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Impact of protein–glycan interactions in the regulation of autoimmunity and chronic inflammation

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Abstract

Protein–glycan interactions control essential immunological processes, including T-cell activation, differentiation and survival. Galectins, carbohydrate-binding proteins, defined by shared consensus amino acid sequences and affinity for β-galactose-containing oligosaccharides, participate in a wide spectrum of immunological processes. These carbohydrate-binding proteins regulate the development of pathogenic T-cell responses by influencing T-cell survival, activation and cytokine secretion. Administration of recombinant galectins or their genetic delivery modulate the development and severity of chronic inflammatory responses in experimental models of autoimmunity by triggering different and potentially overlapping immunoregulatory mechanisms. Given the potential use of galectins as novel anti-inflammatory agents or targets for immunosuppressive drugs, we will summarize here recent findings on the influence of these carbohydrate-binding proteins in autoimmune and chronic inflammatory disorders.

Keywords: Apoptosis; Autoimmunity; Galectins; Galectin-1; Glycosylation; Immunoregulation

Contents

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1. Protein–glycan interactions in immunoregulation: an overview

Glycans decorate the surfaces of all mammalian cells and the extracellular matrix with which they interact [1]. Recent evidence indicates that differential glycosylation of cell surface proteins can control critical immunological processes, including T-cell activation, migration and apoptosis [1]. The mission of decoding glycan information is assigned in part to a great variety of mammalian glycan-binding proteins or lectins including the selectins, pentraxins, siglecs and galectins [2].

Galectins, a family of highly conserved glycan-binding proteins, are characterized by their ability to recognize *N*-acetyllactosamine sequences, which can be displayed on both *N*- and *O*-glycans on cell surface glycoconjugates [3]. All galectins contain conserved carbohydrate-recognition domains (CRDs) that are responsible for carbohydrate binding. So far, 15 mammalian galectins have been identified, which can be subdivided into three groups: those containing one CRD (galectin-1, -2, -5, -7, -10, -11, -13, -14, -15), those containing two distinct CRDs in tandem (galectin-4, -6, -8, -9, -12) and galectin-3 which consists of unusual tandem repeats stretches fused onto the CRD (reviewed in [4]). Different galectins are specific for different carbohydrate ligands, as they differ in their ability to accommodate certain saccharides attached to galactose and can form ordered arrays of complexes when they bind to multivalent glycoconjugates [4]. As galectins can bind either bivalently or multivalently, they can cross-link cell-surface glycoconjugates, which, like many other receptor–ligand systems, can trigger a cascade of transmembrane signaling events [4]. Through this mechanism, galectins can modulate a wide variety of immunological processes including T-cell apoptosis, activation, cell adhesion and cytokine secretion [5].

2. Galectins in immune-mediated disorders: novel regulators of autoimmunity, chronic inflammation and cancer

During the past decade, compelling evidence has been accumulated regarding the immunoregulatory effects of galectins in T-cell-mediated inflammatory disorders [4,5]. Here we will summarize the clinical and immunological consequences of prophylactic or therapeutic administration of galectins (in particular galectin-1) in chronic inflammatory disorders, autoimmunity and cancer (Table 1).

2.1. Experimental autoimmune myasthenia gravis

Levi et al. [6] were pioneers in describing the prophylactic and therapeutic effects of electrolectin, a β-galactoside-binding lectin from the fish *Electrophorus electricus* in experimental autoimmune myasthenia gravis (EAMG) [6]. The administration of electrolectin to myasthenic rabbits led to clinical recovery. Although the authors suggested that electrolectin might play a role in the regulation of immune tolerance to self-antigens, clear evidence was not available at that time with regards to the potential mechanisms involved in galectin-mediated immunoregulation.

2.2. Experimental autoimmune encephalomyelitis

Offner et al. [7] demonstrated that galectin-1 prevents the development of clinical and histopathological signs of experimental autoimmune encephalomyelitis (EAE) in Lewis rats [7]. Although the mechanisms of action of the immunoregulatory activity of galectin-1 were not investigated in this study, the authors proposed that this protein might block the activation or sensitization of encephalitogenic T cells [7]. These pioneer studies in EAMG and EAE prompted us to investigate in vitro and in vivo the molecular mechanisms underlying the immunoregulatory effects of galectin-1.

Of particular relevance, Zhu et al. recently identified galectin-9 as a specific binding partner for the Th1-specific molecule Tim-3 [8]. Interestingly, the authors demonstrated that galectin-9 can trigger an apoptotic signal in Tim-3-positive Th1 cells and reduce the severity of pathology in murine models of EAE [8].

2.3. Collagen-induced arthritis

By using gene and protein therapy strategies, we have demonstrated that galectin-1 ameliorates the

Table 1
Immunoregulatory effects of galectins in experimental models of autoimmunity, chronic inflammation and cancer

Autoimmunity and chronic inflammation			
Experimental models	Strategies used	Clinical outcome	Potential mechanisms involved
Experimental autoimmune myasthenia gravis (EAMG)	• Injection of electrolectin to rabbits	• Complete clinical recovery and delayed onset	• No changes in circulating autoantibodies or modifications at the muscular level
Experimental autoimmune encephalomyelitis in (EAE)	• Prophylactic administration of Gal-1 to MBP-immunized Lewis rats	• Prevention of clinical and histopathological signs of the disease	• ND (blockade of sensitization of pathogenic T cells?)
Collagen-induced arthritis (CIA)	• Gal-1 gene therapy and protein administration to DBA/1 mice	• Suppression of clinical and histopathological manifestations	• Increased IL-5 and decreased IFN-γ production • Increased T-cell susceptibility to activation-induced cell death
Concanavalin A-induced hepatitis	• Prophylactic administration of Gal-1 in BALB/c mice	• Prevention of liver injury and T-helper cell liver infiltration	• Suppressed tumor necrosis factor-α and IFN-γ production • Increased apoptosis of activated T cells
Inflammatory bowel disease (TNBS-induced colitis)	• Prophylactic and therapeutic administration of Gal-1 in BALB/c mice	• Suppression of clinical and histopathological manifestations	• Reduced ability of mucosal T cells to produce IFN-γ •Increased number of apoptotic T cells within mucosal tissue
Nephrotoxic nephritis (induced by anti-glomerular basement membrane serum)	• Gal-1, Gal-3, Gal-9 administration to Wistar Kyoto rats	• Clinical recovery	• Gal-9 induces apoptosis of activated $CD8^+$ cells • Gal-1 and Gal-3 block the accumulation of macrophages
Graft vs. host disease	• Gal-1 administration to mice	• Increased host survival following allogeneic hematopoietic stem cell transplant	• Reduced production of IFN-γ and IL-2 •Reduced alloreactivity
Experimental autoimmune encephalomyelitis	• Gal-9 injection to MOG-immunized C57BL/6 mice	• Reduced severity and mortality	• Selective loss of IFN-γ-producing cells. Apoptosis of Tim-3+ Th1 cells
	• siRNA *gal-9* to PLP-immunized SJL mice	• Increased severity of the disease	
Inflammatory bowel disease (TNBS-colitis)	• Gal-4 reactivity	• Exacerbates intestinal inflammation	• Stimulates IL-6 production by $CD4^+$ T cells

Cancer			
Experimental models	Strategies used	Clinical outcome	Immunological outcome
B16 melanoma	• Knockdown clones (antisense *gal-1*)	• Tumour rejection	• Increased tumour-specific IFN-γ and IL-2 production

Abbreviations: Gal: galectin, MBP: myelin-basic protein, MOG: myelin oligodendrocyte glycoprotein, PLP: myelin proteolipid protein, siRNA: small interfering RNA, TNBS: 2,4,6-trinitrobenzene sulfonic acid.

severity of the inflammatory response in a collagen-induced arthritis (CIA) model [9]. A single injection of synovial fibroblasts engineered to secrete galectin-1 at the day of the disease onset was able to abrogate clinical and histopathological manifestations of arthritis in DBA/1 mice [9]. Examination of the mechanisms involved in this immunoregulatory effect revealed a clear shift from a Th1 to a Th2-polarized immune response. This effect was manifested by reduced levels IFN-γ and increased levels of IL-5 in draining lymph nodes from mice treated with galectin-1 [9]. In addition, sera from galectin-1-treated mice showed reduced levels of anti-collagen type II IgG2a and increased levels of anti-collagen type II IgG1 antibodies. Remarkably, lymph node cells from galectin-1-treated mice showed an increased susceptibility to antigen-induced apoptosis. In addition, galectin-1-expressing fibroblasts showed an inhibitory effect in antigen-dependent IL-2 production to a collagen type II-specific T cell hybridoma clone [9]. This study provided a clear correlation between the apoptotic properties of galectin-1 and its therapeutic potential in vivo. In agreement, we also found a strong correlation between the levels of galectin-1 expression and the regulation of apoptosis in synovial tissue from patients with juvenile rheumatoid arthritis [10]. On the other hand, Ohshima et al. [11] found that galectin-3,

another member of the galectin family with pro-inflammatory activity, is elevated in sera and sinovial fluids from rheumatoid arthritis patients [11].

2.4. Concanavalin A-induced hepatitis

Using in vitro and in vivo experiments, Santucci et al. [12] found that galectin-1 pre-treatment prevents liver injury and $CD4^+$ T-cell liver infiltration in concanavalin A (Con A)-induced hepatitis in mice [12]. The authors showed protective effects of galectin-1 in this model and confirmed that galectin-1 acts in vivo by promoting selective elimination of antigen-activated T cells and blocking the synthesis of pro-inflammatory cytokines [12].

2.5. Inflammatory bowel disease

Recombinant galectin-1 also showed immunosuppressive activity in 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced colitis, a Th1-mediated model of inflammatory bowel disease [13]. The authors demonstrated that prophylactic and therapeutic administration of galectin-1 results in striking improvement of the clinical and histopathological manifestations of the disease [13]. Interestingly, galectin-1-treated mice experienced a marked reduction in the secretion of pro-inflammatory cytokines and decreased viability of hapten-activated mucosal T cells. Thus, galectin-1 exerts protective and immunoregulatory activity in TNBS-induced colitis.

Interestingly, Hokama et al. [14] demonstrated that galectin-4 exacerbates TNBS-induced colitis and delays the recovery from acute intestinal injury through a mechanism involving abnormal activation of $CD4^+$ T cells and increased secretion of IL-6 [14]. These findings suggest that different members of the galectin family may trigger different immunological mechanisms, which may differentially influence the clinical outcome of chronic inflammatory disorders.

2.6. Immune-mediated renal diseases

In a comparative study, Tsuchiyama et al. [15] investigated the efficacy of different members of the galectin family in the amelioration of nephrotoxic serum nephritis, an immune-mediated renal disease characterized by glomerular influx of $CD8^+$ cells [15]. The authors found that galectin-9 induces apoptosis of activated $CD8^+$ T cells, while galectin-1 and galectin-3 block the accumulation of macrophages in the renal glomeruli [15].

2.7. Experimental autoimmune uveitis

Given the potential role of galectin-1 in the maintenance of immune privilege in organs such as the eye [5], we have recently investigated the immunoregulatory effects of this protein in experimental autoimmune uveitis (EAU), a Th-1-mediated model of retinal disease [16]. Interestingly, treatment with galectin-1 either early or late during the course of EAU was sufficient to suppress clinical ocular pathology, inhibit leukocyte infiltration and counteract pathogenic Th1 cells [16]. Administration of galectin-1 ameliorated retinal inflammation by skewing the uveitogenic response towards non-pathogenic Th2 or T regulatory (IL-10 and TGF-β)-mediated anti-inflammatory responses [16]. In addition, increased levels of apoptosis were detected in lymph nodes from mice treated with recombinant galectin-1 during the efferent phase of the disease [16]. These results highlight the ability of this endogenous lectin to counteract Th1-mediated responses through different, but potentially overlapping anti-inflammatory mechanisms. In addition, we found a striking correlation between the levels of anti-retinal galectin-1 autoantibodies in sera from uveitic patients and the severity of autoimmune retinal inflammation [17].

2.8. Other immune-mediated disorders: graft versus host disease

In addition to its role in autoimmune disorders, galectin-1 also showed immunosuppressive activity in a murine experimental model of graft versus host disease (GVHD) [18]. Galectin-1 treatment in vivo resulted in reduced inflammatory infiltrates in target tissues and a selective reduction of Th1 cytokines [18].

2.9. Cancer: the "sweet" escape

The strong association between galectin-1 expression and the aggressiveness of tumour cells [4] prompted us to investigate the role of galectin-1 in tumor-immune escape. Through a combination of in vitro and in vivo strategies, we have established a link between galectin-1-mediated immunoregulation and its contribution to tumor-immune escape [19]. Blockade of the immunosuppressive activity of galectin-1 within tumour tissue resulted in reduced tumour growth and heightened T-cell-mediated tumor rejection in an experimental model of murine melanoma [19].

Supporting our findings, Le et al. [20] recently identified galectin-1 as a molecular link between tumour hypoxia and tumour-immune privilege and found a strong inverse correlation between galectin-1 expression and

CD3 staining in tumour sections corresponding to head and neck squamous cell carcinoma patients [20]. Taken together, these results support the concept that galectin-1 may contribute to immune privilege of tumours by modulating survival and differentiation of effector T cells.

3. Molecular mechanisms underlying galectin-mediated immunoregulation

3.1. Regulation of T cell survival

How galectins exert their immunoregulatory and anti-inflammatory effects is poorly understood, primarily because of their pleiotropic activities (Fig. 1) and the perception of their redundant nature [3–5]. The most extensively studied function of galectins is their ability to regulate T-cell growth and survival [4,5]. So far, galectin-1, -2, -3 and -9 have been shown to modulate T-cell apoptosis through binding to specific glycoconjugates [21–27].

Different glycoproteins on the surface of activated T cells appear to be primary receptors for galectins, including CD45, CD43, CD7, CD29 and Tim-3 [8,22,24,26] However, recent studies indicate that some of these receptors are not essential for cell death and that individual galectins may trigger apoptotic signals through a different set of glycoreceptors [8,26,28]. In this regard, it has been demonstrated that the presence of poly-*N*-acetyllactosamine ligands decorating specific glycoreceptors may be critical in determining susceptibility to galectin-1-induced cell death [29,30]. Galvan et al. [29] showed that $CD45^{+}$ T cells lacking the core-2-β-1,6-*N*-acetylglucosaminyltransferase (C2GnT) are resistant to galectin-1-induced cell death [29]. This enzyme is responsible for creating branched structures on *O*-glycans of T-cell surface glycoproteins, such as CD45. On the other hand, incorporation of α2,6-linked sialic acids to lactosamine units by the ST6Gal-I sialyltransferase has been shown to block galectin-1 binding by interfering with lactosamine insertion into the binding pocket of galectin-1 [30]. Moreover, recent findings provided new insights into the signal transduction pathways leading to galectin-1-induced cell death. These include $p56^{lck}$ and ZAP-70-mediated tyrosine phosphorylation [31], caspase-3 and caspase-8 activation [23], cytochrome *c* release [23], and modulation of mitochondrial budding and fission [23]. Likewise, galectin-2 triggers T-cell apoptosis through caspase activation, cytochrome *c* release and disruption of the mitochondrial membrane potential [24]. However, a recent study shows that apoptosis induced by galectin-1 in a T-cell line is not dependent on

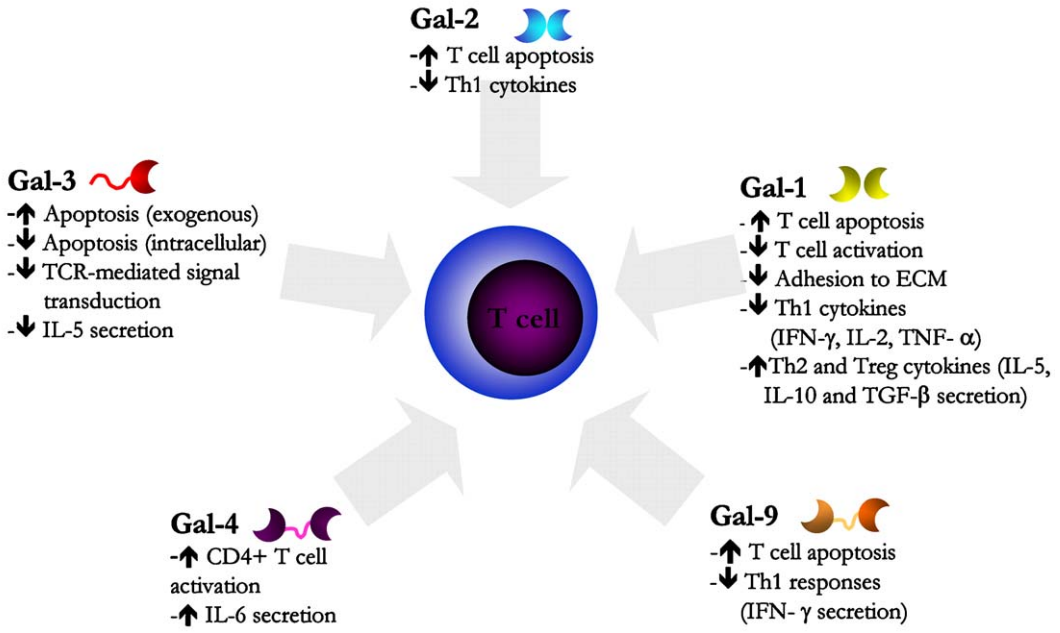

Fig. 1. Role of different members of the galectin family in the regulation of T-cell physiology. This scheme illustrates the influence of individual members of the galectin family on different T-cell functions including T-cell apoptosis, activation and cytokine secretion. Galectins are represented according to their biochemical structure (Gal-1 and Gal-2 are one-CRD galectins which may dimerize; Gal-4 and Gal-9 have two distinct CRDs in tandem, connected by a linker of up to 70 amino acids; and Gal-3 consists of unusual tandem repeats of proline- and glycine-rich short stretches fused onto the CRD). There is still scarce information regarding the immunoregulatory role of other members of the galectin family.

the activation of caspase-3 or on cytochrome *c* release [32]. Therefore, it seems evident that galectins might trigger different death pathways or different apoptosis end points in different cell types.

One of the most striking findings is that galectin-3 acts in a dual manner either protecting cells from apoptosis or stimulating cell death depending on whether the protein is found in the intracellular compartment [25] or whether it acts extracellularly [26,27]. In this regard, Yang and colleagues [25] demonstrated that T-cell transfectants overexpressing galectin-3 are protected from apoptosis induced by a variety of agents including Fas ligand and staurosporine [24]. In contrast, extracellular galectin-3 can signal apoptosis of human T cells through caspase-3, but not caspase-8 activation [26]. Furthermore, recent evidence suggests a functional cross-talk between intracellular and extracellular galectins in the regulation of T-cell death [32]. Hahn et al. demonstrated that galectin-1-induced cell death is inhibited by intracellular expression of galectin-3 [32]. In addition, galectin-9 also induces apoptosis of peripheral $CD4^+$ and $CD8^+$ T cells through a Ca^{2+}-calpain-caspase 1 signaling pathway [33]. Interestingly, this "two-CRD" galectin has been recently reported to be a specific binding partner for the Th1-specific molecule Tim-3 and contribute to Th1 cell survival [8]. Taken together, these findings suggest that different members of the galectin family might act in concert to modulate T-cell survival and regulate the inflammatory response.

3.2. Regulation of T-cell activation

Galectins have been also shown to influence different events associated with T-cell activation (Fig. 1). In addition to the role of galectin-1 in the modulation of T-cell survival, Vespa et al. [34] showed that this protein modulates T-cell receptor (TCR) signaling and antagonizes TCR-induced IL-2 production in a murine T-cell hybridoma clone [34]. Interestingly, the same group further demonstrated that galectin-1 is able to antagonize TCR responses known to require costimulation and processive protein tyrosine phosphorylation, such as IL-2 production, while it is permissive for TCR responses that only require partial TCR signals, such as CD69 up-regulation and apoptosis [35]. Thus, by acting at early events of TCR signaling, galectin-1 may also exert a control on T-cell activation.

In this context, Demetriou et al. [36] reported that galectin-3 might play a role in restricting TCR complex-initiated signal transduction. The authors hypothesized that galectin-3 might form multivalent complexes with *N*-glycans on the TCR, thereby restraining the lateral mobility of TCR complexes [36]. This effect was abrogated in mice deficient in the β1,6 *N*-acetylglucosaminiltransferase (Mgat5), a crucial enzyme in the *N*-glycosylation pathway.

3.3. Modulation of the Th1/Th2 cytokine balance

It has been demonstrated that galectins can differentially modulate the cytokine balance in different autoimmune and inflammatory conditions (Fig. 1). While galectin-1 inhibits the secretion of IL-2, IFN-γ and TNF-α [35,37], it can dramatically increase IL-5 and IL-10 secretion by activated T cells [9,38]. In addition, in vivo studies revealed the ability of this protein to skew the balance towards Th2 or T-regulatory (Tr1) cytokine profiles [9,12,13,16,18]. Likewise, recent observations indicate that galectin-2 may also shift the cytokine balance towards a Th2 profile [24]. In contrast, it has been demonstrated that galectin-3 may interrupt IL-5 synthesis and silence Th2-mediated chronic airway inflammation [39]. However, a recent study indicates that galectin-3-deficient mice develop higher Th1 responses in a model of airway inflammation in vivo [40]. These discrepancies might be explained by the different strategies used by the authors to evaluate the role of galectin-3 in vivo (i.e. *gal-3* gene therapy versus induction of inflammation in *gal-3*$^{-/-}$ mice). Finally, galectin-4 has been shown to exacerbate intestinal inflammation by inducing the secretion of T-cell-derived IL-6 [14]. Therefore, it seems evident that different members of the galectin family may differentially influence the Th1/Th2 cytokine balance and modulate the inflammatory response in vivo. Current research is aimed at dissecting the individual role of particular members of the galectin family in immune-mediated disorders by targeted disruption of single or multiple galectin genes.

4. Concluding remarks

Galectins have pleiotropic activities in immune regulation being capable of modulating T-cell survival, activation and cytokine secretion. Recent evidence indicates the relevance of different members of the galectin family in the regulation of T-cell physiology and chronic inflammatory disorders in vivo. This body of knowledge, documenting the coming of age of galectins as potential immunomodulatory agents or targets for immunosuppressive drugs, represents a sound basis to further explore their immunoregulatory properties in the development of immunomodulatory therapies for autoimmune diseases, GVHD, chronic inflammation and cancer.

Take-home messages

- Protein–glycan interactions control critical immunological processes involved in T-cell homeostasis.
- Galectins, a family of glycan-binding proteins with affinity for β-galactoside containing oligosaccharides, can regulate the inflammatory response by influencing T-cell survival, activation and cytokine synthesis.
- The most extensively studied function of galectins is the regulation of apoptosis; some galectins can induce apoptosis when added exogenously to cells, whereas others regulate apoptosis through intracellular mechanisms.
- Administration of recombinant galectins in vivo can influence the severity of pathogenic responses in experimental models of chronic inflammation and autoimmunity.
- Recent evidence indicates that galectin-1 may also function as a soluble mediator employed by tumour cells to evade the immune response.
- Understanding the molecular mechanisms involved in the immunoregulatory functions of galectins might help to delineate novel therapeutic targets based on protein–carbohydrate interactions for autoimmune and chronic inflammatory disorders.

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Anti-Ro/SSA antibodies in rheumatoid arthritis: clinical and immunologic associations.

To assess the prevalence of anti-Ro/SSA in rheumatoid arthritis (RA), and to analyze clinical and serological features of anti-Ro/SSA positive patients with RA. Cavazzana I. et. al. (Clin Exp Rheumatol 2006; 24: 59-64) assessed anti-Ro/SSA antibodies in 195 consecutive patients affected by RA. Anti-Ro was found in 12 patients, with a prevalence of 6%. These 12 patients were pooled with other 15 patients known to have anti-Ro/SSA antibodies and RA, in order to evaluate their clinical and laboratory features. Anti-Ro positive patients showed a common pattern of joint involvement at onset and a comparable progression of disease compared to anti-Ro negative subjects. In addition, extra-articular manifestations and peculiar autoantibody profile were found significantly associated to anti-Ro/SSA positivity. Anti-TNF-alpha treatment did not cause further progression of autoimmunity neither on laboratory nor on clinical ground. Anti-Ro/SSA can be detected in about 6% of patients affected by RA. These patients presented a peculiar clinical picture characterized by extra-articular manifestations some of which are known to be anti-Ro/SSA correlated, while others are more disease-specific. Anti-Ro/SSA is significantly associated with other autoantibodies not specific for RA such as anti-dsDNA.