Cytokine 119 (2019) 113–118

Contents lists available at ScienceDirect

Cytokine

journal homepage: www.elsevier.com/locate/cytokine

IL-18 induced IL-23/IL-17 expression impairs Aβ clearance in cultured THP-1 and BV2 cells☆

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ARTICLE INFO

Keywords:
Alzheimer's disease
Cytokines
Interleukin
Inflammation
Amyloid

ABSTRACT

Recent studies have provided overwhelming evidence of the involvement of microglia-related molecular networks in the pathogenesis of Alzheimer's diseases (AD). The potential involvement of pro-inflammatory cytokines interleukin (IL)-18, IL-23 and IL-17 on amyloid (Aβ) clearance is still unclear. In this study, we addressed that there might be a net relationship among IL-18, IL-23, and IL-17 and they can affect Aβ clearance in cultured macrophage/microglia cells. In human macrophage cell line THP-1, Aβ42 incubation could increase the expression of IL-18, IL-23 and IL-17 in a concentration dependent manner. THP-1 cell could clear Aβ42 in the culture medium time-dependently, but its capacity of Aβ clearance was impaired by IL-18, IL-23 or IL-17 treatment. Similarly, the capacity of the microglia cell line BV2 to clear Aβ42 was impaired by IL-18, IL-23 or IL-17 treatment. In co-cultures of BV2 with APP/PS1 neuron, Aβ was efficiently cleared by BV2 cell, but Aβ clearance was impaired by IL-18, IL-23 or IL-17 treatment. The effects of IL-18, IL-23 and IL-17 could be blocked by their corresponding neutralizing antibodies. In addition, the inhibitory effects of IL-18 were blocked by IL-23 or IL-17 neutralizing antibodies while the inhibitory effects of IL-23 were blocked by IL-17 neutralizing antibodies. Our study provides evidences showing that amyloid induced IL-18/IL-23/IL-17 axis could impair macrophage and microglia-mediated Aβ clearance. Thus, IL-18/IL-23/IL-17 axis might be a therapeutic target in AD.

1. Introduction

Neuroinflammation plays a crucial role in the pathogenesis of Alzheimer's disease (AD) [1–3]. Cytokines, secreted by microglia and astrocytes, are involved in the regulation of the brain immune response [4]. Studies suggest that AD patients are accompanied by higher peripheral concentrations of interleukin (IL)-18, IL-23 and IL-17 [5]. IL-18, also known as IL-1γ or interferon-γ-inducing factor (IGIF), is elevated in post-mortem brains of AD patients[6] and can increase AD-associated amyloid (Aβ) in human neuron-like cells [7,8]. IL-23 is composed of p40 and p19 subunits. AD-associated pathology and cognitive deficits could be ameliorated by modulating the subunit of p40 [9,10]. Th17 cell-mediated neuro-inflammation may participate in various chronic inflammatory conditions, such as atherosclerosis and AD [3]. Besides, via IL-23/Th17 pathway, cholesterol can significantly accelerate the progress of atherosclerosis in IL-18 deficiency, which demonstrates a new role for Th17 in chronic inflammation [11]. Experimental data have shown that both Th17 and IL-23 were increased in the supernatant of Aβ stimulating vitro cells from AD patients [12]. However, the detailed role of IL-18, IL-23 and IL-17 in the AD pathogenesis has not been established.

The extracellular deposition of Aβ in the form of parenchymal plaques is the major pathology marker of AD [4]. In addition, AD is frequently associated with inflammation and microglia activation in AD patient brains [4]. It has long been recognized that Aβ plaques are surrounded by activated microglial cells [13,14], however, the underlying mechanism still remains a matter of debate. Glial cells, especially Aβ-activated microglia could release pro-inflammatory cytokines in AD [9,15]. IL-23 displayed a synergistic effect with IL-18 on stimulating Th17 for IL-17 production in experimental autoimmune

☆ Summary sentence: IL-18/IL-23/IL-17 axis impairs Aβ clearance.

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https://doi.org/10.1016/j.cyto.2019.03.003
Received 27 November 2018; Received in revised form 28 February 2019; Accepted 11 March 2019
Available online 21 March 2019
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encephalomyelitis (EAE) [16] and psoriasis-like epidermal hyperplasia [17]. IL-18, IL-23 and IL-17 have been shown to have correlations with AD [5,8,10]. In this study, we aimed to study whether IL-18, IL-23, and IL-17 could affect Aβ clearance in cultured macrophage and microglia cells.

2. Materials and methods

2.1. Materials

THP-1 cells were obtained from ATCC (Cat#TIB-202; http://www.atcc.org, Research Resource Identifier (RRID): CVCL_0006). BV2 cells were obtained from ICLC (Cat#ATL03001; RRID: CVCL_0182). Human IL-18 ELISA (Cat# RAB0543), Mouse IL-18 ELISA (Cat# RAB0810), Human IL-17 ELISA (Cat#RAB0262), Mouse IL-17 ELISA (Cat# RAB0263), Human IL-23 ELISA (Cat#RAB0697) and Mouse IL-23 ELISA (Cat# RAB0813) were purchased from Sigma (St. Louis, MO, USA). Human IL-18 antibody (Cat# AHC8181, RRID: AB_1500350), Human IL-18 (Cat# PHC0186), Mouse IL-18 (Cat# PMC0184), Human IL-17 (Cat# PHC0174), Mouse IL-17 (Cat# PMC0175), Human IL-23 (Cat# PHC9324), Aβ42 human ELISA Kit (Cat#KHB3442), Aβ42 Mouse ELISA Kit (Cat#KMB3441) and Aβ40 Mouse ELISA Kit (Cat#KMB3481) were purchased from Invitrogen (Carlsbad, CA, USA). Human IL-17 antibody (Cat#16–7178-85, RRID: AB_494122), Mouse IL-17 antibody (Cat#16–7178-853,RRID: AB_763585), Human IL-23 antibody (Cat#16–5236-85, RRID: AB_201657), Mouse IL-23 antibody (Cat#16–7232-85, RRID: AB_469241), Mouse IL-23 (Cat#14–8231-63) were purchased from eBioscience (San Diego, CA, USA). Mouse IL-18 antibody (Cat# D048-3, RRID: AB_592011) was purchased from MBL (Nagoya, Japan).

2.2. Preparation of Aβ42 peptide

Aβ42 peptide was synthesized by ChinaPeptides (Shanghai, China) and solubilized in dimethyl sulfoxide (DMSO) at 1 mg/ml. The peptide aliquots were stored at −20 °C. For Aβ42 clearance assay, the peptide was further dissolved in serum-free culture medium at 1 μg/ml.

2.3. Cell culture

The THP-1 cells were maintained in RPMI-1640 with 10% fetal bovine serum (FBS). BV2 cells were maintained in DMEM with 10% FBS. Cells were incubated at 37 °C in a 5% CO_2/95% air humidified atmosphere. BV-2 and THP-1 cells were authenticated one month before our study began and they are not listed as commonly misidentified cell line by the International Cell Line Authentication Committee. Cell experiments were repeated at least three times.

2.4. Primary neurons and co-culture system

APP/PS1 mice were obtained from Jackson laboratory (Cat#004462, Bar Harbor, ME, USA, RRID: MGI: 5702670). These mice co-overexpress Aβ precursor protein with the Swedish double mutation and presenilin 1 with deletion of exon 9 under the control of mouse prion promoter and breed like a single transgenic mouse line [18]. The genotyping was performed on embryonic day 17 (E17) using Extract-N-Amp™ Tissue PCR Kit (Sigma). Mouse primary cortical neurons were isolated from embryonic day 17 mouse brains of positive embryos. Briefly, mouse cerebral cortices were isolated in cold DMEM and digested for 6 min at 37 °C in 0.25% trypsin followed by adding DMEM with 10% FBS to terminate digestion. After filtered with 70 μm cell strainer, cells were centrifuged at 1000 rpm for 3 min and resuspended in DMEM with 10% FBS. Cells were plated in poly-D-lysine coated dishes and further cultured in Neurobasal supplemented with B27, 0.5 mM glutamax and 5-fluorouracil (5-FU) for 10–12 days. The study was not pre-registered. All animal experiments were done in strict accordance with the Laboratory Animal Welfare Act, the National Institutes of Health Guide for the Care and Use of Laboratory Animals. The study and protocols were approved by the Institutional Animal Care and Use Committee of Shanghai Jiao Tong University School of Medicine (ECRN.2014.17).

The co-culture system consists of lower and upper chambers which were separated by a selectively permeable membrane with 0.4 μm-diameter pores (Corning, Transwell 3450). The primary APP/PS1 mouse neurons were plated in the lower chamber and maintained to 10 days in vitro (DIV10). BV-2 cells were plated in the upper chamber and were co-cultured with neurons to simulate the Central Nervous System (CNS) microenvironment.

2.5. ELISA for IL-18, IL-23 and IL-17 production

The levels of IL-18, IL-23 and IL-17 were measured by commercial ELISA kit according to the instructions of its manufacturer. The minimum detectable concentrations were 3.0 pg/ml for IL-18, 0.05 pg/ml for IL-17 and 0.1 pg/ml for IL-23. Moreover, according to the manufacturer guidelines the coefficient of variations (CV) was 4.2%, 4.8% and 4.1% for the assessments of IL-18, IL-17 and IL- 23, respectively.

2.6. ELISA for Aβ

Culture medium was collected and centrifuged to avoid cells and debris. Culture medium was stored at −80 °C until ELISA experiments. Human Aβ42 levels in the medium were quantified by ELISA kit (Invitrogen, Cat#KHB3442). Mouse Aβ42 and Aβ40 derived from cultured neurons were quantified by ELISA kit (Invitrogen, Cat#KMB3441 and Cat#KMB3481).

2.7. Real-time PCR for IL-23mRNA, IL-17mRNA and IL-18mRNA

After cells collection, the total RNA was extracted by Trizol reagent and was dissolved in 20 μL DEPC treating water. The concentration of total RNA was measured by NanoDrop (Thermo, American). One μg total RNA was reverse-transcribed using RT-PCR Kit (Takara). The quantitative real-time PCR was performed with qPCR machine (ABI 7500, American) and SYBR Green kit (Takara). With β-actin as a reference gene, the relative gene expression level was calculated by $2^{-\Delta\Delta Ct}$ method. The primers were synthesized by Shanghai Huagene Biotechnology Company. Primer sequences are as follows (F, forward; R, reverse): IL-18, F-ACTGGTTCAGCAGCCATCTT, R-TGCAGTCTACAC AGCTTCGG; IL-23, F-CCACACTGGATATGGGGAAC, R-ACTCAGTGCCA GCAGCTTTC; IL-17, F-GGGGACAGAGTTCATGTGGT, R-CCACCTCACC TTGGAATCTC.

2.8. Statistical analysis

Data are expressed as mean ± standard deviations (n = 3, the "n" describes number of independent experiments). Group differences were analyzed by unpaired Student's *t* test for two groups and one-way ANOVA was used for multiple groups in the time-dependent manner. Data collection was made based on the availability and feasibility, and no sample calculation was performed. No blinding and no randomization were performed. Statistical analyses were performed using GraphPad Prism (version 6.01) software (GraphPad Software Inc., San Diego, CA, USA). All *p* values were based on two-sided tests. For all, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$. An assessment of the normality of data was carried out by Shapiro-Wilk normality test using GraphPad Prism6 for each test. No test for outliers was conducted on the data.

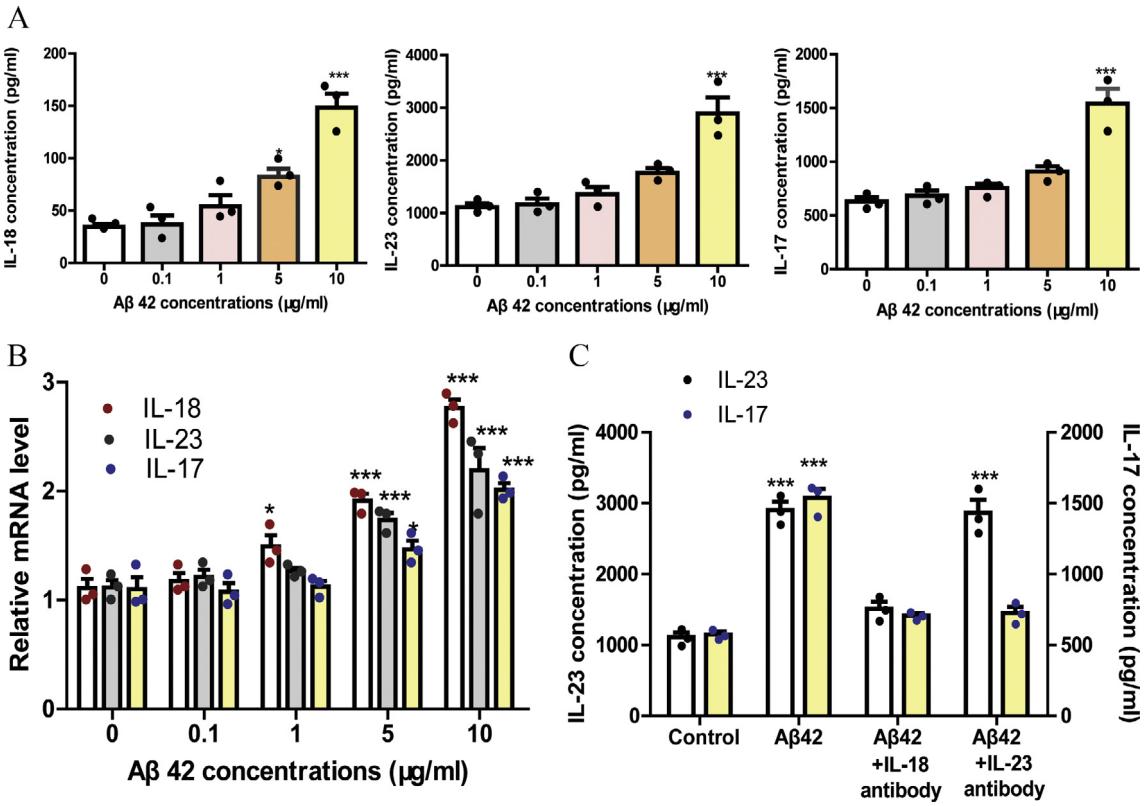

Fig. 1. Amyloid (Aβ) 42 induces interleukin (IL)-23/IL-17 expression by increasing IL-18 in macrophage cells. A. Results of the concentration of IL-18, IL-23, IL-17 measured by ELISA in presence of various concentrations of Aβ42 pre-treated THP-1 cells. B. Results of the level of IL-18mRNA, IL-23mRNA, IL-17mRNA by qRT-PCR in presence of various concentrations of Aβ42 pre-treated THP-1 cells. C. Results of IL-18 antibody and IL-23 antibody blocked the increased concentration of IL-23 and IL-17 induced by Aβ42 in the THP-1 cells. Experiments were repeated three times with similar results (n = 3, the "n" describes number of independent experiments). For all, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

3. Results

3.1. Aβ42 induces IL-23/IL-17 by increasing IL-18 level in THP-1 macrophage

We cultured macrophage cell line THP-1 in presence of various concentrations of Aβ42 and analyzed the concentration of IL-17, IL-18, and IL-23 in the culture medium of THP-1. The concentrations of IL-17, IL-18 and IL-23 were increased dose-dependently by Aβ42 (Fig. 1A). Similarly, qRT-PCR analysis showed IL-17mRNA, IL-18 mRNA and IL-23 mRNA levels in THP-1 cell were also increased dose-dependently by Aβ42 (Fig. 1B). It's important to note that lower Aβ42 concentration was sufficient for IL18 induction but higher Aβ42 concentration was required for IL23 and IL17.

It is reported that IL-18 can combine with IL-23 to stimulate IL-17 production [16,19]. To study potential interactions among IL-17, IL-18 and IL-23 on Aβ, we used IL-18 antibody and IL-23 antibody as blocking agents. Aβ42 (10 μg/ml) induced the concentrations of both IL-17 and IL-23 in THP-1. IL-18 antibody blocked both IL23 and IL17 induction while IL23antibody only blocked IL-17 induction (Fig. 1C). It suggests that IL18 acts in the upstream of IL23/IL17.

3.2. IL-18 induced IL-23/IL-17 expression impairs the capacity of macrophage Aβ clearance

To characterize the capacity of macrophage mediated β-amyloid clearance, we incubated THP-1 cells with Aβ for different time points. A significantly decrease of Aβ concentration in the culture medium began at 4 h and continued in a time-dependent manner, (Fig. 2A). To assess the impact of IL-18, IL-23 and IL-17 on THP-1 mediated Aβ clearance, THP-1 cell was treated with Aβ alone or co-treated with IL-18, IL-23 and IL-17 ("1" stands for 1 ng/ml, "2" stands for 10 ng/ml, "3" stands for 100 ng/ml). The results showed that IL-18, IL-23 and IL-17 could dose-dependently impair Aβ clearance, respectively (Fig. 2B). Then, we used IL-18 antibody, IL-23 antibody and IL-17 antibody as blocking agents. The results showed the effect of IL18 was blocked by IL-18, IL-23 and IL-17 antibodies; the effect of IL23 was blocked by IL-23 and IL-17 antibodies, but not by IL-18 antibody; the effect of IL17 was only blocked by IL-17 antibody (Fig. 2C).

3.3. IL-18 induced IL-23/IL-17 expression impairs the capacity of microglia amyloid clearance

Since IL-18 can induce IL-23/IL-17 expression and impair the capacity of macrophage to clear Aβ (Fig. 2), it is valuable to explore whether microglia, the macrophage in central nervous system (CNS), is also affected. In this study, we used microglia cell line BV-2. To determine whether IL-18, IL-23 and IL-17 can impair the capacity of microglia to clear amyloid, we first showed that BV2 cell was able to clear Aβ in the culture medium time-dependently (Fig. 3A). Then, BV2 cell was treated with Aβ alone or co-treated with IL-18, IL-23 and IL-17 ("1" stands for 1 ng/ml, "2" stands for 10 ng/ml, "3" stands for 100 ng/ml). The results showed that IL-18, IL-23 and IL-17 could dose-dependently impair Aβ clearance, respectively (Fig. 3B). Then, we used IL-18 antibody, IL-23 antibody and IL-17 antibody as blocking agents. The results showed the effect of IL18 was blocked by IL-18, IL-23 and IL-17 antibodies; the effect of IL23 was blocked by IL-23 and IL-17 antibodies, but not by IL-18 antibody; the effect of IL17 was only blocked by IL-17 antibody (Fig. 3C). Taken together, similar results were observed in microglia and these results indicated that IL-18 induced IL-23/IL-17 expression could impair the capacity of macrophage and microglia to clear amyloid.

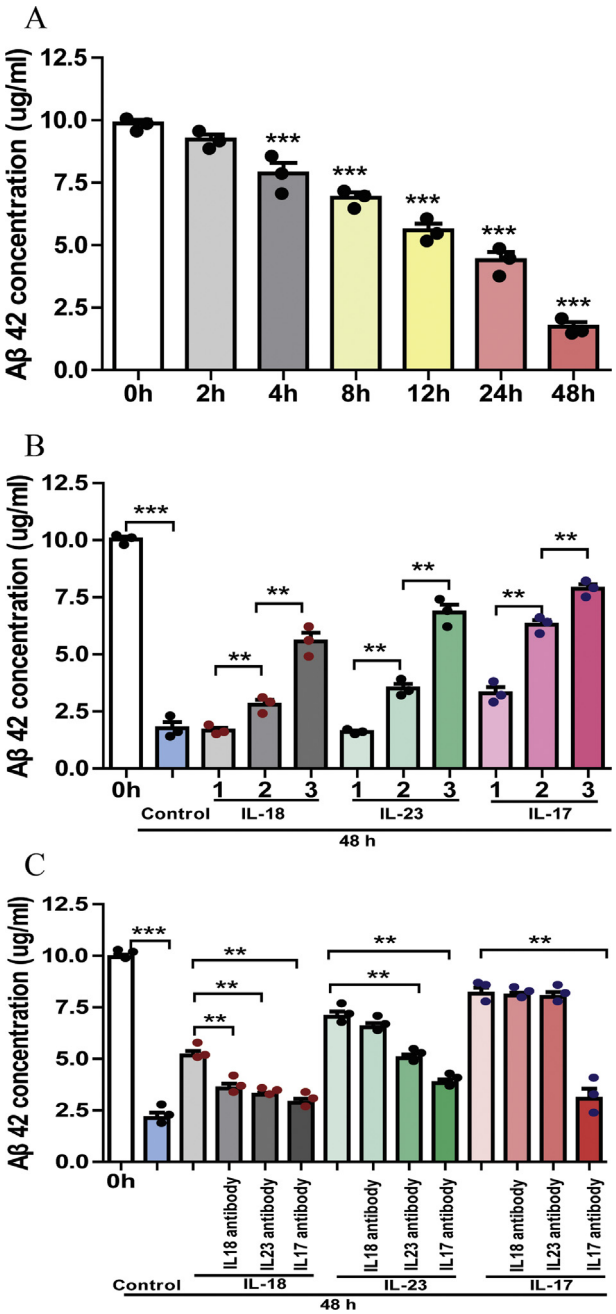

Fig. 2. Interleukin (IL)-18 induced IL-23/IL-17 expression impairs the capacity of macrophage to clear amyloid (Aβ). A. Result of the Aβ concentration measured by ELISA at different time points in Aβ42 pre-treated THP-1 cells. B. Result of the Aβ concentration measured by ELISA in presence of various concentrations of IL-18, IL-23, IL-17 of the Aβ42 pre-treated THP-1 cells for 48 h. (All 1 = 1 ng/ml, 2 = 10 ng/ml, 3 = 100 ng/ml.) C. Results of IL-18 antibody, IL-23 antibody, IL-27 antibody blocked the increased Aβ concentration induced by IL-18 (100 ng/ml), IL-23 (100 ng/ml), IL-17 (100 ng/ml). Experiments were repeated three times with similar results (n = 3, the "n" describes number of independent experiments). For all, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

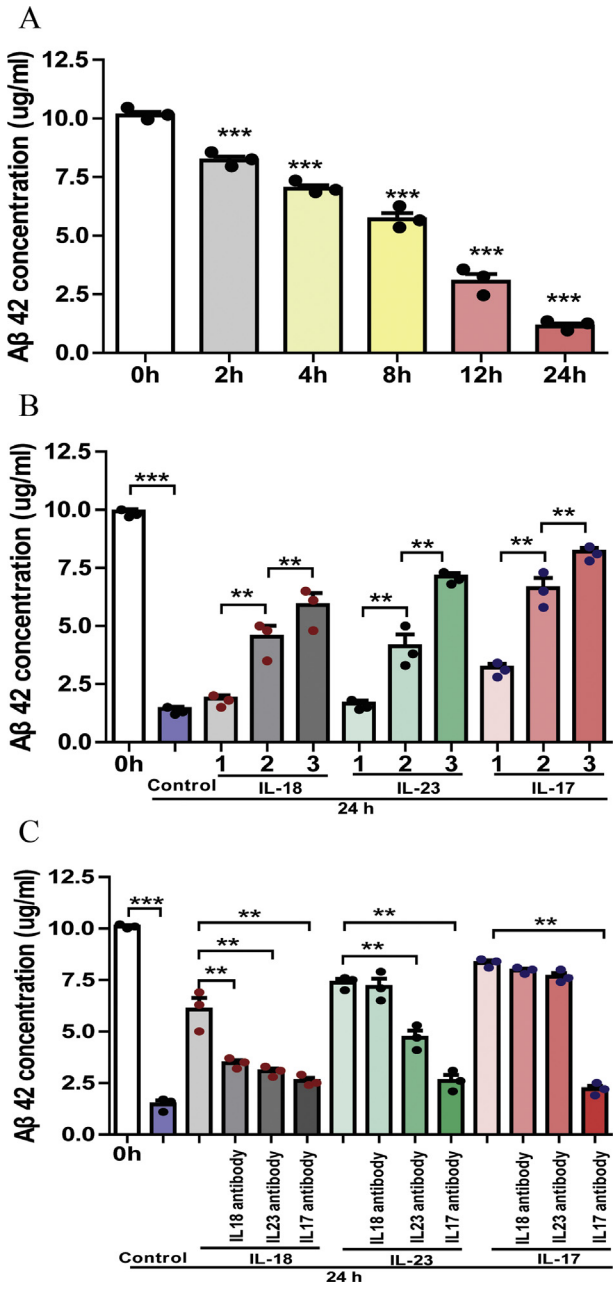

Fig. 3. Interleukin (IL)-18 induced IL-23/IL-17 expression impairs the capacity of microglia to clear amyloid (Aβ). A. Result of the Aβ concentration measured by ELISA at different time points in the Aβ42 pre-treated BV2 cell. B. Result of the Aβ concentration measured by ELISA in presence of various concentration of IL-18, IL-23, IL-17 of the Aβ42 pre-treated BV2 cells for 24 h (1 = 1 ng/ml, 2 = 10 ng/ml, 3 = 100 ng/ml). C. Results of IL-18 antibody, IL-23 antibody, IL-27 antibody blocked the increased Aβ concentration induced by IL-18 (100 ng/ml), IL-23 (100 ng/ml), IL-17 (100 ng/ml). Experiments were repeated three times with similar results (n = 3, the "n" describes number of independent experiments). For all, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

3.4. IL-18 induced IL-23/IL-17 expression impairs microglia-mediated amyloid clearance in co-culture system

To further validate the experiment that IL-18 induced IL-23/IL-17 expression could impair the capacity of microglia to clear Aβ, we used the co-cultures of BV2 and primary neurons from APP/PS1 mice to mimic the in-vivo CNS microenvironment (Fig. 4A).

First, we showed that BV2 could efficiently clear the APP/PS1 neuron-derived human Aβ42 and mouse endogenous Aβ40/42 (Fig. 4B). Next, we assessed the impacts of IL-18, IL-23 and IL-17 on Aβ clearance in co-culture system. The results showed that IL-18, IL-23 and IL-17 dose-dependently impaired the clearance of human Aβ42 and mouse Aβ40/42) (Fig. 4C).

Then, we used IL-18 antibody, IL-23 antibody and IL-17 antibody as blocking agents. The results showed the effect of IL18 was blocked by IL-18, IL-23 and IL-17 antibodies; the effect of IL23 was blocked by IL-

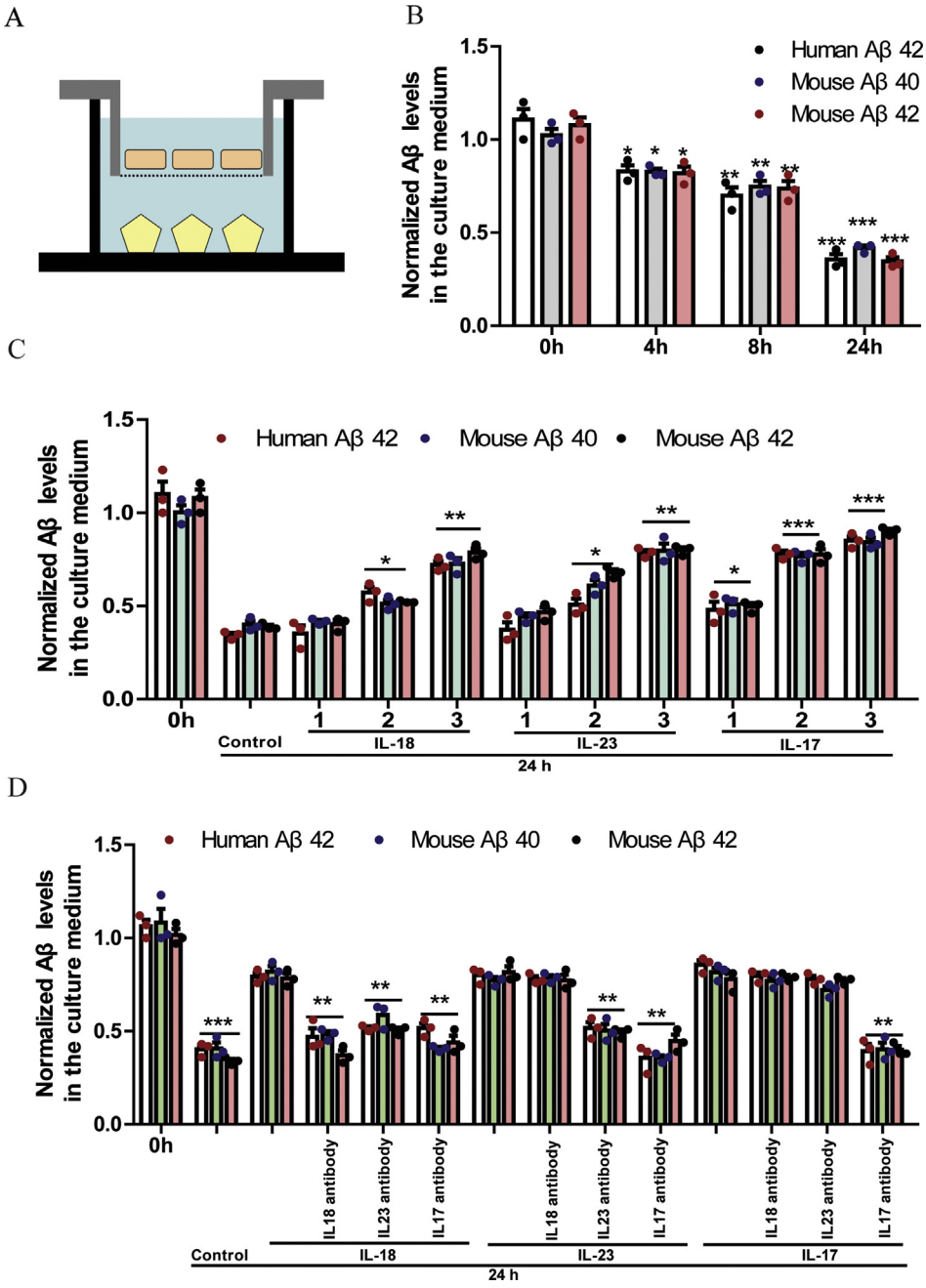

Fig. 4. Interleukin (IL)-18 induced IL-23/IL-17 expression impairs the capacity of microglia to clear amyloid (Aβ). A. The simulation of central nervous system microenvironment by co-culture primary neuron derived from APP/PS1 mice and BV2 cells. B. Result of the Aβ concentration (human Aβ42, mouse Aβ40/42) measured by ELISA at different time points in the culture medium. C. Result of the Aβ concentration (human Aβ42, mouse Aβ40/42) measured by ELISA in presence of various concentrations of IL-18, IL-23, IL-17 of the Aβ42 pre-treated simulation of central nervous system microenvironment for 24 h (1 = 1 ng/ml, 2 = 10 ng/ml, 3 = 100 ng/ml). D. Results of IL-18 antibody, IL-23 antibody, IL-27 antibody blocked the increased Aβ concentration (including human Aβ42, mouse Aβ40/42) induced by IL-18 (100 ng/ml), IL-23 (100 ng/ml) and IL-17 (100 ng/ml). Experiments were repeated three times with similar results (n = 3, the "n" describes number of independent experiments). For all, $^{*}P < 0.05$, $^{**}P < 0.01$, $^{***}P < 0.001$.

23 and IL-17 antibodies, but not by IL-18 antibody; the effect of IL17 was only blocked by IL-17 antibody (Fig. 4D). The results indicated that IL-18 induced IL-23/IL-17 expression might also impair the capacity of microglia to clear amyloid from neurons in in-vivo environment.

4. Discussion

In this study, we demonstrate that IL-18 induced IL-23/IL-17 expression can impair Aβ clearance by macrophage and microglia. It supports that inflammatory networks involving IL-18, IL-23 and IL-17 play important roles in the pathogenesis of AD.

Macrophages, monocytes and microglia contribute to Aβ clearance and play a neuroprotective role by promoting Aβ phagocytosis, degradation and clearance [4,20]. The exposure of macrophage to Aβ can trigger an inflammatory response and activation of inflammatory transcription factors leading to the release of a variety of pro-inflammatory and neurotoxic factors [21–23]. These studies are consistent with the $A\beta_{42}$ induced expression of IL-17, IL-18 and IL-23 in our current study as well as our previous epidemiological survey [5].

Although IL-18, IL-23 and IL-17 have been implicated in a variety of diseases, including bacterial infections [24] and autoimmune disorders such as multiple sclerosis [25], Crohn's disease [26] and ankylosing spondylitis [27], their involvement in AD have not been established. Lalor [16] examined the role of caspase-1-processed cytokines in IL-17 production and in induction of EAE and found that overexpression of IL-18 bp, an endogenous inhibitor of IL-18, reduced Th17 responses and the severity of EAE in mice, indicating that IL-18 might synergize with IL-23 to stimulate the expansion of Th17 cells. In this study, we examined the potential interactions among IL-17, IL-18 and IL-23 on Aβ by using IL-18, IL-23 and blocking antibodies. These results suggested that IL-18 might regulate the production of IL-23 and IL-17 while IL-23 could only regulate the production of IL-17. This is consistent with previous studies showing that IL-18 could combine with IL-23 to stimulate IL-17 production [16,19]. Our study is also consistent with a

report showing that IL-17 was produced by microglia in response to IL-23 treatment [28].

In the present study, we mimic the in-vivo microenvironment of CNS by using co-cultures of primary neurons from APP/PS1 mice and BV2 cell line. Using the SAMP8 model of accelerated aging, Tan [10] observed the p40 (the IL-12/23 common subunit) in the brain was upregulated and knockdown of brain p40 could reduce the Aβ production in brain. Sun [1] investigated the lipopolysaccharide (LPS)-induced rats and found that neutralizing IL-17 could prevent neuroinflammation and reduce amyloid level. Tian [2] found IL-17-related cognitive dysfunction may be due to the activation of astrocytes and TGFβ/Smad pathway dependent Aβ accumulation. Increased IL-18 [7,8] and IL-17 [1,2] were involved in the procession of Aβ accumulation. These results supported the paradigm that pro-inflammatory IL-18, IL-23 and IL-17 could also promote the Aβ production in the brain.

Our study provides novel evidence for the importance of pro-inflammatory cytokines of IL-18, IL-23, and IL-17 in macrophage and microglia-mediated Aβ clearance. The results in the current study deserves further validation in in-vivo studies.

Disclosures

The authors declare that they have no conflicts of interest.

Availability of data and materials

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

Authors' contributions

J.-M.C, Q.-W.L., G.-X.J., J.-S.L. and Q.C. conceived and designed the experiments. J.-M.C., J.-S.L. and Q.-W.L. performed the experiments. G.-X.J. acquired and analyzed the data. J.-M.C. and Q.-W.L. drafted the manuscript. All authors approved and reviewed the final manuscript.

Acknowledgements

This study was supported by funds from Natural Science Foundation of China (81070958 & 81371218).

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