Chronic Toxoplasmosis Modulates the Induction of Contact Hypersensitivity by TNCB in Mouse Model

Zhaoshou Yang, Hye-Jin Ahn, Ho-Woo Nam*
Department of Parasitology, College of Medicine, The Catholic University of Korea, Seoul 06591, Korea

Abstract: Mouse models of chronic toxoplasmosis and atopic dermatitis (AD) were combined to clarify the effect of opportunistic Toxoplasma gondii infection on the development of AD. AD was induced as a chronic contact hypersensitivity (CHS) with repeated challenge of 2,4,6-trinitro-1-chlorobenzene (TNCB) on the dorsal skin of mice. TNCB induced skin thickness increases in both normal and toxoplasmic mice. The changing patterns were different from the sigmoidal which saturated at 20 days in normal mice to the convex saturated at 12 days in toxoplasmic mice with the crossing at 18 days. Compared to normal mice, toxoplasmic mice presented CHS more severely in earlier times and then moderately in later times. These data suggest that host immune modification by T. gondii infection enhances CHS in early times of atopic stimulation but soothes the reaction of CHS in later times in mouse model.

Key words: Toxoplasma gondii, toxoplasmosis, contact hypersensitivity, atopic dermatitis, animal model
Ity of dermatitis and more rapid hair re-growth in T. gondii-infected mice. Control mice mostly exhibited severe symptoms of dermatitis including hemorrhage, edema, excoriation/erosion, and dyne/scaling, while T. gondii-infected mice presented with mild or moderate clinical skin severity (Fig. 2). These differences may derive from the immune response of mice infected with T. gondii and CHS mice model induced by TNCB. At the acute phase of Me49 infection, T-helper (Th) 1-type immune response is dominantly activated [2]. The activation of CD4+ T cell can enhance the inflammation and dissemination of T. gondii in mouse body including the brain [7]. At the acute phase of CHS induced by TNCB, Th1-type immune response is dominantly activated. Meanwhile, T. gondii induce the activation of signal transducer and activator of transcription 6 (STAT6) [8], which play a critical role in the induction phase of CHS [9]. From acute phase to chronic phase of Me49 infection, the immune responses of host shift from Th1-type to Th2-type dominant response accompanying with stronger CD8+ T cell responses [2]. In addition, CD8+ T cell responses control the dissemination of T. gondii. Accompanying with the other responses of host immunity, T. gondii is transformed from fast growing tachyzoites to slowly growing bradyzoites and eventually forms tissue cysts [2]. Meanwhile, T cell function was impaired by T. gondii infection [3]. At the acute phase of CHS induced by TNCB, Th1-type immune response is dominantly activated [4]. While at the chronic phase of CHS induced by TNCB, the immune responses of host shift from Th1-type to a Th2-type response.

In the present study, mice were in the chronic phase of Me49 infection. At the acute phase of CHS induced by TNCB,
the stronger CD4+ T cell activation, Th1-type response, enhances the inflammation by *T. gondii*. The immune responses of *T. gondii* inflammation [10], such as IL-4 independent activation of STAT6, contribute to the steep increment of dorsal skin under which there are plenty of lymph organs preferred to be infected by *T. gondii*. At chronic phase of CHS induced by TNCB, the immune responses at the chronic phase of Me49 infection, in particular CD8+ T cell activation and impairment of T cell function may have an immunosuppressive effect on the clinical severity of AD-like skin lesions.

Taken together, the preliminary data has showed BALB/c mice in the chronic phase of Me49 infection are sensitive to TNCB biphasically but resistant to AD-like skin lesions induced by TNCB. These results will hopefully facilitate the understanding of the effect of autoimmune diseases on those *T. gondii*-infected population.

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**REFERENCES**

1. Yang Z, Cho PY, Ahn SK, Ahn HJ, Kim TS, Chong CK, Hong SI, Cha SH, Nam HW. A surge in the seroprevalence of toxoplasmosis among the residents of islands in Gangwva-gun, Incheon, Korea. Korean J Parasitol 2012; 50: 191-197.
2. Hunter CA, Sibley LD. Modulation of innate immunity by *Toxoplasma gondii* virulence effectors. Nat Rev Microbiol 2012; 10: 766-778.
3. Rodrigues V, Cordeiro-da-Silva A, Laforge M, Ouaisi A, Akharid K, Silvestre R, Estaquier J. Impairment of T cell function in parasitic infections. PLoS Negl Trop Dis 2014; 8: e2567.
4. Harada D, Takada C, Tsukumo Y, Takaba K, Manabe H. Analyses of a mouse model of the dermatitis caused by 2,4,6-trinitro-1-chlorobenzene (TNCB)-repeated application. J Dermatol Sci 2005; 37: 159-167.
5. Subauste C. Animal models for *Toxoplasma gondii* infection. Curr Protoc Immunol 2012; Chapter 19: Unit 19.3. 1-23.
6. Matsumoto K, Mizukoshi K, Oyobikawa M, Ohshima H, Tagami H. Establishment of an atopic dermatitis-like skin model in a hairless mouse by repeated elicitation of contact hypersensitivity that enables to conduct functional analyses of the stratum corneum with various non-invasive biophysical instruments. Skin Res Technol 2004; 10: 122-129.
7. Kamerkar S, Davis PH. *Toxoplasma* on the brain: understanding host-pathogen interactions in chronic CNS infection. J Parasitol Res 2012; 2012: 589295.
8. Ahn HJ, Kim JY, Nam HW. IL-4 independent nuclear translocalization of STAT6 in HeLa cells by entry of *Toxoplasma gondii*. Korean J Parasitol 2009; 47: 117-124.
9. Yokozeki H, Ghoreishi M, Takagawa S, Takayama K, Satoh T, Katayama I, Takeda K, Akira S, Nishioka K. Signal transducer and activator of transcription 6 is essential in the induction of contact hypersensitivity. J Exp Med 2000; 191: 995-1004.
10. Melo MB, Jensen KD, Saeij JP. *Toxoplasma gondii* effectors are master regulators of the inflammatory response. Trends Parasitol 2011; 27: 487-495.
