**eISSN: 09748369, www.biolmedonline.com**

# Does intrinsic immune defect against common microbial pathogens play an important role in arthritic manifestation?

***S Subramanian, S Dhivya**
Department of Biotechnology, International Research Institute for the Deaf (IRID), An Institute under Acoustical Foundation for Education and Charitable Trust (AFECT),
Chennai, India.

*Corresponding author: sambandam.subramanian@gmail.com

**Abstract**
The autoimmune diseases are characterized by inflammation and resulting degradation of macromolecules of specific foci. Etiopathogenesis of arthritis is still unclear. In recent times many studies have been published, giving satisfactory explanation of infection and defective immune mechanisms for arthritic etio-pathogenesis. Understanding etio-pathogenesis is the most important and fundamental aspect of any particular problem. Many have given their different views on the above to educate the society. Out of these views, very few clear views were brought to the notice on immune dysfunction to common microbial infections. Convincingly, the above may have a strong connection to the disorder. Generally, it is thought that common microbial infections cause known problems but in unforeseen situation the dysregulation of immune function may also have acceptable reason behind the etio-pathogenesis. Vice-versa, defective immune functions like defective B cell function, defective B Cell Receptor signaling mechanism, dysregulated cytokine function, auto-antibodies' cross reactivity to self antigens, inappropriate complement cascade events and defective apoptosis are few privileged environments which are discussed here for possible explanation of etiology of rheumatoid arthritis. This review deals with infection connection and defective immune mechanism of rheumatoid manifestation for further better understanding of etiopathogenesis.

**Keywords:** Autoimmunity; Arthritis; Inflammation; Defective immune response; Common microbial pathogens.

## Introduction

Etiology for rheumatoid arthritis hypothesized it could be an infectious disease and possibly of other conditions as many as endocrine, psychosomatic, hereditary and defective apoptosis (Cutolo, 1997; Pittoni, 2002) etc., Many suggested mechanisms to etiology of the disease is still believed relevant to the manifestation, particularly infectious connection posted for etiopathology gives satisfactory explanation. Similarly inflammatory joint disease may develop following an extra-articular infection. The complex interactions between the triggering microbe and the defense mechanisms of the host in arthritis have been studied in several laboratories around the world, and interesting observations has been made. The demonstration of antigens of an infective agent at specific foci in association with a specific local immune response suggests the pathogenetic importance of the agent. In addition to microbial candidates, defective immune arm connection giving satisfactory explanation to etiology. Some of the common microbial candidates and defective immune function against common microbes has been tabled (tab 1&2).

Both humoral and cell mediated immune responses against common microbes are thought to participate in chronic inflammatory joint disease. These immune responses may reflect either a normal response to usual antigenic stimulation or to a regulatory dysfunction or both. Similarly, individuals with primary or acquired immunodeficiency has increased incidence of autoimmunity. This classified as disorders of cell-mediated immunity, humoral immunity, phagocyte cell function, and the complement system (Barrett and Sleasman 1990). Several antibody deficiencies are also found associated with autoimmune diseases. Combined cellular and antibody deficiencies, such as Wiskott-Aldrich syndrome, carry an increased risk for juvenile rheumatoid arthritis. Concomitantly immunologic defect in eliminating microbial antigens resulting in chronic immunologic activation predispose to both autoimmunity and immunodeficiency. Defects within one component of the immune system may alter the way a pathogen-induced immune response and lead to inappropriate immune response.

Immunodeficiency commonly proceed to development of autoimmunity, it is possible that immunodeficient state renders individuals more susceptible to infectious agents, which then trigger an autoimmune condition. This hypothesis could be applied to the association

of autoimmunity with many inflammatory diseases of autoimmune origin. Another possibility is that, chronic infection resulted failure in clearing circulating immune complexes may leads to autoimmunity through immune complex deposition in the tissues. These mechanisms may play important role in the development of autoimmune diseases in patients with complement deficiencies. Deficiencies of the complement system to systemic lupus erythematosus (SLE), glomerulonephritis, vasculitis and abnormal inflammatory stimuli may be an additional factor in the pathogenesis of RA (Chikanza et al., 1992). Furthermore, immunological mechanisms to the tissue damage caused by the initial inflammatory reactions play a central role in the etiopathogenesis, because findings in chronic RA suggest a defective down-regulation of the immune response. On the above understanding the immunologic defects that contribute to the development of autoimmunity will provide an insight into the pathogenesis of the autoimmune process.

**Table 1. List of intrinsic defect to rheumatoid arthritis**

| **T cell** | |
|---|---|
| **Function** | **Disease** |
| Abnormal clonal expression and suppressed proliferation | RA |
| Dysfunctional effect on the regulation of autoantibodies | SLE |
| **B cell** | |
| Defective B cell antigenic stimulation | Hypogammaglobulinemia |
| Dysregulaton of B cell homeostasis associated to B cell stimulation | RA |
| Quantitative and Qualitative defect in dentritic cell | RA and SLE |
| Defective apoptosis promoted survival of autoreactive cells | Ra and SLE |

**Table 2. List of intrinsic defect in RA to microbial antigen**

| **T cell** | | |
|---|---|---|
| **Function** | **Disease** | **Organism** |
| Qualitative reduction of T cells | AS | K. pneumonia |
| Quantitative reduction of synovial T cells | RA | Microbial glycolipids |
| Defective suppressor T cells function | RA/SLE | EBV |
| T cell IL-12 deficiency | CNS Pathology | Semliki Forest Virus |
| Functionally defective Fc(IgG)+ T cell | SLE | Retroviral |
| **B cell** | | |
| Downstream B cell signaling pathway | SLE | Microbial LPS |
| Autoreactive B cell defective tolerance checkpoint | SLE | Microbial LPS |
| Class switch-defect | RA | Parvovirus B 19 |
| Defective B cell function | RA/SLE | EBV |
| Defective antibody regulation | RA | Parvovirus B 19 |
| **CSF** | | |
| TNF deficiency relate to reduced expression of IgE receptor | RA/SLE | *in vitro* study |
| IFN deficiency relate to decreased IgM, B cell, Macrophage and Granulocytes function | RA/SLE | *In vitro* study |
| **Complements** | | |
| C1q deficiency associated defective apoptosis | RA/SLE/Crohn's disease/SS | Neisseria meningitides Streptococcus pneumonia |
| Terminal complement component deficiency | Raynaud's phenomena | |
| **MMPs** | | |
| MMP - 9 deficiency | RA | Staphylococcus sp. |
| MMP – 7 deficiency | Allograft rejection | Viral sp. |
| Fas defective MRL-mice | RA | Staphylococcus sp. Mycoplasma sp. |
| Depressed phagocytic activity | RA/SLE | Mycoplasma sp. |
| Defective apoptosis associated CTL activity | RA | Mycobacterium sp. |

**T cells**

Diagnosis of arthritis using various laboratory methods identified microbe-specific T-lymphocytes and its lymphokines in autoimmune diseases speculate importance of the infectious connection to the above manifestation. Impaired antigen-specific proliferation of T-lymphocytes providing insights to study its role for rheumatoid arthritic etiology. The factors that play important role in driving T cell function mainly relate to nature and amount of microbial antigens. Similarly, regulatory T cell mechanism is essential for preventing autoimmune disorders but it may also facilitate the establishment of latent infections via suppression of the host immune response. An absolute defect in regulatory T cell function may contribute to the development of autoimmune disorders such as rheumatoid arthritis, type 1 diabetes mellitus, multiple sclerosis and chronic inflammatory bowel diseases etc., (Kelsen, 2006 ). Similarly number of phenotypic and functional T-cell defects has been described in RA, including abnormal clonal expansions and suppressed proliferative responses against microbial antigen suggest a defect in T-cell differentiation. Defective T cell and its lymphokine function resulted with increased risk of mycobacterial and Salmonella infection reported (Barnett, 1992).

Cell-mediated immunity (Coaccioli, 2000) and defective mononuclear/macrophage response in patients with SLE attributed to increased susceptibility to infection (Passero, 1981). In addition encapsulated bacterial pathogens like *Pneumococcus* or *Haemophilus influenzae* stimulate microbial clearance through T-cell independent pathway documented [Galin and Malech 1990]. Similarly defect within the particular component of the immune system will result in an alteration in the way the pathogen activated immune response. For example, quantitative reduction of K pneumoniae-responsive T cells in Ankylosing Spondolysis (AS) patients showed defective peripheral T cell defense against *Klebsiella sp.* and further it allows bacterial antigens to reach the synovium (Hermann et al., 1995). It seems that defect in T cell arm further perpetuate infection which might prove its vulnerability in autoimmune phenomena, because multiple infection at one time may have deleterious defects in the host.

Fine specificity of T cell responses to antigenic epitopes of a particular microbe has importance in providing tolerance. In adjuvant arthritic model T cell clones specific for nine amino-acid sequence of *Mycobacterium tuberculosis* antigen provided significant tolerance and resistance against adjuvant arthritis speculates importance of T cell regulatory mechanism (Gaston, 1989; Wegner, 2005; Skapenko, 2005). Hence defective regulatory immune mechanism might allow the breakdown of peripheral tolerance, following which the detrimental T-cell-driven immune response evolves and proceeds to chronic inflammation. It is possible that immunologic defects alter the common mechanism in which a pathogen is cleared by the host. Examples would include deficiencies involving the complement cascade or antibody production. This results in shift towards a cellular immune response with predominated activation of either Thl or Th2 of T cells subclass. In high synovial inflammation patients with RA showed low CD1a+, CD1b+, and CD1c+ synovial cells count. Such a defect may leads to an insufficient immune response against microbial glycolipids, which causes inadequate response to infection (Weidler, 2004). Neuronal necrosis more severe in interleukin (IL)-12-defective mice correlated with higher virus titer in the brain. This indicates type-1 T cell interleukin-12 impairment in the control of Semliki Forest virus (SFV) replication in the CNS pathogenesis (Keogh, 2002). Gamma/delta+ T cells in the pathological immune response showed poor proliferation to defective interleukin-2 (IL-2) synthesis, which implicated to provide defective helper effect in inducing B cells to secrete immunoglobulins (Gerli et al., 1993). Concomitantly, functionally defective Fc(IgG)+ T cells' important role in impaired immune regulation to SLE patients has also been demonstrated (Sakane et al., 1978).

In addition evidence of T-cell differentiation defect in RA could explain some of the well-characterized immunologic features of the disease (Ponchel et al., 2002). CD4+ memory T cells from patients with early untreated RA manifest an intrinsic abnormality in their ability to differentiate into specific cytokine-producing effector cells that might contribute to the characteristic Th1-dominated chronic autoimmune inflammation in RA (Mangelli, 2003; Boyle, 2001). Concomitantly active RA patients showed abnormal CD28 up-regulation suggest modulated CD28 surface levels (Romagnani 1994). Though such experimental evidences from different authors could be taken together to suggest principle defect in determining microbial antigen through T cell function will leads to defective consequences which cause deleterious effects in the host. Corresponding to initial dysregulation or malfunction in T cell arm may serve undesirable effects later in the

tolerance against common microbial antigens. Such intrigue would be given more importance for studies relate to defective cascading events.

**B cells**

Person who develops RA may have aberrant immune response to common microbial antigens or other antigens in the environment. Such response might be caused by intrinsic defects in B cell arm in the immune system. Defective B cells involvement to arthritic manifestation has been deled widely for their involvement in autoimmune manifestation. Studies on the B cell population and its antibody production in human and animal models have suggested involvement of both intrinsic B cell defect and abnormal regulation to common microbe for arthritic manifestation. Defects in B cell tolerance play an important role in the pathogenesis of systemic autoimmune diseases. Recruitment of B cells depends on antigenic milieu-established threshold for B cell receptor signaling, which is modulated by numerous co-receptors, which implicates upon their importance in development of autoimmunity. B cell responses are mediated by different patterns of gene expressions, BCR signaling threshold and cellular interactions. Aberrant B cell responses are reviewed in the light of these principles taking into account the molecular and architectural aspects of immunopathology. B cell hyper-reactivity may arise from altered BCR signaling thresholds in autoimmunity. Defects in such stimuli may guide for intrinsic response to microbial antigen and defective B cell gene expression. On the above, the interaction between immune cells cellular and signaling components involvement in B cell development and maintenance has prime role in understanding RA manifestation. Because modulated expressions of presumed key regulatory or signaling components have resulted in subsequent development of immune dysfunction and autoimmune disease. The B cell traverse is tightly regulated development pathway from early progenitors to terminally differentiated plasma cells. Many of these developmental steps are dependent on signals mediated through receptor-ligand interactions. Recent results shows that RA patients suffer from defective central and peripheral B cell tolerance checkpoints may favor the development of autoimmunity (Samuels, 2005; Yurasov, 2005; Currier, 2000). Using tonsil biopsy study on autoreactive B cells provided evidence for defective tolerance checkpoint that appears to be specific for human systemic lupus erythematosus (SLE) (Cappione, 2005). Recently Pugh (2006) demonstrated B cells of SLE patients with molecular signaling defect, which likely to contribute to pathogenesis of the disease and explain the characteristic hyperactivity of B cells in active disease.

On the above, microbial antigen connection to defective BCR signaling much speculate upon their role in autoimmunity. Autoimmunity-associated B cell defective BCR signaling and subsequently regulation of microbial lippo-polysaccharides-driven antibody responses has number of downstream events in signaling pathways of B cells. Hence it may be proposed that defective BCR mediated signals altering intracellular signal, and thereby changing the strength of signals needed to initiate BCR mediated activation. In addition inherent abnormality of B cells and its lymphokines to external signal such as bacterial lipo-polysaccharides and similar bacterial products has been well documented (Defranco, 1993). The defect can result from aberrant regulation of antigen processing for IgM production; this may be a predisposing factor in systemic autoimmune diseases (Roy, 2005). Mice develop lupus-like syndrome to defective autoantibody production possess immunologic abnormalities suggest B cell tolerance may be defective against common microbial antigens (Anderson, 1995).

Similarly defective auto-antigen signaling through BCR signal may have role in generation and maintenance of self-reactivity of B cells in primary immune deficiency (PID). Arthritis most commonly occurs chiefly in humoral PIDs like agammaglobulinemia, common variable immunodeficiency, hyper-IgM syndromes, IgA deficiency, chronic granulomatous disease and Wiskott-Aldrich syndrome etc., Arthritic patients with PID is usually infectious in nature, the most common causative organism is being Mycoplasma, followed by *Staphylococcus, Streptococcus, and Haemophilus*. These bacteria's can induce not only synovial infections but also aseptic arthritogenic inflammatory responses. PID syndromes provide insight into the pathophysiology of bone and joint abnormalities associated with immune dysfunction (Cuomo, 1995).

Many studies proposed several infectious agents leads to recognition of self-antigens consequently to the disordered immune response and dysregulation of cytokines production, which initiates and maintains the disease (Tedder, 1997; Sordet, 2005). Patients infected with B19 virus showed elevated IgM antibodies and lack of specificity against viral minor capsid species suggested a

class switch defect (Bijlsma, 1999). It is also suggested that patients with congenital acquired immunodeficiency may produce antibodies that fail to react with the viral capsid protein epitopes. On the above, some experimental evidences pertains to disordered immune response against common virus infection needs to be discussed. Epstein-Barr virus infections of B cells cause the cell to display increased binding sites on the cell surface for human Herpesvirus-6, thereby increasing susceptibility to super-infection (Fish, 1989). Lymphocytes from EBV-immune RA patients infected with EBV in culture produced increased number of immunoglobulin-secreting cells suggesting defect in suppressor-T cell function related to EBV specificity. Since EBV persists in host B cells, the potential stimulus for immunoglobulin production. This virus persistence along with a specific regulatory T-cell defect, may contribute to many of the immune abnormalities underlying rheumatoid arthritis (Tosato, 1981). Lymphocytes and polyclonal B cells of RA patients cultured with Epstein-Barr virus (EBV) produced less IgM after one week and increased IgM secretion at the end of second week and greater IgM after fifth week suggest that defective B and T cell responses to EBV in lymphocytes of RA patients (Irving, 1985). Considering above studies viral infection with disordered immune response has role in RA like diseases. Hence it may be suggested that immune deficiency might have contributory role in autoimmune phenomena, but only with causative organism gives more satisfactory explanation. In age related syndrome effective memory B cell activity is more importantly necessary to maintain avoiding cross-reactivity. Re-infection of same old microbial antigens always frequently deled by memory B cells. Memory B cells elicited weak primary response to antigen of re-infection on transfer to immunodeficient mice has been reported (Inman, 2006). In addition maintenance of memory B cell population by exposure to environmental antigens including viruses, bacteria and other parasites provided intermittent immune stimulation through cross-reactive epitopes.

Furthermore, RA patients' B cells failed to proliferate against interleukin-2 &10 supplements, supports the notion that these cells play important role in the pathophysiology of RA (Reparon-Schuijt et al., 2001). Defective B cell auto-regulation involvement in the pathogenesis and chronicity of the disease also reported (White, 1986). Taken together the experimental evidences pertain to defective B cell function giving satisfactory explanation for autoimmune phenomena. Thus, B cell defective function and defective BCR signaling on the regulation of bacterial antigen-driven antibody response accounting for architectural aspect of immunopathology, which would render deleterious effects in the host.

**Colony Stimulating Factors (CSFs) and Cytokines**

Colony Stimulating Factors (CSF) being as chemotactic in nature has led RA pathogenesis lies in the comprehension of arthrotopism of antigens and inflammatory cells for joints. Immunological studies have learned that host defense against disseminated microbes is based on the complex interplay between innate and cell-mediated immunity and their CSF with cytokine function (Barrett and Sleasman, 1990). Large body of clinical experience on the adverse consequences of cytokine administration has accumulated since the last decade. Side effects reported after the therapeutic use of cytokines has provided evidence for activation of immune response may sometimes have deleterious consequences. Several effects appeared as a direct consequence of the immune activation induced by cytokines. Cytokine-induced exacerbations of immune dysregulation were growing concern. Interferon-alpha (IFN-alpha) treatment clearly linked with the exacerbation or the occurrence of several types of autoimmune diseases like thyroiditis, systemic lupus erythematosus and arthritis. Growth factors and CSF are more specifically linked with the development of dermatological inflammatory diseases through neutrophils, monocytes, macrophages or eosinophils activation. *Candida albicans* infection with defective immune response (Vonk et al., 2006) and granulocyte-macrophage colony-stimulating factor-deficient mice failed response against antigen alpha-galactosylceramide showed intrinsic defect and defective immune cell differentiation and development (Bezbradica et al., 2006). Concomitantly phenotypical or morphological analysis of cells from GM-CSF-supplemented-bone marrow-culture showed quantitative and qualitative alterations of the dentritic cell (DC) lineage and increased generation. It has been proposed that, high number of granulocytes favors inflammatory environment by interfering with DC development because unbalanced antigen presenting cell function, which leads to T cell autoimmunity (Fuhler, 2004). Likewise TNF-deficient cells found less responsive to infectious agents. Recently Wright (2006)

demonstrated *in vitro* cultured mast cells from TNF-deficient mice with reduced expression of high affinity IgE receptors and reduced number of peritoneal mast cell.

In addition, IFN-beta-/- mice showed reduced spleen and bone marrow (BM) macrophages, defective B cell maturation, decreased CD43-ve bone marrow (BM)-derived cells, reduced IgM, and CD23 expression. Likewise circulating IgM, Macrophages and Granulocytes positive cells found decreased in IFN-beta-/- mice. The decreased number of circulating macrophages and granulocytes likely to reflect defective maturation of primitive bone marrow hematopoiesis and reduced colony-forming units (Deonarain, 2003), thus providing insights into importance of CSF in the events of primary and secondary immune responses. Concomitantly, qualitative defect in white blood cell count altered white blood cell function and increased susceptibility to infection as well. Similarly release of immature white blood cells into the circulation caused defect in clear infection and increased propensity to organ failure (Livingston 2003). Joint inflammation in -/Delta vav mice characterized by increased number of neutrophils in the inflamed synovium, bone marrow, peripheral blood and spleen most likely due to enhanced responsiveness to G-CSF and IL-6 during arthritis (Kerr, 2004). Likewise impaired viral clearance in IL-18-deficient mice implicated for RA (Nakanishi, 2001). Furthermore in GM-CSF exacerbated collagen induced arthritis (CIA), GM-CSF administration at the antigenic site has been recognized as effective adjuvant for increasing cellular and humoral immunity to peptide/protein antigens. Thus, studies corroborate the importance of defect in immune response against common microbial antigens are related to deficient CSF network or cytokine modulation. From the above experimental evidences, deficient CSF network, TNF-deficiency induced less effective IgE immunoglobulin synthesis and IFN-deficient mice with defective maturation of B cells are strongly advocate those that principal defects upon their role in autoimmunity. Those intrinsic defects while dealing microbial antigens may serve potential and favorable environment for infectious agents to facilitate undesirable effects in the host.

**Neutrophils**

Polymorphonuclear neutrophils (PMN) play a central role in the elimination of most extracellular pathogenic microorganisms. Impairment of its functions therefore predisposes to defective immune response. Neutrophils are fundamental to the inflammatory process, they migrate into inflammatory foci where they manufacture and release numerous substances, which if not controlled may injure the tissues they come in contact with. This enhanced activity is responsible for the degenerative reaction, which occurs in rheumatoid arthritis. Recently it has been shown that granulocyte–colony-stimulating factor (G-CSF) and interferon-γ (IFN-γ)–activated human neutrophil released remarkable amounts of soluble B-lymphocyte stimulator (BLyS) in vitro. Similarly, pro-inflammatory stimuli such as chemotactic factors, cytokines, immune complexes, and bacteria-derived lipo-polysaccharides (LPS) trigger and greatly amplify the release of BLyS by inflammatory neutrophils. This B-lymphocyte stimulator (BlyS) released by neutrophils implicated to dysregulated B-cell homeostasis (Patrizia Scapini 2005). In addition abnormal synovial fluid neutrophil function to different susceptibility against various infections in patients with rheumatic disorders have been well documented (Wong, 2006; Dolganiuc, 2000).

The association between complementary protein C1q and autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus (SLE) are well established. Deficiency in C1q considered strong susceptibility factor for development of rheumatic diseases. Similarly the observation of the presence of high-affinity autoantibodies against C1q antibodies in patients with SLE provides strong correlation between C1q and inflammatory process. Recent evidence using C1q-deficient mice has showed presence of glomerulonephritis with immune deposits and large number of apoptotic bodies in the diseased glomeruli suggesting a defect in the apoptotic activity by macrophages and dendritic cells (DCs). These data's are consistent with the hypothesis that, C1q deficiency may induce a generalized failure to clear immune complexes. Furthermore, low serum complement levels found in patients with autoimmune diseases generally reflect increased consumption of complement proteins as a result of immune complex-mediated inflammation (Ghebrehiwet and Peerschke, 2004).

Inherited deficiencies in the complement components of the classic cascade carry risk for the development of systemic lupus erythematosus (SLE) and juvenile arthritis. Patients reported to have homozygous C4 deficiency with clinical manifestations of autoimmunity. Approximately

one-half of the individuals with symptomatic C2 deficiency have autoimmune disease (Hauptmann, 1998). C2 deficiency observed with increased incidence of bacterial pneumonia, meningitis, and sepsis. Similarly deficiency of Cl inhibitor showed uncontrolled activation of classic pathway components and consumption of C2 and C4 that leads to recurrent episodes of angioedema of the viscera, soft tissues, and airway, and high risk of SLE, Crohn's disease, and Sjogren's syndrome (Brickman, 1986).

In addition SLE, systemic vasculitis, and glomerulonephritis reported with C3 deficiency (Borzy, 1988). Raynaud's phenomena and lupus-like syndromes reported with defects in terminal complement components (Ross and Densen, 1984). Cytolysis by terminal complement components is important in host defense against Gram-negative organisms like *Neisseria* and brucella species. Defects in the alternative complement pathway are more commonly associated with recurrent pyogenic infections, particularly infections with *Neisseria meningitidis* and *Streptococcus pneumoniae*. Chronic granulomatous disease (CGD) is an X-linked recessive condition characterized with recurrent infection of catalase-positive organism *Staphylococcus aureus* (Galin and Malech, 1991). In the chronic phase of Chlamydia-induced arthritis the Rac-deficient mice developed more severe arthritis and demonstrated defective clearance of the pathogen from the joint (Zhang, 2005). Balb/c mice defective with IL-10 gene intravenously inoculated along with bacteria showed more frequent and destructive arthritis with higher bacterial load in blood and kidneys (Gjertsson, 2002). In addition, peripheral blood, synovial fluid and synovial tissue samples from patients with recent *Salmonella* infection of RA patients study showed positive levels of macrophage receptor. This suggest defective host defense against gram-negative bacteria (Seta, 2001). Furthermore the defects in PMN function observed in murine model of autoimmunity with spontaneous production of TGF-beta possibly play a crucial role in the pathogenesis by infection (Gresham et al., 1991).

In G-CSF receptor (G-CSFR) deficient mice with impaired IL-8 activity demonstrated selective defects in PMN activation (Betsuyaku et al., 1999). Neutrophils from SLE patients displayed increased DNA damage and demonstrated defective repair of oxidative DNA damage (McConnell, 2002). From the above experimental evidences includes LPS-induced B lymphocytes stimulating factors from neutrophils and its relation to dysregulation of B cell homeostasis, deficient complementary protein activity induced defective clearance of immune complexes by apoptotic cells are corroborate the idea that defective neutrophil function has satisfactory explanation for development of autoimmunity. Because immune-complexes may have potential immunogens and those can induce re-stimulation of immune system. Concomitantly complement deficiency with increased incidence of bacterial infection herewith pursues the importance of defective complement cascade relation to development of RA like inflammatory diseases.

**Matrix metalloproteinases (MMPs)**

In rheumatoid arthritis cartilage damage guess protease enzymes connection to erosion at the site of inflammation. The regulation and expression of MMPs considered multi-factorial, and it considered a micro environmental process prevails in the inflammatory region, their release being stimulated by exposure to specific activating factors or stimulatory factors such as IL-1 and TNF alpha (Cronstin, 1993; Arend, 1995; Poole; 1993). Pro-inflammatory cytokines induced matrix metalloproteinase enzymes up regulates mediators such as adhesion molecules and further reinforces the inflammatory activity (Kuo, 2006). Elevated levels of MMP-9 demonstrated in synovial fluids of rheumatoid arthritis correlated to the severity of the disease. MMP-9 knockout mice inoculated intravenously with *Staphylococcus aureus* displayed significantly higher frequency and severity of arthritis. This knockout mouse also proved to harbour increased number of bacteria locally in joints and systemically in kidneys and leukocyte deficiency against infection (Feldman, 1996). This indicates that deficiency in MMP-9 increases the degree of joint inflammation due to decreased bacterial clearance. In addition damage to the respiratory epithelium by viral infection in MMP7-Knock out mice lead consistent chronic allograft rejection, suggesting a role for MMPs in epithelial injury in bronchiolitis obliterans syndrome (Conley, 1985). Those data's assume the defective MMP regulations are connected with joint inflammation and bacterial clearance.

**Defective apoptosis**

Apoptosis plays an important role in autoimmune diseases. Defective apoptosis the idea has been introduced to autoimmune like degenerative diseases with induction of many proteases which damage and clear macromolecules of the cartilage region. A common feature systemic lupus

erythematosus (SLE) is breakdown of tolerance to self-antigens, a consequence of which is the production of autoantibodies reactive with multiple self-proteins. Many evidences are accumulating for modification of autoantigens during apoptosis leading to the development of autoantibodies. Similarly defective apoptosis can cause autoimmunity by allowing the survival of autoreactive T and B cells. Defective apoptosis acts as source of immunogen and accelerates abnormal processing of apoptotic cell, which could leads to auto-antibody production. Defective T cell apoptotic pathway promotes survival of potential autoreactive proinflammatory cells. Thus failure to eliminate activated cells can result in prolonged effector function and inappropriate survival of primed autoantibody-producing B cells (Mulherin, 1996). Furthermore, it has been suggested that defects in the modulation of programmed cell death may lead to autoimmune disease. Altogether, the idea that defects in the apoptotic process could be important for explaining autoimmune diseases and makes research on the different factors in this pathway valuable for achieving a better understanding of the etiopathogenesis of autoimmune diseases. Infiltration mononuclear cells lead destruction of parenchymal tissue showed apoptosis of the acinar and ductal epithelial cells of the salivary and lachrymal glands suggested possible impairment of secretary function in Sjogren Syndrome (SS).

In the fas-defective MRL-lpr/lpr mice staphylococcal enterotoxin super-antigen systematic administration caused inflammatory arthritis in the knee joints (Edwards, 1996), and human endogenous retrovirus HERV-K18 super-antigen level in the JRA patients suggesting a possible mechanism for autoimmunity by super-antigen stimulated autoreactive T cells (Sicat, 2005). Phagocytic activity of mice estimated by the carbon clearance test following injection of *Mycoplasma arthritidis* showed significantly depressed phagocytic activity in post-infection may be related to super-antigen activity with the production of mediator like macrophage deactivating factor (Kaklamani 1993). Recently our study related to arthritic model using heat killed Mycobacterium suspended adjuvant in rats showed invasion of cytotoxic T lymphocytes in knee joints region, which implicated to damage and clearing of cartilage macromoleules (Subramanian and Ramalingam, 2005). On the above it may be suggested that defective apoptosis may responsible for CTL activity against Mycobacterium tuberculosis super-antigen.

In addition, increased rate of epithelial cell apoptosis in SS may result from either the imbalance between the down-regulated apoptosis-inhibitor (autocrine) or by the up-regulated apoptosis-inducer (paracrine or Fas/FasL) interaction. Defective Fas/FasL-mediated apoptosis of T cells renders arthritis-resistant B6 mice susceptible to the development of chronic erosive arthritis subsequent to mycoplasma infection (Hsu et al., 2001). Eguchi (2001) demonstrated T and B cell defective apoptosis with failure in proper clearance of immune cells and defective down-modulated immune response in mice, which speculates apoptosis defects, including defects in Fas, Fas ligand and Fas apoptosis signaling, may play a role in defective down-modulation of hyper-immune response in human autoimmune diseases (Eguchi, 2001). In addition defective apoptosis has been reviewed along with promoting autoreactive T cells and pro-inflammatory cells production and failure in clearing activated cells resulted in prolonged survival of autoantibody producing B cells. This implicates upon their role in RA like immunopathology diseases. Especially breakdown of tolerance to self-antigen consequent with autoantibodies reactive with self-antigens has possible explanation for defective apoptosis involvement to arthritic phenomena.

**Conclusion**

One way or another, the autoimmune mechanism has potential and satisfactory explanation for infectious connection. Obviously, immunity to common microbial antigen is the pre-requisite for induction of immune cascading events. Trigger of immune response to denatured fragments of post infection or to denature self- molecules throw the way for intrigue or undesirable effects in the host. Obviously defective immune response against a common microbial antigen might favour the undesirable situation in the host. RA is one in that, hence immune deficiency has contributory role in autoimmune phenomena but only with causative organism giving satisfactory explanation for etiology. Especially defective B cell function, defective BCR signaling mechanism, dysregulated cytokine function, autoantibodies cross reactivity to self-antigens, inappropriate complement cascade and defective apoptosis are few privileged environments needs to be understood in-depth. From the above experimental evidences it may be understood that not only infectious connection is the fact

behind etiology but also defect in normal immune arm serve the important contributory role in development and maintenance of autoimmunity. On the above it's very important to look for many more experimental evidences pertains to important and necessary defective responses against common microbial antigen to understand reason behind autoimmunity.

**References**

Anderson CC, Cairns E, Rudofsky UH, Sinclair NR. 1995. Defective antigen-receptor-mediated regulation of immunoglobulin production in B cells from autoimmune strains of mice. Cell Immunology. 164(1):141-9.

Arend W.P, Dayer J.M. 1995. Inhibition of the production and efforts of interleukin -1 and tumour necrosis factor alpha in rheumatoid disease, Arthritis Rheumatism 38:151-160.

Barnett LA, Fujimani RS. 1992. Molecular mimicry: a mechanism for autoimmune injury. FASEB Journal 6:840-844.

Barrett DJ, Sleasman JW. 1990. Immunodeficiency disorders in infants and children. In: Current therapy in infectious disease. Kass EH, Platt R, editors. Philadelphia, PA: Decker. 51-68.

Betsuyaku T, Liu F, Senior RM, Haug JS, Brown EJ, Jones SL, Matsushima K, Link DC., 1999. A functional granulocyte colony-stimulating factor receptor is required for normal chemoattractant-induced neutrophil activation. Journal of Clinical Investigation. 103(6):825-32.

Bezbradica JS, Gordy LE, Stanic AK, Dragovic S, Hill T, Hawiger J, Unutmaz D, Van Kaer L, Joyce S., 2006. Granulocyte-macrophage colony-stimulating factor regulates effector differentiation of invariant natural killer T cells during thymic ontogeny. : Immunity. 25(3):487-97.

Bijlsma JW, Cutolo M, Masi AT, Chikanza IC. 1999. The neuroendocrine immune basis of rheumatic diseases. Immunology Today 20(7):298-301.

Borzy MS, Gewurz A, Wolff L, Houghton D, Lovrien E., 1988. Inherited C3 Deficiency with recurrent infectionsand glomerulonephritis. American Journal of Diseases of Children 142:79-83.

Boyle LH, Goodall JC, Opat SS, Gaston JS. 2001. The recognition of HLA-B27 by human CD4(+) T lymphocytes. Journal of Immunology. 1;167(5):2619-24.

Brickman CM, Tsokos GC, Balow JE, Lawley TJ, Santaella M, Hammer CH., 1986. Immunoregulatory disorders associated with hereditary angio-oedema. I. Clinical manifestation of autoimmune disease. Journal of Allergy and Clinical Immunology. 11:149-151.

Cappione A 3rd, Anolik JH, Pugh-Bernard A, Barnard J, Dutcher P, Silverman G, Sanz I., 2005. Germinal center exclusion of autoreactive B cells is defective in human systemic lupus erythematosus. Journal of Clinical Investigation. 115(11):3205-16.

Chikanza IC, Petrou P, Kingsley G, Chrousos G, Panayi GS. 1992. Defective hypothalamic response to immune and inflammatory stimuli in patients with rheumatoid arthritis. Arthritis Rheumatism . 35(11):1281-8.

Coaccioli S, Di Cato L, Marioli D, Patucchi E, Pizzuti C, Ponteggia M, Puxeddu A. Impaired cutaneous cell-mediated immunity in newly diagnosed rheumatoid arthritis. Panminerva Medica. 2000 Dec;42(4):263-6.

Conley ME. 1985. B cells in patients with X-linked agammaglobulinemia. Journal of Immunology 134:370-3074.

Cronstin B.N, Weissman G. 1993. Neutrophil structure and functions. In: D.J. McCatty, W.J. Koopman (eds): "Arthritis and allied conditions, A textbook of rheumatology" vol.1. Philadelphia: Lea & Febiger 389-408.

Cuomo L, Angeloni A, Zompetta C, Cirone M, Calogero A, Frati L, Ragona G, Faggioni A., 1995 Human herpes virus 6 variant A, but not variant B, infects EBV-positive B lymphoid cells, activating the latent EBV genome through a BZLF-1-dependent mechanism. AIDS Research Human Retroviruses 11(10):1241-5

Currier N.L, Sun L.Z, Miller S.C., 2000. Exogenous melatonin: qualitative enhancement in vivo of cells mediating non-specific immunity. Journal of Neuroimmunol ogy. 104 :101-108.

Cutolo M. 1997. Do sex hormone modulate the synovial macrophages in rheumatoid arthritis, Annals of Rheumatic Diseases. 56: 281-286.

DeFranco A.L., 1993. Lymphocyte activation, In: Paul WE (eds) Fundamental immunology, 3rd ed:, New York, Raven Press 505-549.

Deonarain R, Verma A, Porter AC, Gewert DR, Platanias LC, Fish EN., 2003. Critical roles for IFN-beta in lymphoid development, myelopoiesis, and tumor development: links to tumor necrosis factor alpha. Proceedings of National Academy of Sciences U S A. 11;100(23):13453-8.

Dolganiuc A, Stavaru C, Anghel M, Baltaru D, Georgescu E, Olinescu A., 2000. The migratory and phagocytic activity of polymorphonuclear leukocytes in rheumatoid arthritis and osteoarthritis patients. Romanian Archives of Microbiology and Immunology. 59(1-2):43-53.

Edwards CK 3rd, Zhou T, Zhang J, Baker TJ, De M, Long RE, Borcherding DR, Bowlin TL, Bluethmann H, Mountz JD. 1996. Inhibition of superantigen-induced proinflammatory cytokine production and inflammatory arthritis in MRL-lpr/lpr mice by a transcriptional inhibitor of TNF-alpha. Journal of Immunology. 15;157(4):1758-72.

Eguchi K., 2001. Apoptosis in autoimmune diseases. International Medicine. 40(4):275-84.

Feldman M., Brennan FM., Aaini RN. 1996. Role of cytokines in rheumatoid arthritis., Annual Review Immunology. 14:397-440.

Fish S, Zenowich E, Fleming M, Manser T., 1989. Molecular analysis of origin antigenic sin I. Clonal selection, somatic mutation and isotype switching during a memory B cell response. Journal of Experimental Medicine. 179:1191.

Fuhler GM, Cadwallader KA, Knol GJ, Chilvers ER, Drayer AL, Vellenga E., 2004. Disturbed granulocyte macrophage-colony stimulating factor priming of phosphatidylinositol 3,4,5-trisphosphate accumulation and Rac activation in fMLP-stimulated neutrophils from patients with myelodysplasia. Journal of Leukocyte Biology. 76(1):254-62.

Galin JI, Malech HL: Update on chronicgranulomatous diseases of childhood. Journal of American Medical Association. 1991, 263:1533-1537.

Gaston JS, Life PF, Bailey LC, Bacon PA. 1989. In vitro responses to a 65-kilodalton mycobacterial protein by synovial T cells from inflammatory arthritis patients. Journal of Immunology. 15;143(8):2494-500.

Gerli R, Agea E, Muscat C, Bertotto A, Ercolani R, Bistoni O, Bini P, Spinozzi F, Venanzi F. 1993. Functional characterization of T cells bearing the gamma/delta T-cell receptor in patients with primary Sjogren's syndrome. Clin ical and Experimental Rheumatology. 11(3):295-9.

Ghebrehiwet B, Peerschke EI. 2004. Role of C1q and C1q receptors in the pathogenesis of systemic lupus erythematosus. Current Directions in Autoimmunity. 7:87-97.

Gjertsson I, Hultgren OH, Tarkowski A. 2002. Interleukin-10 ameliorates the outcome of Staphylococcus aureus arthritis by promoting bacterial clearance. Clinical and Experimental Immunology. 130(3):409-14.

Gresham HD, Ray CJ, O'Sullivan FX. 1991. Defective neutrophil function in the autoimmune mouse strain MRL/lpr. Potential role of transforming growth factor-beta. Journal of Immunology. 1;146(11):3911-21.

Hauptmann G, Tappeiner G, Schifferli JA., 1998. Inherited deficiency of the fourth component of human complement. Immunodeficiency Review. 1:3-22.

Hermann E, Sucke B, Droste U, Meyer zum Buschenfelde KH. 1995. Klebsiella pneumoniae-reactive T cells in blood and synovial fluid of patients with ankylosing spondylitis. Comparison with HLA-B27+ healthy control subjects in a limiting dilution study and determination of the specificity of synovial fluid T cell clones. Arthritis Rheumatism. 38(9):1277-82

Hsu HC, Zhang HG, Song GG, Xie J, Liu D, Yang PA, Fleck M, Wintersberger W, Zhou T, Edwards CK 3rd, Mountz JD. 2001. Defective Fas ligand-mediated apoptosis predisposes to development of a chronic erosive arthritis subsequent to Mycoplasma pulmonis infection. Arthritis Rheumatism. 44(9):2146-59.

Inman RD. 2006. Mechanisms of disease: infection and spondyloarthritis. National Clinical Practical Rheumatology 2(3):163-9.

Irving WL, Walker PR, Lydyard PM. 1985. Abnormal responses of rheumatoid arthritis lymphocytes to Epstein-Barr virus infection in vitro: evidence for multiple defects. Annals of Rheumatic Dissases. 44(7):462-8.

Kaklamani E, Karalis D, Koumandaki Y, Kaklamanis P, Katsouyanni E, Tzanetea R, Blackwell CC, Sparos L, Weir DM, Trichopoulos D. 1993. The effect of Mycoplasma arthritidis infection on the kinetics of colloidal carbon clearance in mice. FEMS Immunology and Medical Microbiology. 6(4):299-305.

Kelsen J, Hvas CL, Agnholt J, Dahlerup JF. 2006. CD4 + CD25 + regulatory T cells and their importance to human illnesses, Ugeskr Laeger. 3;168(1):32-7.

Keogh B, Atkins GJ, Mills KH, Sheahan BJ., 2002. Avirulent Semliki Forest virus replication and pathology in the central nervous system is enhanced in IL-12-defective and reduced in IL-4-defective mice: a role for Th1 cells in the protective immunity. Journal of Neuroimmunology. 125(1-2):15-22.

Kerr JR, Cunniffe VS, Kelleher P, Coats AJ, Mattey DL. 2004. Circulating cytokines and chemokines in acute symptomatic parvovirus B19 infection: negative association between levels of pro-inflammatory cytokines and development of B19-associated arthritis, Journal of Medical Virology. 74(1):147-55

Kuo E, Bharat A, Shih J, Street T, Norris J, Liu W, Parks W, Walter M, Patterson GA, Mohanakumar T. 2006. Role of airway epithelial injury in murine orthotopic tracheal allograft rejection. Annals of Thoracic Surgery. 82(4):1226-33.

Livingston DH, Anjaria D, Wu J, Hauser CJ, Chang V, Deitch EA, Rameshwar P. 2003. Bone marrow

failure following severe injury in humans. Annals of Surgery. 238(5):748-53.

Manganelli P, Fietta P. 2003. Apoptosis and Sjogren syndrome. Semin Arthritis Rheumatism. 33(1):49-65.

McConnell JR, Crockard AD, Cairns AP, Bell AL., 2002. Neutrophils from systemic lupus erythematosus patients demonstrate increased nuclear DNA damage. Clinical Experimental Rheumatology. 20(5):653-60.

Mulherin D.M, Veale D.J, Belch J.J.E, Bresnihan B, Filzgerald O. 1996. Adhesion molecule in unrelated inflammatory arthritis, Quarterly Journal of Medicine. 89:195-203.

Nakanishi K, Yoshimoto T, Tsutsui H, Okamura H. 2001. Interleukin-18 is a unique cytokine that stimulates both Th1 and Th2 responses depending on its cytokine milieu. Cytokine Growth Factor Review. 12(1):53-72.

Passero FC, Myers AR. 1981. Decreased numbers of monocytes in inflammatory exudates in systemic lupus erythematosus. Journal of Rheumatology. 8(1):62-8.

Patrizia Scapini, Antonio Carletto, Bernardetta Nardelli, Federica Calzetti, Viktor Roschke, Flavia Merigo, Nicola Tamassia, Sara Pieropan, Domenico Biasi, Andrea Sbarbati, Silvano Sozzani, Lisa Bambara, and Marco A. Cassatella., 2005. Proinflammatory mediators elicit secretion of the intracellular B-lymphocyte stimulator pool (BLyS) that is stored in activated neutrophils: implications for inflammatory diseases, Blood, 15-105(2): 830-837.

Pittoni V, Valesini G. 2002. The clearance of apoptotic cells: implications for autoimmunity. Autoimmunity Review. 1(3):154-61.

Ponchel F, Morgan AW, Bingham SJ, Quinn M, Buch M, Verburg RJ, Henwood J, Douglas SH, Masurel A, Conaghan P, Gesinde M, Taylor J, Markham AF, Emery P, van Laar JM, Isaacs JD. 2002. Dysregulated lymphocyte proliferation and differentiation in patients with rheumatoid arthritis. Blood. 15;100(13):4550-6.

Poole A.R. 1993. Cartilage in health and disease. In: McCarty DJ, Koopman WJ, (eds) arthritis and allied conditions, A textbook of rheumatology vol.1, Philadelphia: Lea & Febiger 279-334.

Pugh-Bernard AE, Cambier JC. 2006 B cell receptor signaling in human systemic lupus erythematosus. Curr ent Opinion in Rheumatology. 18(5):451-5.

Reparon-Schuijt CC, van Esch WJ, van Kooten C, Ezendam NP, Levarht EW, Breedveld FC, Verweij CL., 2001. Presence of a population of CD20+, CD38- B lymphocytes with defective proliferative responsiveness in the synovial compartment of patients with rheumatoid arthritis. Arthritis Rheumatism. 44(9):2029-37

Romagnani S., 1994. Lymphokine production by human Tcells in disease states. Annual Review Immunology 12:227-257.

Ross SC, Denson P., 1984. Complement deficiency states and infection: epidemiology, pathogenesis, and consequences of neisserial and other infections in an immune deficiency. Medicine 63:243-273.

Roy V, Chang NH, Cai Y, Bonventi G, Wither J. 2005. Aberrant IgM signaling promotes survival of transitional T1 B cells and prevents tolerance induction in lupus-prone New Zealand black mice. Journal of Immunology. 1;175(11):7363-71.

Sakane T, Steinberg AD, Green I., 1978. Failure of autologous mixed lymphocyte reactions between T and non-T cells in patients with systemic lupus erythematosus. Proceedings of National Academy of Sciences U S A. 75(7):3464-8.

Samuels J, Ng YS, Coupillaud C, Paget D, Meffre E., 2005. Human B cell tolerance and its failure in rheumatoid arthritis. Annals of New York Academy of Sciences. 1062:116-26

Seta N, Granfors K, Sahly H, Kuipers JG, Song YW, Baeten D, Veys EM, Maksymowych W, Marker-Hermann E, Gu J, Huang F, Kirveskari J, Yu DT. 2001. Expression of host defense scavenger receptors in spondylarthropathy. Arthritis Rheumatism. 44(4):931-9.

Sicat J, Sutkowski N, Huber BT. 2005. Expression of human endogenous retrovirus HERV-K18 superantigen is elevated in juvenile rheumatoid arthritis. Journal of Rheumatology. 32(9):1821-31.

Skapenko A, Leipe J, Lipsky PE, Schulze-Koops H. 2005. The role of the T cell in autoimmune inflammation. Arthritis Research Therapy. 7 Suppl 2:S4-14.

Sordet C, Cantagrel A, Schaeverbeke T, Sibilia J. 2005. Bone and joint disease associated with primary immune deficiencies. Joint Bone Spine 72(6):503-14.

Subramanian, S and Ramalingam, K. 2005. Electron microscopic evidence on the participation of Cytotoxic T-lymphocyte and macrophages in MTB- adjuvant induced connective tissue inflammation and arthritogenesis in Rattus norvegicus. Asian Journal of Microbiology, Biotechnology & Environmental Sciences 7(2) 227-233.

Tedder T.F, Tuscano J, Sato S, Kehrl J.H., 1997. A B lymphocyte-specific adhesion molecule that regulates antigen receptor signaling, Annual Review Immunology. 15: 481-504.

Tosato G, Steinberg AD, Blaese RM. 1981. Defective EBV-specific suppressor T-cell function in

rheumatoid arthritis. : New England Journal of Medicine. 19;305(21):1238-

Vonk AG, Netea MG, van der Meer JW, Kullberg BJ., 2006. Host defence against disseminated Candida albicans infection and implications for antifungal immunotherapy Expert Opinion Biology Therapy 6(9):891-903

Wagner U, Schulze-Koops H. 2005. T-lymphocytes--do they control rheumatic immune responses?. Rheumatology. 64(6):377-82.

Weidler C, Kroll R, Miller LE, Scholmerich J, Grifka J, Straub RH., 2004. Low density of CD1+ cells in the synovial tissue of patients with rheumatoid arthritis. Clinical Experimental Rheumatology. 22(4):433-40.

White RE, Pisko EJ, Foster SL, Panetti M, Turner RA., 1986. Decreased suppressive B cell factor (SBF) in rheumatoid arthritis: evidence for a defect in B cell autoregulation. Journal of Immunology. 15;136(6):2151-7.

Wong PK, Egan PJ, Croker BA, O'Donnell K, Sims NA, Drake S, Kiu H, McManus EJ, Alexander WS, Roberts AW, Wicks IP., 2006. SOCS-3 negatively regulates innate and adaptive immune mechanisms in acute IL-1-dependent inflammatory arthritis. Journal of Clinical Investigation. 116(6):1571-81.

Wright HV, Bailey D, Kashyap M, Kepley CL, Drutskaya MS, Nedospasov SA, Ryan JJ., 2006. IL-3-mediated TNF production is necessary for mast cell development. J ournal of Immunology. 15;176(4):2114-21

Yurasov S, Wardemann H, Hammersen J, Tsuiji M, Meffre E, Pascual V, Nussenzweig MC., 2005. Defective B cell tolerance checkpoints in systemic lupus erythematosus. J ournal of Experimental Medicine. 7;201(5):703-11.

Zhang X, Glogauer M, Zhu F, Kim TH, Chiu B, Inman RD. 2005. Innate immunity and arthritis: neutrophil Rac and toll-like receptor 4 expression define outcomes in infection-triggered arthritis. Arthritis Rheumatism. 52(4):1297-304.