whereas, the proportion of CD4⁺MAIT cells displayed increased levels. Previous researches have depicted that obese adults displayed a depletion of circulating MAIT cells [20, 21]. Touch et al. have revealed that obese human showed an impaired frequency of MAIT cells [37]. Recent study investigated by Li et al. has suggested that considerable decrease of MAIT cells frequency and distinct dysfunctional state of MAIT cells in obese patients [38]. CD8⁺MAIT cells were the majority of MAIT cells, we implied that the lipid metabolic disorder was mainly affected by the decreased amount and weakened function of

CD8⁺ MAIT cells in PCOS patients [16]. We indicated that the reduction of CD8⁺ MAIT cells might promote the development of obesity in PCOS patients.

MDSCs have been indicated to have a close relation with MAIT cells in various pathological processes [28]. Haeryfar et al. suggested that MAIT cells could induce MDSCs [26]. Nevertheless, a direct connection between MAIT cells and MDSCs has not been identified in PCOS. In our study, we found a significant reduction of MDSCs and a positive relationship between MAIT cells and MDSCs in the PB of PCOS patients. One explanation would be that lessened MAIT cells have an impaired function of induction of MDSCs. Till now there are no studies about the role of MDSCs in PCOS, however, another group of immunosuppressive cells, Tregs, has been indicated to be reduced in PCOS patients [11, 39]. Based on the immunosuppressive properties of MDSCs and Tregs, the two populations are expected to share a similar role in different diseases [40, 41]. Reduced immunosuppression is a key factor in the overreaction in inflammatory response. As mentioned previously, patients with PCOS have a strong chronic inflammatory background. Therefore, we suggested that an impaired immunosuppressive microenvironment with reduced MDSCs might be a cause of long-term chronic inflammation in PCOS.

Furthermore, our findings also revealed that PCOS patients with disorders of glucose metabolism had a strong reduction of MDSCs and Mo-MDSCs. What's more, with the progression of glucose metabolic dysfunction, the frequencies of MDSCs and Mo-MDSCs decreased. The roles of MDSCs in metabolic diseases have been widely studied. Yin et al. have demonstrated that transferred MDSCs could down-regulate autoimmune responses and prevent diabetes onset in mice model [42]. Researchers have previously clarified that MDSCs could improve metabolic dysfunctions and act as a protector in obesity [43]. Combined with these results, our study indicated that a decreased frequency of MDSCs and Mo-MDSCs might induce the occurrence of metabolic dysfunction in PCOS patients.

5. Conclusion

The outcomes of our research gave a clue that the combined reduction of CD8⁺MAIT cells and MDSCs, and increased population of CD4⁺MAIT cells might contribute to the pathogenesis of PCOS and its metabolic disorders. We propose that the prominently reduced amount of CD8⁺MAIT cells and MDSCs, shown in PCOS patients' PB, probably promote the chronic inflammation in PCOS immune microenvironment, therefore might promote the onset of PCOS and increase the severity of PCOS. The results suggested that inducing CD8⁺MAIT cells and MDSCs might be a potential therapeutic target for PCOS patients. However, the limitation of this study is that we only analyzed the PB from PCOS patients, which might not present the immune status in ovary microenvironment. In-depth researches about the mechanisms of MAIT cells and MDSCs could lead to new therapeutic ideas.

Abbreviations

PCOS, polycystic ovary syndrome; Tregs, T regulatory cells; MAIT cell, Mucosal-associated invariant T cell; TCR, T cell receptor; DN, double negative; PB, peripheral blood; T2D, type 2 diabetes mellitus; MDSC,

Myeloid-derived suppressor cell; Mo-MDSC, monocytic myeloid-derived suppressor cell; PMN-MDSC, polymorphonuclear myeloid-derived suppressor cell; TGF, transforming growth factor; IL, Interleukin; IFN- γ , Interferon- γ ; BMI, body mass index; NW, normal weight; AG, abnormal weight; NG, normal glucose; AG, abnormal glucose; HOMA-IR, homeostasis model assessment of insulin resistance;

Declarations

Ethics approval and consent to participate

The process was approved by The Ethics Review Board of the First Affiliated Hospital of Anhui Medical University (No. PJ2020-12-38).

Consent for publication

All participants volunteered to enroll in this study and signed a written consent inform.

Availability of data and materials

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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Author contributions

Mengting Zhu: conceptualization, study conduct, data analysis, writing - original draft. Caihua Li: writing - review & editing, investigation. Yuping Xu: conceptualization, supervision, writing – review & editing. Zhimin Lu: methodology, supervision. Kaihuan Bi: supervision. Kangxia Wang: supervision. Peipei Guo: resources, supervision. Huanhuan Jiang: conceptualization, investigation, writing - review & editing. Yunxia Cao: conceptualization, methodology, supervision, writing - review & editing.

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Tables

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HOMA-IR	4.35±3.81	2.16±0.80	0.0182

Table 1. This table represented the clinical and biochemical characteristics of PCOS patients (n =68) and controls (n =20). All values were expressed as mean±SD. P-values were calculated by using an unpaired Student's t-test. BMI, body mass index; FSH, follicular stimulating hormone; LH, luteinizing hormone; E2,estradiol; T, testosterone; PRL, prolactin; FPG, fasting plasma glucose ; 2h PG, 2hour plasma glucose; FINS, fasting insulin; 2h INS, 2hour insulin; HOMA-IR, homeostasis model assessment of insulin resistance;

Figures

Figure 1

Analysis of MAIT cells and MDSCs in peripheral blood from patients by flow cytometry. Representative pseudocolor with the gating strategy identifying CD8⁺, CD4⁺, DN MAIT (A). CD3⁺CD161⁺ Va7.2⁺ cells were gated at first. Basing on CD4 and CD8, and three subsets were identified: CD8⁺, CD4⁺ and DN MAIT cells. At last, cells which had expression of CD38 (CD38⁺) were selected. The gating strategy identifying MDSCs (B). Firstly, CD33⁺ cells were gated and then HLA-DR^{-/low} and CD11b⁺ cells were isolated. Next, based on CD14 and CD15, the cells were divided into Mo-MDSC(CD14⁺CD15⁻) and PMN-MDSC(CD14⁻CD15⁺). MAIT cell, mucosal-associated invariant T cell; MDSC, myeloid-derived suppressor cell; DN, double negative; Mo-MDSC, monocytic myeloid-derived suppressor cell; PMN-MDSC, polymorphonuclear myeloid-derived suppressor cell.

Figure 2

Percentages of MAIT cells subsets and MDSCs in circulation of PCOS patients without metabolic dysfunction and control group. (A) displayed lower expression of CD8+MAIT cells in the PCOS group. PCOS patients exhibited a remarkable down-regulation of CD38 on CD8+ MAIT cells than the control group (B). CD4+MAIT cells showed an enhancement in PB of PCOS group(C). Expression of MDSCs significantly reduced in PCOS patients than the control group (D). MAIT cells was positively correlated with MDSCs (E). *P < 0.05, **P < 0.01. PCOS, polycystic ovary syndrome; CG, control group; MAIT cell, mucosal-associated invariant T cell; PB, peripheral blood; MDSC, myeloid-derived suppressor cell.

Figure 3

Histogram represents frequency of MAIT cells subsets in NW and AW cohorts. CD8⁺MAIT cells and CD38⁺CD8⁺ MAIT cells showed higher expression in the NW group (A, B). Patients of AW group showed a dramatic elevation of CD4⁺MAIT cells (C). The negative correlation between the frequency of CD8⁺MAIT cells as well as CD38⁺CD8⁺ MAIT cells and BMI (D, E). A positive association between the CD4⁺MAIT cells and BMI was discovered (F). *P < 0.05, ***P < 0.001. MAIT cell, mucosal-associated invariant T cell; PB, peripheral blood; NW, normal weight; AG, abnormal weight; BMI, body mass index.

Figure 4

Histogram showing MDSCs and Mo-MDSC frequency in two groups, including NG group and AG group. Compared to NG group, MDSCs frequency of AG group were significantly decreased (A). The percentage of Mo-MDSCs decreased significantly in AG group (B). C-D displayed the negative associations between Mo-MDSCs and the level of 2hour PG and HOMA-IR index of PCOS patients. * $P < 0.05$. MDSC, myeloid-derived suppressor cell; Mo-MDSC, monocyte myeloid-derived suppressor cell; PB, peripheral blood; NG, normal glucose; AG, abnormal glucose; 2h PG, 2hour plasma glucose; HOMA-IR, homeostasis model assessment of insulin resistance.