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Review

The roles of galectins in parasitic infections

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ABSTRACT

Galectins is a family of multifunctional lectins. Fifteen galectins have been identified from a variety of cells and tissues of vertebrates and invertebrates. Galectins have been shown to play pivotal roles in host–pathogen interaction such as adhesion of pathogens to host cells and activation of host innate and adaptive immunity. In recent years, the roles of galectins during parasite infections have gained increasing attention. Galectins produced by different hosts can act as pattern recognition receptors detecting conserved pathogen-associated molecular patterns of parasites, while galectins produced by parasites can modulate host responses. This review summarizes some recent studies on the roles of galectins produced by parasitic protozoa, nematodes, and trematodes and their hosts. Understanding the roles of galectins in host–parasite interactions may provide targets for immune intervention and therapies of parasitic infections.

1. Galectins, their expressions and functions

Galectins, a family of lectins that binds *N*-acetyllactosamine-containing glycans, have diverse roles in many cellular processes and are receiving increasing interest as therapeutic targets because of their roles in immune signaling pathways (Farhadi and Hudalla, 2016; Rabinovich and Toscano, 2009). Galectins are widely distributed in organisms from lower invertebrates to mammals. In mammals, galectin family consists of 15 proteins, galectin (Gal)-1 to -15, which can be divided into three groups (prototype, chimera type, and tandem-repeat type) based on their structures (Balan et al., 2010). The prototype group includes Gal-1, -2, -5, -7, -10, -11, -13, and -14, whereas the chimera type only contains Gal-3 that can form homodimers. Both the prototype and the chimera type galectins have a single carbohydrate recognition domain (CRD). The chimera type Gal-3 has an extended N-terminal peptide. The tandem-repeat type includes Gal-4, -6, -8, -9, and -12 and has two non-identical CRDs linked by a short peptide (Unajak et al., 2015). Gal-15, also known as OVGAL11, is a member of the galectin family of secreted beta-galactoside lectins containing a conserved carbohydrate recognition domain and a putative integrin binding domain. It was originally found to be induced in gastrointestinal tissue and secreted into the intestinal lumen in response to infection of a nematode parasite *Haemonchus contortus* in sheep (Dunphy et al., 2000; Gray et al., 2004).

Most galectins are both intracellularly and extracellularly distributed throughout the body of an organism. Extracellular galectins interact with glycans on the cell surface and induce various cellular responses (Elola et al., 2007). Galectins are expressed in many types of immune cells, including monocytes, macrophages (Mφ), dendritic cells (DCs), mast cells, B cells, and T cells (Dhirapong et al., 2009). The ubiquitous expression of galectins in a large number of cell types and tissues dictates their diverse functions in the developmental processes and defense pathways against invading pathogens. Here we briefly summarize the known properties and major functions of galectins and discuss some examples of host and parasite galectins in regulating host-parasite interactions, including host responses to infections of various parasites.

Gal-1, encoded by lectin galactoside binding soluble (LGALS) 1 gene, is a homodimer of 14 kD subunits that belongs to a family of soluble galactoside-binding proteins (Astorgues-Xerri et al., 2014). It binds β-galactosides and is a potent anti-inflammatory and immunoregulatory molecule that plays a role in pathogenesis of various immune/inflammatory diseases (Yang et al., 2008; Zúñiga et al., 2001a). Gal-3 is an important modulator of biological processes and an emerging player in the pathogenesis of various immune/inflammatory diseases (Dumic et al., 2006). Gal-2 and -4 are mainly expressed in the gastrointestinal tract (Sturm et al., 2004; Kim et al., 2013) and are

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found to promote intestinal epithelial wound healing (Paclik et al., 2008). Additionally, Gal-4 plays an important role in mucosal immunity and has been shown to have bactericidal activity (Cao and Guo, 2016). Gal-2 may contribute to the development of gestational disease because the expression level of Gal-2 was decreased in placentas of preeclampsia patients (Hutter et al., 2015). Gal-5 is identified in rat red blood cells and may function in erythropoiesis (Barrès et al., 2010; Skutelsky and Bayer, 1983). Gal-6 is the homolog of Gal-4 and is gut-specific (Gitt et al., 1998). A recent study suggests that Gal-6 also has anti-microbial activity on the skin (Natsuga and Watt, 2016). Gal-7 is expressed in the stratified squamous epithelium of the gut and skin (Nio-Kobayashi, 2017) and is associated with the differentiation and development of pluristratified epithelia (Saussez and Kiss, 2006). Gal-8 is expressed in various organs and tissues (Hadari et al., 2000); it can bind glycans to regulate immune cell functions, including pathogen recognition and cellular adaptive immune and inflammatory responses (Rabinovich and Toscano, 2009). Gal-9, expressed by T cells, eosinophils, endothelial cells, Mφ, DCs, Kupffer cells, vascular endothelial cells, and intestinal epithelial cells, can act as a co-inhibitory receptor inducing cell death via interaction with T cell immunoglobulin and mucin domain–3 (Tim3) (Zhu et al., 2005). Gal-10 is mainly expressed in $CD4^+CD25^+$ regulatory T (Treg) cells, eosinophils, and basophils and plays a role in Treg cell function (Ackerman et al., 1982; Kubach et al., 2007). Gal-11 is expressed in the nucleus and cytoplasm of upper epithelial cells and can be secreted into the mucus of the infected abomasum of animals; it may have functions in proliferation and differentiation of epithelial cells (Dunphy et al., 2000). Gal-12 is expressed mainly in adipose tissue and is required for adipogenic signaling and adipocyte differentiation, suggesting a regulatory function in adipose tissue development (Yang et al., 2004). Gal-13, also known as Placental Protein 13 (PP13) with immunoregulatory activities, is predominantly expressed by the syncytiotrophoblast and is released from the placenta into the maternal circulation (Than et al., 2014). Gal-14 is mainly expressed and released by tissue eosinophils; however, Gal-14 secretion by peripheral blood eosinophils can be induced after *in vitro* activation (Dunphy et al., 2002; Young et al., 2009). Gal-14 release has also been observed in the lungs after allergen challenge (Dunphy et al., 2002). Galectins can be produced by both parasites and their host. Parasite galectin may play an important role in host-parasite interactions (Young and Meeusen, 2004). In summary, galectins are expressed by different types of cells and tissues, have diverse functions, and play important roles in host responses to infections of parasites and other pathogens.

2. Galectins in parasitic infections

Parasites contain a variety of complex carbohydrates on their surfaces, namely glycolipids, glycoproteins, and glycosylated phosphatidylinositol glycolipids (Nyame et al., 2004). Parasite glycoconjugates play important roles in host cell invasion, and specific interactions between host galectins and parasite glycoconjugates are considered to be critical for pathogen recognition (Vasta, 2009). Carbohydrates and glycoconjugates exert pro-inflammatory effects on DCs and elicit pathogen-induced innate immunity and antigen processing (Mascanfroni et al., 2011). Herein we summarized some recent advances in functional roles of host galectins during infections of selected parasitic protozoa, nematodes, and trematodes. We also discussed the potential roles of galectins produced by parasites in modulating host immune responses.

2.1. Galectins in protozoan infections

2.1.1. Galectins in Leishmania major infection

L. major is the pathogen of cutaneous and visceral leishmaniasis. These diseases are associated with inflammation due to production of pro- and anti-inflammatory cytokines such as tumor necrosis factor (TNF)-α, interferon (IFN)-γ, interlukin (IL)-1β, and IL-10 (Mougneau et al., 2011). Gal-3 can act as a danger-associated molecular pattern to facilitate early neutrophil migration to the infected sites, which is beneficial for controlling *Leishmania* infection. After intradermal infection with *L. major* substrain LV39, Gal-$3^{-/-}$ mice showed significantly impaired neutrophil recruitment in the footpads and draining lymph nodes and higher parasite load in the footpads (Bhaumik et al., 2013). In another study, after infection with *L. major* substrain LV39, *Lgals3*$^{-/-}$ mice displays higher frequency of $CD4^+CD25^+Foxp3^+$ Treg cells in draining lymph nodes and significantly enhanced IL-10 production from Treg cells compared to wild-type (WT) mice. Both Treg and T effector cells from *Lgals3*$^{-/-}$ mice show higher expression of Notch1 and the Notch targetted gene Hes-1. Thus, Gal-3 reduces the frequency and function of $CD4^+CD25^+Foxp3^+$ Treg cells during *L. major* infection via modulation of the Notch signaling pathway (Fermino et al., 2013).

2.1.2. Galectins in Perkinsus marinus infection

P. marinus is a protozoan causes “Dermo” disease in the eastern oyster *Crassostrea virginica*. Inside oyster hemocytes, trophozoites can resist oxidative killing, proliferate, and spread throughout the host. Oyster hemocytes recognize *P. marinus* via *C. virginica* galectin (CvGal) that displays four canonical galectin CRDs, a domain organization unlike any known galectin types. CvGal is produced by hemocytes and secreted to the surrounding plasma to recognize various microbial pathogens, unicellular algae, and particularly *Perkinsus* spp. trophozoites. Exposure of *Perkinsus* spp. trophozoites to hemocytes enhances CvGal secretion and binding to the plasma membrane (Tasumi and Vasta, 2007). CvGal may function as a hemocyte surface receptor for the parasite and mediate parasite entry into oyster hemocytes (Feng et al., 2013). Further study shows that CvGal2 from the eastern oyster (*C. virginica*) binds to *P. marinus* trophozoites in a dose-dependent and β-galactoside-specific manner (Feng et al., 2015).

2.1.3. Galectins in Plasmodium spp. infections

Malaria is a serious disease with a spectrum of symptoms, and various galectins have been found to play an important role in host-malaria parasite interaction. Gal-9 concentration in the plasma of patients with acute *Plasmodium falciparum* malaria was significantly increased and correlated with disease severity (Dembele et al., 2016). Mice infected with *P. berghei* ANKA had significantly increased mRNA levels of Gal-9 in the lungs, mediastinal lymph nodes, livers, and spleens (Liu et al., 2016b; Xiao et al., 2016). Further, blockage of galectin-receptor interactions by α-lactose exacerbated *P. berghei* ANKA-induced pulmonary immunopathology (Liu et al., 2016a), indicating that Gal-9 can significantly alter the pathogenic course of murine malaria. Another galectin that can affect malaria infection is Gal-3 that is overexpressed in mice exhibiting symptoms of experimental cerebral malaria (ECM). Gal-3-deficient (gal$3^{-/-}$) mice are partially protected against *P. berghei* ANKA induced ECM (Oakley et al., 2009). Additionally, the lack of Gal-3 significantly reduces *P. yoelii* 17XNL parasitaemia, indicating that Gal-3 can affect *P. yoelii* 17XNL replication or infectivity. However, no differences in parasitaemia between Gal-3-deficient (*Lgals3*$^{-/-}$) and WT mice infected with *P. berghei* ANKA or *P. chabaudi* AS are observed in another study (Toscano et al., 2012), suggesting that Gal-3 may or may not contribute to parasitemia control. The observations of different Gal-3 effects on disease outcomes after infections with *P. berghei* and *P. chabaudi* could be due to variations in both host and parasite genetic background.

2.1.4. Galectins in Toxoplasma gondii infection

T. gondii is an obligate intracellular protozoan parasite that infects virtually all warm-blooded animals and invades many cell types. The disease is usually started with an acute phase accompanied by rapid tachyzoite proliferation, followed by a chronic stage characterized with cyst formation in the central nervous system (CNS) and skeletal muscles (Saouros et al., 2005; Yap and Sher, 1999).