Int J Pharm Bio Sci 2016 July ; 7(3): (B) 337 - 342

Review Article **Immunobiology**

International Journal of Pharma and Bio Sciences **ISSN 0975-6299**

MAMMALIAN GLYCANS AS MODULATOR OF INFLAMMATORY RESPONSES

Maheswara Reddy Mallu*, Siva Reddy Golamari, Sandeep Vemula AND Srinivasa Reddy Ronda

Centre for Bioprocess Technology, Department of Biotechnology, K L University,Vaddeswaram, Guntur District, Andhra Pradesh, India.

ABSTRACT

In the perspective of the genetic code, a new concept for coding information is emerging: the sugar code. This describes glycans as a third class of bio-informative macromolecules, next to nucleic acids and proteins. As a first step, the complexity of all glycans being produced in an organism, the glycome is being identified. In the past, the lack of possibilities to analyze glycan chains in detail was a main reason why scientists did not pay adequate attention to the potential information-encoding system hidden in sugar structures. Today, sophisticated analytical procedures are at hand and thus these problems have been elegantly mastered. Glycan, a unique member of the growing family of β-galactoside binding lectins, contains a single carbohydrate recognition domain and a glycine rich N-terminal domain, through which it can form oligomers and functions to cross-link both carbohydrate and non-carbohydrate ligands. Glycans are widely expressed in adult tissues, particularly on and secreted by activated macrophages, monocytes and adipocytes. Glycans have been implicated in many facets of the inflammatory response including neutrophil and macrophage activation and function.

KEYWORDS: **Glycan, inflammation, macrophage, glycobiology, adipocytes, LGALS.**

Maheswara Reddy Mallu
Centre for Bioprocess Technology, Department of Biotechnology, K L University, Vaddeswaram, Guntur District, Andhra Pradesh, India

INTRODUCTION

Barondes initially proposed the general name 'galectins' in 1994 for all the S-type lectins [1]. Before acceptance of the universal nomenclature, the glycans were known by different names, mostly reflecting on the circumstances of their discovery. Two minimal criteria were advocated by Barondes for membership into the glycan family: "affinity for β-galactosides and significant degree of sequence similarity in the carbohydrate recognition site". A wide range of proteins discovered from different species exhibited conserved structure-function relationships and accordingly were grouped and numbered sequentially following Barondes' proposal [2]. Glycan is widely expressed in many cells and tissues of the adults. It has been localized on activated macrophages and monocytes [3,4], basophils and mast cells [5], intestinal and renal epithelial cells [6,7,8] and fibroblasts including adipocytes [9]. Intracellular distribution of glycan can be influenced by cell cycle, as quiescent fibroblasts contain cytoplasmic glycan, whereas in proliferating fibroblasts, the protein is located mainly in the nucleus [9]. Glycan expression can be regulated by differentiation- it is up regulated when monocytes differentiate into macrophages [4] and down regulated when macrophages further differentiate into neuronal dendritic cells [10].

Glycan expression and regulation

The gene regulation of glycan entails a complex mechanism involving various transcription factors and signaling mediators and depends on cell type, degree and severity of stimuli and environmental conditions. *LGALS3*, the gene coding for human glycan is located on chromosome 14, locus q21-q22 [11]. The human and mouse *LGALS3* genes are composed each of six exons and five introns. Exon I along with part of exon II encodes the untranslated region (UTR) upstream of the translation initiation site located on exon II. Exon III of both the mouse and human *LGALS3* gene encodes the N-terminal domain. In mouse, the CRD is encoded by exons IV, V and VI [12], whereas in human the sequence encoding the CRD is within the exon V [13]. The expression of glycan at both mRNA and protein levels are regulated by various stimuli. Glycan protein and transcript levels are found to be higher in proliferating fibroblasts compared to quiescent cells [9,14]. Glycan is considered a macrophage differentiation marker – because glycan levels increase in macrophages after their differentiation from monocytes [4] and decrease after differentiation into dendritic cells [10]. Glycan is also regarded as a macrophage activation marker due to the fact that glycan is upregulated by the activation of the monocytic THP-1 cell line by phorbol myristoyl acetate[15] and in macrophages exposed to granulocyte-macrophage colony stimulating factor (GM-CSF) [16]. Despite availability of enormous data concerning glycan expression, the mechanisms of regulation of glycan expression are relatively poorly defined. However, it is significant that from the previous study, glycans promote regulation in inflammatory responses in both macrophage and adipocyte culture systems [17]. Recombinant glycans are also found to regulate the inflammatory responses in context of metabolic pathologies and chronic inflammation in obesity [18].Both human and murine *LGALS3* promoters do not contain the TATA box upstream of the transcription initiation site. However, multiple GC motifs for binding of *Sp1* transcription factor are found, which is a common feature of constitutively expressed, or the so-called housekeeping genes [13]. In addition to five putative Sp1 binding sites, the promoter region of the human *LGALS3* gene contains 5 cAMP-dependent response elements (CRE), 4 AP-1 transcription factor binding sites and 1 AP-4-like consensus sequence, two NF-κB-like motifs, 1 sis-inducible element (SIE) and a consensus basic helix-loop-helix (bHLH) core sequence. Although the *LGALS3* promoter is similar to that of a housekeeping gene, glycan expression increases in response to serum stimulation, indicating it as an immediate-early gene. The SIE is important for growth factor-induced transcriptional activation of other immediate-early genes and it has been suggested that SIE is a possible candidate for the growth factor-induced activation of *LGALS3* expression, caused by the addition of serum [16]. The presence of CRE and NF-κB-like sites in the promoter region suggests that glycan expression could be regulated through metabolic/signaling pathways involving the cAMP-response element-binding protein (CREB) or the NF-κB transcription factor that is at the core of inflammatory pathways. The involvement of NF-κB and Jun protein in the regulation of glycan expression has been widely confirmed [19,20].

Chronic inflammation and infection

Macrophages play an important role in the regulation and orchestration of tissue responses following chronic inflammation. In particular, recent studies have demonstrated that macrophages display phenotypical heterogeneity in response to environmental factors that affect their role in inflammation. N-glycans that promote chronic inflammation, lead to the elevation of systemic autoantibody titers, cell activation and apoptotic death, and kidney failure [21].

Classical macrophage activation

The classically activated (M1 polarised) macrophage (Figure 1) is the best studied macrophage phenotype and develops following an initial pro-inflammatory response during which T helper 1 (Th1)-type lymphocytes and natural killer (NK) cells produce interferon-γ (IFN-γ) and antigen presenting cells (APCs) produce an array of cytokines such as glycans including IL-12 and IL-18 [22]. After an infection, LPS, a microbial trigger, classically activates macrophages following priming by IFN-γ. Once classically activated, macrophages produce glycans and the pro-inflammatory cytokines IL-6 and tumour necrosis factor-α (TNF-α) [23,24]. They also produce nitrites including nitric oxide (NO) by an inducible nitric oxide synthase (NOS2) [25,26], which is important for microbial killing. In contrast, the resolution phase of inflammation is driven by alternatively activated (M2 polarised) macrophages, which are hypo-responsive to pro-inflammatory stimuli. Macrophages undergo alternative activation when

stimulated with the glycans, Th2 cytokines, IL-4 or IL-13 [22,27,26]. Initially it was believed that IL-4 and IL-13 resulted in a deactivated phenotype similar to that seen with IL-10, whereby there is a deactivation of the respiratory burst and of inflammatory cytokine production, particularly TNF-α. However, it was discovered that the regulatory role of IL-4 and IL-13 on immune responses appeared to be more complex than first thought [28]. Incubation of macrophages with IL-4 or IL-13 causes upregulation of mannose receptor expression [29], arginase-1 activity [26], YM-1 (chitinase-like lectin) [30] and FIZZ-1 (found in inflammatory zone-1, a resistin-like secreted protein) expression [31]. One mechanism by which Th1 and Th2 cytokines induce opposing macrophage phenotypes is through differential regulation of NOS2 or arginase-1 [26](Figure 1). Th1 cytokines IFNγ and TNF-α cause macrophages to metabolise L-arginine by NOS2 to NO and L-citrulline. The intermediate product, L-hydroxyarginine, inhibits arginase-1 activity resulting in a classical (M1) phenotype. If Th2 cytokines IL-4 and IL-13 are present, less L-hydroxyarginine is produced and arginase-1 activity is not inhibited. Consequently, the common substrate L-arginine is metabolised by arginase-1 resulting in the production of L-ornithine and an alte rnative (M2) phenotype. L-ornithine is a necessary metabolite for the production of proline (a critical amino acid for the synthesis of collagen) which links arginase activity to fibrosis [26,32,33].

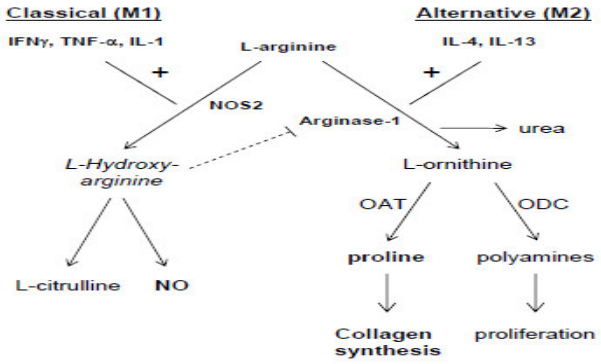

Figure 1

Classical (M1) and alternative (M2) activation of macrophages.* (*Macrophages can be classically (M1) or alternatively (M2) activated as a result of competition between nitric oxide synthase 2 (NOS2) and arginase-1 for the common substrate L-arginine producing either nitric oxide (NO) or L-ornithine respectively. (OAT; ornithine aminotransferase, ODC; ornithine decarboxylase) (adapted from Gordon et al. [22]).

Alternative macrophage activation

Alternatively activated macrophages (figure 1) have been widely implicated in the progression of parasitic infections. It has been shown that the M2 macrophage contributes to the susceptibility of cutaneous leishmaniasis [34] and that certain parasitic infections result in the generation of alternatively activated macrophages. Infection with the helminth parasite *Fasciola hepatica* induces a polarised Th2 immune response resulting in the alternative activation of macrophages [35,36]. In earlier studies, IL-4 (KO) mice, which mounted a Th1 response, demonstrated the lowest level of liver damage. Similar results have been shown with other helminth infections including Brugia malayi and Schistosoma [37,38]. For example, in acute tissue damage glycan like galectin-3 is a key component in the host defense against microbes such as *Streptococcus pneumonia* [39]. Some research into the role of alternatively activated macrophages during bacterial infections has been carried out in recent years. The presence of alternatively activated macrophages during progressive tuberculosis results in an inability to control bacterial replication [40]. Alternative macrophage phenotype has also been observed in Whipple Disease, a rare systemic disease caused by the bacterium *Tropheryma whipplei* [41]. Alternatively activated macrophages, it has been suggested, contribute to the pathophysiological properties of this disease.

Regulation of the immune response

Glycan is highly expressed and secreted from activated macrophages and acts as a powerful pro-inflammatory signal. As stated above, extracellular glycan mediates cell adhesion, activation and acts as a chemoattractant for various cell types. Numerous studies have been carried out investigating the effects of glycan on the cells involved in immune responses (Figure 2). Glycan promotes the respiratory burst in neutrophils and monocytes [42,4] and this activity is dependent on the lectin property of the protein as it is inhibitable by lactose; it induces mediator release from mast cells [43] and down regulates interleukin-5 (IL-5) production from eosinophils [44]. Glycan promotes the survival of B cells by blocking the final differentiation into plasma cells thus allowing the rising of a memory B cell phenotype [45]. This process is important when the host meets a pathogen which it has previously encountered. A good deal of research has been carried out investigating the effect of glycan on T lymphocytes.

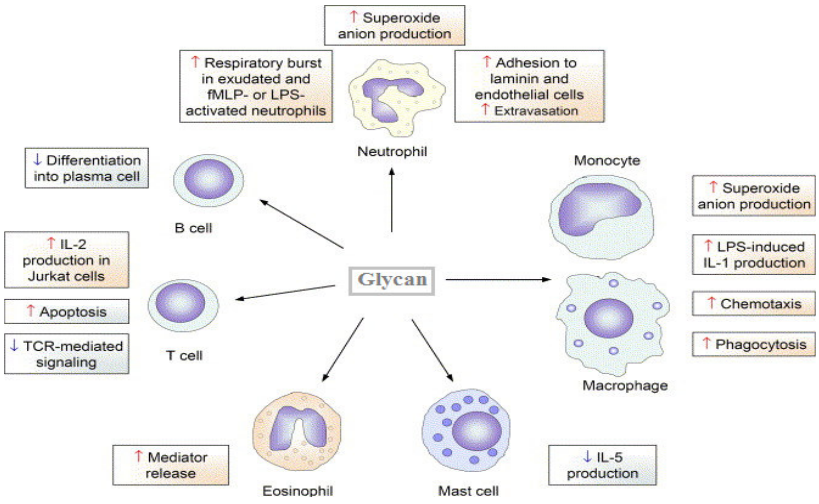

Figure 2

The effect of glycan on immune cell function (The effects of glycan on immune cells. Red upwards arrows indicate positive effects, blue downwards arrows indicate negative effects, adapted from Dumic et al [46]).

Glycan is expressed in activated, but not resting T lymphocytes [47]. Extracellular glycan induces T cell apoptosis [48] whereas intracellular glycan results in an inhibition of apoptosis [49]. Over expressing glycan in the human leukemia T cell line Jurkat enhances proliferation and confers resistance to apoptosis induced by anti-Fas antibody and staurosporine [49]. Furthermore, anti-sense oligonucleotides specific for murine glycan inhibit the proliferation of activated T lymphocytes [49]. Inhibition of glycan reduces naive T-lymphocyte-dendritic cell interactions [50], a process crucial for the induction of immune responses. Finally, Mgat5-dependent association of glycan with T cell receptor (TCR) complex proteins restricts TCR recruitment to the site of antigen presentation thus inhibiting TCR-mediated signaling [51].

CONCLUSION

Recent advances in the understanding of the contribution of cell surface glycoconjugates and carbohydrate binding proteins to inflammatory processes have motivated the design of synthetic glycoconjugates or lectins as candidates for future generations of therapeutic drugs. Despite the extensive research in the area of glycoproteins, concerning structure and function of glycans, lectins and glycosylation processes, many aspects are still left unexplored. The aim of this review was to improve our understanding of this dense field, predominantly focusing on various aspects of glycan functions in macrophage activation and its role in regulation of immune system. Glycans can serve as a macrophage pattern recognition receptor conveyed by its CRD binding to glycan moieties on invading pathogens. Besides regulating inflammation and tissue remodeling through its roles in phagocytosis, pattern recognition and signaling, an emerging view connects glycans to intracellular sorting and trafficking of glycoproteins. Related publications hitherto used mostly polarized cells or cell systems other than macrophages, yet it is plausible that glycans would also direct trafficking of glycoproteins related to macrophages'functions.

ACKNOWLEDGEMENT

The authors thank the management of K L Univeristy for their kind support and encouragement.

CONFLICT OF INTEREST

All the authors declare that no conflict of interest exist among them.

REFERENCES

1. Barondes SH, Castronovo V, Cooper DN, Cummings RD, Drickamer K, Felzi T, Gitt MA, Hirabayashi J, Hughes C, Kasai KI, Leffler H. Galectins: a family of animal β-galactoside-binding lectins. Cell. 1994 Feb 25;76(4):597-8.
2. Barondes SH, Cooper DN, Gitt MA, Leffler H. Galectins. Structure and function of a large family of animal lectins. Journal of Biological Chemistry. 1994 Aug 19;269:20807-.
3. Ho MK, Springer TA. Mac-2, a novel 32,000 Mr mouse macrophage subpopulation-specific antigen defined by monoclonal antibodies. The Journal of Immunology. 1982 Mar 1;128(3):1221-8.
4. Liu FT, Hsu DK, Zuberi RI, Kuwabara I, Chi EY, Henderson Jr WR. Expression and function of galectin-3, a beta-galactoside-binding lectin, in human monocytes and macrophages. The American journal of pathology. 1995 Oct;147(4):1016.
5. Liu FT. S-type mammalian lectins in allergic inflammation. Immunology today. 1993 Oct 1;14(10):486-90.

6. Lotz MM, Andrews CW, Korzelius CA, Lee EC, Steele GD, Clarke A, Mercurio AM. Decreased expression of Mac-2 (carbohydrate binding protein 35) and loss of its nuclear localization are associated with the neoplastic progression of colon carcinoma. Proceedings of the National Academy of Sciences. 1993 Apr 15;90(8):3466-70.
7. CASTRONOVO V, VAN DEN BRÛLE FA, Jackers P, Clausse N, LIU FT, Gillet C, Sobel ME. DECREASED EXPRESSION OF GALECTIN-3 IS ASSOCIATED WITH PROGRESSION OF HUMAN BREAST CANCER. The Journal of pathology. 1996 May 1;179(1):43-8.
8. Bao Q, Hughes RC. Galectin-3 expression and effects on cyst enlargement and tubulogenesis in kidney epithelial MDCK cells cultured in three-dimensional matrices in vitro. Journal of Cell Science. 1995 Aug 1;108(8):2791-800.
9. Moutsatsos IK, Wade M, Schindler M, Wang JL. Endogenous lectins from cultured cells: nuclear localization of carbohydrate-binding protein 35 in proliferating 3T3 fibroblasts. Proceedings of the National Academy of Sciences. 1987 Sep 1;84(18):6452-6.
10. Dietz AB, Bulur PA, Knutson GJ, Matasić R, Vuk-Pavlović S. Maturation of human monocyte-derived dendritic cells studied by microarray hybridization. Biochemical and biophysical research communications. 2000 Sep 7;275(3):731-8.
11. Raimond J, Zimonjic DB, Mignon C, Mattei MG, Popescu NC, Monsigny M, Legrand A. Mapping of the galectin-3 gene (LGALS3) to human chromosome 14 at region 14q21-22. Mammalian genome. 1997 Sep 1;8(9):706-7.
12. Gritzmacher CA, Mehl VS, Liu FT. Genomic cloning of the gene for an IgE-binding lectin reveals unusual utilization of 5'untranslated regions. Biochemistry. 1992 Oct;31(40):9533-8.
13. Kadrofske MM, Openo KP, Wang JL. The HumanLGALS3 (Galectin-3) Gene: Determination of the Gene Structure and Functional Characterization of the Promoter. Archives of biochemistry and biophysics. 1998 Jan 1;349(1):7-20.
14. Agrwal N, Wang JL, Voss PG. Carbohydrate-binding protein 35. Levels of transcription and mRNA accumulation in quiescent and proliferating cells. Journal of Biological Chemistry. 1989 Oct 15;264(29):17236-42.
15. Dabelic S, Supraha S, Dumic J, Glycan in macrophage-like cells exposed to immunomodulatory drugs. Biochim. Biophys. Acta. 2005;1760: 710-709.
16. Saada A, Reichert F, Rotshenker S. Granulocyte macrophage colony stimulating factor produced in lesioned peripheral nerves induces the up-regulation of cell surface expression of MAC-2 by macrophages and Schwann cells. The Journal of cell biology. 1996 Apr 1;133(1):159-67.
17. Vemuri PK, Talluri B, Veeravalli S, Bodiga VL. GALECTIN-3 IN REGULATION OF INFLAMMATORY RESPONSES MEDIATED BY LIPOPOLYSACCHARIDE IN MACROPHAGES AND ADIPOCYTES CULTURE SYSTEMS. International Journal of Pharmacy and Pharmaceutical Sciences. 2016 Mar 1;8(3):356-60.
18. Kumar VP, Suryanarayana V, Sudhakar P, Rao KR. Study of the anti-inflammatory effects of recombinant human galectin-3 in the context of metabolic pathologies and chronic inflammation in obesity. Int. Journal of Pharmacy and Biological Sciences. 2013;3(2):627-32.
19. Dumic J, Lauc G, Flögel M. Expression of galectin-3 in cells exposed to stress-roles of jun and NF-κB. Cellular Physiology and Biochemistry. 2000;10(3):149-58.
20. Kim K, Mayer EP, Nachtigal M. Galectin-3 expression in macrophages is signaled by Ras/MAP kinase pathway and up-regulated by modified lipoproteins. Biochimica et Biophysica Acta (BBA)-Molecular Cell Research. 2003 Jun 17;1641(1):13-23.
21. Green RS, Stone EL, Tenno M, Lehtonen E, Farquhar MG, Marth JD. Mammalian N-glycan branching protects against innate immune self-recognition and inflammation in autoimmune disease pathogenesis. Immunity. 2007 Aug 24;27(2):308-20.
22. Gordon S, Alternative activation of macrophages. Nat. Rev. Immunol.2003; 3: 23-35.
23. Munder M, Eichmann K, Modolell M. Alternative metabolic states in murine macrophages reflected by the nitric oxide synthase/arginase balance: competitive regulation by CD4+ T cells correlates with Th1/Th2 phenotype. The Journal of Immunology. 1998 Jun 1;160(11):5347-54.
24. Welch JS, Escoubet-Lozach L, Sykes DB, Liddiard K, Greaves DR, Glass CK. TH2 cytokines and allergic challenge induce Ym1 expression in macrophages by a STAT6-dependent mechanism. Journal of Biological Chemistry. 2002 Nov 8;277(45):42821-9.
25. Hauschildt S, Bassenge E, Bessler W, Busse R, Mülsch A. L-arginine-dependent nitric oxide formation and nitrite release in bone marrow-derived macrophages stimulated with bacterial lipopeptide and lipopolysaccharide. Immunology. 1990 Jul;70(3):332.
26. Hesse M, Modolell M, La Flamme AC, Schito M, Fuentes JM, Cheever AW, Pearce EJ, Wynn TA. Differential regulation of nitric oxide synthase-2 and arginase-1 by type 1/type 2 cytokines in vivo: granulomatous pathology is shaped by the pattern of L-arginine metabolism. The Journal of Immunology. 2001 Dec 1;167(11):6533-44.
27. Munder M, Eichmann K, Morán JM, Centeno F, Soler G, Modolell M. Th1/Th2-regulated expression of arginase isoforms in murine macrophages and dendritic cells. The Journal of Immunology. 1999 Oct 1;163(7):3771-7.
28. D'Andrea A, Ma X, Aste-Amezaga M, Paganin C, Trinchieri G. Stimulatory and inhibitory effects of interleukin (IL)-4 and IL-13 on the production of cytokines by human peripheral blood mononuclear cells: priming for IL-12 and tumor necrosis factor alpha production. The Journal of

experimental medicine. 1995 Feb 1;181(2):537-46.
29. Henderson NC, Sethi T. The regulation of inflammation by galectin-3. Immunological reviews. 2009 Jul 1;230(1):160-71.
30. Stein M, Keshav S, Harris N, Gordon S. Interleukin 4 potently enhances murine macrophage mannose receptor activity: a marker of alternative immunologic macrophage activation. The Journal of experimental medicine. 1992 Jul 1;176(1):287-92.
31. Nair MG, Gallagher IJ, Taylor MD, Loke PN, Coulson PS, Wilson RA, Maizels RM, Allen JE. Chitinase and Fizz family members are a generalized feature of nematode infection with selective upregulation of Ym1 and Fizz1 by antigen-presenting cells. Infection and immunity. 2005 Jan 1;73(1):385-94.
32. De'Broski RH, Hölscher C, Mohrs M, Arendse B, Schwegmann A, Radwanska M, Leeto M, Kirsch R, Hall P, Mossmann H, Claussen B. Alternative macrophage activation is essential for survival during schistosomiasis and downmodulates T helper 1 responses and immunopathology. Immunity. 2004 May 31;20(5):623-35.
33. Misson P, Van Den Brûle S, Barbarin V, Lison D, Huaux F. Markers of macrophage differentiation in experimental silicosis. Journal of leukocyte biology. 2004 Nov 1;76(5):926-32.
34. Endo M, Oyadomari S, Terasaki Y, Takeya M, Suga M, Mori M, Gotoh T. Induction of arginase I and II in bleomycin-induced fibrosis of mouse lung. American Journal of Physiology-Lung Cellular and Molecular Physiology. 2003 Aug 1;285(2):L313-21.
35. Hölscher C, Arendse B, Schwegmann A, Myburgh E, Brombacher F. Impairment of alternative macrophage activation delays cutaneous leishmaniasis in nonhealing BALB/c mice. The Journal of Immunology. 2006 Jan 15;176(2):1115-21.
36. O'neill SM, Brady MT, Callanan JJ, Mulcahy G, Joyce P, Mills KH, Dalton JP. Fasciola hepatica infection downregulates Th1 responses in mice. Parasite immunology. 2000 Mar 1;22(3):147-55.
37. Donnelly S, O'Neill SM, Sekiya M, Mulcahy G, Dalton JP. Thioredoxin peroxidase secreted by Fasciola hepatica induces the alternative activation of macrophages. Infection and immunity. 2005 Jan 1;73(1):166-73.
38. P'ng Loke AS, Robb A, Maizels RM, Allen JE. Alternatively activated macrophages induced by nematode infection inhibit proliferation via cell-to-cell contact. Eur J Immunol. 2000;30:2669-78.
39. Noël W, Raes G, Ghassabeh GH, De Baetselier P, Beschin A. Alternatively activated macrophages during parasite infections. Trends in parasitology. 2004 Mar 31;20(3):126-33.
40. Kahnert A, Seiler P, Stein M, Bandermann S, Hahnke K, Mollenkopf H, Kaufmann SH. Alternative activation deprives macrophages of a coordinated defense program to Mycobacterium tuberculosis. European journal of immunology. 2006 Mar 1;36(3):631-47.
41. Desnues B, Lepidi H, Raoult D, Mege JL. Whipple disease: intestinal infiltrating cells exhibit a transcriptional pattern of M2/alternatively activated macrophages. Journal of Infectious Diseases. 2005 Nov 1;192(9):1642-6.
42. Yamaoka A, Kuwabara I, Frigeri LG, Liu FT. A human lectin, galectin-3 (epsilon bp/Mac-2), stimulates superoxide production by neutrophils. The Journal of Immunology. 1995 Apr 1;154(7):3479-87.
43. Frigeri LG, Zuberi RI, Liu FT, epsilon BP. beta.-galactoside-binding animal lectin, recognizes IgE receptor (Fc. epsilon. RI) and activates mast cells. Biochemistry. 1993 Aug;32(30):7644-9.
44. Cortegano I, Del PV., Cardaba B, De Andres B, Gallardo S, Del Amo A, Arrieta I, Jurado A, Palomino P, Liu FT, Lahoz C, Glycan down-regulates IL-5 gene expression on different cell types. J. Immunol. 1998; 161: 385-389.
45. Acosta-Rodriguez EV, Montes CL, Motran CC, Zuniga EI, Liu FT, Rabinovich GA, Gruppi A, Glycan mediates IL-4-induced survival and differentiation of B cells: functional cross-talk and implications during Trypanosoma cruzi infection. J. Immunol. 2004; 172: 493-502.
46. Joo HG, Goedegebuure PS, Sadanaga N, Nagoshi M, Von Bernstorff W, Eberlein TJ. Expression and function of galectin-3, a β-galactoside-binding protein in activated T lymphocytes. Journal of Leukocyte Biology. 2001 Apr 1;69(4):555-64.
47. Fukumori T, Takenaka Y, Yoshii T, Kim HR, Hogan V, Inohara H, Kagawa S, Raz A. CD29 and CD7 mediate galectin-3-induced type II T-cell apoptosis. Cancer research. 2003 Dec 1;63(23):8302-11.
48. Yang RY, Hsu DK, LIu FT. Expression of galectin-3 modulates T-cell growth and apoptosis. Proceedings of the National Academy of Sciences. 1996 Jun 25;93(13):6737-42.
49. Swarte VV, Mebius RE, Joziasse DH, Van den Eijnden DH, Kraal G. Lymphocyte triggering via L-selectin leads to enhanced galectin-3-mediated binding to dendritic cells. European journal of immunology. 1998 Sep 1;28(9):2864-71.
50. Demetriou M, Granovsky M, Quaggin S, Dennis JW. Negative regulation of T-cell activation and autoimmunity by Mgat5 N-glycosylation. Nature. 2001 Feb 8;409(6821):733-9.
51. Dumic J, Dabelic S, Flögel M. Galectin-3: an open-ended story. Biochimica et Biophysica Acta (BBA)-General Subjects. 2006 Apr 30;1760(4):616-35.

.