Tropical Journal of Pharmaceutical Research July 2019; 18 (7): 1527-1532
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v18i7.24

Original Research Article

Macrophages induce natural killer cell dysfunction via KIR2DL1 during *Echinococcus multilocularis* infection

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Sent for review: 9 January 2019 *Revised accepted: 17 June 2019*

Abstract

Purpose: *To investigate the mechanism by which natural killer (NK) cells are compromised by infection with Echinococcus multilocularis in patients with alveolar echinococcosis (AE).*
Methods: *NK cells from AE patients and healthy individuals were measured by flow cytometry and quantitative real-time polymerase chain reaction (PCR) to identify the frequency of different types of NK cells and assess their function. E. multilocularis cyst fluid (EMF) was applied to human monocytic leukaemia cells (THP-1 cells) to assess its effect on their differentiation. In a co-culture system with NK and EMF-THP-1 cells, the function of NK cells were analyzed by enzyme-linked immunosorbent assay (ELISA) with or without antibody against KIR2DL1.*
Results: *Blood from AE patients had fewer CD56low NK cells ($p < 0.01$) with decreased production of IFN-γ and granzyme B due to the elevated expression of KIR2DL1 ($p < 0.001$). Treatment of THP-1 cells with EMF induced a tolerogenic phenotype upon activation. Incubation of these EMF-THP-1 cells with NK cells isolated from AE patients significantly impaired the cytotoxic function of NK cells, but this effect was largely blocked by an anti-KIR2DL1 antibody ($p < 0.001$).*
Conclusion: *E. multilocularis modulates infection macrophages to induce NK cell dysfunction via interaction with KIR2DL1. These results provide a new insight into the mechanisms of parasitic infection-induced dysfunction of NK cells, and may be helpful for the development of therapeutic strategies for the treatment of alveolar echinococcosis.*

Keywords: *Echinococcus multilocularis, Chronic helminthic diseases, Macrophages, NK cells, Killer-cell immunoglobulin-like receptors*

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INTRODUCTION

Alveolar echinococcosis (AE) is a group of diseases induced by the larvae of the parasitic tapeworm *Echinococcus multilocularis* (*E. multilocularis*) [1,2]. Propagation of *E. multilocularis* in human hosts evokes both adaptive and innate immune responses which result in extensive infiltration of blood lymphocytes into the pathogen-induced lesions [3,4]. Without appropriate treatment, the mortality rate within the followed 10 years of infection is

approximately 75 - 94 % [5]. However, host immunity is always insufficient to eliminate *E. multilocularis*. Antigens associated with the larvae may subvert host immune responses through mechanisms including inhibiting chemotaxis of neutrophils, impeding maturation of dendritic cells, or interfering with dendritic cell function [6,7]. Overall, evidence suggests that the human host exhibits a prominent tolerant status during AE.

Alveolar echinococcosis first affects the liver which is the source of many of the cells of the innate immune system, such as macrophages and natural killer (NK) cells [8]. However, the mechanism by which *E. multilocularis* infection compromises NK cells is unknown. Recent evidence showed that NK cells express a series of activating receptors or inhibitory receptors to activate immune responses or promote self-tolerance, respectively [9]. Killer-cell immunoglobulin-like receptors (KIRs) are primarily expressed on the cell surface of NK cells, and also on a small number of T cells [10]. These receptors can interact with major histocompatibility (MHC) class I molecules to regulate the “master switch” of NK cells. A potential relationship between macrophages and NK cells has been suspected in several diseases or immune disorders [11-13]. During *E. multilocularis* infection, macrophages are ideally poised, spatially and temporally, to contact the parasite [14]. Based on this background, it was hypothesized that infection by *E. multilocularis* altered macrophages, and in turn, had an impact on NK cells.

In the present study, the interaction between macrophages and NK cells during *E. multilocularis* infection was explored.

METHODS

Patients and healthy subjects

Blood samples were collected from 15 patients (age: 45 year ± 10.1) with *E. multilocularis* infection in the later phase, without progressive symptoms, and from 10 healthy adults (age: 43.0 ± 7.2 years). The later stage was diagnosed by PNM system (P = parasitic mass in the liver, N = involvement of neighbouring organs, and M = metastasis) according to a clinical classification for AE (WHO) [15]. The study was approved by the ethics committee of The First Affiliated Hospital of Xinjiang Medical University (approval no. XST2017357). and conducted according to the principles of Declaration of Helsinki [16]. All participants provided written informed consent.

Cell culture

Human monocytic leukaemia cell line THP-1 was purchased from American Type Culture Collection (ATCC, Manassas, Virginia, USA) and cultured in RPMI 1640 medium (Thermo Fisher Scientific, Inc., Waltham, MA, USA) supplemented with 10% fetal bovine serum (FBS, Gibco; Thermo Fisher Scientific, Inc., Waltham, MA, USA), 100 mg/mL penicillin, and 100 mg/mL streptomycin (Thermo Fisher Scientific, Inc) at 37 °C in a 5 % CO_2 cell incubator. Electromotive force was collected from established fluid-filled hydatid cysts by crushing and centrifugation. Normal human serum diluted to the same protein concentration served as control. Differentiation of THP-1 cells was induced by 100 ng/mL phorbol myristate acetate (PMA; Sigma-Aldrich; Merck KGaA) in the presence or absence of EMF.

Isolation of PBMCs from blood and the purification of NK cells

Peripheral blood mononuclear cells were enriched by Ficoll-Isopaque (GE Healthcare, Finland). The intermediate layer was harvested and washed three times with phosphate buffer (PBS) containing 3 % FBS. The harvested and washed cells were used either for fluorescence-activated cell sorting (FACS) analysis or further NK cell purification with an NK cell isolation kit (Miltenyi Biotec, Germany) according to the manufacturer’s instructions. Cells with CD3-CD14-CD56 markers (NK cells) of > 95 % purity for subsequent experiments were selected.

Flow cytometry

Peripheral blood mononuclear cells were stained with a mixture of anti-CD16 (BD Biosciences, San Jose, CA, USA), anti-CD3 (BD Biosciences), and anti-CD56 (BD Biosciences) antibodies. For *in vitro* analysis of IFN-γ produced by NK cells, cells were stimulated with Leukocyte Activation Cocktail (BD Biosciences) at 37 °C. In addition to staining the cells with surface makers, they were fixed, made permeable with Cytofix/Cytoperm Buffer (BD Biosciences), and stained with anti-IFN-γ (BD Biosciences). After washing three times with PBS, the cells were analyzed with flow cytometry.

Quantitative real-time polymerase chain reaction

Total RNA was extracted from purified NK cells in PBMCs or activated THP-1 cells with the TRIzol reagent (Thermo Fisher Scientific, Inc.). Complementary DNAwas prepared using reverse

transcriptase (Thermo Fisher Scientific, Inc.). The primers used to detect mRNA levels are shown in Table 1.

In vitro co-culture model

THP-1 cells were treated with EMF as described above (EMF-THP-1 cells), and were co-cultured with NK cells isolated from AE patients. Specifically, 10^5 EMF-THP-1 cells were washed and plated in a 96-well V-bottom plate. Isotype or anti-KIR2DL1 antibodies (Biolegend, San Jose, CA, USA) were added to the wells at a concentration of 10 μg/mL. Phorbol-12-myristate-13-acetate was added during the last 5 h of the 24-h co-culture to activate NK cells.

Assessment of cytokine production

The supernatant of THP-1 culture was collected for cytokine detection. The levels of interleukin (IL)-1β, IL-6, IL-10, and transforming growth factor (TGF)-β1 in the culture supernatant were analyzed by the corresponding ELISA kits (Cusabio, Wuhan, China). Levels of interferon (IFN)-γ and tumor necrosis factor (TNF)-α levels in the supernatants of co-culture system were analyzed by the corresponding ELISA kits (Cusabio). All the procedures were performed according to the manufacturer's introduction. Absorbance values were acquired by a microplate reader.

Statistical analysis

Data are presented as mean ± SEM. All data were processed by Graphpad Prism 5.0 software (USA). Significance difference between two groups was determined with Mann–Whitney U test or among multiple groups by one-way ANOVA. A two-tailed value of $p < 0.05$ was considered statistically significant.

RESULTS

E. multilocularis infection impaired NK cell function by increasing the expression of KIR2DL1. Natural Killer cells from the blood of patients infected with *E. multilocularis* functioned abnormally and showed increased expression of KIR2DL1 compared to cells from blood of non-infected controls

To investigate the role of NK cells in *E. multilocularis* infection, the function of NK cells in peripheral blood from infected patients during the chronic phase of AE with NK cells from healthy adults were analyzed. The percentage of cells producing IFN-γ in the populations that had high, intermediate, or diminished expression of CD56 ($CD56_{high}$, $CD56_{int}$, or $CD56_{dim}$, respectively) was determined. As shown in Figure 1A, almost 40 % of the NK cells in the blood from the healthy cohort produced IFN-γ after activation, while there were significantly fewer IFN-γ-producing NK cells in blood from the infected patients ($p < 0.05$). Infected patients also had markedly fewer $CD56^{int}$ NK cells among the cells that did produce IFN-γ ($p < 0.05$).

Next, the levels of several markers for activation (IFN-γ, granzyme B, and CD69) or inhibition (KIR2DL1 and NKG2A) of NK cells were analyzed. From the results of quantitative real-time PCR, we conclude that expression of IFN-γ, granzyme B, and CD69 were decreased, but KIR2DL1 and NKG2A were increased in the NK cells from AE patients compared to healthy patients (Figure 1B). Based on these results, it was conclude that the function of NK cells from *E. multilocularis*-infected patients was impaired and that the expression of KIR2DL1 was increased when compared to those from healthy individuals.

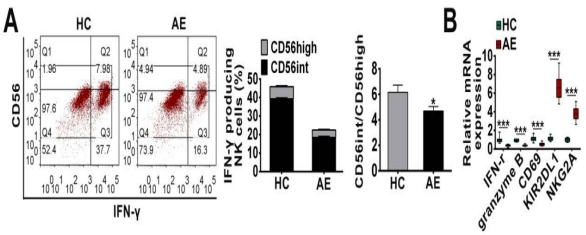

Figure 1: The functional changes of natural killer (NK) cells from alveolar echinococcosis (AE) patients. (A) Typical response of NK cells to activation. The frequency of $CD56_{high}$ and $CD56_{int}$ IFN-γ + NK cells on CD56 cells. Ratio of $CD56^{int}/CD56^{high}$ NK cells. (B) Expression of IFN-γ, granzyme B, CD69, KIR2DL1, and NKG2A in NK cells isolated from peripheral blood mononuclear cells, acquired from quantitative real-time PCR analysis. (HC, healthy control patients; data are presented as mean ± SEM (n = 10 to 15); *$p < 0.05$; ***$p < 0.001$)

Effect of EMF treatment on the function of macrophages and their phenotype

There were significantly lower levels of the pro-inflammatory cytokines IL-1β and IL-6 levels in the THP-1 cells cultured with EMF than those cultured with serum from normal humans, but IL-10 and TGF-β1 levels were greater in the EMF-treated cells (Fig. 2A). Arginase-1, CD206, CD163, and iNOS mRNA were measured in the sediments from the cultures. Based on qRT-PCR, it was concluded that M2 polarized makers—arginase-1, CD206, and CD163—in the EMF-treated cells were present in greater amounts than in the cells treated with serum from

healthy controls, while iNOS expression was not significantly different in the two groups (Fig. 2B). Therefore, EMF altered the differentiation of macrophages, and they tended to differentiate into the M2 phenotype.

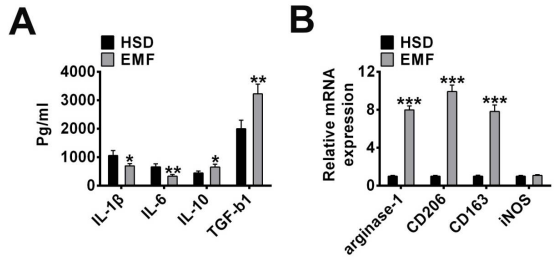

Figure 2: Effect of *E. multilocularis* cyst fluid (EMF) treatment on macrophage function and phenotype. THP-1 cells were induced to differentiate into macrophages by PMA in the presence of human serum dilution (HSD) or EMF. (A) Concentrations of IL-1β, IL-6, IL-10, and TGF-β1 in the culture supernatants as detected by ELISA. (B) Levels of mRNA for arginase-1, CD206, CD163, and iNOS in the pellets of culture were analyzed by quantitative real-time PCR. Data are presented as mean ± SEM; *$p < 0.05$; **$p < 0.01$; ***$p < 0.001$

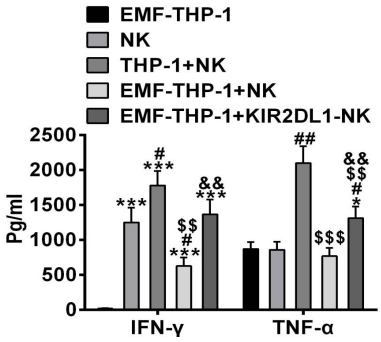

Figure 3: Effect of *E. multilocularis* cyst fluid (EMF)-treated macrophages on NK cell function. NK cells were isolated from alveolar echinococcosis patients by magnetic cell sorting. Macrophages differentiated from THP-1 cells that had been stimulated by EMF were co-cultured with NK cells, and then the NK cells were activated. The IFN-γ and TNF-α production in the supernatant of culture were detected by ELISA. Data are presented as mean ± SEM; *$p < 0.05$; ***$p < 0.001$ (vs EMF-THP-1 group); $^{\#}p < 0.05$; $^{\#\#}p < 0.01$ compared to the NK group; $^{\$\$}p < 0.01$, $^{\$\$\$}p < 0.001$, compared to the THP-1 + NK group; &&, $p < 0.01$ (compared to the EMF-THP-1 + NK group)

EMF-treated macrophages impaired NK cell function via KIR2DL1

Culture supernatants from EMF-THP-1 + NK cohort had significantly lower levels of IFN-γ and TNF-α than those from the THP-1+NK cohort. When NK cells were preincubated with the neutralizing antibody against KIR2DL, the levels of these cytokines were nearly equal to those of the THP-1+NK cohort. Therefore, the macrophages that came into contact with EMF impaired NK cell function via KIR2DL1.

DISCUSSION

In this study, a possible mechanism by which *E. multilocularis* infection results in NK cell dysfunction was examined. It has been well established that several surface receptors on NK cells, including NKG2D, CD28, and CD40L, result in NK cell activation. However, receptors on NK cells that inhibit activation have been less well characterized. In a recent study, it was suggested that KIR-associated HIV-1 sequence polymorphisms improve the binding of KIRs to HIV-infected T-helper cells. It was also noted that the NK cells that had high expression of inhibitory KIRs were markedly less effective against viruses than those with lower expression [17]. In another study with a KIR transgenic murine model, when mice with lymphomas were co-administered anti-KIR and anti-CD20 antibodies, no tolerogenic interaction was observed and the spontaneous cytotoxicity of NK cells was enhanced. Thus, KIRs may be critical for NK cell inhibition in several diseases [18].

In the present study, NK cells isolated from PBMCs of AE patients had high KIR2DL1 expression when compared to healthy individuals, but produced significantly less IFN-γ and granzyme B. In addition, fewer $CD56^{dim}$ NK cells on PBMCs and IFN-γ-producing cells on NK cells were observed in AE patients. Therefore, it seems that long-term *E. multilocularis* infection results in NK cell dysfunction, and is associated with up-regulation of KIR2DL1.

Studies on acute viral hepatitis have revealed a critical role for a macrophage–NK cell interaction in the alleviation of liver injury [19]. Macrophages may affect the function of NK cells by several pathways. For example, they may cause the release of pro-inflammatory cytokines, or they may engage activating or inhibiting receptors through cell-cell contact [20-22]. Thus, an investigation on the effect of EMF on macrophages during differentiation of THP-1 cells in culture was carried out. Addition of EMF to the culture resulted in the decreased levels of pro-inflammatory cytokines IL-1β and IL-6, and increased levels of anti-inflammatory cytokines IL-10 and TGF-β1 in the supernatant. It is possible that EMF caused a shift in macrophage function, from triggering to impeding inflammation. Indeed, other researchers have observed impaired function of macrophages in mice with chronic *E. multilocularis* infection. Impaired function was characterized as the

reduced ability of the macrophages to present antigen as well as down-regulation of CD40 and inhibition of expansion of T cells [23,24].

Dendritic cells isolated from the peritoneal cavities of mice infected with *E. multilocularis* had relatively high expression of TGF-β1, consistent with these results here [25]. In contrast, there was no increase of co-stimulatory molecules in the murine dendritic cells, which may mean they are not effective in conferring immunity [25,26]. In addition, the outer laminated layer of hydatid cysts contributes to the impairment of the pro-inflammatory response against *E. multilocularis* [7]. There may be a type of "epithelioid cells" from a monocytic lineage lining the outer laminated layer of host lesions [27], with cells that produce a large amount of IL-10, as well as strongly expressing MHC class I chain-related molecules, which can interact with NK or activated CD8 + T cells via NKG2D [28]. However, NKG2D is absent in NK cells or CD8 + T cells in AE [28]. Here, this study hypothesized that KIR2DL1 has a crucial role in the crosstalk between macrophages and NK cells in the chronic phase of AE. These results were further verified by the co-culture model as strong evidence that EMF-THP-1 cells compromised the function of NK cells, while blocking KIR2DL1 largely restored the IFN-γ production.

CONCLUSION

The findings of this study show that *E. multilocularis* infection changed the function of macrophages, which induced the expression of KIR2DL1 on NK cells and impaired their function. These results may be helpful for the development of therapeutic strategies for alveolar echinococcosis.

DECLARATIONS

Acknowledgement

This work was supported by a research grant (no. 8156040098) from National Natural Science Foundation of China

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the researchers listed in this manuscript. All liabilities related with the content of this article will be borne by the authors. Yingmei Shao and Tuerganaili Aji designed all the experiments and revised the manuscript. Bo Ran and Tieming Jiang performed the experiments, Wulan Tongbayier and Bayindala wrote the paper.

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