Recent Progress in the Understanding of B-Cell Functions in Autoimmunity

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Our early concepts of the normal role of B cells in immunity focused on their ability to produce antibodies (Ab) and in the case of autoimmune diseases autoAbs, some of which were pathogenic. Over the past 10 years, it has become apparent that B cells display a variety of characteristics, other than Ab production, which could contribute to autoimmunity. They normally play a role in the development of lymphoid architecture, regulating T-cell subsets and dendritic cell (DC) function through cytokine production, and in activation of T cells. Receptors editing is also important in B cells which aids in immunity to infection and, possibly, prevention of autoimmunity. Transgenic animal models have now shown that B cells are necessary for many autoimmune diseases although their Ab products are not required in some cases. Negative signalling by CD5 and other molecules, such as CD22, in maintaining tolerance through recruitment of src-homology two domain-containing protein tyrosine phosphatase-1 has also been documented. In fact, we have now reached a new era whereby the B cell has returned as an important contributor to autoimmune disorders, so that the race is on to characterize signalling regulation via the B-cell receptor and coreceptors. Identification of such molecules and their potential defects should lead to effective ways of controlling the immune response and in particular preventing the development of autoimmune states. The classical view of B cells in the biology of immune responses to infectious and self-antigens (Ag) that they promote immunity primarily by producing Ab turns out to be rather naïve. Indeed, studies over the last few years indicate that this view is far from complete, and suggest that B lymphocytes have extraordinarily diverse functions within the immune system. Furthermore, it is becoming increasingly clear that the pathogenesis of autoimmune diseases cannot solely be accounted for by T cells, and intrinsic abnormalities of B cells have been described in such conditions. In this brief review we highlight some recent observations in the context of B lymphocyte in pathophysiology, and focus on their revival as pivotal players the pathophysiology in autoimmune diseases. Yet, it remains difficult to provide a model of how important B cells are in immunity and autoimmunity.

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B LYMPHOCYTES AND THE REGULATION OF THE IMMUNE SYSTEM

B lymphocytes influence the formation of follicular DC networks and secondary lymphoid architecture

Recent studies of the prominent and influential pro-inflammatory cytokines, such as tumour necrosis factor (TNF)-α and lymphotoxin (LT)-α and LT-β have unravelled intriguing new insights, not only into their diverse functions, but also into the signals that establish and/or preserve the architecture of secondary lymphoid organs (Table 1). Thus, there is now evidence that both TNF-α and LT-α/-β are involved in establishing and maintaining normal splenic architecture, as

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shown by the findings that LT-α [1], LT-β [2], TNF receptor-I [3], and TNF-α [4], knock-out (KO) mice all have abnormal splenic architecture, as do mice in which LT-α and/or LT-β signalling is disrupted [5–7]. Although it is still not exactly apparent why defects in signalling by TNF/LT create such disturbances in splenic architecture, it is intriguing that DC networks, conspicuous components of B-cell follicles, are not present in any of the different TNF/LT-KO mice [1–7]. The basic link between the production of these cytokines, B lymphocytes and the formation of DC networks was initially suggested in SCID mice which lack mature B lymphocytes and DCs [8–10]. Subsequent studies established that host-derived DCs differentiate in the spleen of SCID mice after transfer of wild-type lymphocytes [8–10]. The recent elegant studies by Gonzalez et al. [11] are even more relevant to the role of B lymphocytes in that they showed that B cells induce the appearance of DCs through the expression of membrane LT-α. These investigators observed that, following the transfer of B cells from membrane LT-α+/+ but not LT-α−/−, the expression of LT-α/−β on B lymphocytes, but not T lymphocytes, was critical for the formation of DC nettings. Furthermore, an intimate interaction between the B cells and DC precursors was essential for the DC function. These studies confirmed previous suggestions of a direct role for B cells in the DC development. For example, Cerny, Zinkernagel and Groscurth have reported that DCs are absent in the lymphoid organs of mice deprived of B cells [12]. It has also been demonstrated that purified B cells obtained after exhaustive elimination of T cells are sufficient to induce DCs in SCID mice [10]. The requirement for LT-α expression on B cells was seen in the presence of LT-α-expressing T cells, and within a white pulp expressing LT-α.

**Table 1. Various commitments of B cells**

<table>
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<th>Commitment</th>
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<tr>
<td>Induce the appearance of dendritic cells (DCs)</td>
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<td>Co-ordinate T-cell migration and differentiation</td>
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<tr>
<td>Modulate the production of cytokines by DCs</td>
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<tr>
<td>Prime T cells in contact sensitivity</td>
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<td>Process and present antigens to T cells</td>
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**B lymphocytes co-ordinate T lymphocyte migration and differentiation in secondary lymphoid organs**

Pathways of T-lymphocyte activation and differentiation into effector Th1 and Th2 cells have been the focus of intensive research over the last decade [14]. This has been owing to the impact that the T-lymphocyte differentiation along these two pathways has on developing appropriate immunity to deal with infectious pathogens and also on susceptibility to autoimmune pathology. In this respect the role of different costimulatory molecules CD28-B7 [14] CD40-CD40 Ligand (L) [15] interactions, and more recently the OX40-OX40L pathway [16] have been extensively investigated. CD28 whose engagement by its ligands CD80 and CD86 (constitutively expressed by mature DCs) is an absolute requisite for T-cell-dependent germinal centre (GC) formation, whereas this has a limited role in the T-cell subset differentiation [17]. The CD40L, which is upregulated following the initial stimulation by Ag and the CD28-CD80/86 interaction, is involved in stimulating DCs to release interleukin (IL)-12, which in turn influences the differentiation of effector T cells into Th1 cells [18]. Studies on the expression of CXCXR5 and the migration of the activated T cells to GC have highlighted the importance of the OX-40/OX-40L juncture that is induced in a CD28-dependent pathway [19]. Interestingly, it has also been demonstrated that OX40 signals from DCs co-ordinate the selection, migration, and cytokine-mediated differentiation of both Th1 and Th2 CD4 T-cell help for B-cell GCs [20]. However, it appears that Ag-specific interaction of B and T lymphocytes and the engagement of OX40 on activated T cells by OX40L on activated B cells induces IL-4 production, suppresses interferon (IFN)-γ production and results in the differentiation of Th2 cells and plasma cells under the influence of IL-4 that has just been released [21].

**B lymphocytes influence the pattern of immune responses through the production of cytokines**

The paradigm that there exist two distinct effector lymphocyte populations, Th1 and Th2, has been strongly substantiated. These subpopulations produce distinct spectra of cytokines compatible with the kind of response required to particular Ags. Thus, it is known that Th1 cells secrete IFN-γ and IL-2, whilst Th2 cells produce IL-4, IL-5 and IL-6. The latter cytokines influence the activation and maturation of B lymphocytes. In addition, Th1 cytokines enhance further production of Th1 cells whereas inhibiting Th2 cells, and vice versa. Although it has long been known that B cells produce cytokines, such as IL-10, IL-6 and TNF-α they also acquire the ability to express IL-2, IFN-γ, IL-4 and IL-12 when stimulated with Ag in the presence of effector Th1 cells [22–25]. It is extremely important that more recent studies demonstrate that naïve B cells differentiated themselves into polarized B cells with different cytokine profiles, following stimulation with Ag and polarized effector Th1 and Th2. Polarized B cells have been termed Be1 and Be2, respectively [26], inasmuch as, once induced, these lymphocytes regulate the level of Th1 and Th2 cells. Consequently, Be1 cells, by virtue of their production of IFN-γ and presentation of specific Ag to T lymphocyte, promote the expansion of Th1 cells. In contrast, IL-4 produced by Be2 cells promotes Th2-cell development. Therefore, Be1 and Be2 cells behave as classical antigen-presenting cells (APC) that can potentially regulate the profile of the immune response. The fact that Th1/Th2 and Be1/Be2 cells can cross-regulate the differentiation of naïve B and T cells leads to the possibility of a significant amplification of immune responses. Such positive feedback amplification, if out of control, could potentially lead to autoimmunity [27]. The precise origin of the Be1 and Be2 cells remains, however, to be defined.
**B cells influence the production of cytokines by DCs**

In addition to the increased awareness of the role of B lymphocytes in affecting effector T-lymphocyte differentiation, and by inference their ability to induce Th1- or Th2-type cytokines, it has been demonstrated that B cells regulate the production of cytokines by DCs, as a result of their ability to produce IL-10. This cytokine, produced by B cells among other cells, has indeed been shown to inhibit the production of IL-12 by DCs [28,29]. In turn, IL-12 induces IFN-γ production by Th1 cells, and acts to suppress Th2 development, as well as favour Th1-cell expansion. Hence, not only do B cells directly affect the differentiation of Th cells in an immune response, but they can also influence Th differentiation by DCs through an IL-10-dependent pathway.

**B cells prime T cells in a contact sensitivity model**

In a murine models [reviewed in 30] it has been established that B cells are necessary for the induction of the contact sensitivity to picryl chloride and 4-ethoxymethylene-2-phenyl-2-oxazolin-5-one. It has therefore been concluded that the B cells produce immunoglobulin (Ig)M that form immune complexes with the inciting Ag, and lead to complement fixation. Activation of mast cells through C5a, and subsequent release of TNF-α and 5-hydroxytryptamine, results in the recruitment of T cells. Interestingly, these B cells have been shown to express CD5 and therefore are of the B-1a type (see below).

**B lymphocytes and tolerance to self antigens**

The capacity of B lymphocytes to capture, process and present Ags to T cells has been extensively investigated. In general, there is a consensus that naïve B lymphocytes cannot activate Ag-specific T cells. On the contrary, it has been argued that naïve B cells, by virtue of their lack of costimulatory molecules, can render T lymphocytes anergic. Recently, numerous investigators have claimed that B lymphocytes have the capability to induce the differentiation of Th2 cells. In elegant experiments, Mason and colleagues [31,32] showed that, by targeting Ags to B cells for presentation, the pattern of T-cell differentiation can be altered to Th2 cells when these Ags have been shown to induce Th1 cells under normal circumstances. Intriguingly, even more recent studies have shown that a population of B cells, B-1 cells (analyzed for their role in autoimmune since 20 years), may in fact contribute to maintaining self-tolerance.

B-1 cells, that express the CD5 Ag, first described as T-cell markers, have long been investigated for their ability to produce polyreactive Abs and examined for their cellular origin. The CD5 Ag, which is a transmembrane glycoprotein was first identified on malignant B cells [reviewed in 33], and subsequently shown to be expressed by a minor proportion of normal B cells [34]. This finding led to the concept that there are at least two main populations of B cells, B-1 and B-2 [35]. The first population encompasses the CD5-positive B cells, and the second represents the conventional CD5-negative B cells. B-1 lymphocytes are self-replenishing, mostly found in serous cavities, and associated with the production of low-affinity polyreactive autoAbs, as well as an increased propensity for malignant transformation [36]. Advances in leukocyte phenotyping have since allowed the B-1 population to be further divided into B-1a and B-1b cell subpopulations. B-1b lymphocytes lack surface CD5, but share all other phenotypic and functional attributes of B-1a cells. However, there are no precursors for B-1a cells in the adult, while a few precursors for B-1b cells persists in the bone-marrow (BM) throughout life. It remains unresolved as to whether or not the presence of CD5 on B cells, at least in man, indicates an activation or a separate lineage marker. We have postulated [37] that two discrete kinds of CD5 + B cells coexist, ‘classical’ CD5 + B cells and ‘induced’ CD5 + B cells.

Studies, using the hen egg lysozyme/immunoglobulin (HEL-Ig) transgenic (Tg) mouse model, have suggested that B-1 cells play a role in retaining tolerance to self Ags. Mice Tg for HEL-Ig and a soluble form of the self-Ag HEL generate B cells that are functionally impaired [38]. Breeding of this transgenic model onto the CD5-KO background resulted in the spontaneous loss of B-cell tolerance [39], raising the possibility that regulation exerted by CD5 results in tolerization of the autoreactive B cells. This loss of tolerance in anergic B-1a might be accounted for by polymorphisms (alternative splicing?) or point mutations involving the cytoplasmic tail of CD5 that participates in the negative regulation of B-cell receptor (BCR) signalling.

**The primary and secondary repertoires**

The importance of self-Ags in negative selection in the BM, originally postulated in the clonal selection hypothesis, is now established. It has, however, been difficult to test whether self-Ags also play a role in the positive selection of B cells [40]. In view of recent contrasting observations this issue appears to be most essential. By modifying the specificity of their BCR in the BM, auto-reactive B cells may initiate new Ig light chain rearrangements [41,42]. Self-reactive BCRs generated during the preceding stochastic gene recombination process can thus be eliminated, not only by classical deletion, but also by continued recombination, i.e. receptor editing [43]. Those immature B cells that undergo receptor editing express recombinase-activating genes, RAG1 and RAG2, encoding the recombination signal sequence – specific endonucleases that activate V(D)J recombinations [44]. Such genes are then extinguished by a feedback mechanism from the BCR. Assembly of Ag-receptor genes can, however, be reactivated in response to Ag in mature B cells in secondary lymphoid organs. These secondary rearrangements have indeed been described in a number of systems [43]. For example, it has been reported that RAG1 and RAG2 may be re-expressed in a subset of activated mature murine B cells population the GCs of draining lymph nodes.
[45], spleen and Peyer’s patches [46]. A similar phenomenon has recently been reported to occur in human tonsilar B lymphocytes [47]. If, once re-expressed, the RAG gene products are functional, an unfavourable surface Ig receptor may be revised again, and auto-reactive B cells arising by hypermutations in the dark zone of GCs can escape deletion. Alternatively, the interpretation has been maintained that new Ag receptor assembly in cells that fail to bind Ag may contribute to repertoire diversification by improving the affinity of some receptors [48].

Contrasting observations have recently been reported regarding the positive selection of mature B cells by self-Ags. There is compelling evidence that recruitment of mature short-lived B cells into the pool of recirculating B cells is dependent on BCR engagement by self-Ags [49]. Mature B cells which produce ‘natural’ self-reactive Abs have also been shown to express RAG1 and RAG2 genes [50], whereas other investigators have been unable to induce RAG1 expression in such B lymphocytes [51]. GCs of ectopic lymphoid follicle [52,53] are likely to be relevant to these secondary rearrangements in RA and primary Sjögren’s syndrome (pSS). Such secondary rearrangements have been demonstrated in rheumatoid pseudo-GC [54], and could possibly operate in salivary glands of patients with primary Sjögren’s syndrome (pSS). In fact, replacement events could either maintain or break the self-tolerance.

**B CELLS IN AUTOIMMUNE DISEASES**

*B cells are required for the initiation of many autoimmune diseases*

The MRL/1pr mouse strain develops a spectrum of disease manifestations similar to human systemic lupus erythematosus (SLE), including nephritis, vasculitis, sialoadenitis and skin disease [55]. B-cell-deprived mice of this strain, not only lack the immune deposit manifestations of nephritis such as glomerulonephritis, but also have no cellular infiltrates in the kidney or vasculitis [56]. In this same model, it was shown that B cells were required for the activation of the T cells. The exact role of B cells in this model remained unclear. More recently the same group has, however, shown that Ab produced by the B cells is not an absolute requirement for the development of the disease in mice expressing a mutant Tg of surface Ig which did not allow Ig secretion [57]. The authors favour the explanation that the B cells act as APCs to autoreactive T cells rather than contribute directly to pathogenesis perhaps through cytokine production. The nonobese diabetic (NOD) mouse model of diabetes – an organ-specific autoimmune disease also needs B cells where it is thought they play a role in Ag presentation [58,59].

In the Tg K/BxN T-cell receptor (TCR) mouse model of rheumatoid arthritis (RA), B cells are necessary for the production of specific pathogenic autoAbs to the self Ag glucose-6-phosphatase isomerase that are important in the disease [60,61]. In this model therefore, unlike the murine lupus or NOD mouse, it is the Ab itself and not the B cells acting as APCs, that give rise to the autoimmune disease.

B cells have recently been shown to be important in human RA. Although the mechanism remains elusive, it has been postulated that the B cells produce an IgG rheumatoid factor that can activate macrophages carrying FcyRIIIa to produce TNF-α [62]. Whatever the mechanism, refractory RA patients treated with CD20 to remove B cells, together with conventional therapy, has reached some success [63]. Although clearly important for the initiation of autoreactive T-cell activation or the production of autoAbs, B cells are not required for all models of autoimmune diseases, e.g. experimental autoimmune encephalomyelitis [64]. B cells in autoimmunity have recently been the subject of a mini review [65].

**B-cell signalling**

Recent years have seen a significant increase in the interest and understanding of the intracellular signalling pathways that regulate B-lymphocyte response and tolerance from the BCR (Table 2). Most of these works have been based on the realization that natural selection within the immune system is aimed at establishing a balance between the ability to combat a variety of infectious pathogens and yet preventing the danger of generating life-threatening autoimmune diseases. In this respect, there has been a plethora of studies of assessing the role of various BCR-associated signalling molecules and membrane molecules in B-lymphocyte responses [66]. Within seconds of the Ag interaction with the BCR, there is phosphorylation of tyrosine residues located within the immunoreceptor tyrosine-based activation motifs (ITAM) of the transducer elements Iglα and Iglβ. Thus, Ag recognition triggers the sequential binding to ITAMs and the activation of protein tyrosine kinases (PTK), such as lyn which is a member of the src family kinases family, and syk which is recruited by previously phosphorylated ITAM [67].

At the appropriate time, cytosolic phosphatases dephosphorylate these tyrosin residues to terminate signal transduction. The inability to properly terminate activation may therefore result in inappropriate responses. In this regard, it has been shown in SLE that B cells have abnormal Ag receptor-mediated early signal transduction events [68]. The authors showed that following the Ag receptor ligation, Ca2+ responses and PTK phosphorylation were abnormally high compared with other autoimmune diseases and controls.

<table>
<thead>
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<th>Table 2. B cells in autoimmunity</th>
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<td>Deficiency in lyn</td>
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<tr>
<td>Deficit in B-1 differentiation</td>
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<tr>
<td>Deficiency in CD22</td>
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<tr>
<td>Over-expression of CD19</td>
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<tr>
<td>Deficiency in src-homology 2 domain-containing protein tyrosine phosphatase</td>
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Role of polymorphism in signalling molecules in determining the fate and responses of B lymphocytes

In general terms, B-lymphocyte hyperactivity stemming from polymorphic variations in molecules that regulate qualitative and quantitative BCR signalling has been associated with increased susceptibility to autoimmune diseases. For example, a B lymphocyte hyperactivity syndrome associated with deficiency in lyn resulted in a disease resembling SLE in mice [69,70]. In accord with the fact that lyn is involved in both the initiation of BCR signals and their subsequent downregulation [71,72], it has been noted that it is an essential inhibitory component of BCR that acts as a modulator of BCR ligation-generated signalling. Thus, lyn KO mice show a delayed but increased Ca$^{2+}$ flux and exaggerated negative selection responses in the presence of Ag and spontaneous hyperactivity in its absence [73].

Some surface molecules important in negative signalling of B cells that play a role in maintenance of tolerance

CD5. CD5 was first shown to control TCR-mediated signalling in the developing thymocytes [74]. Pani et al. [75] have since established an association between the BCR and the src-homology 2 domain-containing protein tyrosine phosphatase (SHP)-1, so that cross-linking of the BCR results in an immediate dissociation of SHP-1. Furthermore, SHP-1 has homology 2 domain-containing protein tyrosine phosphatase (SHP)-1, so that cross-linking of the BCR results in an increased Ca$^{2+}$ flux and exaggerated negative selection responses in the presence of Ag and spontaneous hyperactivity in its absence [73].

Intriguingly, initiation of BCR signals and their subsequent downregulation might thus be a factor in the loss of tolerance to Sm and provide insight into the low prevalence of the anti-Sm response in murine and human SLE [86]. Furthermore, manipulation of the coreceptors CD19 and CD22 in this system, confirmed that the differentiation of B-1 and tolerance is dependent on the strength of the BCR signalling. Imbalance between CD19 that reduces the threshold and CD22 that enhances it, might be associated with the production of pathogenic autoAbs [87,88].

This is consistent with the interpretation that lymphocytes with a functional B-1a phenotype can be induced from adult precursors by appropriate Ags [89] and with the fact that CD5-positive and CD5-negative human B cells converge to an indistinguishable population on signalling through BCR and CD40 [90]. As stated before, there is, nonetheless, still much debate over the lineage origin of B-1, relative to B-2 cells, which have been assigned to separate development lineage by other groups, as discussed in [91].

CD19 and CD22. CD19 [92] and CD22 [93] are B-cell-associated transmembrane glycoproteins. CD19 is coupled with surface Ig and essential in the development of the B-1 cells [94]. This coreceptor amplifies the BCR signalling by increasing the PTK activity [93–97], allowing amplification of lyn activation [98]. B lymphocytes from CD19-defective mice become hyperresponsive to transmembrane signals, whereas those from mice that over-express CD19, even to a small extent, become hyperresponsive [99]. It is of great interest that modest changes in the expression or function of CD19 may shift the balance between CD19 and tolerance and immunity to autoimmunity, as suggested in systemic sclerosis [87,93].

In contrast, CD22 acts to dampen signals generated through the BCR and correlates with the development of autoAbs. This coreceptor might substitute for CD5 in B-1b and B-2 cells to recruit SHP-1 [87,100]. Deficiency in CD22 is sufficient to predispose to development of high-affinity autoAbs [101]. Furthermore, because the PTK lyn phosphorylates CD22, mice in which the lyn gene has been disrupted exhibit hyperactive B cells and autoAbs [100]. However, B cells in CD22-deficient
mice are much less severely affected than those in SHP-1-deficient mice, suggesting that SHP-1 regulates the BCR transduction by associating with other coreceptors, such as FcγRIIb or CD72. The latter B cell-specific lectin constitutes an additional substrate for SHP-1 [102]. It has been claimed that CD72 plays a negative role in the B-cell activation by recruiting SHP-1 [103]. Given that tyrosine phosphorylation of CD72 is associated with BCR-induced apoptosis, following strong stimulation, this molecule may rather have a net positive effect on BCR signalling.

**Genetic abnormalities in signalling.** The fate of B lymphocytes is dependent on BCR-induced signals, which are modulated by a number of genetically controlled cell surface coreceptors. It has been estimated that genetic factors account for between 61 and 96% of variance in levels of blood cells of 392 pairs of twins [104]. The expression of CD22 has been shown to be genetically controlled [101], and a quantitative genetic variation in the CD19 expression also correlate with autoimmunity. Autoimmune diseases may therefore result from subtle genetic alterations in PTK or phosphatases, that control the expression in the cell-surface signalling molecules. In addition to CD22 and CD19, the size of the B-1a cell pool appears to be under genetic regulation. It has indeed been established that twins have the same levels of B-1a [105], and that the relatives of patients with RA offer a similar frequency of B-1a cells as the proband [106].

**CONCLUSIONS**

In conclusion, B cells are more important contributors to autoimmune conditions than they were thought to be. They present a variety of characteristics other than the Ab production which could be instrumental in autoimmunity. Unexpectedly, the interplay between CD5, CD19, CD22 and FcγRIIB seem to be the key mechanism in the balance between immunity and autoimmunity. As highlighted by Stevenson and Natvig [107], there are many potential and rational approaches to immune therapy that are emerging from our increased understanding of the B cell pivotal role in nonorgan-specific autoimmune diseases.

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