DOI: 10.53469/jcmp.2026.08(03).13

Research Progress on the Mechanism of Th1/Th2 Immune Response Imbalance in Hepatic Multilocular Echinococcosis

Jiawen Deng[1], Li Ren[2,*]

[1]School of Clinical Medicine, Qinghai University, Xining 810003, Qinghai, China
[2]Department of General Surgery, The Affiliated Hospital of Qinghai University, Xining 810001, Qinghai, China
**Correspondence Author*

Abstract: ***Hepatic multilocular echinococcosis (Em) is a parasitic disease caused by infection with Echinococcus multilocularis (Em). Its pathological characteristics are that the lesion is composed of vesicles with a diameter of millimeters, which grow and proliferate in the liver, forming a central liquefaction necrosis and patchy calcification, with liver tissue infiltrating the "lesion" [1]. Research has found that Echinococcus can survive and proliferate in the host's body for a long time, highly dependent on its ability to evade host immune surveillance and attacks. By actively regulating the host's immune response, it gradually forms a series of complex and sophisticated immune regulatory mechanisms [2]. At present, it is believed that the immune evasion response caused by hepatic echinococcosis is closely related to the mutual regulation of Th cells and their secreted cytokines. The research results of Rigano et al. indicate that the imbalance of Th1/Th2 immune response plays an important role in the immune response to hydatid infection [3]. This study elucidates the immune regulatory mechanism of hepatic multilocular echinococcosis, with a focus on the central role of Th cell-mediated immune response imbalance in the occurrence and development of the disease.***

Keywords: Multilocular echinococcosis, Immune microenvironment, Immune regulation, Parasitic immunity**.**

1. Introduction

Alveolar echinococcosis is a zoonotic disease caused by infection with multilocular echinococcosis. Adults parasitize canids and infect humans orally after infecting the environment with insect eggs [4]. After years of prevention and control, the prevalence rate in China has declined, but the epidemic situation in Xinjiang, Qinghai, Xizang and other places is still serious [5]. This pathogen originates in the liver, with invasive growth of vesicles that can damage liver tissue and metastasize to other organs. Due to its malignant growth pattern, it is known as "worm cancer" [6,7]. Parasites actively regulate host immunity to form escape mechanisms [2]. Elucidating the immune microenvironment constructed locally in the liver is of great significance for revealing the characteristics of "insect cancer" and developing new prevention and treatment strategies.

2. The Manifestation of Th1/Th2 Immune Response Imbalance in Hepatic Multilocular Echinococcosis

During the infectious process, the T cell lineage plays a dominant role in orchestrating the transition of immune responses. In the early stage of infection, the immune profile is predominantly characterized by a Th1-type response. This is marked by a significant upregulation of interferon-gamma (IFN-γ) expression, which serves as a key cytokine driving cellular immunity. Elevated IFN-γ levels activate macrophages, enhancing their effector functions. These activated macrophages subsequently produce substantial amounts of reactive oxygen species (ROS) and nitric oxide (NO), both of which possess potent microbiicidal and cytotoxic properties capable of directly damaging pathogens. Thus, the early Th1-polarized response, mediated through IFN-γ and downstream macrophage activation, constitutes a critical front-line defense mechanism against invading parasites [8,9]; In the later stages of infection, the immune response shifts toward a predominant Th2-type profile. $CD4^+$ T lymphocytes, also known as helper T cells, can be functionally categorized into two major subgroups: Th1 and Th2 cells. The Th1 subset primarily secretes interferon-gamma (IFN-γ), which plays a central role in promoting cellular immunity, such as activating macrophages and enhancing cytotoxic T cell responses. In contrast, the Th2 subset mainly produces interleukin-4 (IL-4), a cytokine that directs humoral and allergic-type immune reactions, including eosinophil activation, IgE production, and alternative macrophage polarization, thereby modulating the anti-parasitic immune response. This Th2-biased environment often supports parasite persistence and is associated with chronic infection outcomes [10-12]. Multi locular echinococcosis infection actually induces a Th1/Th2 mixed immune pattern, and the dynamic balance of the two jointly affects the infection process and outcome [13]. The dynamic changes and immunological significance of $CD4^+$ T cell-mediated Th1/Th2 immune response during multilocular echinococcosis infection. Parasites regulate the Th1/Th2 balance to form an immune microenvironment that is conducive to their own survival; In the early stage of infection, Th1 response is predominant, and anti infection effects are exerted through effector molecules such as IFN - γ; In the late stage of infection, there is a shift towards Th2 response, which is associated with the chronicity of the disease. Th1 and Th2 cells each have their own focus in anti infection, while multilocular echinococcosis infection induces a mixed immune response pattern, whose dynamic balance profoundly affects the infection process and outcome.

3. The Pathological Impact of Th1/Th2 Imbalance on Disease Progression

Both experimental models and clinical observations have

consistently demonstrated that substantial recruitment of T lymphocytes occurs at the site of multilocular echinococcosis infection. Notably, among the infiltrating immune cells, $CD4^+$ T cells show a marked and significant increase in number, highlighting their prominent role in the local immune response to the parasite [14,15]. These infiltrating T cells exhibit a high degree of functional heterogeneity, encompassing both activated effector states that contribute to anti-parasitic immunity and regulatory or exhausted phenotypes that promote immunosuppression. Together, these divergent T-cell subsets contribute to the formation of a complex and dynamically evolving immune microenvironment at the infection site. A key mechanism underlying the establishment of chronic infection is the progressive dysfunction of T cells, primarily characterized by exhaustion and anergy. Under conditions of persistent antigen exposure, T cells gradually lose their effector capacities, upregulate inhibitory receptors such as PD-1 and TIM-3, and become increasingly unresponsive to antigenic stimulation, thereby compromising the host's ability to clear the pathogen [16-19]. This dysfunction impairs immune clearance, facilitating long-term parasite immune escape and disease progression. T cells are extensively recruited at infection sites in both experimental models and patient lesions, exhibiting a heterogeneous mix of activated and suppressed states that shape a dynamic immune microenvironment. T cell exhaustion and anergy—characterized by loss of effector function and upregulated inhibitory receptors—are key drivers of chronic infection, enabling immune evasion and disease advancement. These insights underscore the central role of T-cell responses in multilocular echinococcosis immunopathology and support therapeutic strategies aimed at restoring T-cell function.

4. The Role of Key Immune Cells in Th1/Th2 Imbalance

NKT cells represent a distinct and important immune regulatory subpopulation that has garnered considerable attention in the field of anti-tumor immunology due to their unique ability to rapidly produce cytokines and bridge innate and adaptive immunity. However, their specific functions and mechanistic contributions in the context of parasitic infections remain poorly defined and represent a significant gap in current immunological understanding [20]. NKT cells can be rapidly activated during the early phase of infection, responding to pathogenic signals by secreting a diverse array of cytokines—including interferon-gamma (IFN-γ), interleukin-4 (IL-4), interleukin-10 (IL-10), and interleukin-17 (IL-17). This prompt cytokine release enables NKT cells to modulate the local immune milieu, thereby effectively bridging the innate and adaptive arms of the immune system and shaping subsequent antigen-specific responses [21]. The intensity of multilocular echinococcosis infection significantly influences the phenotypic profile of NKT cells. Under conditions of low to moderate infection, $CD8^+$ NKT cells become the predominant subset, suggesting their potential involvement in mediating immune clearance of the parasite. In contrast, during high-intensity infection, there is a marked increase in double-negative (DN) NKT cells. This subset may contribute to parasite survival by suppressing the proliferation and function of $CD4^+$ T cells in a cell-contact-dependent manner, thereby promoting an environment conducive to immune escape and chronic infection [22,23]. Activated NKT cells exert anti-infective effects both directly and indirectly, primarily through the rapid secretion of a broad spectrum of cytokines, which can enhance the effector functions of other immune cells and contribute to pathogen control [24]. However, parasites have evolved strategies to evade NKT-cell surveillance. For instance, some parasites release specific lipid-based molecules that interfere with CD1d-mediated antigen presentation, thereby inhibiting the recognition and activation of NKT cells. Alternatively, parasites can skew NKT-cell responses toward a Th2-polarized profile by inducing the secretion of cytokines such as IL-4, IL-10, and IL-17. This shift promotes an immunosuppressive microenvironment that favors parasite survival and chronic infection [25,26]. The mechanism of NKT cells in parasitic infection immunity and their dual role in the infection process. NKT cells participate in the anti parasitic immune response through early activation and cytokine secretion, but can also promote immune suppression through functional imbalance or phenotype transformation under high infection conditions. At the same time, parasites can escape the immune surveillance of NKT cells by interfering with antigen presentation or inducing immune shifts.

5. Conclusions and Prospects

This review systematically elucidates the core mechanisms and pathological effects of Th1/Th2 immune response imbalance in hepatic multilocular echinococcosis. Multi locular Echinococcus actively regulates the differentiation and function of $CD4^+$ T cells, inducing a shift from early Th1 immune response to late Th2 immune response, and forming an immune tolerant microenvironment conducive to parasite survival. Th1/Th2 imbalance not only weakens the host's ability to resist infection, but also promotes disease chronicity and invasive progression through T cell depletion and abnormal activation of inhibitory immune cells (such as regulatory T cells and NKT cells). Key immune cells, such as NKT cells, play a dual role in infection, participating in early immune clearance and transforming into "accomplices" of immune suppression under parasitic escape mechanisms. These findings reveal the pivotal role of Th1/Th2 imbalance in immune escape of multilocular echinococcosis, providing an immunological basis for understanding the "parasite cancer" characteristics of the disease.

Fund Project

(1) Qinghai Provincial Science and Technology Program Project, No.2019-ZJ-7031.

(2) 2023 Qinghai Province "Kunlun Talent" Action Plan Project (Qing Talent Document No. [2024]1).

References

[1] Becce F, Pomoni A, Uldry E, et al. Alveolar echinococcosis of the liver: diffusion-weighted MRI findings and potential role in lesion characterisation [J]. European Journal of Radiology, 2014, 83(4): 625-631.

[2] Sacks D, Sher A. Evasion of innate immunity by parasitic protozoa [J]. Nature Immunology, 2002, 3(11): 1041-1047.
[3] Riganò R, Buttari B, De Falco E, et al. Echinococcus granulosus-specific T-cell lines derived from patients at various clinical stages of cystic echinococcosis [J]. Parasite Immunology, 2004, 26(1): 45-52.
[4] Graeter T, Kratzer W, Oeztuerk S, et al. Proposal of a computed tomography classification for hepatic alveolar echinococcosis [J]. World Journal of Gastroenterology, 2016, 22(13): 3621-3631.
[5] Han Shuai, Li Shizhu Current situation and key prevention and control measures of echinococcosis in China [J]. Chinese Journal of Parasitology and Parasitic Diseases, 2025, 43 (1): 1-5
[6] Jensenius M, Mørch K, Yaqub S, et al. Alveolar echinococcosis [J]. Tidsskrift for Den Norske Laegeforening: Tidsskrift for Praktisk Medicin, Ny Raekke, 2024, 144(10).
[7] Gauthiez E, Uldry E, Coste A T, et al. [2023 update on alveolar echinococcosis] [J]. Revue Medicale Suisse, 2023, 19(822): 708-712.
[8] Rodrigues V, Cordeiro-da-Silva A, Laforge M, et al. Impairment of T cell function in parasitic infections [J]. PLoS Neglected Tropical Diseases, 2014, 8(2): e2567.
[9] Bellanger A P, Mougey V, Pallandre J R, et al. Echinococcus multilocularis vesicular fluid inhibits activation and proliferation of natural killer cells [J]. Folia Parasitologica, 2017, 64: 2017.029.
[10] Mosmann T R, Cherwinski H, Bond M W, et al. Two types of murine helper T cell clone. I. Definition according to profiles of lymphokine activities and secreted proteins [J]. Journal of Immunology, 1986, 136(7): 2348-2357.
[11] Li Zhi, Yang Tingting, Xu Weijia Research progress on the relationship between CD4+T lymphocytes and autoimmune diseases [J]. International Journal of Laboratory Medicine, 2012, 33 (23): 2891-2894
[12] Romagnani S. T cell subpopulations [M]//Bergmann K C, Ring J. Chemical immunology and allergy: Vol. 100. S. Karger AG, 2014: 155-164.
[13] Wen H, Vuitton L, Tuxun T, et al. Echinococcosis: advances in the 21st century [J]. Clinical microbiology reviews, 2019, 32(2): e00075-18.
[14] Ab F. Suppression of T cell responses in the tumor microenvironment [J]. Vaccine, 2015, 33(51).
[15] Lodygin D, Flügel A. Intravital real-time analysis of T-cell activation in health and disease [J]. Cell Calcium, 2017, 64: 118-129.
[16] Zhang C, Lin R, Li Z, et al. Immune exhaustion of T cells in alveolar echinococcosis patients and its reversal by blocking checkpoint receptor TIGIT in a murine model [J]. Hepatology, 2020, 71(4): 1297-1315.
[17] Mejri N, Gottstein B. Intraperitoneal echinococcus multilocularis infection in C57BL/6 mice affects CD40 and B7 costimulator expression on peritoneal macrophages and impairs peritoneal T cell activation [J]. Parasite Immunology, 2006, 28(8): 373-385.
[18] Hou Xinling, Li Liang, Li Linghui, etc The effect of cysticercosis infection on immune exhaustion of CD8+T cells in the spleen of mice [J]. Chinese Journal of Schistosomiasis Control and Prevention, 2020, 32 (6): 591-597604
[19] Vuitton D A, Bresson-Hadni S, Laroche L, et al. Cellular immune response in Echinococcus multilocularis infection in humans. II. Natural killer cell activity and cell subpopulations in the blood and in the periparasitic granuloma of patients with alveolar echinococcosis [J]. Clinical and Experimental Immunology, 1989, 78(1): 67-74.
[20] Kriegsmann K, Kriegsmann M, von Bergwelt-Baildon M, et al. NKT cells - New players in CAR cell immunotherapy? [J]. European Journal of Haematology, 2018, 101(6): 750-757.
[21] Robertson F C, Berzofsky J A, Terabe M. NKT cell networks in the regulation of tumor immunity [J]. Frontiers in Immunology, 2014, 5: 543.
[22] Wei G, Tabel H. Regulatory T cells prevent control of experimental african trypanosomiasis [J]. Journal of Immunology, 2008, 180(4): 2514-2521.
[23] Antúnez M I, Cardoni R L. Trypanosoma cruzi: the expansion of NK, T, and NKT cells in the experimental infection [J]. Experimental Parasitology, 2004, 106(3-4): 85-94.
[24] Yang J Q, Zhou Y, Singh R R. Effects of invariant NKT cells on parasite infections and hygiene hypothesis [J]. Journal of Immunology Research, 2016, 2016: 2395645.
[25] Mallevaey T, Fontaine J, Breuilh L, et al. Invariant and noninvariant natural killer T cells exert opposite regulatory functions on the immune response during murine schistosomiasis [J]. Infection and Immunity, 2007, 75(5): 2171-2180.
[26] Zamora-Chimal J, Hernández-Ruiz J, Becker I. NKT cells in leishmaniasis [J]. Immunobiology, 2017, 222(4): 641-646.