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Dendritic cells in autoimmune diseases and neuroinflammatory disorders

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1. ABSTRACT

Dendritic cells are the most potent antigen presenting cells and have long been recognized as key regulators of the immune system, linking both stimulatory and inhibitory components of normal immunity. While DCs are fully characterized with respect to primary and secondary immune responses, their unique role in coordinating central and peripheral tolerance is just emerging. It is increasingly evident that the failure of DCs ability to maintain tolerance can lead to autoimmune and/or inflammatory diseases. However, existing literature highlighting participation of DCs in several autoimmune phenomena is scattered and remains underappreciated. This review is a comprehensive account of current knowledge characterizing the role of DCs in various autoimmune diseases including psoriasis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and diabetes. Additionally, it provides a rare description of DCs participation in various neuroinflammatory disorders including multiple sclerosis, HAM/TSP, Alzheimer disease and prion-associated diseases. Finally, a detailed description of the possible mechanisms of DC involvement in regulating immune response towards self versus non-self is discussed. Overall, the goal of this review is to establish DCs in the interface of tolerance and autoimmunity and generate a global interest in this field in order to exploit DC potential for the therapy of inflammatory diseases.

2. INTRODUCTION

One of the hallmarks of the immune system is its ability to protect the host from an abundance of potentially pathogenic microorganisms while avoiding the pathologic consequences of self-constituents. This avoidance is called self-tolerance, the failure of which can lead to debilitating immunological disorders thereby causing autoimmune phenomenon. Although the etiology of autoimmune disease is largely unknown at present, self-reactive immunoglobulins or autoantibodies, have been shown to be the key players in a number of autoimmune disorders (1-4). In addition, self-reactive T cells are also shown to play an important role in various autoimmune phenomena (5-10). In the bone marrow, immature B cells that express autoantibodies, which bind to self-peptides presented with major histocompatibility complex (MHC) class I molecules on bone marrow stromal cells, are negatively selected and thus undergo apoptosis. However, a few of these cells are able to escape negative selection and reach the periphery. On the other hand, immature T cells undergo a double selection procedure, first positive then negative. During the positive selection, only cells whose T cell receptors (TCRs) recognize self-MHC are selected, while the rest undergo apoptosis. As a result of positive selection, TCR repertoire with a spectrum of affinities to self-MHC are selected. Following positive selection, negative selection removes those cells that react too strongly with self-peptides expressed on MHC or self-MHC alone and thus undergo

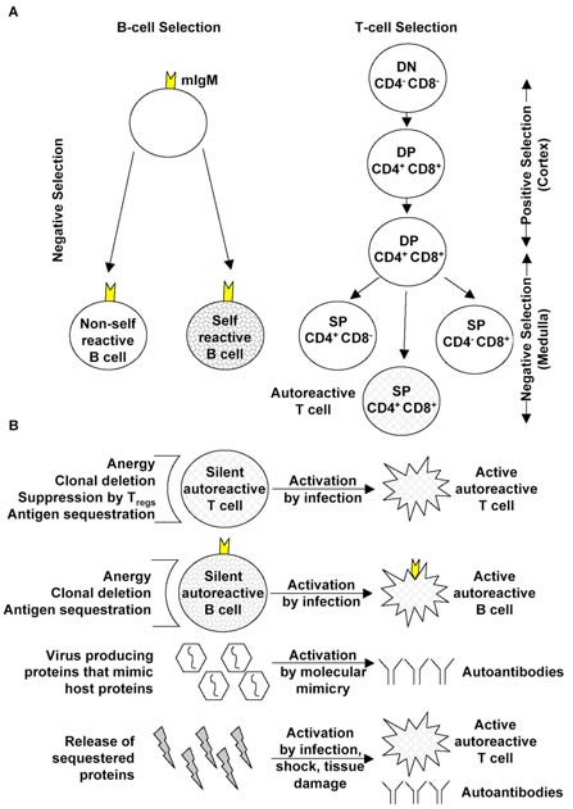

Figure 1. Mechanism of B and T lymphocyte selection, generation and activation of autoimmune cells. (A) In the bone marrow, immature B cells that express autoantibodies are negatively selected and thus undergo apoptosis. A few of these cells are able to escape negative selection and reach the periphery. The immature T cells undergo positive selection first in which only those cells whose TCR recognize self-MHC are selected, while the rest undergo apoptosis. Negative selection follows, in which cells that react too strongly with self-peptides or self-MHC undergo apoptosis. As with B cells, some autoreactive T cells manage to evade this selection process and then reach the periphery where they become activated and thus proliferate. (B) The escaped autoreactive cells lie in the periphery and are usually kept in check by anergy, protein sequestration or T_{regs} (only for T cells), however during infection these cells may get triggered and lead to autoimmunity. Viruses can produce proteins that mimic host proteins thus allowing the host immune system to target self-proteins. Yet another cause of autoimmunity is the release of sequestered self-proteins after injury.

apoptosis. However, certain autoreactive T cells manage to evade this double selection process and reach the periphery where they can become activated and proliferate. A number of back-up mechanisms are known to exist to ensure that these silent autoreactive T cells do not become activated. These mechanisms include anergy, clonal deletion by activation induced cell death, and antigen (Ag) sequestration. The development of an autoimmune disease involves the inheritance of susceptibility genes interacting with environmental triggers, which promote the stimulation of autoreactive T cells. These susceptibility genes may also be responsible for maintaining self-tolerance. Additionally, certain infections may upregulate the expression of costimulatory molecules on antigen presenting cells (APCs), which may result in the breakdown of anergy and the activation of T cells specific for self-antigen. Certain virus-derived products can mimic host proteins resulting in targeting of self-proteins by that antigen-specific immune response. Another cause of autoimmunity is the release of cryptic Ag that is normally hidden from the immune system. After injury, shock or stress these Ags are identified as foreign and, therefore, an autoimmune response is mounted against them. Figure 1 depicts the selection of B cells and T cells in bone marrow and thymus, respectively, and induction of autoimmune phenomenon by various foreign agents. Although several proposed mechanisms of autoimmunity exist, one single mechanism underlying all autoimmune pathogenesis has not been defined. Moreover, the role played by dendritic cells (DCs), the most potent APCs, in this process is just beginning to be explored.

DCs, first discovered by Steinman and Cohn (11), are primed to efficiently take up, process, and present Ag to T cells during both primary and secondary immune responses (12, 13). Four major categories of DCs are recognized: interstitial DCs, Langerhans DCs (lDCs), myeloid DCs (mDCs), and plasmacytoid DCs (pDCs). Thymic DCs are thought to arise from both common lymphoid and common myeloid precursors; however, peripheral DCs are primarily of myeloid origin (14). DCs have three intricate and innate properties that account for their roles in the immune system: (i) special mechanisms for Ag capture and processing, (ii) a unique capacity to migrate to defined sites in lymphoid organs, especially the T cell areas, to initiate immunity, and (iii) their rapid differentiation or maturation in response to a variety of stimuli ranging from Toll-like receptor (TLR) ligands to many other non-microbial factors such as cytokines, innate lymphocytes, and immune complexes (reviewed in (15)). Uptake of soluble Ag by DCs can be mediated by endocytosis, pinocytosis, and macropinocytosis (16). In addition to their classical role as an APC, DCs are shown to play critical roles during autoreactive responses (17-22). Another subtype of DCs, follicular DCs (fDCs), do not possess the classic Ag presentation role, but act as a depot for many pathogens. Follicular DCs have Fc receptors for antibody binding, which subsequently traps Ag. Many investigations have highlighted the role of these specialized DCs in autoimmunity. Furthermore, DCs have also been shown to induce a specialized set of regulatory T cell that aid in protecting against autoimmunity, known as T regulatory cells (T_{regs}) (23).

This review provides a comprehensive account of current existing knowledge characterizing the role of DCs in various autoimmune diseases. We are particularly interested in virus-associated inflammatory diseases and have been studying DCs role in a classical autoimmune neuroinflammatory disease known as HAM/TSP (human T cell leukemia virus-associated myelopathy/tropical spastic paraparesis), a chronic debilitating disorder very similar to multiple sclerosis (24-30). To this end, we have shown that

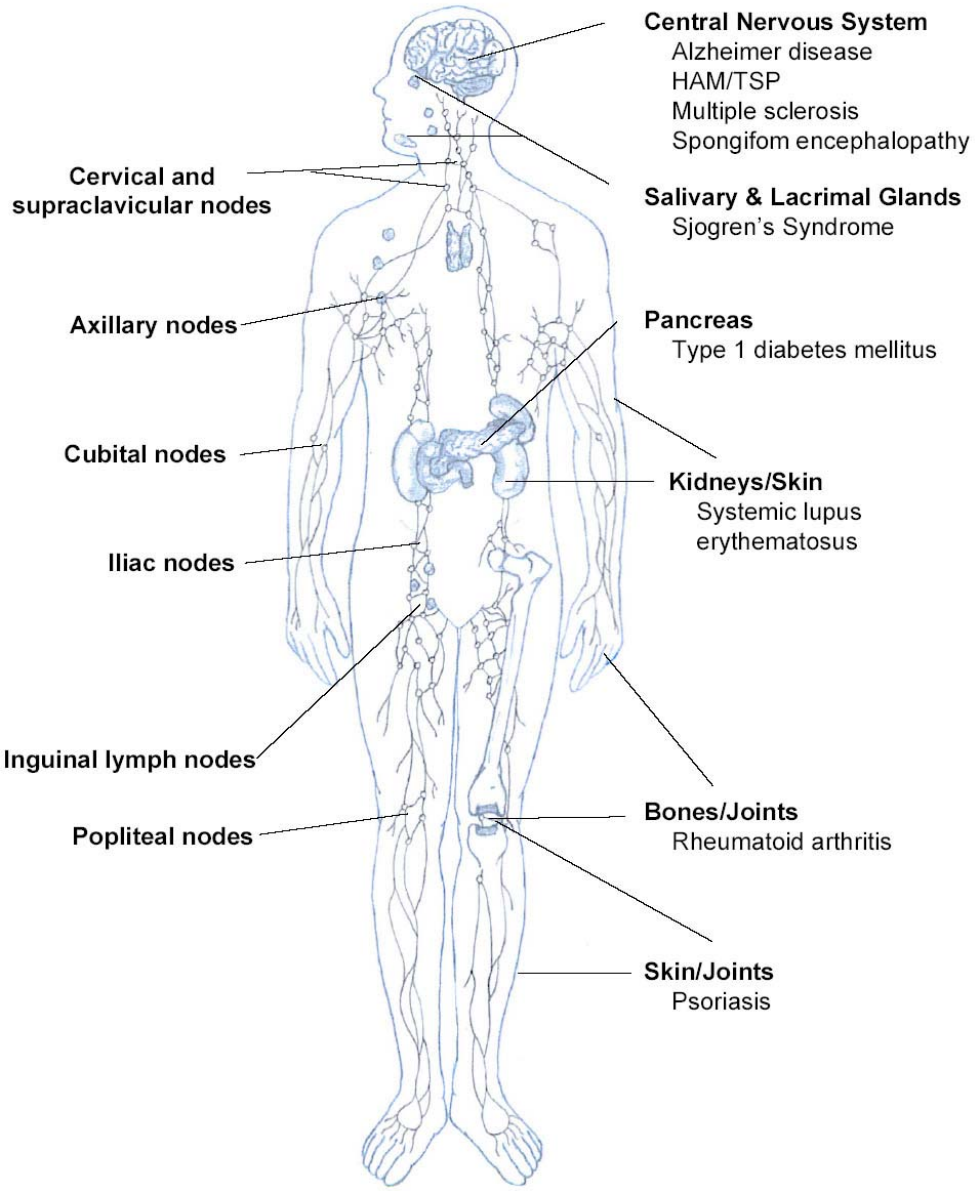

Figure 2. Common autoimmune diseases along with their sites of manifestation and their nearby lymph nodes.

HTLV-1 transactivator protein Tax (26-28, 30-33) can activate DCs and modulate its function leading to the intense proliferation of autoreactive T cells thereby playing a major role in priming immune and inflammatory responses observed in HAM/TSP (24, 29, 34, 35). Therefore, using HAM/TSP as a disease model of autoimmunity and neuroinflammation, we hope to develop a more conclusive understanding of major underlying mechanisms of other virus-associated autoimmune diseases. However, over the years it has become obvious that a need exists for a comprehensive review summarizing underappreciated literature that exists in this important field. Therefore, an attempt has been made to overview all the current existing literature that characterizes DC participation in various autoimmune and neuroinflammatory diseases. In this context, several autoimmune diseases including psoriasis, rheumatoid arthritis, systemic lupus erythematosus, Sjögren's syndrome, and diabetes have been discussed. Additionally, rare descriptions of the role of DCs in selected neuroinflammatory disorders have been provided including multiple sclerosis, HAM/TSP, Alzheimer's disease and prion-associated diseases such as transmissible spongiform encephalopathies. Finally, a detailed description of the possible mechanisms of DC involvement in regulating immune response towards self versus non-self is discussed. The collective overview of the relative literature has revealed the critical role that DCs play in regulating autoimmunity and inflammation. Figure 2 grossly depicts common autoimmune diseases along with their sites of

manifestation and the neighboring regional lymph nodes. The discussion that follows summarizes the participation of DCs in the immunopathogenesis of each one of these diseases in the context of available clinical and research observations.

3. RHEUMATIC DISEASES AND DCs

3.1. Psoriasis

Psoriasis is a chronic autoimmune inflammatory dermatosis affecting as many as 125 million people worldwide (36) and approximately 2% of people in the United States (37). It is a T cell-mediated disease in which there is increased keratinocyte proliferation (38). In psoriasis, it is likely that APCs in the skin, such as resident DCs, interact with infiltrated $CD4^+$ T cells to initiate the disease, providing signals for the activation of $CD8^+$ T cells in the epidermis. These infiltrated lymphocytes also produce growth factors for keratinocytes (38). The resulting interactions give rise to a vast array of Th1 cytokines including IL-12, IFN-gamma, and TNF-alpha. McGregor *et al* (39) demonstrated that epidermal DCs in psoriasis and other cutaneous inflammatory diseases express molecules that are known to be crucial for Langerhans cell driven T cell activation *in vitro*. Another study (40) demonstrated an accumulation of mature DCs within psoriatic lesions. From the results of this study, it was noted that T cell activation was dependent on the B7-CD28/CD152 costimulatory pathway to maintain the pathology of psoriasis. Lowes *et al* (41) identified a type of DC, which had proinflammatory effects in psoriasis through nitric oxide and TNF-alpha production. An additional study (42) revealed that pDCs, natural IFN-alpha-producing cells, infiltrate the skin of psoriatic patients and become activated to produce IFN-alpha during the early stages of disease. Moreover, the pDC-derived IFN-alpha was found to be essential to drive the development of psoriasis *in vivo*. Boyman *et al* (43) recently have reported on the local, rather than systemic, components of the immune system and suggested that a psoriatic lesion can be triggered and sustained by the local network of skin-resident immune cells. Due to these collective findings it is believed that DCs do in fact contribute to the inflammatory processes observed in psoriasis. Additionally, several hypotheses regarding the pathogenesis of psoriasis exists, many of which include DC-based mechanisms. Some believe psoriasis to be primarily a keratinocyte proliferation; others believe it involves abnormal activation of acquired immunity, while some separate investigators suggest a pathological activation of innate immunity pathways (44). Taniguchi *et al* (45) have noted that DC interactions with NK cells may be relevant in psoriasis (44), while other investigators have observed dendritic epidermal cells and pDCs in psoriatic lesions (46). These cells are known to be activated and possibly a source of TNF-alpha (47). Currently more focus is being placed on the genomics and immunopathogenesis of psoriasis and it is thought that targeting the early events of this disease may be an efficacious method toward remission in active psoriasis and psoriatic arthritis (44).

3.2. Rheumatoid arthritis

Rheumatoid arthritis (RA) is a highly inflammatory polyarthritis characterized by the proliferation of synovial tissue, often leading to joint destruction, deformity, and loss of function. Additive, symmetric swelling of peripheral joints is the hallmark of this disease. A characteristic histological feature is pannus (a mass of synovium and stroma consisting of inflammatory cells, granulation tissue, and fibroblasts) formation resulting in erosion of articular cartilage (38). Extra-articular features and systemic symptoms can commonly occur and may antedate the onset of joint symptoms. Chronic pain, disability, and excess mortality are unfortunate sequelae. According to investigators at the John's Hopkins Arthritis Center (48), RA affects individuals around the world with an estimated prevalence of 1 to 2% of the global population, affecting women about three times more frequently than men. Prevalence increases with age, reaching about 5% in women over age 55. The average incidence in the United States is about 70 per 100,000 annually. Although RA may present at any age, patients most commonly are first affected in the third to sixth decades of life.

An important role has been suggested for DCs in synovial inflammation (49-53), supporting the theory that utilizing DCs as a therapeutic agent is likely to be beneficial in RA. It is generally agreed that the disease process involves abnormal presentation of self-antigen by APCs, leading to activation of autoreactive T lymphocytes that are a significant component of RA pathogenesis (38). Additionally, autoantibodies from activated B cells can form immune complexes with self-antigen, which ultimately can lead to joint destruction (38). A number of observations support this conclusion, including histological studies demonstrating MHC class II^+ APCs clustered with T cells close to blood vessels, evidence of T cell activation in the synovial tissue and the synovial fluid, and improvement in the disease after functional inactivation of $CD4^+$ T cells (20, 54-57). Leung *et al* (49) demonstrated that DCs primed with collagen are able to induce inflammatory arthritis after transfer to joints. Consistent with DC trafficking into the joint, studies of the chemokine/chemokine receptor system in RA have indicated that there is selective recruitment of DC precursors that express inflammatory chemokines such as macrophage inhibitory protein 3 (MIP3)-alpha and chemokine receptors such as CCR1, CCR2, CCR5, and CCR6 (58). In addition, monocyte-derived dendritic cells (MDDCs) from RA patients were found to express high levels of TLRs and were found to react more strongly upon TLR ligand stimulation as compared to healthy controls (59). This has suggested active involvement of MDDCs in the inflammatory process (59). Furthermore, pDCs have also been identified in RA synovial tissue and comprise an APC population distinct from the previously described nuclear $RelB^+$ synovial DCs indicating a significant contribution to the local inflammatory environment (60). In a separate study investigators (61) found that immature DCs in synovial fluid may contribute to the perpetuation of inflammation via sampling of the inflamed synovial environment, and *in situ* presentation of arthritogenic Ag.

Collectively, these results indicate that DCs are involved in the onset and perpetuation of the inflammatory circle of synovitis. Wenink *et al* (62) have suggested novel mechanisms of how triggering of the Fc gamma receptor might be used to manipulate DC function and combat autoimmunity. As a consequence this suggests that DCs may serve as a potential tool in treating RA (62).

3.3. Systemic lupus erythematosus

Systemic lupus erythematosus (SLE), also referred to as lupus, is a multi-system autoimmune disease characterized by a vast array of autoantibodies, particularly antinuclear antibodies (ANAs), febrile illness, and injury to the skin, joints, kidney, and serosal membranes. It may be acute or insidious in its onset and predominantly affects women of childbearing age (38). The worldwide prevalence of SLE is 4 to 250 per 100,000 people (63). According to the National Women's Health Information Center (NWHIC) (64), lupus affects an estimated 239,000 people in the United States, of these about 9 out of 10 individuals are women. SLE appears to be more prevalent in women of African, Asian, Hispanic and Native American origin probably due to socio-economic factors (38). According to the Centers for Disease Control (CDC) (65), approximately one third of deaths occur among men and women younger than 45 years. During 1979-1998, the annual number of deaths from lupus rose from 879 to 1,406 and the crude death rate increased from 39 to 52 per million populations with a total of 22,861 deaths reported during this 20-year period. However, due to the lack of definitive epidemiological information on lupus, the exact number of people with lupus on a global scale is unknown. Patients with lupus produce abnormal antibodies in their blood that target their own tissues rather than foreign infectious agents. Because the antibodies and accompanying cells of inflammation can involve tissues anywhere in the body, lupus has the potential to affect different parts of the body. Many factors may contribute to developing SLE, but the specific etiology remains to be determined. Of the cellular factors, a number of investigations have identified DCs to play an important role in this immunopathogenic process.

Gill *et al* (66) have suggested that the pathogenesis of SLE may be due to altered DC homeostasis and identified the tumor necrosis factor (TNF) pathway as an underlying mechanistic defect in the observed DC alterations. According to Shodell *et al* (67), pDCs have been implicated in the pathogenesis of SLE due to their production of IFN-alpha. An additional study (68) identified a correlation between peripheral blood DC subsets and serum levels of IFN-alpha and IFN-gamma, thus suggesting a possible relationship between these cytokines in the pathogenesis of SLE. Additionally, Zhu and colleagues (69) provided evidence indicating that intrinsic abnormalities in DCs and possibly other myeloid cells may dictate several of the phenotypes associated with systemic lupus, including ANA formation and T cell hyperactivity. Another study (70) indicated that SLE patients had a reduced number of both BDCA-2^+ pDCs and $CD11c^+$ mDCs and concluded that these alterations in DC subsets may drive the autoimmune response observed in SLE. Many investigators also suggest that apoptotic cells serve as a significant source of autoantigens. The results of a study performed by Frisoni *et al* (71) suggested that DC uptake of opsonized histones and other nuclear Ags from apoptotic cells is a novel pathway for the presentation of nuclear Ags contributing to the inflammation in SLE. In an additional study (72), a positive correlation was found between lymphocyte apoptosis and peripheral blood DC count as well as the level of complement proteins in patients with SLE. It was concluded from this study that the apoptotic lymphocytes may attract peripheral blood DCs, contributing to SLE pathogenesis (72). It was also demonstrated that during apoptosis nuclear components are strongly modified through enzymatic reactions. If these cells are not cleared efficiently, auto-antigens may be released, taken up, and presented by mDCs, and possibly pDCs, in tissues or presented by fDCs within the lymph nodes to T and B cells. This occurrence could, therefore, be a mechanism for breaking peripheral self-tolerance (73). High circulating levels of type I interferon and DC abnormalities have also been reported to correlate with disease severity in SLE (74). It has also been demonstrated in both lupus-prone and normal mouse strains, that strong anti-double stranded DNA antibody responses can be induced by DCs that have been ingested by syngeneic necrotic, but not apoptotic, cells. Therefore, it is thought that these necrotic DCs play a significant role in the pathogenesis of SLE (75). Other studies have suggested that TLRs induce inflammation in SLE through the induction of IFN-alpha by pDCs (76, 77). Decker *et al* (78) showed that MDDCs from SLE patients were pre-activated suggesting that they might behave as more efficient APCs. An additional study (18) discovered a direct link between self-epitopes from apoptotic cells presented by DCs and autoreactive T-cell activation and demonstrated that apoptotic cells are critical for the induction of autoimmunity *in vivo* (18). In a more recent study (79), it was discovered that SLE patients display selective down-regulation of the DC maturation marker CD83 and had abnormal responses to maturation stimuli. These abnormal DCs were able to significantly increase proliferation and activation of allogeneic T cells when compared to control DCs. Therefore, it was concluded that mDCs from SLE patients display significant changes in phenotype, which promote aberrant T cell function and could contribute to the pathogenesis of SLE and organ damage (79). Furthermore, Wan *et al* (80) have recently reported that mouse SLE^+ DCs impair T_{reg} function through their overproduction of IL-6. These studies partly explain how the peripheral tolerance is broken in SLE; however, further characterization of the mechanism of autoimmune response in SLE is required.

3.4. Sjögren's syndrome

Sjögren's syndrome (SS) is an autoimmune exocrinopathy characterized by lymphocyte infiltration of salivary and lacrimal glands that leads to progressive xerostomia and xerophthalmia. This syndrome affects 1-2 million people worldwide (81) and strikes as many as 4 million Americans according to the Sjögren's Syndrome Foundation (82). One-third of patients suffer from systemic manifestations including arthritis, fever, fatigue, and mucosal dryness whereas those with major salivary

involvement show an increased risk to develop low-grade non-Hodgkin lymphomas. In addition, a minority of patients present with symptoms related to progressive hearing loss whose pathogenesis remains undefined. Deposition of autoantibodies to Ags of the inner-ear structures and infiltration by autoreactive T cells has both been implicated in the pathogenesis of SS. In this context, high levels of autoantibodies to both cardiolipin and M3 muscarinic receptors as well as to ciliar epitopes of the cochlear cells have been recently described (83). Typical antibodies that are found in most, but not all, patients include SS-A and SS-B antibodies, rheumatoid factor, thyroid antibodies, and others. Salivary glands can become larger and harden or become tender. Currently there is no cure for this syndrome and more advanced therapeutic approaches are being sought. In order to accomplish this, one must understand the mechanisms of autoimmunity and continue to search for the etiologic agent. In this regard, many reports have identified a link between DCs and the immunopathogenesis of SS.

Various subtypes of DCs found within the inflammatory lesions observed in SS have been reported (83-88). According to Oxholm *et al* (89), a characteristic feature of SS is IgG-binding to the surface of lDCs. They further demonstrated a qualitative and quantitative defect in lDCs as measured on epidermal sheets of SS patients. In another *in vivo* study (90) using the brown Norway rat as an animal model for focal sialoadenitis in SS, it was observed that T cells and DCs dominated the early infiltrates, whereas B cells were absent. Aziz *et al* (91) have suggested that fDCs may be of importance in the immune responses involved in SS and the retention of infiltrating lymphocytes in the glands. In another study (92), it was suggested that SS patients have dysfunctional DCs, with abnormalities in cell surface Ag and the inability to stimulate autologous T cells effectively. Another *in vivo* study (93) reported the detection of increased numbers of DCs, before lymphocytic infiltration, in the submandibular glands of non-obese diabetic (NOD) mice compared to those in control suggesting that DCs play a role in the initiation of sialoadenitis in NOD mice. Differences observed in other strains of mice included composition and organization of inflammatory infiltrates suggesting that there are two types of sialoadenitis found in mouse models for SS. Therefore, it is possible that different types of sialoadenitis also exist in humans and that the pathogenetic process in both the early and late phases of the autoimmune reaction differs among patients (93). Ozaki *et al* (94) have concluded from their results that there is selective trafficking of $CD11c^+$/ $CD1a^+$ DCs into focal sites of inflammation in SS and a subsequent promotion of T helper 1 (Th1) balance indicating a novel pathogenesis of SS. It has also been suggested that these $CD11c^+$/$CD1a^+$ DCs present Ag to autoreactive naïve T cells in the lymph nodes at the initial stages of the disease (95). Another study performed by Bave *et al* (96) suggested that RNA-containing immune complexes activate pDCs to prolong IFN-alpha production at the tissue level, which promotes the autoimmune process with increased autoantibody production and formation of more endogenous IFN-alpha inducers. Finally, a recent study (97) reported a more frequent presence of IFN-producing pDCs in SS patients as compared to controls. These studies clearly indicate that DCs are critical in the immunopathogenesis of Sjögren's syndrome.

4. DIABETES AND DCs

Type 1 diabetes mellitus (T1DM) is the most common metabolic disease of childhood, with a yearly incidence of 15 cases per 100,000 people younger than 18 years. Roughly 5-15% of all cases of diabetes are T1DM. Approximately 1 million Americans have T1DM, and physicians diagnose 10,000 new cases every year. Scandinavia is known to have the highest prevalence rates for T1DM, while China and Japan have the lowest prevalence rates, with less than 1% of all people with diabetes. T1DM is essentially an autoimmune disease characterized by an absolute deficiency of insulin caused by destruction of pancreatic beta cells. This destruction is due to autoreactive T cells acting against beta cell Ags. Insulin is a hormone that is essential for the metabolism of carbohydrates, lipids, and proteins. Without insulin, the glucose formed from these energy sources cannot enter cells and remains in blood at high concentration, thus resulting in hyperglycemia.

Consistent with their roles in other autoimmune diseases, DCs are found to play a role in diabetes. Papaccio *et al* (98) demonstrated that the disappearance of DCs from the infiltrate is concomitant with both the formation of intra-islet infiltration and the increase in proinflammatory Th1 cytokine levels. This study proposed that DCs might exert a protective role against the development of diabetes. Another study (99) reported that treatment with human gamma globulin pulsed DCs was associated with increased levels of IL-4, IL-10, and, to a lesser extent, IFN-gamma and diminished levels of TNF-alpha in the supernatants of islets from NOD mice, a widely used animal model of T1DM. This observation (99) may be related to the fact that exogenous IL-4 and IL-10 are known to exert anti-diabetogenic effects in NOD mice and early blockade of endogenous TNF-alpha prevents NOD mouse diabetes. Although some studies have found DCs to be protective, other studies suggest that DCs infiltrated into the pancreatic islets are capable of stimulating T cells by the MHC class II-antigenic peptide complex, together with costimulatory molecules, which eventually lead to the beta-cell destruction in NOD mice (100). Additionally, another *in vivo* study (101) demonstrated that DCs derived from NOD mice were more sensitive to various forms of stimulation compared to those from C57BL/6 and BALB/c mice, resulting in increased IL-12 secretion. These investigators concluded that an enhanced capacity of NOD DCs to secrete IL-12 would be expected to contribute to the development of a pathogenic Th1 response during the diabetogenic process (101). The results of an additional study (102) have suggested that NOD DCs are inherently biased towards abnormally high costimulation and Th1-induction, two features that would be expected to confer activation and persistence of autoreactive T cells. Another study (103) reported that DCs were located around the pancreatic islets in type 1

diabetic patients, but were absent in pancreatic tissue of normal controls. Additionally, Liang *et al* (104) recently have shown that administration of liver $B220^+$ DCs, a subset of DCs with regulatory properties, protected 60% of NOD mice from the development of diabetes. Several studies have demonstrated successful prevention of TIDM using DC therapy initiated early in the process of islet destruction in NOD mice. However, further investigation is needed to establish whether DC-based therapies block disease onset at advanced stages of islet destruction or even reverse acute-onset T1DM. Lo and Clare-Salzler (105) have proposed a therapeutic DC-based vaccine for T1DM in which the timing of DC therapy and selection of antigenic peptide(s) for DC loading may be critical for the success of this approach. In this vaccine, DCs are loaded with Ag from pancreatic draining lymph nodes or islets, and injected intravenously or subcutaneously. Furthermore, Krueger *et al* (106) demonstrated that vaccination with insulin-pulsed NOD-DC1, a cell line with a phenotype of mDCs ($CD11c^+$, $CD11b^+$, $DEC\text{-}205^+$) that express MHC class II and co-stimulatory molecules (CD40, CD80, CD86), results in an antigen-specific prevention of diabetes. Therefore, it will be of great interest to determine whether DC-based therapy can provide an effective approach to T1DM prevention in human clinical trials.

5. NEUROINFLAMMATORY DISEASES AND DCs

In addition to the above discussed autoimmune diseases, the role of DCs is very well characterized in several neuroinflammatory diseases. Traditionally, the CNS has been regarded as an immune-privileged site where inflammatory cells, such as DCs and other cells of the immune system, could not gain access. It was not until 1996 that the presence of DCs in the CNS was first described (30). Although it is known that certain CNS pathogens and Ags may escape adaptive immune responses in the brain, these pathogens can still be targeted by T cell responses, leading to neuroinflammation as reviewed by Peszkowski *et al* (90). These T cell responses are believed to be initiated by APCs such as DCs (107). Additionally, McMahon *et al* (108) have suggested a tolerogenic role for CNS-resident DCs and that a thorough characterization of CNS DC phenotype and function is greatly needed. It is known that DCs accumulate in the CNS parenchyma during a vast array of immune responses (108). However, there still remains some controversy regarding the origin of these CNS APCs and their role in neuroinflammatory disease. Regardless of this current debate, several investigators have described the role of DCs in various CNS pathologies as detailed in the following discussion.

5.1. Multiple Sclerosis

Multiple Sclerosis (MS) is a relapsing, demyelinating disease that affects the CNS. MS more frequently affects populations located in higher latitudes (above the 40° latitude) away from the equator, than in lower latitudes, closer to the equator (109, 110), affecting as many as 2.5 million people worldwide (111). There are estimated to be 400,000 people currently in the U.S. with MS, most commonly affecting people between 20 and 40 years of age as per the statistics provided by the National Multiple Sclerosis Society (109). MS is more prevalent among Caucasians (particularly those of northern European ancestry) as compared to other ethnic groups. MS is considered to be a neuroinflammatory autoimmune disease specifically attacking myelin, a fatty tissue in the CNS that surrounds nerve fibers and allows electrical impulses to be conducted (112, 113). Loss of myelin in multiple areas leads to sclerotic scar tissue formation known as plaques or lesions. The nerve fibers can also become damaged disrupting the ability of nerves to conduct electrical impulses to and from the brain. The clinical symptoms of MS include severe neurological dysfunction ranging from blurred vision to paralysis (114). It is divided into three distinct, clinically defined subtypes: relapsing-remitting MS, secondary progressive MS, and primary progressive MS. One of the most significant themes describing the pathogenesis of MS is that of epitope spreading, first reported by Sercarz and colleagues (115). These investigators demonstrated that inflammatory processes initiated by T cell recognition of one myelin protein epitope subsequently leads to the activation of autoreactive T cells recognizing other epitopes of the same protein (115). Concurrently, there is activation of T cells recognizing other myelin proteins that presumably get degraded and then loaded into the MHC of local APCs. The complete etiology of MS is currently unknown; however, many reports suggest the involvement of DCs in its pathogenesis.

Increased frequency of pDCs and mDCs have been reported in the CSF of MS patients, with the latter subpopulation having a more mature phenotype in CSF than those in the blood (116). Additionally, myelin-specific APCs have been identified in the cervical lymph nodes of MS patients (117) suggesting that these APCs may be able to migrate to secondary lymphoid organs, carrying myelin Ags to these areas and resulting in T cell activation (108). In an additional study (118), DCs were found to be localized to occasional perivascular cuffs in demyelinated lesions in MS autopsy tissue. Pettersson *et al* (119) showed that estrogen may induce tolerogenic properties of DCs and interferon beta reduces the secretion of proinflammatory cytokines as well as delays differentiation of DCs from monocytes (120). An *in vivo* study (17) using a mouse model showed that $CD11c^+$ mDCs alone are sufficient to present Ag to primed myelin-reactive T cells in order to trigger CNS inflammation. Other investigators (17) have found that a population of $CD11c^+$ DCs is sufficient to present Ag to autoreactive T cells in order to mediate CNS inflammation and clinical disease development. They have also observed DC-SIGN (dendritic cell-specific ICAM-3-grabbing non-integrin) positive cells in close proximity to invading T cells in acute and chronic active human MS lesions. This study also confirmed the presence of DCs at the blood-brain barrier and meninges in mice. Additionally, analogous $DC\text{-}SIGN^+$ cells were found in non-inflamed human brain tissue, suggesting that initial Ag presentation could potentially occur at the blood-brain barrier, which may promote entry of T cells into the CNS. Furthermore, Karni *et al* (121) demonstrated that slow progressive MS patients had an increased percentage of DCs expressing the costimulatory molecule CD80, a decreased percentage expressing

programmed death ligand 1 (PD-L1), and an increased percentage producing the immunoreactive cytokines IL-12 and TNF-alpha compared to those with relapsing MS or healthy controls. Also there was an upregulation of CD40 expression by DCs from both relapsing and slow progressive MS patients compared to controls. Other observations included varied induction of Th1 versus Th2 cytokines in which DCs from relapsing MS patients induced higher levels of both types of cytokines compared to controls while DCs from slow progressive MS patients only induced a Th1 response (121). The results of another study (122) suggested an impaired maturation state of DCs in primary progressive MS patients. In a different study (123), when stimulated with IL-3 and CD40L, pDCs of MS patients demonstrated lower or delayed upregulation of maturation markers CD86, CD137 (4-1BBL), CD40, and CD83. Additionally, depletion of pDCs in MS patients, but not in controls, had no effect on generation of T_{regs}. Therefore, these observations suggest a functional abnormality of pDCs in MS patients and offer some clues regarding the immune dysregulation observed in this disease. Therefore, these studies concluded that abnormalities of DCs existed in MS patients and may correlate with pathogenesis and stage of disease. Other studies have suggested that DCs that are recruited into MS lesions may play a role in the stimulation and generation of autoreactive T cells, thus leading to neuropathology (124). Additionally, during certain viral infections, cytokines produced from DCs, such as IL-12 and INF-gamma, can activate autoreactive T cells. It was thus suggested that viral proteins that exhibit molecular mimicry with CNS proteins could prime a genetically susceptible individual leading to autoimmunity through bystander activation by cytokines (125).

Due to the key component of inflammation observed in MS, many investigators have turned their focus toward anti-inflammatory mechanisms. Liu *et al* (126) have demonstrated that microglia release reactive oxygen species into the local environment resulting in inflammation. Olsson *et al* (127) have taken an alternative approach, targeting gene candidates that may be key genes that link to aggressive neuroinflammation. Others suggest that specific complement components may be proinflammatory, as well as neuroprotective and play key roles in MS pathogenesis (128). Thus, specific immune responses have been suggested, but one single pathway has yet to be indisputably identified. These collective findings do suggest DCs as key players in MS pathogenesis; however, further characterization is required to formulate a more conclusive mechanism.

5.2. HTLV-1 associated myelopathy/tropical spastic paraparesis or HAM/TSP

HAM/TSP is a chronic debilitating neurologic disorder with similarities to MS (129-132) but with a defined causative agent. HAM/TSP is caused by human T cell leukemia virus type 1 (HTLV-1), which was discovered in the early 1980s and is considered to be the first human retrovirus identified (133). HTLV-1 causes a number of abnormalities, the most prominent being a progressive lymphoma designated as adult T cell leukemia (ATL) and HAM/TSP. HTLV-1 infects over 20 million people worldwide (133) and is endemic in southern Japan, Caribbean, Central and South America, Middle East, and Africa (134). While a majority of the infected individuals are asymptomatic carriers, about 2-3% develop ATL while an additional 0.5-3% develop HAM/TSP (135). HAM/TSP is a chronic progressive disease of the CNS characterized by weakness and stiffness in the lower extremities, lower back pain, urinary dysfunction, thoracic myelopathy, and paraplegia. The development of HAM/TSP is closely associated with the intense proliferation of T cells that are HTLV-1-specific but may cross-react with neural Ags (136), thus characterizing HAM/TSP as an autoimmune disease. It has also been demonstrated that the majority of HAM/TSP patients develop antibodies to the HTLV-1 transcriptional transactivator protein Tax that cross-reacts with the neuronal protein hnRNP (heterogeneous nuclear ribonuclear protein) A1 indicating molecular mimicry between the viral and host proteins (131, 132). Previous studies also demonstrated that the M9 epitope of hnRNP A1 is the one that is recognized by the cross-reactive antibodies and is a critical sequence, necessary for transporting this protein in and out of the nucleus. Investigators also found that these cross-reactive antibodies inhibited normal neuronal firing, contributing to the potential neurodegeneration, dysfunction, and death. Additionally, pathologic observations indicate a symmetrical loss of myelin and axonal dystrophy in the thoracic and lumbar regions of the spinal cord thus affecting the corticospinal tract (137). The similar characteristics shared between MS and HAM/TSP is contributed to the hnRNP A2 protein, which has homology to hnRNP A1 and is involved in transporting myelin basic protein into oligodendrocytes. Future studies may provide more in depth insight into the specific role of hnRNPs in neuroinflammation associated with both of these diseases.

Not much is known as to what determines disease outcomes of ATL versus HAM/TSP, but it is thought to be associated with several factors, including viral strain, viral load, human histocompatibility leukocyte antigen (HLA), and the immune response. These observations have been previously reviewed by Barmak *et al* (26). The most characteristic feature during the course of HAM/TSP is the spontaneous proliferation of lymphocytes (SPL), the levels of which reflect the severity of the disease (138). Depletion of DCs from the patients' peripheral blood mononuclear cells (PBMCs) abolishes SPL while supplementing DCs, but not B cells or macrophages (other potent APCs), restores proliferation. Furthermore, SPL can be blocked by monoclonal antibodies to MHC class II, CD86, and CD58 indicating a DC-dependent mechanism (139). Additionally, this disease features a robust highly stimulated immune response including the oligoclonal expansion of $CD8^+$ cytotoxic T lymphocytes (CTL) specific for the viral oncoprotein Tax (24, 29, 140). Hanon and colleagues (141) have reported that $CD8^+$ lymphocytes selectively kill Tax-expressing $CD4^+$ lymphocytes *in vitro*. Studies have also shown that there is a dominant protective effect associated with certain HLA class 1 alleles (e.g. HLA-A*201), suggesting that class 1-restricted T lymphocytes play an important role in controlling HTLV-1

proviral DNA load *in vivo* (142). DCs are also known to be infected with HTLV-1 *in vitro* and lead to T cell proliferation (136, 143). These studies strongly suggest that DCs play a critical role during the progression of HAM/TSP; however, the mechanism of DC activation and the role of activated DCs in the generation of a Tax-specific immune response have not been fully delineated. It was hypothesized that the presentation of Tax peptides by activated DCs to naïve T cells likely plays an important role in the continuous stimulation of T cells as well as in the induction of a Tax-specific CTL response observed during HAM/TSP. Studies of DCs in both HIV-1 and HTLV-1 disease indicate that infection of DCs may play a critical role in development of T cell abnormalities (144). DCs have specific antigen-presentation pathways that allow them to cross present HLA class 1-restricted antigens, from virus-infected host cells, to antigen-specific $CD8^+$ cells. Cell-free Tax has also been found in the cerebrospinal fluid of HAM/TSP patients of all disease stages (145). It is associated with lesions in the CNS resulting in the progressive weakness, stiffness, and paralysis of the legs observed in HAM/TSP (146). It has been found that high viral load correlates with immune response by demonstrating high titers in those affected by this disease (114). Infiltrating lymphocytes, local cytokine production, and immunoglobulins can also be found. Therefore, immune mechanisms are thought to play a major role in the pathogenesis of this disease (114). Previous studies by Wigdahl and coworkers (24, 26-29, 31) and others (136, 143, 147) have suggested that DCs represent a major factor of HAM/TSP pathogenesis. Specifically, we have shown that DCs, once exposed to Tax, can undergo activation providing constant Ag presentation and costimulation to T cells leading to the intense T cell proliferation and inflammatory responses underlying HAM/TSP (35). We have also shown that soluble Tax can selectively bind to both immature and mature DCs and drive immature DC activation and maturation to a Th1 phenotype (24). DCs are also known to be infected by HTLV-1 both *in vitro* and *in vivo* particularly in HAM/TSP patients (24, 29, 136, 148, 149). Moreover, progression of HAM/TSP is extensively dependent on MHC class II, found only on APCs (150). In one study, DCs infected *in vitro* survived longer than 6 days and did not induce apoptosis or syncytial formation of the stimulated T cells. It has also been demonstrated that autologous infected DCs, as well as those pulsed with inactivated HTLV-1 virions, can lead to a strong proliferative response of both $CD4^+$ and $CD8^+$ T cells (136, 147). These investigations strongly support our current working hypothesis that presentation of Tax peptides by activated DCs to naive $CD8^+$ T cells plays an important role in the induction of a Tax-specific CTL response and the eventual neurologic dysfunction observed in HAM/TSP (24, 29, 34, 35).

5.3. Alzheimer disease

Alzheimer disease **(**AD) is the most common cause of dementia in the elderly. The disease usually becomes clinically apparent as an insidious impairment of higher cognitive function, with alterations in mood and behavior. Later, progressive disorientation, memory loss, and aphasia indicate severe cortical dysfunction, and eventually, in 5 to 10 years, the patient becomes significantly disabled (151). Symptoms are uncommon prior to the age of 50, except for those individuals with trisomy 21 who survive beyond 45 years. The worldwide prevalence of AD is 15 million people (152). According to statistics provided by the Alzheimer's Association (153), an estimated 4.5 million Americans, more than double since 1980, have Alzheimer disease (154). The incidence of the disease rises with age, and the prevalence roughly doubles every five years, starting from a level of 1% for the 60 to 64 year-old population and reaching 40% or more for the 85 to 89 year-old cohort (155-157). Most cases are sporadic, although at least 5% to 10% of cases are familial. The neuropathologic hallmarks of this disease include extracellular amyloid plaques (largely comprised of beta-amyloid peptides, derived from the proteolysis of amyloid precursor protein) and intracellular neurofibrillary tangles (158). Beta-amyloid has been determined to be the critical component in AD pathogenesis; however, the specific types of beta-amyloid that induce neurodegeneration are yet to be determined. Additionally, the types of neurons that are susceptible to AD pathology were previously unknown. To address this gap in knowledge Capetillo-Zarate *et al* (159) have recently reported that the vulnerability of different types of neurons to beta-amyloid was related to the complexity of the morphology of their dendrites. Reports regarding AD pathogenesis focus specifically on the role of microglia. Meda *et al* (160) and McGeer *et al* (161) have reported that activated microglia secrete proinflammatory cytokines resulting in neuronal injury and thus suggesting a role for these cells in AD pathogenesis (158). Other studies, performed in Dr. Frederick Maxfield's laboratory, have shown that challenge of microglia with labeled beta-amyloid peptides promotes phagocytosis but poor degradation of soluble or fibrillar beta-amyloid *via* scavenger receptors (162-164). Using knockout mice, Chung *et al* (165) showed that the class A scavenger receptor (type I and II) is the predominant scavenger receptor responsible for beta-amyloid uptake by microglia, with other scavenger receptors playing a more minor role (including the class B scavenger receptor CD36). Although the role of DCs has not been fully characterized in AD, many investigators believe that these cells participate in the the pathogenesis of AD. The etiology of AD is based on the accumulation of amyloid within the CNS. Schmitt *et al* (166) discovered that amyloid may escape immune recognition by its failure to activate APCs and by inhibiting MHC class II surface expression. However, more extensive studies need to be performed before attributing any role of DCs in AD pathogenesis or investigating therapeutic approaches involving DCs.

5.4. Prion diseases

Prions are the etiologic agent of transmissible spongiform encephalopathies (TSEs) including kuru (associated with human cannibalism), Creutzfeldt-Jakob disease (CJD; associated with corneal transplants), bovine spongiform encephalopathy (BSE; better known as mad cow disease), and variant Creutzfeldt-Jakob disease (vCJD; likely transmitted to humans from BSE-infected cattle) (167). These infectious particles, smaller than viruses and

Table 1. Mechanisms of Specific Autoimmune and Neuroinflammatory Diseases

Disease	Site	Known Mechanism(s)	Reference
HAM/TSP	CNS	HTLV-1 specific T cells cross react with neural Ags; Tax-mediated immunoregulation	136
MS	CNS	T cell recognition of one myelin protein epitope resulting in activation of autoreactive T cells recognizing other epitopes of the same protein	115
Spongiform encephalopathy	CNS	Conformational change of normal prion protein, resulting in abnormal protein and accumulation of this abnormal protein results in inflammation	168
Alzheimer disease	CNS	Accumulation of amyloid protein resulting in inflammation	38
Rheumatoid Arthritis	bones joints	Abnormal presentation of self-antigen within synovial tissue by APCs, leading to activation of autoreactive T lymphocytes	57
Sjogren's Syndrome	salivary glands lacrimal glands	Deposition of autoantibodies to Ags of the inner-ear structures and infiltration by autoreactive T-cells	83
SLE (Lupus)	systemic - mostly Skin - kidney	A failure of the mechanisms that maintain self-tolerance resulting in an array of antibodies targeted against nuclear and cytoplasmic components of the cell that are neither organ nor species specific	38
Psoriasis	skin possibly joints	APCs in the skin interact with $CD4^+$ T cells to initiate the disease, providing signals for the activation of $CD8^+$ T cells as well as keratinocyte proliferation	39
Diabetes	pancreas	Autoreactive T cells acting against beta-cell Ags	38

viroids are composed of abnormal forms of a host protein, termed prion protein (PrP) (168). Since these particles do not contain nucleic acid, some refer to them as defective viruses (previously reviewed by Vojvodic (169)). PrP is normally found in neurons; however, disease can occur if the prion protein undergoes a conformational change that confers resistance to proteases. The accumulation of this abnormal form of protein, called PrP^{SC}, results in neuronal damage and distinctive spongiform pathologic changes in the brain. Spontaneous or inherited mutations in PrP, which make PrP protease resistant, have been observed in the sporadic and familial forms of CJD, respectively (170). The most common clinical presentation is CJD. The sporadic form occurs with an annual incidence of approximately 0.6 to 1.2 million people worldwide (171) and accounts for the majority, approximately 85% (65), of cases of CJD. In the United States, fewer than 300 cases per year are reported (65).

Many investigators have studied the mechanisms behind the CNS pathology observed in prion diseases and have found DCs to be critical players in these disorders. The pathogenesis of TSEs often includes a replication phase in lymphoid tissues before infection spreads to the CNS (172). TSEs undergo long incubation periods at the beginning of which the titer of infectious agents (prions) increases or "propagates" in peripheral lymphoid organs. The propagation of infectious particles leads to a progressive invasion of the CNS and appears to be supported by fDCs. However, the subsequent steps ultimately leading to CNS invasion remain obscure (173). $CD11c^+$ DCs are candidate vectors for prion propagation. Brown *et al* (174) found that fDCs themselves produce PrP and that replication of a mouse-passaged scrapie strain in spleen depends on PrP-expressing fDCs rather than on lymphocytes or other bone marrow-derived cells. In an additional study, performed by Aucouturier *et al* (173), a high infectivity titer in splenic DCs from prion-infected mice was observed, suggesting that DCs can carry the prion infection. These investigators have also discovered that injection of infected DCs induced scrapie without accumulation of prions in the spleen, suggesting that $CD11c^+$ DCs can propagate prions from the periphery to the CNS in the absence of any additional lymphoid element. Another study (175) also supports the idea that replication in the spleen and subsequent neuroinvasion is critically dependent upon mature fDCs. Others have demonstrated that Ags are trapped and retained on the surface of fDCs through interactions between complement and cellular complement receptors (176). Huang *et al* (177) demonstrated that DCs acquire PrP^{SC} *in vitro*, and transport intestinally administered PrP^{SC} directly into lymphoid tissues *in vivo*, suggesting that DCs are a "cellular bridge" between the gut lumen and the lymphoid TSE replicative machinery. Other results have suggested that Langerhans cells and keratinocytes may be the targets of peripheral infection with prions (178). Other investigators (179) have speculated that $CD11c^+$ DCs may play a dual role in prion infections: facilitating neuroinvasion by transfer of the infectious agent as suggested from *in vivo* studies, but may also protect against the infection by causing an efficient degradation of PrP^{SC}. Prinz *et al* (180) discovered that the prion neuroimmune transition occurs between fDCs and sympathetic nerves, and relative positioning of fDCs with neurons controls the efficiency of peripheral prion infection. Mohan *et al* (181) have concluded from their studies that Langerhans cells are not involved in PrP^{SC} transport to draining lymphoid tissues but might have the potential to degrade PrP^{SC} in the skin. A separate *in vivo* study (182) demonstrated that DCs can enter the CNS of prion-infected mice, suggesting a possible role for these cells in the pathogenesis of prion disorders. Collectively, these studies support the current thinking regarding DCs as a key component associated with these fatal diseases. For comparative purposes we have summarized the known mechanisms of various autoimmune and neuroinflammatory disorders (Table 1).

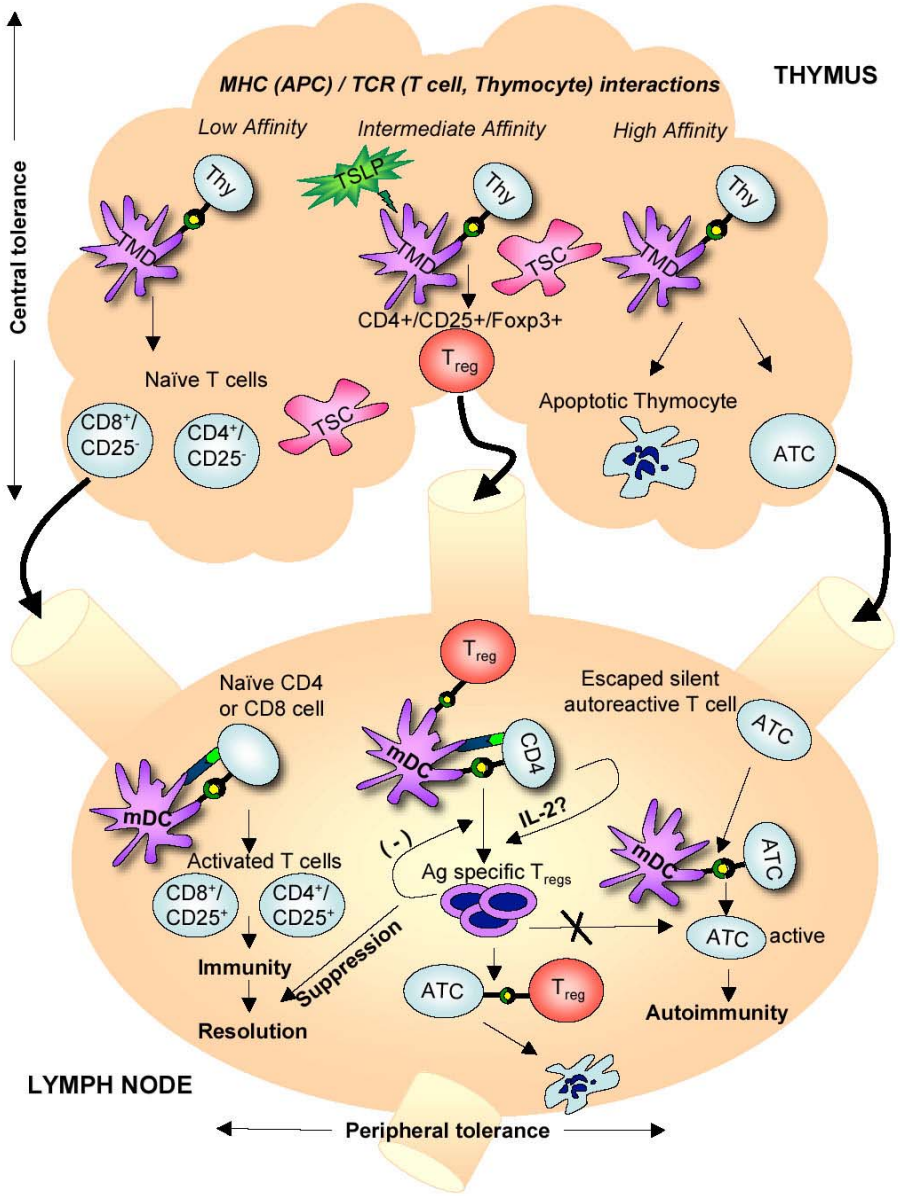

Figure 3. Thymocyte and thymic medullary dendritic cell (TMD) interactions. Thymic stromal lymphopoietin (TSLP) conditioned DCs induce $CD4^+/CD25^-$ thymocytes (Thy) that have intermediate affinity for self-antigen to undergo proliferation and differentiation to $CD4^+/CD25^+$ thymocytes. Low affinity interactions with self-antigen, allow for the differentiation of naïve T cells. High affinity interactions allow for the possible escape of autoreactive T cells (ATC) if not deleted in the lymph node. In the periphery, matured myeloid DCs (mDCs) interact with normal naïve T cells resulting in normal immunity and resolution of the immune response. In addition, mDCs can interact with non-Ag specific T_{regs}, resulting in Ag-specific T_{regs} that can suppress T cells of other Ag specificities. Furthermore, these Ag-specific T_{regs} downregulate DC-mediated T_{reg} expansion through negative feedback. These mature $CD86^+$ DCs may also induce secretion of IL-2 from naïve $Foxp3^-/CD4^+/CD25^-$ T cells. Autoimmunity can occur when there is an inability for the Ag-specific T_{regs} to develop or function properly.

6. POSSIBLE MECHANISMS OF DC INVOLVEMENT IN AUTOIMMUNE DISEASES

Although many have studied various mechanisms of autoimmunity, not one single model of pathogenesis has been proposed for all autoimmune diseases. Since DCs are the major professional APC of the immune system, it is possible that the key mechanism behind autoimmunity can be contributed to this cell type. Figure 3 represents our model of DC interplay in normal immunity, central tolerance, peripheral tolerance, autoimmunity, and the conditions that lead to the failure of this tolerance (Figure 3). DCs have been shown to contribute to T cell tolerance, a function that is inconsistent with the conventional view that these cells are primarily involved in innate and adaptive immunity to infections and other Ags *in vivo*

(183). The family of T_{regs} encompasses T cell populations with distinct suppressive mechanisms, which includes naturally occurring $CD4^+/CD25^+$ T_{reg} cells, T helper type 3 cells, and T_{reg} type 1 cells (184). T_{regs} may also be known as $Foxp3^+$ cells due to a unique marker, forkhead box protein 3. The job of this suppressive/regulatory T cell family is to maintain antigen-specific T cell tolerance within the host, which is seen in both mice and humans (184).

DCs are thought to regulate tolerance induction versus immunization by transferring Ags and peripheral signals to draining lymph nodes (117). The evidence has shown that DCs prepared *ex vivo* and exposed to Ags in the absence of full-maturation stimuli down-regulate immunity and induce T_{reg} cells (183). Also, there is *in vitro* evidence demonstrating that T_{regs} can modify DCs to downregulate the expression of MHC class II, costimulatory molecules, and IL-12, which suggests that DCs might be the direct target of T_{reg} actions (185-190), which has been previously reviewed by Tang and Bluestone (190). Another study (191), using an *in vitro* model system, demonstrated that immature DCs exposed to T_{reg} cells can increase the expression of inhibitory molecules needed for the tolerogenic activity of DCs, and that tolerogenic DCs, in turn, can induce anergy in alloreactive $CD4^+$ T cells, thus establishing an inhibitory feedback loop. Live tissue and intravital imaging has provided evidence that T cells initially probe DCs for cognate ligands by repeated transient engagements, during which T cells appear to be swarming around the DCs (192, 193). Studies performed by Hugues *et al* (194) have suggested that productive activation of T cells require their persistent interaction with APCs. Thus, the concept has emerged that dialogue between T_{reg} cells and tolerogenic DCs is crucial for the regulation of alloimmune responses (195). Recent studies have also shown that thymic stromal lymphopoietin (TSLP) conditioned DCs can induce $CD4^+/CD25^-$ thymocytes to undergo proliferation and differentiation to $CD4^+/CD25^+$ thymocytes (196) (Figure 3) (23). DCs are also alerted when tissues are under stress, even in the absence of a microbial Ag. Stressed or damaged cells express and release heat-shock proteins, which activate DCs and, in association with the autoantigen, endow them with the ability to induce autoimmunity. The autoimmune response may cause further damage of involved tissues, thus enforcing a vicious circle sustaining DC activation, autoantigen presentation by mature DCs, and sustained autoimmunity. In turn, autoantibodies bind to dying cells and opsonize them, thus possibly further skewing the response to tissue damage *in vivo* (197). DCs have also been found to induce T_{regs}. The efficacy of this induction depends on the nature of the DC maturation stimulus, with inflammatory cytokine-treated DCs being the most effective T_{reg} inducers (198). Results of a study performed by Banerjee *et al* (198) demonstrated a role for DCs in increasing the number of functional $Foxp3^{high}$ T_{regs} in humans. In addition, Yamazaki *et al* (199) have suggested in a recent review of T_{regs} that in the periphery (mainly the lymph node) mature DCs may induce secretion of IL-2 from naïve $Foxp3^-/CD4^+/CD25^-$ T cells as well as expand T_{regs} specific for the Ag presented by the mature DC (Figure 3). Therefore, sufficient evidence exists to support the role of DCs in maintaining T cell tolerance.

Some investigators (190) have posed the question of whether or not autoimmune diseases develop as a consequence of reduced T_{reg} number or function. In normal immune responses, DCs present foreign Ag to both $CD4^+$ and $CD8^+$ T cells, which subsequently triggers an immune response. This response is then resolved by T_{regs} through anti-inflammatory cytokines, IL-10 and IL-4, and other mechanisms. T_{regs} also act to suppress and kill autoreactive T cells, thus playing a role in peripheral tolerance (Figure 3). Autoimmune diseases develop as a consequence of failure in central and/or peripheral tolerance. Thymic deletion does not completely eliminate all autoreactive T cells, thus some cells escape to the periphery allowing healthy individuals to harbor an autoimmune repertoire (200). However, most people and animals do not develop autoimmune diseases. According to Tang and Bluestone (190), failure of T_{regs} to maintain peripheral tolerance may be the underlying cause of many autoimmune diseases. One may wonder how such a small number of these autoreactive T cells develop into destructive effector cells. Autoreactive T cells behave as naïve T cells by circulating throughout the body, entering lymph nodes through high endothelial venules, and homing to T cell zones in response to chemokines CCL19 and CCL21 (201). In the presence of cognate Ag, T cells accumulate in an area bordering the paracortical T cell zone and B cell follicles, where they become activated by tissue emigrant DCs (202, 203) resulting in the expansion of the autoreactive population. This process, referred to as lymph node priming, is believed to be the first crucial step leading to autoimmune diseases (reviewed in (190)). Some studies have demonstrated that LN priming is essential for the pathogenesis of certain autoimmune diseases, such as type I diabetes, by expanding the population of low-frequency autoreactive T cells (5-7, 10). To further support the role of DCs and T_{regs} in autoimmunity, more recent studies have suggested that T_{regs} control lymph node priming of autoreactive T cells at an early stage by preventing persistent T cell conjugation with the DCs (204). This study as well as another study also demonstrated that T_{regs} prevent clonal expansion of autoreactive Th cells in the steady state by limiting their access to DCs (204, 205). Another recent study (23) also suggested that distinct states of DC differentiation or maturation are likely to be important for the emerging roles of DCs in the biology of T_{regs}, particularly the control of autoimmunity in an antigen-dependent manner.

The ability to actively suppress an immune response makes T_{regs} an attractive candidate as a novel therapeutic agent for treating autoimmune diseases and transplant rejection (190). Some have investigated DC-mediated activation of T_{regs} as a potential therapeutic option for type 1 diabetes (206). A separate study (207) has indicated that DCs can generate $CD4^+/CD25^+$ T cells that suppress autoimmune disease *in vivo*. Therefore it was concluded that this might be harnessed as a new avenue for immunotherapy for autoimmune diseases such as type 1 DM, especially since $CD4^+/CD25^+$ regulatory cells

responsive to a single autoantigen can inhibit diabetes mediated by reactivity to multiple Ags (207). According to Tang and Bluestone (190), DCs have been used to expand antigen-specific T_{regs}. Therefore, it is possible to stimulate DCs to upregulate T_{regs} in order to restore self-tolerance and attack autoimmunity. However, more extensive studies need to be performed in order to gain a better understanding of the interactions between T_{regs} and autoreactive T cells in autoimmune diseases to improve T_{reg} associated approaches.

7. CONCLUSIONS AND PERSPECTIVES

DCs have recently emerged as an exciting new topic of investigation in the fields of autoimmunity and neuroinflammation. In addition to the mechanisms of DC-associated tolerance depicted in this review, other novel approaches have recently been described. Specifically apoptosis and apoptotic pathways are receiving attention regarding roles in immunity. Some investigators have noted that apoptosis of DCs can participate in the regulation of DC homeostasis and immune responses. Chen *et al* (208) recently reported that Bim (a BH3-only protein of the Bcl-2 family) is important for regulating spontaneous cell death in DCs, and Bim-deficient DCs may contribute to the development of autoimmune diseases in $Bim^{-/-}$ mice. Also, as noted before, apoptotic cells can serve as sources of self-antigen resulting in immune responses against host self components. Another mechanism involved in maintaining tolerance is phagosome maturation, which allows for compartmentalization or classification of Ag types. Blander and Medzhitov (209) have reported a TLR-based mechanism in which they have shown that DCs can classify different sources of Ags as self or non-self so that self-antigen is excluded from MHC class II presentation. Therefore, there exist other potential mechanisms in which glitches can occur and result in the breakdown of normal immunity. These investigators have also noted that the mechanism by which tolerogenic DCs present apoptotic cell-derived Ags *in vivo* is of significance. As new literature becomes available, it is becoming increasingly apparent that DCs play a role in autoimmunity and neuroinflammation.

Our overall goal of this review is to reveal the role of DCs in both immune and tolerogenic mechanisms. As described above, DC interactions with B and T cells allow for positive and negative selection as well as keeping immune responses in check. They also interact with T_{regs} so that peripheral tolerance occurs. However, these systems in susceptible individuals may not be fully functional. The question still remains as to what causes these disruptions of tolerance, and although several proposed mechanisms are described, one single underlying mechanism has not been disclosed. Additionally, there exist a need for more extensive therapeutic options that focus on preventing or treating the cause of the disease versus treating only symptoms. It remains to be determined if DCs can be exploited as a universal therapeutic tool in treating all autoimmune and neuroinfammatory diseases. If so, what specific subset should be targeted? It is noted in several reports that there are subtle differences among DC subsets in the types of cytokines they secrete, their ability to stimulate T cells, their ability to induce tolerance, and their anatomic localization. It may be these subtleties that require further characterization in order to arrive at a solution to neuroinflammation and maintaining tolerance. Although, some work has been performed utilizing DCs in a therapeutic vaccine for diabetes, much more investigation needs to be completed in targeting other diseases. Furthermore, the recruitment of DCs into the CNS remains controversial and not completely characterized. Some have noted the migration of peripheral DCs into the CNS may be a route of neuroinvasion for some infectious agents, such as prion proteins (108). Therefore, it is becoming evident that these specialized cells are important in all aspects of immunity and it will be of great significance to extensively study their potential as treatment interventions in autoimmune and neuroinflammatory disorders.

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Abbreviations: APC, antigen presenting cell; Ag, antigen; DC, dendritic cell; pDC, plasmacytoid dendritic cell; mDC, myeloid dendritic cell; fDC, follicular dendritic cell; MDDC, monocyte-derived dendritic cell; MHC, major histocompatibility complex; T_{reg}, regulatory T cell; lDC, Langerhan dendritic cell; HTLV-1, Human T-cell leukemia virus type 1; HAM/TSP, HTLV associated myelopathy/tropical spastic paraparesis; Th1, T helper cell type 1; Th2, T helper cell type 2; SLE, systemic lupus erythematosus; MS, multiple sclerosis; SS, Sjogren's syndrome; TSEs, transmissible spongiform encephalopathies

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