

Review articles

Toxoplasma gondii and mast cells

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ABSTRACT. Mast cells, discovered by Paul Burnet over one century ago, have been long recognized only as inductors of IgE-dependent allergic diseases (allergy of type I, Th2 lymphocytes dependent). However, numerous recent studies have indicated that they play an essential role in many other immunological and non-immunological processes. Infection with *Toxoplasma gondii* elicits the induction of a strong cell-mediated immunity characterized by a highly-polarized Th1 response, which can protect against allergy. Knowledge of the contribution of mast cells to *Toxoplasma* invasion is still limited, and the present article discusses aspects of the relationship between mast cells and *T. gondii*.

Key words: mast cells (MCs), *Toxoplasma gondii*

Mast cells

Mast cells (Mastzellen) were described at the end of 19th century by a medical student, Paul Burnet, the father of modern immunology. Their name derives from a German word "*mast*" (fattening), from the numerous granules that fill them and which were believed to feed surrounding cells [1]. Mast cells (MCs) are primitive immune cells that appeared early in evolution and have since evolved solely in invertebrates into multifunctional cells taking part in both protective and pathological processes [2]. The huge variety of bioactive compounds released by these cells and the presence of numerous cell receptors within them represent the basis for their flexible nature. Mast cells surround the blood vessels and nerves within most tissues, such as the skin, the mucosa of the respiratory and digestive tracts, and the conjunctiva.

The best known function of mast cells is the induction of type I allergic processes, mediated by an allergen-specific IgE antibody. In the primary phase, the cells are sensitized to the antigen by being bound to monomeric IgE via FcεR1 receptors, so that upon the second contact with the same antigen, the cell undergoes direct activation and releases a battery of mediators responsible for the type I allergic reactions [3,4].

Mast cells are crucial effector cells in host defence against parasite infections [reviewed shortly in 5]. They have a potent arsenal to combat infections, including antimicrobial peptides, proteases, chemokines and cytokines for the recruitment and activation of other immune cells, and control of the infection [6]. Although data on the role of mast cells in *Toxoplasma gondii* invasion is still very limited, some information is presented below.

Toxoplasma gondii

Toxoplasma gondii is a widespread protozoan parasite that infects all species of endothermic animals and humans with a high prevalence. The biological success of *T. gondii* is associated with the formation of a specific relationship between the parasite and host cells leading to the establishment of a latent, chronic infection. Although *T. gondii* primary infection occurs asymptomatically in most immunocompetent hosts, the quick-replicating tachyzoites transform into slow-replicating, "dormant" forms, bradyzoites, at the end of the acute infection stage under the pressure of specific Th1 lymphocyte-dependent cellular immunity. The bradyzoites, enclosed in tissue cysts, preferentially occupy the brain, musculature and eyes. In the late 1980s, IFN-γ produced by CD4+ and CD8+ T cells was identified as the major mediator of protection

against *T. gondii.* Cytotoxic CD8+ lymhocytes kill host cells infected with the parasite, whereas CD4+ cells predominantly regulate the immune response to *T. gondii* [7].

T. gondii is well known as a potent type 1 cytokine inducer, and while these cytokines are required by the host to survive infection, their overproduction may lead to pathology and the death of the host [8]. The survival of both the host and the parasite is associated with the conversion of tachyzoites into dormant bradyzoites and their encystation in tissues under the pressure of host immune response. The mechanisms that control the tachyzoite replication in the infected tissues involve both an innate acute inflammatory response and an antigen-specific inflammatory response. MCs have been regarded as powerful cells, due to their effector and regulatory functions [4].

Leukotrienes (LTBs) are biological mediators which are biosynthesized *de novo* under the influence of 5-lipooxygenase (5-LO) in mast cells from an arachidonic acid precursor, liberated from cell membrane phospholipids of allergen-activated mastocytes. After incubation with *Toxoplasma gondii*, MCs degranulate and release LTB4, which damages *T. gondii* tachyzoites [8]. The generation and release of LTB4 can be inhibited by 5-LO specific inhibitors.

Early research on mast cells in *T. gondii* invasion suggested that these cells play an essential role. Using a rodent model (*Calomys callosus*) highly susceptible to toxoplasmosis, it was found that the experimental infection was associated with an increase in the level of mastocytes and their activation [9]. Further detailed *in vivo* and *in vitro* studies revealed a significant influx of mast cells into the peritoneal cavity after 1 h of intraperitoneal infection, but this was followed by a progressive decrease in the number of mastocytes 48 hours later, with the number eventually being significantly lower than in control animals. A remarkable increase in the influx of neutrophils toward the peritoneal cavity of the infected animals took place 12 h post-infection, after an intensive mast cell degranulation process [10]. Morphological changes of MCs from infected animals suggested that they had become degranulated: fusion of the cytoplasmic granules, intracytoplasmic channels and cytoplasmic granules with flocculent material, plasma membrane rupture and the presence of granule contents in the extracellular environment. Tachyzoites were found in granular content secreted by the mast cells. Extracellular parasites appeared to be destroyed during the interaction with mast cells. This data suggests that mast cells play an important role in the acute inflammatory response against *T. gondii*.

T. gondii infection is acquired by an oral route, and mucosal immunity, also including mast cell reactivity plays a predominant role in the protection of the host. Knockout W/W^v (mast cells-deficient) mice succumbed within 15 days of infection with the relatively low-virulent ME49 *T. gondii* strain. The speed of the death of the animals was correlated with increased IFN-γ and IL-2 levels, suggesting the presence of a delayed Th1 response [11].

Earlier studies identified serglycin proteoglycan as an important factor in the storage and activity of mast cell proteases. Although severely reduced levels of cell-bound mast cell proteases were noted in serglycin-deficient mice, an ongoing *T. gondii* infection up-regulated release of active MC proteases in both serglycin-deficient and wild type mice [12], which strongly suggests that the serglycin proteoglycan is only required for the correct storage of proteases in naïve resting MCs but it is not necessary for normal secretion of proteases in response to *T. gondii.* However, further research is required to clarify this issue.

The mediators of activated mast cells may play an important role in modulating acute inflammatory pathogenesis and parasite clearance in *T. gondii* infection. Huang et al. [13] describe the activity of mast cells in mice infected intraperitoneally with the highly virulent *T. gondii* strain and treated with either an MC activator or an MC inhibitor. Having evaluated the inflammation degree in the spleen, liver and mesentery, as well as the parasite burden in the peritoneum and the change in the level of pivotal cytokines (IFN-γ, TNF-α, IL-12p40, IL-4 and IL-10), the authors conclude that the induction or inhibition of mast cells is a key factor determining the fate of the infection and associated immunopathology. In summary, MC stimulators intensified the pathology and increased the parasite load, whereas MC stabilizers improved the pathology and decreased the parasite burden in *T. gondii*-infected mice. Hence, chemical interference with mast cell activity may represent a possible therapeutic approach to the prevention and control of *T. gondii* infection.

To reach the immune-privileged sites of a host, such as the brain, musculature or eye, *Toxoplasma gondii* must pass through the extracellular matrix

(EXM) and cross such biological barriers as the intestine, placenta or brain-blood barrier. Matrix metalloproteinases produced by *T. gondii*-activated mast cells degrade ECM [14] and may contribute to the transfer of mast cell progenitors to the sites of inflammation, and thus, parasite transmigration. Inhibition of the Erk1/2/NFκB signalling pathway might offer a potential tool to control early *T. gondii* infection.

On the other hand, *Toxoplasma gondii* itself inhibits mast cell degranulation by suppressing the mobilization of intracellular Ca^{2+} mediated by C-phospholipase. Inhibition of IgE/Fc-RI signaling persists when the tachyzoite invasion is stopped by cytochalasin D, which suggests the inhibition is mediated by a parasite derived factor secreted into the cell during invasion [15].

Allergic asthma is an inflammatory disorder associated with the intense influx of inflammatory cells to the airway wall driven by the activation of Th2 lymphocytes, mast cells and eosinophils. A large body of epidemiological data shows that respiratory allergy is less frequent in developing than in developed countries, and in people who are extensively exposed to such foodborne microbes as *T. gondii*. The parasite infection was found to inhibit the development of airway inflammation in mice [16]. This effect might be related to the development of a strong Th1 response to the parasite. Another possible mechanism is the action of regulatory T cells. Thoracic lymph node cells taken from mice with chronic toxoplasmosis demonstrated suppressor activity in both *in vitro* and *in vivo* experiments. This effect was found to be related to the presence of high levels of $CD4^{+}Fox^{+}$ cells and TGF-β [17].

Many recent studies clearly indicate that the field of mast cell biology has significantly expanded beyond the boundaries of atopic disorders and anaphylaxis on which it has been historically focused. The abundance of numerous bioactive compounds within activated MCs allows the modulation of many immunological processes, including the immune response to parasites. A considerable body of research indicates that mast cells contribute to susceptibility and systemic inflammation in the course of *T. gondii* invasion.

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