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Review Article

Dentistry Section

Immunopathological Concepts Behind Autoimmunity

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ABSTRACT

Autoimmunity is the failure of self-tolerance of an organism, which empowers immune response against its own cells and tissues generating autoimmune diseases. Autoimmune diseases are exceeding 100 million people globally. Autoimmune mechanisms underline many diseases, some are organ-specific and others are systemic in distribution. Aberrations in central and peripheral tolerance, molecular mimicry, bystander activation, cryptic antigenic and super-antigenic exposure are found to be associated with immune response against self-antigens. As the molecular biology behind autoimmune diseases is obscure, an insight on immune pathways, impaired immunity and evolution of autoimmune diseases can supplement on the therapeutic modalities of immunological diseases.

Keywords: Autoimmunity, Cryptic antigen, Epitope spreading, Molecular mimicry, Self tolerance

INTRODUCTION

Immune system refers to the assortment of defence cells against foreign antigens. The line of defence in the immune system encompasses Innate and Adaptive immune responses [1]. D2-Immune system is under the control and regulation of inflammatory cells which safeguard and prevent body from cellular injury and infections. Inflammatory cells can also act as a "double-edged sword" in both protective and destructive manner emphasizing the role of immune cells in autoimmune mechanism wherein self antigens are recognised as antigenic. Instant recognition of encroaching foreign antigen is perceived by innate immune mechanism which is deprived of immunological memory. Adaptive immune response is antigen dependent and specific with immunologic memory which empowers immune mechanism upon succeeding antigenic response [2]. Central intra-thymic deletion of self-reactive T lymphocytic cells which own receptors for self-antigen is self-tolerance [3]. Inhibition of self-antigen reactive immune cells in the periphery is performed by regulatory T-cells (T regs) [4,5]. Some T cells termed as ignorant T-cells are neither deleted in the periphery nor in the thymus due to the diminished amount of their cryptic antigen [6]. D3-Antigen Presenting Cells (APC) along with surface Major histocompatibility complex present antigen to T-lymphocytes. CD4+T cells are restricted by MHC class II antigens and CD8+ cells are restricted by MHC class I antigens. Major histocompatibility (MHC) complex comprising HLA (Human Leukocyte Antigen) class I and HLA class II could perceive foreign antigens and present to T-lymphocytic receptors [7]. Self Non-Self (SNS) model, Infection Non-Self (INS) model, Danger model and Two Signal model are considered as some of the ideal concepts of immune reactions [8]. Autoimmune disease is the sequelae of impairment of self-tolerance to self-antigen.

Autoimmune diseases are exceeding 100 million people globally [9]. Cessation of central and peripheral tolerance is found to be associated with prolonged environmental insults generating immune response against self-antigens. Molecular mimicry, bystander activation, cryptic antigenic and super antigenic exposure can promote autoimmune reactions [10-12].

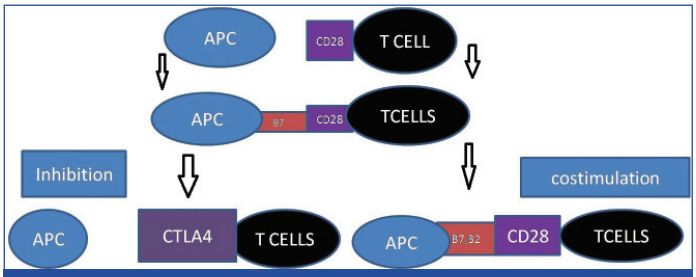
Concepts in Autoimmunity

Self Non-Self model theory and Two Signal model theory: The SNS model theory of immunity states that any non-self or foreign antigen can trigger immune mechanism in the host, whereas self endogenous elements will not provoke an immune reaction in the host. Confrontation of body with any foreign material can bring about immune response. A contrast statement was proposed by Jerne which recommends that a constant negligible reaction should be there by immune cells on self molecules for normal immune surveillance [13]. During lymphocytic selection in the thymus or bone marrow, these immune cells could survive in the primary lymphoid organs only if it reacts on self molecule. Deprivation of weak reaction of circulating lymphocyte on self antigen can result in its cessation. T regulatory lymphocytes which are self immune cells control the normal self lymphocytes during immune functions [14-16]. Immune tolerance of host immune cells to gut bacteria, certain helminths, alloantigenic graft, chimerism and foetomaternal tolerance are countering SNS model theory of immunology [17-20].

In the initial phase of SNS model, it was postulated that interaction of B-cell antigenic receptors and T-cell antigenic receptors with an antigen can generate immune reactions. Subsequently two signal model theory of immunology was implied, declaring that B-cell after processing antigen, re-express it on MHC class II molecule for T-helper cells to identify [21,22]. A consequent theorization was proposed recommending that T-lymphocytes need stimulatory signals from Antigen Presenting Cells (APC) for immune reaction. TCR signalling is monitored by co-stimulatory and co-inhibitory receptors on its surface. After the recognition of antigenic peptides presented by MHC molecules to T-Cell Receptors (TCR), T-cell function and fate is determined by the co-stimulatory and co-inhibitory receptors on T-cells.

According to the two signal hypothesis of immunity, both antigen and secondary stimuli are required for T cell activation. The most complex two signal model, immune regulatory system operates with the conjugation of the co-stimulatory receptor CD28 (ligand, B7-1), and co inhibitory receptor (Cytotoxic T Lymphocyte Antigen-4 (CTLA4), which also binds to B7-1) and a second ligand (B7-2, which binds to both CD28 and CTLA4) [23-25]. Expression of B7-1 and B7-2 is modulated by the activation state of the APC. T cell growth and survival is promoted by CD28 co stimulatory receptor, expressing on the cell surface of naive CD4+ and CD8+T cells upon ligation by B7-1 and B7-2 on antigen-presenting cells (APCs) [26-28]. Instigation of CTLA4, co inhibitory receptor is promoted by the activation of T cell and increased expression of CTLA4 declines

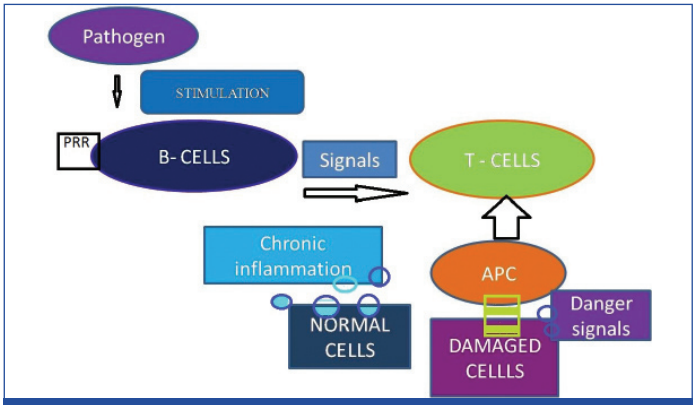
CD28 expression by endocytosis [29-31]. Cellular insults activate APCs and induce transcription, translation and transportation of both B7-1 and B7-2 to the cell surface [32,33]. The formation of the immune synapse allows TCR signalling and co-signalling [34,35] [Table/Fig-1] D1. The central, peripheral and distal Supra-Molecular Activation Complexes (cSMAC, pSMAC and dSMAC) form the immune synapse with TCR which provides evidence for the two-signal model of T cell activation [36,37]. Co signalling ligands and



[Table/Fig-1]: Two signal model hypothesis.
APC: Antigen presenting cells, CD28 (T cells co-stimulating receptor, B7 and B2 (co-stimuating receptor of antigen presenting cell, CTLA4 (co-inhibiting receptor of T cell

counter-receptors are highly expressed on the professional Antigen Presenting Cells (APCs).

Danger model theory: Danger model hypothesis was postulated by Polly Matzinger, according to which the immune system is more concerned with safe guarding the individual from insults rather than discriminating self and non-self. Circumstances like Mechanical stress, DNA damage, heat, cold and hypoxia can result in cellular damage. Injured, distressed, damaged or necrotic cells could liberate danger or alarm signals which stimulate APC whereas healthy cells send calm signals and apoptotic cells convey eat me signals to APC [38-40]. Repeated cellular insults generate danger alarm signals augmenting antigen presentation which in due course recognises, self protein antigenic, precipitating chronic autoimmunity D2 [Table/Fig-2] [41,42]. A S8-Some of the Endogenous signals are



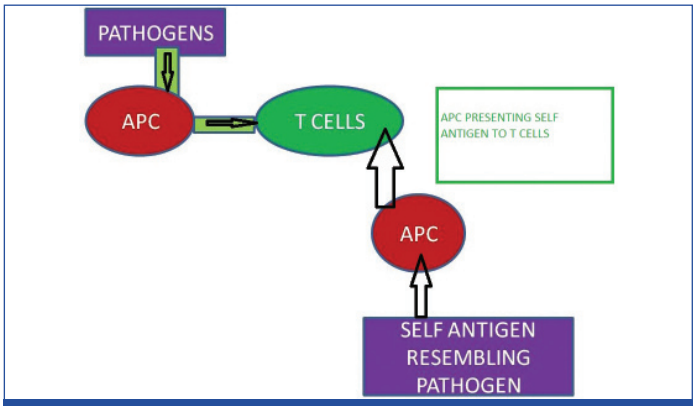
[Table/Fig-2]: Danger model theory.
PRR: Pattern recognising receptors; APC: Antigen presenting cells

Heat Shock Proteins (HSP), hyaluronan, High Mobility Group Box-1 Mediator (HMGB1), Fibronectin fragments, modified low density lipoprotein and extracellular ATP [43-48].

HSP which are released on account of cellular stress could switch on innate immune cell via Toll-Like Receptors (TLRs). HSP induces the production of nitric oxide (NO), down regulation of tumour necrosis factor α, activates IL12 and regulatory T-cells and improves antigen presentation if associated with antigen [49-51]. The sulphated glycosaminoglycans, hyaluronan which is a major component of extracellular matrix is cleaved to hyaluronic acid during tissue injury [52,53]. This signalling response could institute innate immune response and propagation of dendritic cell maturation contributing adaptive immune response. HMGB1 is released from necrosed cells with the aid of macrophages and dendritic cells. HMGB1 with its endogenous stimulatory mechanism can contribute autoimmune reaction with existing chronic inflammation [54,55]. Fibronectin fragments, defensin and modified low density lipoprotein through divergent immune response can contribute to immune reaction.

Immunopathology of Autoimmune Reactions

Molecular Mimicry: Elicitation of immune response against self antigens, when there exist an antigenic resemblance between foreign peptide or pathogen and self peptide is called molecular mimicry [56]. The central and peripheral tolerance which is specifically the positive and negative selection of primitive T cells occurs in the thymus [57]. The selection depends on the competence of T cells to interact with the peptides presented by MHC. T-cells, with negative selection of MHC presented peptides and strong interactions with self antigens are nullified [58,59]. Instead in molecular mimicry a



[Table/Fig-3]: Molecular mimicry.
APC: Antigen presenting cells; T cells: T lypmbocyles

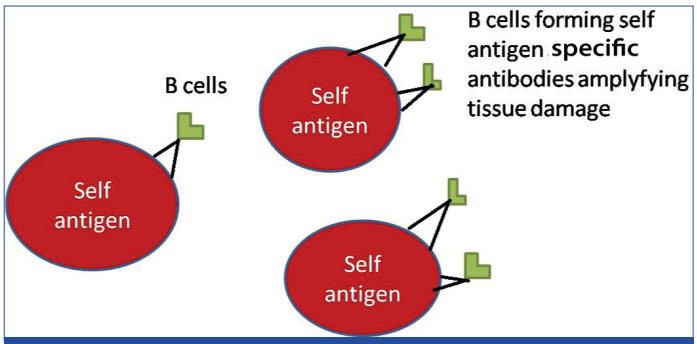
constant immune response against self-antigens is ensued, when the pathogen has a structural and sequential resemblance with self antigens [Table/Fig-3]. Molecular mimicry can also be emerged by virtue of neoepitope formation acquiring via tissue injury. Tissue injury can contribute to the development of self reactive T cells by exposing the self cryptic epitopes [60,61].

AS10-TCR is poly specific in nature. The structural resemblance of pathogens to self antigens creates dilemma to TCR inducing molecular mimicry [62]. A foreign peptide (such as virus) resembling MHC derived peptide can activate T cells, and if the self antigen is also structurally similar, exposure to the foreign peptide results in these activated T cell becoming autoreactive [63,64]. Molecular mimicry is confederated to several autoimmune diseases like Multiple sclerosis, Gullian-Barre syndrome, Acute Rheumatic fever, type 1 Diabetes Mellitus, Lyme arthritis and Ankylosing Spondylitis. A structural homology between Epstein-Barr virus and Myelin basic protein was evident in multiple sclerosis [65]. In Gullian–Barre syndrome post infectious molecular mimicry between nerve antigen and microbes induce autoimmune response [66]. Epitope mimicry between Streptococcal M proteins and human myosin, tropomyosin, keratin, actin, laminin, vimentin and N–acetylglucosamine contribute to acute rheumatic fever [67]. In type 1 diabetes mellitus, mimicry related to viral infection is hypothesized due to the structural similarity between pancreatic beta cell enzyme and viruses [68,69].

Bystander Activation: In bystander activation, viral and bacterial products induce INF α/β (Interferon alfa/beta) secretion which propagates the proliferation and expansion of heterologous polyclonal T cells [70]. Activation of INF α/β D11 (Interferon alfa / beta) leads to the stimulation of APC [71]. APC produce the cytokine, IL -15 which then activates memory phenotype (MP CD+8) T cells. CD8+T cells recognize the infected cells and release cytokines like TNF (Tumour Necrosis Factor), NO (Nitric Oxide) and Lymphocyte Toxins (LT) resulting in the causation of bystander killing of uninfected neighbouring cells D3 [72]. Cytokines released from CD4+T cells can directly kill uninfected cell but the bystander

activation of CD4+T cells are less competent than CD8+T Cells. CD 122 receptor for IL2/IL15 is more expressed by MP CD8+T cells than MP CD4+T which results in limited bystander activation of MP CD4+T [73].

Epitope Spreading: AS13-Epitope spreading can be defined as a specific autoreactive lymphocyte (T or B cell) response to endogenous epitopes, secondary to the release of such self protein during a chronic autoimmune or inflammatory response (Vanderlugt and Miller, 1996) [Table/Fig-4] [74]. Cell mediated and humoral immunities are influenced in epitope spreading by the unmasking of multiple epitopes on a single antigen or from one antigenic molecule to other. The biological events elucidated in epitope spreading



[Table/Fig-4]: Epitope spreading showing clonal expansion of autoantibodies causing damage on self antigens.

include endocytic processing, antigen presentation, and somatic hypermutation. B cell epitope spreading appeared to be inveigled in autoimmune diseases like Systemic lupus erythematous, multiple sclerosis, pemphigus and bullous pemphigoid [75]. T cell epitope spreading is accomplished in Multiple Sclerosis and Autoimmune Encephalomyelitis, by a concurrent regression of primary autoreactivity associated with disease onset [76].

CONCLUSION

Insight on immune pathways, impaired immunity and evolution of autoimmune diseases can supplement on the therapeutic modalities of immunological diseases. Distraction in the suppression of the immune response to the self antigens contributes to autoimmune diseases. Various mechanisms, including the release of sequestered antigens, molecular mimicry, epitope spreading, cytokine deregulation and inappropriate expression of class II MHC molecules propagate autoimmunity.

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