The role of Tolerance, in maintaining immune Cells and Cytokines and as Immuno-modulatory Target in Cancer and Autoimmune Diseases Treatment and Prevention

Dr. Zelalem Kiros Bitsue,
United States of Africa Health Organization "AHO",
Department of Immunology, International Campus, Tehran University of Medical Sciences

Abstract

The immune system provides defenses against invading pathogens while maintaining immune tolerance to self-antigens. This immune homeostasis is harmonized by the direct interactions between immune cells and the cytokine environment in which immune cells develop and function.

Tregs are produced in the thymus as a functionally mature subpopulation of T cells and can also be induced from naive T cells in the periphery. Recent research reveals the cellular and molecular basis of Treg development and function and implicates dysregulation of Tregs in immunological disease.

Current therapies typically involve nonspecific immunosuppression that may prevent the appropriate response to an antigen, thereby decreasing humoral immunity and increasing the risks of patient susceptibility to opportunistic infections, viral reactivation, and neoplasia.

The induction of antigen-specific immunological tolerance to block undesired immune responses to self- or allogeneic antigens, while maintaining the integrity of the remaining immune system, has the potential to transform the current treatment of autoimmune disease. Immunomodulatory approaches to cancer immunotherapy include treatment with agents that enhance and maintain T-cell activation. A growing understanding of immune tolerance has been the foundation for new approaches to cancer immunotherapy.

In this article, I discuss the Immune tolerance and the immune response, Essential role of central tolerance, B cell Tolerance, Peripheral Tolerance, and Role of Dendritic Cells in Central as well as The role of Tolerance, in maintaining immune Cells and Cytokines and as Immuno-modulatory Target in Cancer and Autoimmune diseases Treatment and Prevention

Key Word: Central tolerance, Peripheral Tolerance, B cell Tolerance, Dendritic Cells in Central, Immunomodulatory, Cancer, and Autoimmunity

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1. Introduction

Studies of immune tolerance have generally centered around “self” versus “nonself” recognition. In other words, T and B cells of the immune system recognize specific nonself-antigens derived from invading pathogens and defend the host from infectious diseases. T and B cells that recognize self-antigens are often believed to be eliminated or become nonfunctional. Nonetheless, in the context of T cell development in thymus, the nearly-random V(D)J recombination of αβ-T cell receptor (TCR) gene segments unavoidably creates a repertoire of major histocompatibility Access this article online complex (MHC)-restricted TCRs that potentially recognize self-antigens. The thymocytes that have a TCR potentially recognizing self-antigens undergo apoptosis, a process callednegative selection or central tolerance. However, some selfreactive thymocytes successfully develop into mature T cells and enter the periphery. To ensure immune tolerance to self, the self-reactive T cells entering the periphery can be further deleted, become anergic (a lack of reaction against specific antigen), or be actively suppressed by regulatory T cells (Tregs). The molecular basis underlying these peripheral tolerogenic mechanisms is not fully defined (1). As a hallmark of the adaptive immune system, T cells require antigen-specific activation to exert their effector function. This antigen-specific activation occurs when the T cells receive sufficient signals upon engagement of the TCR by the antigen-MHC complex on the antigen presenting cells (APC) in combination with signals from CD28-B7 co-stimulatory molecules (2). Activated T cells in turn express high affinity interleukin IL-2 receptor (IL-2R) and also produce cytokine IL-2 themselves. The IL-2 signaling pathway drives the proliferative machinery of T cells (3). To date, in addition to CD28-B7 and IL-2, numerous cell surface co-signaling molecules and soluble cytokines have been shown to control T cell activation and function (2). Hence, T cell immunity or tolerance to a particular antigen is regulated not only by TCR recognition, but also by various co-stimulatory and cytokine signals. This is exemplified in mice deficient in cytotoxic T-lymphocyte antigen 4 (CTLA4), a negative regulator that turns off the CD28-B7 signaling, where they develop lethal autoimmunity in weeks after birth (4). In this review, we focus on the cytokine regulation of immune tolerance, with specific emphasis on the peripheral tolerance of T cells, as they are the central players in various human autoimmune diseases.

2. Immune tolerance and the immune response

Illustrates how tolerance is established and maintained and how it fails with ensuing autoimmunity. Specific immune and autoimmune responses involve the same elements. These include (a)an antigen (or autoantigen); (b) a response by interacting families and subsets of cells that include antigen presenting cells, T lymphocytes, and B lymphocytes; (c) messenger molecules, cytokines, chemokines, and their receptors; and (d) signalling and costimulatory molecules on cell surfaces. Many of the functionally important cell surface molecules and their receptors are described by the cluster of differentiation (CD) nomenclature, based on their identification by characterised monoclonal antibodies. The immune system does not normally

respond to self-antigens. This immunological tolerance was postulated over 50 years ago, but its multifactorial basis is still controversial (2), (3), (4). Tolerance is generated at two levels. The "upper level" of central tolerance develops primarily in fetal life, and the "lower level" of peripheral tolerance develops postnatal as a backup process. A faulty central tolerance sows the seeds for autoimmune disease, while faulty peripheral tolerance lead to its eruption.

3. Central tolerance

Lymphocytes learn to react with antigens during lymphopoiesis in central lymphoid organs, thymus, and bone marrow. During the random rearrangements of genes that encode antigen receptors of nascent lymphocytes, the lymphocytes are exposed to antigenic signals from self-molecules. Weak interactions with low affinity signals are stimulatory and select lymphocytes suitable for immune repertoires positive selection. Strong interactions with high affinity signals are lethal, such that self-reactive lymphocytes are eliminated by apoptosis negative selection (4). In bone marrow, developing B lymphocytes receive stimulatory or deletional signals from self-antigens, but selection processes continue in germinal centres of peripheral lymphoid tissues as well (5). Exactly how these selection processes operate is uncertain, but important influences include the extent of representation and level of exposure to tolerogenic self-molecules and, in the thymus, the HLA constitution of the individual (6). In any event, not all self-antigens are available for efficient negative selection, so that central tolerance is "leaky" and results in export to the periphery of self-reactive lymphocytes that require control throughout life.

4. Peripheral tolerance

Peripheral tolerance encompasses various safeguards that prevent activation of self-reactive lymphocytes. These include ignorance, anergy, and homoeostatic control, and regulation. *Ignorance* Autoimmune lymphocytes are kept in ignorance by sequestration of autoantigens behind cel- lular or vascular barriers; by the occurrence of cell death by apoptosis, which normally precludes spillage of autoantigenic intracellular constituents; and by the presence on the surface of potentially autoimmune (but non-activated) T lymphocytes of signaling molecules that preclude entry of the cell into tissue parenchyma (7). *Anergy* describes a state of unstable metabolic arrest affecting lymphocytes that can lead to apoptosis (8). It occurs when a lymphocyte receives an antigenic signal without the normally necessary costimulatory second signal (9). Anergy is a protective (tolerogenic) outcome after interaction between an autoimmune T cell and a self-peptide on a parenchymal cell that is not competent to deliver a costimulatory signal (10). *Homoeostatic control* occurs by expression of cytotoxic T lymphocyte antigen 4 (CTLA-4, CD152) on activated T lymphocytes as an alternative to the CD28 ligand. When CD80/86 on the antigen presenting cell interacts with CTLA-4 the T cell is switched off. *Regulation* by dedicated T cells inhibits the induction or effector functions of other classes of lymphocytes, either by production of down regulatory cytokines or interference with receptor signalling path- ways. More information is needed on markers that identify regulatory T cells (11), and their role in the development of autoimmunity.

5. Immunological Tolerance

5.1. Recessive versus dominant tolerance

The existence of recessive tolerance in the form of apoptotic cell death of immature lymphocytes (12), suggested to some (13), but not others (14), that it excluded the existence of dominant tolerance. In fact, central tolerance was the first tolerance process to be mechanistically defined; however, at the same time strong evidence for the existence of dominant tolerance was presented (15),(16), culminating in the characterization of Treg (17), and an elucidation of the important role of the Foxp3 gene in both the generation as well as the function of at least one set of Treg (18-20). In fact, mutant Foxp3 resulted in strong autoimmune disease in both man and mouse (21), (22), providing immediate genetic evidence for the essential role of dominant tolerance in avoiding autoimmunity. The clear evidence put recessive tolerance in a defensive spot since similarly persuasive evidence for a likewise essential role of recessive tolerance was not available. Nevertheless, I will argue below that failing recessive central tolerance is likely to play a pivotal role in some of the most prevalent autoimmune diseases.

5.1.2. Mechanisms of central tolerance

While initial studies on development of T and B cells were consistent with deletion of immature cells, it became clear that with B cells selfreactivity could be avoided by receptor editing i.e. by a process of antigen-induced continuing rearrangement of Ig receptor gene segments that resulted in a change of specificity of the self-reactive BCR. Most notably, evolutionary selected ‘‘editor’’ Ig-light chains appear to have the role of neutralizing the DNA binding properties of certain Ig-heavy chains, thereby avoiding diseases mediated by antibody-DNA complexes such as lupus erythematosus (23). A similar receptor editing mechanism for T cells was postulated (24), but not convincingly shown. In fact, experiments specifically designed to reveal such mechanisms in T cells have failed to do so(25). While there appears to be no antigen-induced editing in T cells there exists ongoing TCRa rearrangement irrespective of whether an immature T cell expresses an abTCR or not (26), (27). In fact, the TCRa loci of developing T cells will undergo continuing rearrangement until the process is stopped by binding of the abTCR to a ligand (28-30). In the case of a low affinity ligand, this results in survival, and in the case of a high efficient ligand in premature cell death with no apparent rescue by receptor editing (25). In the following I will discuss some mechanistic details of the process of negative selection by apoptotic cell death counteracting previous views on this subject (31),(32), that have, I believe, become widely accepted without validity. I will not, however, discuss B lymphocytes because B-cell tolerance represents an intriguing and well-studied topic that is discussed in an accompanying article (33).TCR transgenic mice carrying a receptor for a ubiquitously expressed ligand (HY, epitope encoded on male chromosome) are characterized by the absence of CD41CD81 double positive (DP) thymocytes in the cortex . Initially, this finding could have been misinterpreted because the premature expression of the transgenic TCR leads to lineage

diversion of some double negative (DN) cells into the DNgd lineage (34),(35), (36). This was taken as evidence that in these mice there was only a developmental arrest at the DN stage rather than deletion of DP thymocytes (37). However, experiments with DP cells from female mice confirmed that such cells could be deleted by antigenic stimulation in suspension culture(12) as well as organ culture (25). Furthermore, analysis of Bim-deficient HY male mice revealed a marked increase in DP thymocytes indicating that in Bim-competent mice CD41CD81 thymocytes were deleted and that the absence of these cells was due to negative selection in the form of cell death rather than a developmental arrest only (38). Finally, recent experiments with HY transgenic mice with expression of the TCRa chain regulated to occur in DP cells have confirmed antigen-induced cell death of DP thymocytes (39), albeit after a detour that disputed the death of cortical thymocytes as an important mechanism of immunological tolerance (40). These results strongly argue against the suggestions that negative selection of cortical thymocytes is a transgenic artifact (31),(32), and also against the previously proposed role for TCR editing (31). In fact, the experiments on negative selection (12), (25), appear to confirm very early experiments where CD3 antibodies in organ culture were shown to induce deletion of DP thymocytes (41). These experiments (12), (25), unlike their in vivo equivalents (42), cannot be explained by stress-induced cell death of cortical thymocytes(39), and hence represent additional support for the concept that negative selection can affect cortical thymocytes even prior to their positive selection (43). It is in fact true that not only DP cortical thymocytes, but also immature medullary single positive (SP) thymocytes can be deleted (32), (44), the latter representing an important mechanism of tolerance when certain antigens are presented by medullary cells only. Presentation in the thymus of tissue-specific antigens derived from the periphery is made possible either by immigration of peripheral antigen-presenting dendritic cells (45), or by promiscuous antigen expression by medullary epithelial cells facilitated by the autoimmune regulator (AIRE) gene (45).

6. Essential role of central tolerance in preventing autoimmunity

As explained in the section Recessive versus dominant tolerance, there exists straightforward genetic evidence for a role of dominant tolerance in preventing autoimmunity (21),(22). Since Treg are generated intrathymically by antigenic stimulation (46),(47), and the same antigen can also cause deletion (47), of cells expressing the same receptor as Treg (a surprising notion which may depend on encounter of antigen in different thymic niches), it is not easy to decide whether certain experimental manipulations have an impact on recessive rather than dominant tolerance. Certainly, there is no formal genetic analysis that examines whether genetic factors that contribute to type 1 diabetes, such as Ptpn 22, Iddm2 or CD25 (48), do so by affecting recessive or dominant tolerance. Strong evidence for an essential role of recessive tolerance appears to be confined to a Mmonogenic autoimmune disease caused by the disruption of the murine autoimmune regulator (AIRE) gene, where both recessive and dominant tolerances were investigated in a specific experimental setting (49), and it was concluded that intrathymic deletion, but not generation, of Treg was impaired; however, additional experiments in

genetically deficient mice that would definitely exclude a role of Treg are still required to disprove dominant tolerance as the key contributor to the prevention of autoimmune disease.

7. B Cell Tolerance Mechanisms and Their Role in Autoimmunity

7.1. B cell Tolerance. This mechanism is essential for maintaining

nonresponsiveness to thymus-independent self-antigens such as lipids and polysaccharides. B cell tolerance is also important in preventing the development of antibody responses to protein antigens. Both central and peripheral mechanisms are implicated in B cell tolerance. In the central tolerance, the immature B lymphocytes that recognize selfantigens in the BM with high affinity are deleted or activate mechanisms to change their specificity by receptor editing. This fate is defined by the strength of BCR signaling: a strong BCR signal by binding with high affinity to an autoantigen will lead to deletion or receptor editing (see below) while an intermediatebinding affinitywill permit B cells to survive and continue to the periphery (50). If a mature B cell recognizes autoantigens in peripheral tissues without specific helper T cell response, this cell may be functionally inactivated by anergy mechanisms or die by apoptosis. The AICDA is required for B cell tolerance in humans. This enzyme is required for CSR and somatic hypermutation. Patients with AICDAdeficit develop primary immunodeficiencies and autoimmune complications. Single B cells from AICDA-deficient patients show an abnormal immunoglobulin (Ig) repertoire and high frequencies of auto reactive antibodies (51).

8. Dendritic Cells: Key Regulators of Immunity and Tolerance

8.1. DC Subsets and Differentiation Stages. DCs originate

from CD34+ hematopoietic progenitor cells in the bone marrow and are generally classified in two groups: myeloid or classical DCs (cDCs) and plasmacytoid DCs (pDCs) (52),(53). pDCs are characterized by expression of CD123 and a high production of type I interferon (IFN). Whereas pDCs differentiate from lymphoid progenitor cells in lymphoid organs, cDCs are derived from myeloid progenitor cells in the bone marrow and differentiate into immature DCs (iDCs) with different features. (i) Langerhans cells are characterized by expression of CD11c and CD1a. Once they enter the blood circulation, they migrate to the epidermis. (ii) Interstitial DCs areCD11c+CD1a− and are found in the interstitiumof various organs including the lungs, the gastrointestinal tract, afferent lymphatic vessels, and the dermis. (iii) During physiological stress, monocyte-derived DCs can originate from CD14+ monocytes under the influence of a combination of stimuli, such as granulocyte-macrophage colony-stimulating factor (GM-CSF), tumor necrosis factor-α (TNF-α), and interleukin (IL)-4. The widespread distribution of DCs underlines their sentinel function. Indeed, DCs are most concentrated in places of the body where invasion of pathogens ismost likely. Additionally, they are also present in organs such as the heart and kidneys and lymphoid structures, including the spleen, lymph nodes, and the thymus. Where present, iDCs take up both foreign as well as self-proteins and structures and process themintracellularly to antigens that are subsequently presented in the context of major

histocompatibility (MHC) class I and II molecules on the cell's surface. Once DCs capture these antigens in the presence of so-called "danger signals," DCs undergo a complex maturation process. For this, DCs are equipped with pathogen-recognition receptors (PRRs) which detect foreign antigens (i.e., pathogenassociated molecular patterns, PAMPs) thereby activating specific signalling pathways to drive biological and immunological responses. These stimuli can be bacterial products, such as lipopolysaccharide (LPS), or viral products, including double-stranded RNA, but also proinflammatory cytokines like TNF-α (52),(54). Uponmaturation, DCs efficiently present the antigen / MHC complex in combination with co-stimulatory molecules, have changed their pattern of cytokine production (55), and willmigrate to the lymph nodes where they eventually activate T cells (52), (56).

9. Cytokines that maintain immune tolerance

The cytokine milieu provides not only proinflammatory but also anti-inflammatory signals to control immune homeostasis and responses. Results from experimental works have revealed that mice deficient in immunosuppressive cytokines are prone to autoimmunity. Defining the biological functions of those cytokines (e.g., transforming growth factor (TGF)-b, IL-10, IL-27, and IL-37) will advance our understanding of immune tolerance and autoimmune diseases.(57).

TGF-ß

TGF-b has three mammalian isoforms, including TGF-b1, TGF-b2, and TGF-b3. Among them, TGF-b1 is uniquely required for establishing and maintaining normal immune homeostasis (58), which is evident by the fact that TGF-b1-deficient mice exhibit severe and lethal multiorgan inflammatory diseases shortly after birth (59). Because of this, the inhibitory effects of TGF-b1 on various immune cell subsets have been extensively investigated. Indeed, TGF-b1 inhibits the maturation and antigen presentation of dendritic cells (DCs) and macrophages, reduces the interferon (IFN)-g production and the cytotoxic activity of natural killer (NK) cells, modulates the differentiation / proliferation and IgA production of B cells, and constrains the differentiation / proliferation and perforin / Fas ligand expression of CD8+ cytotoxic T lymphocytes (CTL) (60). It becomes interesting as to whether the early lethal autoimmunity observed in TGF-b1-deficient mice is attributed to the dysregulation of T cells, as these cells play a central role in breaking and maintaining immune tolerance. Two independent groups addressed this question by crossing the TGFbRII-flox / flox with CD4-Cre mice, which leads to the disruption of TGF-b signals only in T cells (61), (62). They found that TGF-bRII deficiency in T cells results in the generation of highly pathogenic T cell subsets with overexpressed FasL, perforin, granzymes, and IFN-g, which in turn causes early-onset lethal autoimmunity. Hence, TGF-b1 control immune homeostasis mainly, if not entirely, through restraining T cell activation and differentiation. Indeed, TGF-b1 potently inhibits T cell activation by repressing the activation of Tec kinase Itk and calcium influx. Moreover, TGF-b1 diminishes T helper (Th)1 and Th2 cell differentiation by inhibiting the expression of the master regulators T-bet and GATA-3, respectively (60). Exogenous TGF-b1 is frequently used for the in vitro differentiation

of both inducible Treg (iTreg) and Th17 cells. TGF-b1 is thus considered as an important regulator that controls the balance of Th17 and Tregs, (63), but the physiological role of this regulation in vivo is unclear. Taken together, TGF-b1 permits immune tolerance by modulating the activation and differentiation of immune cells, in particular T cells.

IL-10

IL-10 is a cytokine with pleiotropic effects on many immune cells. For instance, IL-10 modulates the function of APCs through inhibiting phagocytosis, downregulating the expression of MHCs and co-stimulatory molecules, and decreasing the production of proinflammatory cytokines and chemokines (64). Moreover, IL-10 directly inhibits the differentiation of Th cells and maintains the suppressive activity of Treg cells (65). IL-10-deficient mice spontaneously develop colitis (66), suggesting that IL-10 exerts in vivo immunoregulatory effects largely in the intestinal tract. In particular, IL-10 produced by Tregs or Tr1 cells as well as IL-10 signaling in Tregs is believed to be required for preventing T-cell mediated colitis (65),(67), (68). In human, IL-10 has also been confirmed as a susceptibility gene for inflammatory bowel disease (IBD) (69). The beneficial effects of IL-10-based therapies to treat IBD in the clinic remain to be determined(70).

IL-27

IL-27 is an IL-12 family cytokine composed of heterodimeric subunits p28 and Epstein-Barr virusinduced gene 3 (EBI3)(71). IL-27 is produced mainly by APCs. The immune-regulatory effects of IL-27 include suppressing Th17 cell differentiation (72), (73), facilitating Treg generation (74), and promoting IL-10-mediated T cell tolerance (75). Results from a recent study (76), indicate that IL-27 also directly acts on DCs themselves. IL-27 signaling induces immunosuppressive DCs to express high levels of CD39, which in turn promotes the differentiation of Tregs. IL-27 signaling in DCs also inhibits the differentiation of Th1 and Th17 cells, and prevents the development of experimental autoimmune encephalomyelitis (76).

IL-37

IL-37 (IL-1 family member 7) is a newly identified anti-inflammatory cytokine affecting both innate and adaptive immunity (77). IL-37 has five splice variants (IL-37a–e). Transgenic expression of IL-37 protects mice from lipopolysaccharide-induced shock and dextran sulfate sodium-induced colitis (78), as well as concanavalin A-induced hepatitis (79), probably through inhibiting the production of pro-inflammatory cytokines IL-17 and tumor necrosis factor (TNF)-α.

10. Central B cell Tolerance Low Avidity Interactions

Early studies based on conventional transgenic mice also indicated that low avidity interactions between immature B cells and self-antigens result in the development of anergic peripheral B cells (80),(81). Given that the extent of clonal deletion was overrepresented by the use of conventional Ig transgenic mouse models, it was important to revisit central B-cell tolerance

toward low avidity self-antigens in a more physiological context. This question was addressed by studying the fate of H chain transgenic þL chain knockin anti-HELB cells developing in the presence of soluble HEL (82). In this model, only half of the low avidity autoreactive B cells developed anergy, whereas the other half underwent receptor editing (82). in contrast to conventional Ig H and L chain transgenic mice in which most B cells were anergic (80). A similar dichotomy in tolerance induction has been observed in wild-type B cells that develop in the presence of low concentrations of a k-macroself- Ag (83). Together these findings suggest that some of the editing B cells in the wild-type repertoire may be low avidity autoreactive immature B cells. The reasons for why some low avidity autoreactive immature B cells undergo receptor editing whereas others develop anergy are still unresolved, but may relate to cell competition for self-Ag in selective marrow microenvironments.

11. Peripheral Tolerance - Role of Toll-Like Receptors

Toll-like receptors (TLRs) are pattern recognition receptors that recognize pathogen associated molecular patterns (PAMPs) (84), (85). TLR-mediated recognition of PAMPS leads to activation of innate immune cells (86). TLR signaling promotes activation and maturation of innate immune cells, which instructs and supports T-cell activation, leading to cell-mediated adaptive immune response. Activated antigen-specific T cells and naïve B cells interact with each other (cognate interaction), which leads to B-cell clonal expansion and differentiation and antibody secretion. Recent evidence suggests that in addition to TLR signaling in cells of the innate immune system, direct TLR mediated activation of B cells is also required for eliciting humoral immune response. However, multiple B cell subsets exists that play distinct roles during humoral immune responses. For example, follicular B cells are shown to be important for T-dependent immune responses whereas marginal zone B cells are important for T-independent immune responses. Marginal zone B cells are shown to be in a preactivated state and respond rapidly to LPS and secrete antibody in vitro. Peyer's patch B cells in the intestine play critical role in mucosal immune response by secreting IgA that binds to pathogens and prevents enteric infections. B-1 B cells, a subset of B cells in the peritoneal cavity is the source of natural IgM present in the serum and plays an important role in immunity against blood borne pathogens (87). It was shown that B-cell subsets express all known TLRs except 5 and 8 (88).

In a series of landmark studies, it was demonstrated that TLRs expressed by B cells can also recognize self-antigens released from host tissues that are damaged, and such self-recognition by the B cell intrinsic TLR can potentially promote the development of autoimmune disease by breaking B-cell tolerance. Studies from transgenic mice reveal that immune complexes (ICs) consisting of IgG bound to mammalian DNA have been shown to effectively activate transgenic rheumatoid factor (RF) specific B cells through a process that involves BCR recognition of the IC and subsequent delivery of the DNA to TLR9 sequestered in an endosomal / lysosomal compartment (89),(90), (91). These low affinity RF specific B cells do not proliferate in response to protein-containing ICs. The chromatin ICs, but not protein ICs, stimulate myeloid and plasmacytoid DCs to secrete cytokines, through coengagement of both FcγRs and TLR9. Under

specific conditions, mammalian DNA can also directly stimulate DNAreactive cells, through a TLR9-dependent process. However, the role of TLR9 in lupus appears more complex since deletion of Tlr9 gene in some mouse models protects against autoimmunity (92). In addition to the DNA and DNA containing ICs, RNA and RNA binding proteins, such as Sm / RNP, constitute a second major category of autoantigens frequently targeted in systemic autoimmune diseases such as systemic lupus erythematosus (SLE). Sm / RNP particles consist of the U1 RNA bound by Sm and other associated proteins. Recent studies suggest that TLR7 and TLR8 act as receptors for single stranded RNA expressed by the viruses. In this context, the ssRNA was found to be a particularly effective ligand for TLR7 and TLR8 (89), (93). These observations raised the possibility that the interactions between BCR and TLRs that lead to DNA dependent activation of autoreactive B cells and DCs, would also apply to TLR7 / 8 involvement in the activation of B cells by RNAassociated autoantigens (92). In agreement with such a concept, TLR7 deficiency ameliorated autoimmunity in murine models (92). Thus, these observations in mouse models are consistent with the fact that autoantibodies reactive with DNA or DNA-associated proteins are the earliest and most commonly prevalent serological markers of human SLE (90). Mechanisms of B-cell tolerance in bone marrow and periphery: Both clonal deletion and anergy are mechanisms utilized in the primary as well as peripheral lymphoid organs. Strength of BCR signaling affects the fate of the B cells undergoing tolerance. Receptor editing occurs primarily in the bone marrow. Transitional B cells are found in the bone marrow and spleen. Peripheral tolerance is primarily found in splenic transitional B cells, which depends on tonic BCR signaling thresholds and survival signals from BAFF.

12. Role of Dendritic Cells in Central and Peripheral Tolerance

Interaction of dendritic cells (DCs) with B cells and T cells plays an important role in the regulation of immune responses. DCs express a variety of TLRs and respond to TLR stimuli. DCs were found to present antigen to both T cells and B cells in a tolerogenic form(94),(95). Immature DCs have been shown to inhibit and tolerize T cells in vivo because of the absence of a costimulatory signal, whereas maturation of DCs by TLR or CD40 overcomes this inhibitory effect on T cells (95),(96). Recent studies suggest that immature bone marrow DCs (iBMDCs) or bone marrow resident DCs, but not mature bone marrow DCs or Splenic resident DCs (97), strongly inhibited B cell proliferation and differentiation responses induced by TLR ligation. iBMDCs specifically inhibited TLR2, TLR3, and TLR4, as well as BCR-induced proliferation, but did not inhibit anti-CD40 or PMA-ionomycininduced B cell proliferation (87),(98). Cell-cycle analysis revealed that iBMDCs block B cell proliferation by inducing G1-S growth arrest(87). Similar to the DC-mediated regulation of T cell responses, maturation of immature BMDCs with TLR ligands overcame the inhibitory effect of DCs on B cells. Many different TLR ligands can mature DCs in either a MyD88-dependent or MyD88- independent manner(99). Maturation of immature BMDCs via the MyD88-dependent pathway (LPS,

peptidoglycan) or the MyD88-independent pathway [poly(I:C)] had similar effects in overcoming the inhibitory effect of iBMDCs on B cells. CD22 expression by B cells is critical for

the immature BMDC-mediated inhibition of TLR-induced B cell proliferation (87). Interestingly, it has been shown that maturation of BMDCs decreases the expression of sialic acid ligands(100), which is consistent with the role of CD22 in DC–B cell interaction. It is also possible that the sialic acid binding proteins such as Siglec G, which have been shown to be important for B-1 cell responses and for Ag-induced tolerance in B cells could play a role in this process(101). Unstimulated splenic resident DCs were immature as evident by low CD86 and class II expression on the surface, compared with LPS mature Spl-RDCs but they did not inhibit TLR-induced B cell responses. In contrast, bone marrow resident DCs strongly inhibited TLR induced proliferation of B cells from both the bone marrow and the spleen. Although immature BMDCs normally are a heterogeneous population of DCs, flow cytometric sorting established that myeloid DCs in this population have potent inhibitory effects on B cells [64]. It is of interest to note that Kilmon et al(102), found that myeloid DCs and macrophages, but not plasmacytoid DCs, inhibited autoantibody production by self-reactive B cells, but not Ab production by normal B cells. In thymus, DCs present self-antigen in the context of their MHC and play a role in the negative selection of T cells. Thus, the DCs in the bone marrow might play a similar role in B cell negative selection by presenting soluble self-antigens to B cells in membrane bound form in the context of CD22/SIGLEC-mediated inhibitory signals. In this context, recently it has been shown that ligation of T-independent Ags with sialic acid epitopes induced B-cell tolerance through their ability to crosslink SIGLEC family proteins(103),(104). It was proposed that self-antigens that behave like T independent Ags may use this pathway for self-tolerance. In support of such an idea, mice doubly deficient for CD22 and Siglec G developed autoantibodies and a moderate form of immune complex mediated glomerular nephritis(104). Although the significance of inhibition of TLR responses of bone marrow B cells is currently unclear, it must be noted that several endogenous TLR ligands have been identified and have been implicated in the breakdown of self-tolerance in several autoimmune models(105),(106). Some of the endogenous TLR ligands such as high mobility group box 1 and heat shock proteins have their origin in cell death(107), which is known to occur extensively during B cell development. Defects in clearance of dead cells have a critical role in the development of autoimmune diseases such as lupus (108). In the periphery, DCs in mucosal areas and epidermal Langerhans cells (sites of extensive cell turnover) have anti-inflammatory properties.

13. Systemic Immune Tolerance

Systemic immune tolertance can be central genetic or peripheral acquired .The peripheral is acquired and may be induced via low dose toleragen (An antigen that induced tolerance state)or it can be intiated with the exposure to high dose toleragen. Tolerance persist whenever the toleragen is exists in contact with the functional immune cells (The immune committed cells).If it is vanished and not being in such contact, tolerance state can be broken. Tolerance is merely a cellular issue rather than whole being immune system of a certain vertebrate animal. Thus there are B cell tolerance and T cell tolerance. T cell tolerance is being easier to induce than that of B cells. The mechanisms behinds the systemic immune tolerance are, clonal cell deletion, clonal cell anergy, Treg activity, and clonal negative selection (109),(110),(111),(112).

14. Oral Mucosal Tolerance

Three points of views are being evident when, one begins to tackle the topic of oral mucosal immune tolerance. First, constitute the theme of general immune tolerance ,the second is that tolerant cells initiated in gut mucosa and migrated to the oral cavity and performs their effects there, while the third, however state that the oral mucosal tolerance represents a state of an active process including delayed type hypersensitivity and antibody formation .It is initiated by the continual exposure of the oral mucosal surfaces to food and microbial related antigens throughout mastication , drinking ,and / or sucking. This state needs pre-requiests and laid on mechanisms .The pre-requiest are, normal immune function, vived normal commensal microflora ,persistent antigen presence ,antigen specific and it diminished with time. The mechanisms are; clonal deletion of T cells ,T cell apoptosis, anergy, Treg .cell activity,Th3 cell function as well as dendritic cell activity and Sc IgA (113),(114),(115).

15. Conclusions

Decades of disappointing clinical trials of cancer vaccines those were based on poor understanding of
the immune system, led some oncologists and cancer researchers at the turn of the century to view cancer immunotherapy as a "failed hypothesis."

Deficiency of genes, in particular *Ctla4*, *Il2*, and *Cd25*, produces severe autoimmunity in mice presumably through an effect on Treg development and function. Similarly, CTLA-4 blockade or IL-2 neutralization for a limited period elicits T cell mediated autoimmune disease in otherwise normal mice. It is therefore possible that the polymorphisms of these genes may alter Treg development or function and thereby render the host susceptible to autoimmune disease.

Tregs display greater proliferation and higher metabolic activity than non-Tregs under physiological conditions. Treg depletion can evoke autoimmunity; it can also provoke and enhance tumor immunity in rodents. In vitro T cell responses against tumor-associated antigens are enhanced by stimulating T cells from cancer patients (or even normal individuals) with tumor antigen after the depletion of natural Tregs.

In addition, Foxp3+ Tregs are abundant in tumors. Thus, natural Tregs that promote self-tolerance may act to impede immune surveillance against cancers in normal individuals and suppress potential responsiveness to autologous tumors in cancer patients.

Targeting Tregs is a promising approach for cancer immunotherapy. Such approaches could include local depletion of Tregs in the tumor mass, attenuation of Treg function at the time of therapeutic vaccination with tumor antigen, and ex vivo expansion of tumor-infiltrating lymphocytes after the depletion of Tregs. Similar to tumor immunity, depletion or reduction of natural Tregs enhances immune responses to pathogenic microbes.

Foxp3+ natural Tregs retain their suppressive function after expansion in vivo and in vitro. By exploiting this stable suppressive activity and proliferative capacity, strategies that clonally expand antigen-specific natural Tregs while inhibiting the activation and expansion of effector T cells will help to induce transplantation tolerance and suppress graft rejection.

It is necessary to find a specific molecular marker that can selectively and reliably differentiate between Tregs and effector T cells. These various approaches to breaking immune tolerance toward cancer have their impact at different points in the complex interaction between the malignancy and the immune system. Therapeutic approaches to cancer therapy are designed to either bypass immune editing or address mechanisms that contribute to peripheral tolerance

Further elucidation of the cellular and molecular processes underlying the development and function of Tregs will help to establish new strategies for the treatment and prevention of immunological diseases and for the control of a wide spectrum of physiological immune responses.

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