

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

4,800

Open access books available

122,000

International authors and editors

135M

Downloads

Our authors are among the

154

Countries delivered to

TOP 1%

most cited scientists

12.2%

Contributors from top 500 universities



WEB OF SCIENCE™

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.

For more information visit [www.intechopen.com](http://www.intechopen.com)



---

# **Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Parallels with Autoimmune Disorders**

---

Ekua W. Brenu, Lotti Tajouri, Kevin J. Ashton,  
Donald R. Staines and Sonya M. Marshall-Gradisnik

Additional information is available at the end of the chapter

<http://dx.doi.org/10.5772/53440>

---

## **1. Introduction**

Autoimmune disorders are known to affect a substantial number of people worldwide and in some cases may be fatal. They occur in the presence of unregulated inflammatory responses including failure in self-tolerance. Some unexplained disorders with immune compromises may demonstrate certain characteristics that suggest an autoimmune disorder including Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME). CFS/ME remains an unsolved disorder with multiple symptoms and no single causative factor. These symptoms may include but are not limited to incapacitating fatigue, weakened short term memory or attentiveness, sore throat, tender cervical or axillary lymph nodes, muscle pain, severe headaches, impaired sleep and postexertional malaise. To date succinct and concise mechanisms that underlie this disorder have not yet being identified although, many hypotheses have been put forward. CFS/ME often occurs as a consequence of a post-infectious episode accompanied by compromises in the immune, endocrine and nervous systems. The sequences of these events have not being clearly identified. Importantly, immune deterioration in CFS/ME is related to heightened or suppressed cell function, differential gene expression, equivocal levels of immune cell numbers and protein secretion promoting adverse inflammatory activation. Both innate and adaptive immune system perturbations persist in CFS/ME. These characteristics are in many respects similar to mechanisms of disease in autoimmune disorders suggesting that the changes in immune response may develop from cellular and molecular changes in immune cells and proteins. We propose here that as the mechanism of CFS/ME may involve certain immunological factors that have been shown to be compromised in other autoimmune diseases, CFS/ME may in some cases have an autoim-

mune component or perhaps the symptoms of CFS/ME are hallmarks of a novel autoimmune disorder yet to be identified.

## 2. Characteristics of CFS/ME

CFS/ME belongs to a class of unexplained disorders whose causal factor(s) remains to be proven. The prevalence rate of CFS/ME worldwide is 0.4-4% with a female to male ratio of 6:1 (Lorusso et al., 2009). A predominant characteristic of patients with this disorder is persistent debilitating fatigue. Apart from the debilitating and unrelenting fatigue, patients may also experience other symptoms which may include sore throat, headaches, post exertional malaise etc (Fukuda et al., 1994). A diagnosis of CFS/ME is affirmed if these symptoms have persisted for at least 6 months. To assist with correct diagnosis of CFS/ME patients, various diagnostic tools have been developed. Currently, most researchers prefer to use two definition criteria, the CDC and the Canadian definition, for assessing their patients.

Occurrences of disparities in immunological, neurological, endocrinological, cardiac and metabolic function have been reported among CFS/ME patients (Klimas et al., 2012). Although, these observations highlight the extent of physiological damage associated with CFS/ME, the findings are most often not consistent across studies thus posing doubt as to whether these reported disparities are associated with CFS/ME. Nonetheless, alterations in immunological function are the most consistent data associated with CFS/ME (Klimas et al., 2012). Important among them is the observation that CFS/ME patients have a significant decrease in cytotoxic activity (Brenu et al., 2010; Brenu et al., 2011; Fletcher et al., 2010; Klimas et al., 1990; Maher et al., 2005). Other factors such as cytokines also vary in CFS/ME patients in comparison to non-CFS individuals (Patarca, 2001). Thus considerable evidence exists to suggest that CFS/ME is an immune dysfunction disorder and therefore it may share homology with some autoimmune disorders.

Autoimmune disorders arise as a consequence of increased creation of pathological antibodies against self-antigens, in other words the body assumes a diseased state and therefore generates antibodies to attack self-cells and molecules. The result of this over active immune system is tissue damage and inflammation. Tissue damage may develop from elevations in antibody or cellular processes. Autoimmune disorders can either be systemic or organ specific, exemplified by the presence of autoantibodies, autoreactivity to autoantigens, loss in B cell tolerance, alterations in regulatory T cells (Treg) function, changes in T cell repertoire, genetic abnormalities or environmental agents (Davidson and Diamond, 2001). In most autoimmune diseases including Multiple Sclerosis (MS), autoimmune Rheumatoid Arthritis (RA) Systemic Lupus Erythematosus (SLE), and Autoimmune Diabetes (AID), disparities in immune cells such as neutrophils, Natural Killer (NK), T and B cells have been reported. Perturbations in the normal function of these cells are contributory factors to the mechanism of these diseases. Incidentally, these cells have also been described in CFS/ME. Hence, the purpose of this chapter is to describe the findings related to the above mentioned cells in

autoimmune disorders and relate these to CFS/ME. At present, a mechanism for CFS/ME remains to be identified. Exploring such parallels between CFS/ME and other autoimmune disorders may highlight components of the CFS/ME mechanism that may suggest an autoimmune profile and may serve as a platform for further research.

CFS/ME is known to affect both the innate and adaptive immune system. To date despite the numerous findings on the immune system there is still no definitive informative description on the extent and nature of damage to the immune system. However, the research on the innate and adaptive immune system has identified important irregularities in patients with CFS/ME.

### **3. The CFS/ME immune system**

#### **3.1. Innate immunity in CFS**

The innate immune system comprises of cells such as neutrophils, monocytes, dendritic cells and NK cells. Using phagocytosis and cytotoxic activity these cells are able to elicit and effectively eliminate pathogens that invade the immune system. Most innate immune cells act as antigen presenting cells and also produce a variety of cytokines that are important in activation, proliferation and development of other immune cells. In CFS/ME, immune cell numbers and cytokines have been investigated and there is evidence suggesting equivocal levels of innate immune cells and reduced functional capacity of most immune cells including neutrophils and NK cells (Brenu et al., 2010; Brenu et al., 2011; Klimas et al., 1990; Maher et al., 2005). Neutrophils are phagocytic cells that mediate immune response against bacteria and other microbes while NK cells are responsible for early response against viral pathogens and tumour cells. NK cells release lytic proteins such as perforin and granzymes that effectively lyse these pathogens thereby preventing infections. In the presence of a compromised immune system involving a decrease in cytotoxic activity, these cells are not able to effectively clear viral pathogens. Reduced cytotoxic activity may in most cases increase susceptibility to viral infections among patients with CFS/ME. Similarly, alterations in the availability of lytic proteins, perforin and granzymes, among CFS/ME patients, may also affect the rate of cytotoxicity in NK cells in response to pathogen infiltration (Brenu et al., 2011; Klimas et al., 2012; Maher et al., 2005). Polymorphism in the NK cell receptors importantly the Killer-cell immunoglobulin-like receptors (KIR) family of receptors may also contribute to the reduced NK activity (Pasi et al., 2011). Compromises to neutrophil function in some CFS /ME patients affect their ability to lyse or clear bacterial pathogens owing to the lack of oxidative phosphorylation (Brenu et al., 2010). A similar mechanism may also exist among the monocyte/macrophages although, this remains to be determined. These findings highlight an inability of the immune cells in CFS/ME patients to eliminate viral, microbial and bacterial pathogens.

During infection there is an immediate immune response involving the release of cytokines such as interleukin (IL)-1 $\alpha$  and  $\beta$ , IL-6, interferon (IFN)- $\alpha$  and tumour necrosis factor (TNF)- $\alpha$  by dendritic cells and monocytes (Borish and Steinke, 2003). The release of these cytokines

stimulates the production of cell adhesion molecules and chemotactic molecules that recruit innate immune cells to the sites of infection. There is currently no apparent consistency in the cytokine profile in CFS/ME, however, deficiencies in these cytokines may affect immune function at the innate level. Importantly, these proteins are responsible for recruiting adaptive immune cells and initiating adaptive immune cell responses.

### 3.2. Adaptive immunity in CFS/ME

The cells of the adaptive immune system include B and T cells. T cells can be sub-grouped into cluster differentiation (CD)4<sup>+</sup> and CD8<sup>+</sup>T cells as they recognise peptides with MHCII and MHCI molecules respectively. CD4<sup>+</sup>T cells can be further subdivided into the T helper (Th) 1, 2, 17 and regulatory T cells (Tregs). CD8<sup>+</sup>T cells are the main cytotoxic cells in the adaptive immune system while CD4<sup>+</sup>T cells are producers of cytokines either pro or anti-inflammatory cytokines. The B cells are important for producing antibodies of various classes. Compared to the innate immune system, initialization of the adaptive immune response is a much slower immune response. Presentation of antigenic peptides via the MHC class I and II complex is an important step in the induction of adaptive immune response in particular T cell related responses (Visvanathan and Lewin, 2006).

The role of B cells in CFS/ME remains to be expounded. However, there are suggestions that in CFS/ME these cells produce equivocal levels of antibodies against various antigens contributing to the persistence of symptoms over long periods of time. Thus in CFS/ME, B cells may be impaired allowing infections to persist in the absence of efficient memory cells to exterminate pathological antigens. Alternatively B cell responses may be aberrantly self-reactive. T cell investigations in CFS/ME have mostly focused on cytokines and cytotoxic activity. Although, only few studies have directly investigated the status of CD8<sup>+</sup>T cells (Brenu et al., 2011), direct investigations of CD4<sup>+</sup>T cells are yet to be undertaken in CFS/ME. Shifts in cytokines causing either a predominant anti- or pro-inflammatory immune profile occur in some cases of CFS/ME confirming perturbations in cytokines (Patarca, 2001). Other CD4<sup>+</sup>T cell proteins such as FOXP3 are elevated in CFS/ME which may signal an over reactive Treg profile (Brenu et al., 2011). A potential over reactive Treg profile may affect the function of other immune cells and this may be important in understanding the CFS/ME immune profile.

## 4. Cells, cellular process and proteins in autoimmune diseases

### 4.1. Neutrophils in autoimmune diseases

Neutrophils are innate immune cells derived from common myeloid progenitor cells in the bone marrow (Eyles et al., 2006). Neutrophils are important in defending the body against antimicrobial pathogens in the presence of various receptor recognition pathways. Activated neutrophils contain factors that are released into the phagosome during pathogen infiltration these include azurophilic, explicit or secondary, gelatinase granules and secretory vesicles (Nathan, 2006). Derivatives of these neutrophil compartments are discharged via

degranulation causing destruction of microbes, modifications in cytokines, chelation of microbial nutrients and heightened sensitivity to inflammatory response (Nathan, 2006). Reactive oxygen species are also generated via oxidative phosphorylation in the neutrophil phagolysosome to ensure effective clearance of pathogens.

Neutrophil function is altered in autoimmune diseases such as AID, MS, RA and SLE (Nemeth and Mocsai, 2012). In RA, considerably high levels of neutrophils are present in the synovial fluid of the diseased joints and cartilage interface (Mohr et al., 1981). These neutrophils are highly active and may be responsible for the release of IL-1 $\beta$  or IL-8 into the synovial fluid thus causing inflammation in the joint (Edwards and Hallett, 1997). Autoantibody mediated RA can be induced by neutrophils through the production of LFA-1, C5aR and Fc $\gamma$ R which are essential for the migration of autoantibodies into the joint (Binstadt et al., 2006). This was confirmed by the observation that removal of neutrophils from the joint terminated the amassing of autoantibodies in the joint (Wipke et al., 2004). Highly reactive neutrophils in RA synovial fluid generate unwarranted amounts of reactive oxygen species (Cedergren et al., 2007).

IFN- $\alpha$  and neutrophils are among the key mediators of immune dysfunction in SLE patients. IFN- $\alpha$  is highly prevalent in the circulation of patients with SLE (Decker, 2011; Lindau et al., 2011). Neutrophil traps have been proposed to cause significant activation of dendritic cells while neutrophil antimicrobial peptide, LL37, in circulating DNA also stimulates plasmacytoid dendritic cells which sequentially release IFN- $\alpha$  (Lande et al., 2011). Neutrophil extracellular traps (NET) are formed during netosis (a form of neutrophil death) and this is responsible for the death of microbes under normal immune conditions (Warde, 2011). However, in SLE, impairments in NETs, may be attributed to DNase I inhibitors such as G-actin or mutations in the DNase I enzyme (Bosch, 2011; Yasutomo et al., 2001). Persistency of microbe infiltration and tissue damage in SLE results from weakened neutrophil phagocytosis, thus, suggesting an increased rate of infection and a failure to recognise pathogens for destruction (de la Fuente et al., 2001). Oxidative burst may also be reduced in SLE demonstrating a failure in complete clearance of pathogens (Marzocchi-Machado et al., 2002). The presence of reactive oxygen species is protective especially in AID as it prevents the destruction of  $\beta$  cells (Chen et al., 2008).

Neutrophils in mice model of AID are able to permeate the pancreas due to stimulatory signals from FasL facilitating entry of the neutrophil into the islets (Savinov et al., 2003). In humans, impairments in neutrophil oxidative burst have been confirmed in AID (Marhoffer et al., 1993). Additionally, the expression of certain receptors on the cell surfaces of neutrophils such as CD11b and CD18 are increased suggesting increased activity of these cells as confirmed in mice models of AID (Grykiel et al., 2001). Deterioration in neutrophil function increases the likelihood of pathogenesis and prevalence of infections. The presence of high incidence of TNF receptors such as sp55 and sp75 is indicative of substantial neutrophil priming in MS patients in particular those with RRMS (Ziaber et al., 1999). (Naegele et al., 2012). This may be related to increased neutrophil oxidative burst in RRMS (Ferretti et al., 2006). Similarly most MS patients demonstrates increased amounts of NETs in the serum and this is indicative of a severe pathological episode (Logters et al., 2009). Other abnormali-

ties of neutrophils in MS include heightened levels of IL-8, TLR2, degranulation, impediment in apoptosis (Naegele et al., 2012).

In CFS/ME, neutrophils have been reported to be highly susceptible to apoptosis in the presence of increased incidence of TNFR1 (tumor necrosis factor receptor 1) and TGF $\beta$ 1 (Transforming growth factor beta 1) (Kennedy et al., 2004). Deregulation in neutrophil function may however arise as a consequence of decreases in oxidative phosphorylation while recognition of pathogen by neutrophils remains unaffected (Brenu et al., 2010). Although, neutrophil related cytokines have not been formally associated with increasing levels of neutrophils, low levels of IL-8 have been observed in CFS/ME patients (Fletcher et al., 2009).

#### 4.2. Natural killer cells in autoimmune diseases

NK cells are primarily responsible for the lysis and destruction of viral infected and tumour cells and they also produce an array of cytokines (Caligiuri, 2008; Vivier et al., 2008). They are distinguished from other lymphocytes by the expression of CD56 (Neural Cell Adhesion Molecule) and CD16 (Fragment Crystallisation Gamma Receptor III (Fc $\gamma$ RIII)) surface molecules (Farag et al., 2002). Thus NK cells can be classified into two main subtypes, CD56<sup>dim</sup>CD16<sup>positive</sup> and CD56<sup>bright</sup>CD16<sup>negative</sup> NK cells which are highly cytotoxic and producers of cytokines respectively (Caligiuri, 2008; Farag et al., 2002). NK cells execute cell death or cytotoxicity against other infected cells via granule independent and dependant pathways. The granule dependant pathways require lytic granules, perforin and granzymes, for cytotoxicity (Bryceson et al., 2006).

NK cells have been found to be decreased in some autoimmune diseases including SLE and RA (Schleinitz et al., 2010). Reduced numbers in NK cells are normally correlated with a decrease in cytotoxic activity (Park et al., 2009; Yabuhara et al., 1996). In AID NK cells have been noticed in pancreatic islets thus they may be involved in obliterating pancreatic beta cells (Willcox et al., 2009). IFN- $\gamma$  producing NK cells are densely populated in the synovial fluids of the inflamed joint (Aramaki et al., 2009; Dalbeth and Callan, 2002). The presence of high levels NK cells especially the CD56 phenotype can influence prolonged joint inflammation as they foster the prevalence of monocyte derived dendritic cells in the inflamed joint (Zhang et al., 2007). These cells encourage pro-inflammatory immune response by increasing the generation of Th1 cells and cytokines in the joint. NK cells can also influence macrophages to become lethal contributing to abnormal immune responses (Nedvetzki et al., 2007). In some autoimmune disorders variations in KIR genes are associated with disease presentation. A reduced expression of inhibitory KIRs occurs in type 1 diabetes (van der Slik et al., 2007), while the expression of certain genotype combinations increases susceptibility to certain autoimmune diseases including psoriatic arthritis (2DS1/2DS2 and HLA-Cw), systemic sclerosis (2DS2<sup>+</sup>/2DL2<sup>-</sup> and 2DS1<sup>+</sup>/2DS2<sup>-</sup>) and SLE (2DS<sup>+</sup>/2DS2<sup>-</sup>) (Momot et al., 2004; Pellett et al., 2007). Similarly, polymorphism in the Fc $\gamma$ RIIIa in SLE affects antibody dependent cellular cytotoxicity (ADCC) thus suggesting a role of CD16 subsets of NK cells as a potential contributory factor to atypical NK function (Jonsen et al., 2007). NK cell activity is reduced in MS, however, this may fluctuate as the disease progresses (Benczur et al., 1980; Kastrukoff et al., 1998). Similarly, the levels of NK cells in MS are significantly reduced in

comparison to non-MS patients (Munschauer et al., 1995). Experimental models of MS, EAE, have demonstrated that removal of NK cells substantially worsens the disease while restoration of NK cell numbers decreased the MS symptoms (Zhang et al., 1997). Components of cytotoxic function such as TRAIL and perforin may be affected in MS contributing to the decreases in cytotoxic activity (Hilliard et al., 2001).

NK cells in the tissues of some autoimmune diseases have similar characteristics to those in the periphery (Park et al., 2009). The morphology of NK cells in tissues of CFS/ME patients is unknown. In CFS/ME patients, genetic variability has been shown in the KIR alleles, increased levels of KIR3DS1 and a lack of KIR2DS5 with an absence of HLA-Bw4IIE80 on KIR3DS1 and KIR3DL1 in CFS/ME patients is possibly associated with the reduced activity and ineffectiveness of NK cells to clear pathogens (Pasi et al., 2011). The importance of NK cells in both immune and physiological function is highly prolific as their interactions with both immune and non-immune cells are vital for disease clearance and health. Hence, interaction between NK cells and dendritic cells regulates the production of immature dendritic cells, maturation of dendritic cells and the proliferation of NK cells (Della Bella et al., 2003).

### 4.3. B cells and autoimmune diseases

B cells are fundamental cells of the adaptive immune system, they can be categorised into plasma B cells, B effector 1, B effector 2 and regulatory B cells (Mauri, 2010). B cells act as antigen presenting cells and are the main source of an array of immunoglobulins (Jonsen et al., 2007). The source of most autoantibodies in most autoimmune diseases is from the B cell (Stevenson and Natvig, 1999) hence, B cells are pathogenic (Edwards et al., 1999). Autoantibodies can exacerbate autoimmune states by activating autoreactive T cell reactions, however, under normal immune conditions they are responsible for the removal of dead cells and reducing autoantigens (Shlomchik et al., 2001). Additionally, pro-inflammatory cytokines such as TNF- $\alpha$ , IFN- $\gamma$  and IL-12 and anti-inflammatory cytokines IL-4 and IL-13 are secreted by B effector 1 and 2 cells respectively (Harris et al., 2000). In humans three important B cell tolerance check points have been described including central, peripheral and an undefined check point. The central check point is described as the point of substantial decrease in self-reactive and poly reactive B cells in immature B cells, the peripheral check point is the point of obliterating auto-reactive B cells and the final check point denotes a considerable decline in auto-reactive B cells in naïve and IgM memory B cells (Pillai et al., 2011). Alterations in these check points contribute to autoimmunity (Menard et al., 2011; Samuels et al., 2005b). Another type of B cell, regulatory B cells (Bregs), has been shown to contribute to autoimmunity. The exact source of these Bregs remains to be determined however, they have been characterised as B cells with high expression of CD1d and predominant secretors of IL-10 (Yanaba et al., 2008). In mice models of autoimmunity, these cells may be responsible for the induction of Foxp3 Tregs, suppression of inflammation, and induction of Th1 and Th17 CD4<sup>+</sup>T cells (Carter et al., 2011). In humans Bregs can be distinguished from other cells via the expression of CD19<sup>+</sup>CD24<sup>hi</sup>CD38<sup>hi</sup> with high levels of CD1d, CD5<sup>+</sup> and IL-10 (Blair et al., 2010; Sims et al., 2005). In many autoimmune diseases, these cells are ineffectual when compared to those from healthy participants.



In SLE, the presence of autoantibodies suggests a disruption in B cell central tolerance (Yurasov et al., 2005). Similarly, gene rearrangement and alterations in somatic hypermutation occurring during the development of memory B cells are frequently imprecise thus encouraging the development of autoantibodies (Cappione et al., 2005). Peripheral tolerance may be impaired as a consequence of mutations in the VH gene rearrangement for anti-DNA antibodies (Zhang et al., 2008). A high level of plasma B cells with excessive levels of HLA-DR is associated with SLE confirming defects in B cell negative selection (Odendahl et al., 2005). The existence of additional abnormal memory cells in SLE such as CD27<sup>+</sup>B cells and CD27<sup>-</sup>/IgD-B (Dorner et al., 2009), may strongly influence immune function by suppressing immune activation (Tiller et al., 2007). Memory B cells in SLE are therefore class switched and highly activated thus they respond to stimulation from IL-21, IL-10, BAFF, BCR and TLR ligands (Jacobi et al., 2008).

The precise mechanism of B cells in RA is not clearly understood however, B cell therapies have shown that depletion of B cells effectively reduces the severity of RA (Menard et al., 2011). Nonetheless, a plausible cause for the pathogenesis of B cells in RA may be attributed to flaws in early B cell development (Meffre and Wardemann, 2008; van Vollenhoven, 2009). Defective selection during VDJ recombination in the bone marrow and in the periphery facilitates the existence of autoreactive B cells overriding the selection criteria at the tolerance check points (Samuels et al., 2005a). In RA, a predominant cytokine that provokes the existence of severe inflammatory responses is the TNF- $\alpha$ , TNF- $\alpha$  alters the predominance of naïve and memory B cells however, following anti-TNF- $\alpha$  therapies adequate levels of memory B cells and naïve B cells were restored (Anolik et al., 2008; Menard et al., 2011; Souto-Carneiro et al., 2009).

B cells with characteristic CD19<sup>+</sup>CD27<sup>+</sup>CD38<sup>-</sup>CD138<sup>-</sup> and CD19<sup>+</sup>CD38<sup>+</sup>CD138<sup>+</sup> (plasmablasts) markers and others with a short life are found in the cerebrospinal fluid (CSF) of MS patients with progressive symptoms (Cepok et al., 2001; Cepok et al., 2005; Pascual et al., 1994). These CSF related B cells are largely responsible for inflammatory reactions in MS (Kuenz et al., 2008). Peripheral B cells are characterised by the expression of CD19<sup>+</sup>CD27<sup>-</sup> and these are mostly naïve B cells (Cepok et al., 2005; Corcione et al., 2004). IgG molecules with oligoclonal patterns are abundant in the synovial fluid and these cells stimulate complement activation (Silverman and Carson, 2003). The pathogenesis of B cells in MS ensues from high levels of chemokine such as CXCL13 in active lesions sites, CSF and intrameningeal follicles (Franciotta et al., 2008). CXCL13 is regulated by B cells during the formation of lymphoid organogenesis resulting in the formation of ectopic lymphoid tissues (Barone et al., 2008). Dyregulation of B cells permits the survival of certain viruses such as EBV which has been linked to the central nervous system (CNS) infection in MS (Opsahl and Kennedy, 2007). In such cases the presence of EBV infected B cells promotes the persistence of EBV in the brain (Buljevac et al., 2005).

B cells are the principal source of autoantibodies in AID, these cells are also implicated as pancreatic regulators (Marino and Cosentino, 2011). Similar to MS depletion of B cells can be effective in reversing the symptoms of autoimmune diabetes. The presence of B cells results in the destruction of the  $\beta$  cells thus their deletion prolongs the life of the  $\beta$  cells (Xiu et al.,

2008). Different subsets of B cells have been found in AID, in comparison to the non-AID individuals these cell numbers deviate from the norm (Marino et al., 2008; Noorchashm et al., 1999; Tian et al., 2006).

In CFS/ME an in-depth study into the various subsets of B cells remains to be described. This may be important in deciphering the concept of compromised immune mechanisms in CFS/ME. In some studies depletion of B cells in patients with CFS/ME led to a substantial improvement in CFS/ME (Fluge et al., 2011; Fluge and Mella, 2009). Improvement in health following B cell depletion has been noticed in cases of MS and RA this presupposes that in CFS/ME there may be a possible defect in the B cell tolerance check point thus increasing the likelihood for errors during positive selection and rearrangement of the VDJ recombination repertoire. Therefore, only cells that are required for the formation of auto reactive B cells may be selected. Hence, depletion of these B cells may effectively improve the health status of the CFS/ME patients. This has not being confirmed however, future studies may be important in identifying the exact role of B cells in CFS/ME patients. Additionally, B cells and T cells interact with each other to assist in mutual activation. Thus, interference in the normal function of these cells may affect the responses that are communicated to the T cell and possibly initiate the presence of autoreactive T cells. B cell memory is a highly important mechanism for regulating subsequent infections and immune responses, in MS, failure in this mechanism has severe consequences on the CNS function as EBV infected B cells have been known to thrive in MS. Nonetheless, changes in the formation of B cell memory suggests a possible genetic predisposition and these need to be investigated in CFS/ME.

#### 4.4. Regulatory T cells and autoimmune diseases

Regulatory T cells (Tregs) of the immune system can be grouped in to CD8<sup>+</sup> Tregs or CD4<sup>+</sup>Tregs. However, for the purposes of this chapter the focus will be on the CD4<sup>+</sup>Tregs which have received much attention in autoimmune diseases currently being reviewed in relation to CFS. IL-3, IL-4, IL-7, IL-15, TGF- $\beta$  and CD28 are important for the development, proliferation and thrive of Treg cells (Josefowicz et al., 2012). Treg profiles in a number of autoimmune disorders maybe perturbed resulting in hypo or hyperactive state in suppression. Deficiencies in Treg suppressive function may ensue from a lack in the expression of certain surface molecules such as CD39, CD95, cytotoxic T lymphocyte antigen 4 (CTLA4) and lymphocyte activation gene 3 (LAG3) (Sakaguchi et al., 2010; Schmetterer et al., 2012; Schmidt et al., 2012). Most autoimmune diseases are characterised by decreases in the function of Tregs with equivocal levels of Tregs in the tissues and periphery (Buckner, 2010).

Most of the studies on Tregs in autoimmune disorders were performed using mice models of increased susceptibility to autoimmune diseases. The state of Tregs in humans is not fully known and animal models have highlighted some important aspects of Treg function in autoimmune disorders. For example in AID, Treg cells and Foxp3 expression Tregs from NOD mice are more likely to be decreased (Clough et al., 2008; D'Alise et al., 2008; You et al., 2005). Incidentally, some patients with AID demonstrate a significant decrease in peripheral CD4<sup>+</sup>CD25<sup>+</sup>Tregs while others have shown no difference in CD4<sup>+</sup>CD25<sup>+</sup>, CD4<sup>+</sup>CD25<sup>hi</sup>, CD4<sup>+</sup>FOXP3<sup>+</sup>CD45RO<sup>+</sup>, CD4<sup>+</sup>FOXP3<sup>+</sup>CD45RA<sup>+</sup> Treg cells or FOXP3 when compared with

non-diabetics (Putnam et al., 2009). Nonetheless, it is thought that discrepancies in Treg function in AID patients may be as a consequence of poor IL-2 function (Bluestone et al., 2008). In the periphery, IL-2 has been shown to be a necessary factor in the survival and maintenance of Tregs while CD28 is important for Treg proliferation (Fontenot and Rudensky, 2004). In mice deficient in CD28, the lack of Tregs led to the progression of autoimmune diabetes, however, adoptive transfer of Tregs into the NOD mice confers protection against AID thus indicating that the presence of Tregs is necessary to guard against diabetes (Salomon et al., 2000).

The mouse model of MS, EAE, has confirmed an involvement of Tregs in the pathogenesis of MS, in these mice depletion of Tregs is a hallmark of EAE (Kohm et al., 2003). In CNS of highly developed MS patients the ability of Tregs to regulate inflammatory processes is impaired (Venken et al., 2008a; Venken et al., 2008b). Reduced FOXP3 expressing Treg cells in MS is more common in patients with relapsing remitting MS (Huang and Elferink, 2005; Venken et al., 2006) and treatment with IFN- $\beta$  normalized the Tregs levels as it caused an increase in the number of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3 Tregs (Chen et al., 2012). Similarly, CD39<sup>+</sup>Tregs are reduced in patients with relapsing-remitting MS (Borsellino et al., 2007). These cells are necessary for the abrogation of Th17 cells in MS patients hence a reduction in these cells promote inflammatory reaction related to IL-17 (Fletcher et al., 2009). In the CNS however, Treg cells are elevated in the CSF (Feger et al., 2007). Defective Tregs cells in MS is characterised by an inability of these cells to suppress the proliferation and production of cytokines such as IFN- $\gamma$  by Th1 cells (Costantino et al., 2008). It has been suggested that this may be linked to decreases in subsets of Tregs such as the CD4<sup>+</sup>CD25<sup>hi</sup> Tregs (Costantino et al., 2008). Similarly in MS patients IL-10 production by the Tr1 subset of Tregs is dysfunctional (Astier et al., 2006). MS patients may present with decreased CD127<sup>+</sup>FOXP3<sup>+</sup> Tregs (Costantino et al., 2008). Although, levels or numbers of Tregs are more likely to differ between patients, there are consistent irregularities in the suppressive capacity of these cells in MS. A hypo-suppressive Treg state transpires in the presence of decreases in IL-10 (Martinez-Forero et al., 2008).

In SLE, equivocal evidence exists for the changes in the levels of Tregs this may be related to inaccuracies in the methodology. Natural Tregs and FOXP3 Tregs in SLE have been shown to be decreased in number (Crispin et al., 2003; Lee et al., 2008; Lee et al., 2006; Miyara et al., 2005). Peripheral CD4<sup>+</sup>CD25<sup>hi</sup> Tregs in SLE are reduced and this correlates with a substantial insufficiency in function and an increased expression of CD69 and CD71 (Bonelli et al., 2008). In the active form of SLE, Tregs are less suppressive and show an inability to produce efficient cytokines the opposite occurs in the dormant SLE (Valencia et al., 2007). Impairment in Treg function may occur as a result of IFN- $\alpha$  producing APCs, CD95 apoptosis and diminishing levels of IL-2 (Katsiari and Tsokos, 2006). Similarly, the observation of defective CD4<sup>+</sup>CD25<sup>+</sup> Tregs or a reduced number of these cells in the lymph nodes and other areas may be due to susceptibility to Fas related apoptosis (Okamoto et al., 2011). TGF- $\beta$  is necessary for the peripheral generation of CD4<sup>+</sup>CD25<sup>+</sup>Tregs incidentally their reduction may be linked to reduced levels of these cytokines in the serum in particular in patients with active SLE (Xing et al., 2012).

Treg numbers in peripheral circulation of patients with RA are also inconsistent (Boissier et al., 2009). In the synovial fluid there are uniformities in the data describing the presence of Tregs which generally tends to be high in RA patients (Cao et al., 2003), however these Tregs may not be able to effectively suppress the generation of anti-inflammatory IFN- $\gamma$  and TNF- $\alpha$  (Leipe et al., 2005). Similarly, CTLA4 signalling in Tregs is ineffective in RA (Fiocco et al., 2008). Other factors may influence the ability of Tregs to confer suppression in the synovial fluid, mainly, the presence of macrophages in the joint resulting in excessive levels of TNF- $\alpha$ , IL-6 and IL-7. Synovial fluids enriched in these cytokines have an altered Treg suppressive function (Pasare and Medzhitov, 2003). High levels of FOXP3 Tregs have been found in the inflamed synovial fluid compared to the peripheral blood in RA (Jiao et al., 2007).

RA is the only disease where an apparent increase in FOXP3 expressing Tregs has been confirmed, this is consistent with what we have found in our CFS/ME patients where FOXP3 expression was higher in the periphery (Brenu et al., 2011). In CFS/ME inflamed sites may appear in the periphery and the CNS thus explaining the presence of high levels of FOXP3 in the periphery. Incidentally, the exact function of these cells in the CFS/ME patients is yet to be determined. In MS, Tregs may remain unchanged while their suppressive function on other cells and cytokine proliferation in particular the pro-inflammatory cytokines is dysfunctional. A similar mechanism may occur in CFS/ME thus likely contributing to the pathogenesis of this disease.

#### **4.5. Immune related proteins in autoimmune diseases**

Cytokines and chemokines are soluble proteins with an involvement in inflammatory reactions as they can either be pro or anti-inflammatory or both. They can also be cytotoxic to certain cells and tissues. CD4<sup>+</sup>T cells are the predominant producers of both anti and pro-inflammatory cytokines. Th1 cells produce IL-2 and IFN- $\gamma$  and are therefore pro-inflammatory while Th2 cells are anti-inflammatory as they produce IL-4, IL-5, IL-10 and IL-13 (Zhou et al., 2009). The pathogenesis of most autoimmune diseases incorporates changes in these inflammatory molecules with augmented levels of these cytokines observed in the periphery and in certain tissues. For example diseases such as RA, SLE and MS are characterised by a predominant Th1 immune profile.

IL-23, IL-17 and IL-27 are the most dominant cytokines in RA as they are necessary for inflammation in the joints (IL-23), osteoclastogenesis formation (IL-17) and activation of pro-inflammatory reactions due to a diminished amount of IL-27 (Baek et al., 2012). The mechanism of cytokine production during RA and other autoimmune diseases may rely heavily on a number of factors such as disease onset, severity, inflammatory state and source of cytokines. RA patients with severe cases of inflammation are known to have high mRNA levels of STAT1 and its associated genes suggesting that disease severity affects the pattern of cytokines in RA (Gordon et al., 2012). RA patients with an early incidence of synovitis express high levels of IL-1, IL-2, IL-4, IL-13 and IL-15 while premature RA results in substantial quantities of IL-2, IL-4, IL-13, and IL-17 in the synovial fluid (Arend, 2001; McInnes and Schett, 2007; Raza et al., 2005). Characteristically high levels of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, IL-13 and IL-15 are found in the serum (Yilmaz et al., 2001). The profile of cytokines in

RA suggests a shift towards a predominant anti-inflammatory response as a consequence of elevated levels of Th2 derived cytokines IL-4 and IL-13 (Wong et al., 2000). Other cytokines including anti-inflammatory IL-10 and IL-20, and pleiotropic IL-7 may be implicated in the pathogenesis of RA (Katsikis et al., 1994; Kunz and Ibrahim, 2009).

Insulinitis lesions in AID provoke inflammatory responses and the recruitment of T cells and islet-infiltrating macrophages (Eizirik et al., 2009). These cells produce cytokines that affect insulin levels in patients (Rabinovitch, 2003; Rabinovitch and Suarez-Pinzon, 2003). Suppression of insulin synthesis, secretion and destruction of  $\beta$  and  $\alpha$  cells occurs in the presence of cytokines such as IL-1, IFN- $\gamma$ , TNF- $\alpha$  and TNF- $\beta$  (Mandrup-Poulsen et al., 1990; Rabinovitch et al., 1993).  $\beta$  cells may indirectly stimulate autoreactive T cells via the production of IFN- $\alpha$  during stress while T cells may stimulate IFN- $\gamma$  which in turn penetrate the islets and cause their destruction (Chakrabarti et al., 1996; Stewart et al., 1993). Similarly increase in the expression of MHC I and Fas increases the likelihood for the destruction of  $\beta$  cells by CD8<sup>+</sup>T cells (Itoh et al., 1993). In serum samples, high levels of Th1 related cytokines have been observed in autoimmune diabetes with no changes in the levels of Th2 cytokines. Contrarily, Th2 cytokines have been shown to be decreased in other patients following activation of peripheral blood mononuclear cells (Kallmann et al., 1997; Rapoport et al., 1998). The levels of cytokines in autoimmune diabetes are discordant across studies and this may be related to factors such as disease severity, and the source of the cytokines.

In MS, cytokines are responsible for the oligodendrocyte cell death, axonal degeneration and neuronal impairments (Bjartmar and Trapp, 2003; Bjartmar et al., 2003; Lucchinetti et al., 2000; Wujek et al., 2002). The most prominent cytokine in MS is IFN- $\gamma$  which is elevated both in MS and in the experimental condition, EAE (Ferber et al., 1996). In EAE mice IFN- $\gamma$  is usually expressed in the CNS during the initial manifestations of MS and increases progressively with disease causing advancement in demyelination (Begolka et al., 1998; Issazadeh et al., 1995). In the absence of IFN- $\gamma$ , EAE is not obliterated as there is evidence to suggest an increase in severity in mice depleted of IFN- $\gamma$  (Hassani et al., 1999). Although, IFN- $\gamma$  may have a deleterious role in EAE it may be necessary for the regulation of other inflammatory activities, deletion of certain components of IFN- $\gamma$  such as STAT4 prevents the occurrence of EAE (Chitnis et al., 2001). Different classes of MS may differ in their cytokine pattern, for example, IFN- $\gamma$  and IL-10 are elevated in RP and SP but not in PP MS patients (Balashov et al., 2000). The presence of TNF- $\alpha$  in the CNS of EAE mice is an indication of severe infiltration and inflammation in the spinal cord and oligodendrocyte cell death (Selmaj and Raine, 1988).

A number of cytokines have been implicated in the pathogenesis of SLE including IL-6, TNF- $\alpha$ , IFN- $\gamma$ , IL-2, IL-21 and IL-17. Serum levels of IL-6 are elevated in SLE patients this is linked to the presence of hyperactive B cells and a high incidence of autoantibodies (Linker-Israeli et al., 1991; Tackey et al., 2004). Similarly CSF levels are higher in SLE patients compared to non-SLE individuals (Alcocer-Varela et al., 1992). The presence of abnormal levels of IL-6 in SLE can have systemic effects as IL-6 is a highly inflammatory cytokine. IFN- $\gamma$  mRNA and serum levels are known to be increased in SLE suggesting an increase in IgG (Csiszar et al., 2000). Similarly, susceptibility to SLE is linked to polymorphism in the IL-21

and its receptor, and in the serum increased secretions of IL-21 are noticed (Sawalha et al., 2008). IL-17 secretions by cells in the plasma and serum are also noted to be increased in SLE (Crispin et al., 2008; Wong et al., 2008; Yang et al., 2009). Elevations in pro-inflammatory cytokines in SLE are important indicators of significant inflammations. Deficiencies in IL-2 occur in SLE and this is possibly linked to over activation of B and T cells (Ohl and Tenbrock, 2011). Importantly IL-2 is a necessary factor in the Treg development and function and increased levels of IL-17 (Brandenburg et al., 2008; Laurence et al., 2007).

In CFS/ME, the cytokine profiles differ from one study to another and this may be due to other factors such as age of onset and severity or cell and tissue specific cytokines. However, it is most likely that the cytokine pattern in CFS/ME resembles that of the above described autoimmune diseases where the cytokines implicated are mainly IL-2, IL-4, IL-10, IFN- $\gamma$  and TNF- $\alpha$ . An in-depth examination of these cytokines is necessary for establishing a definitive mechanism for CFS/ME. Governance of pro-inflammatory over anti-inflammatory or vice versa has been reported in CFS/ME (Patarca et al., 2001) and this has been observed in RA and MS hence, it is possible that in RA and MS the inflammatory status of cytokines is attributed to the diseases.

## 5. Therapy

Currently there are no definitive therapeutic drugs for CFS/ME although current trials with rituximab may be effective in reducing the symptoms of CFS/ME. Other strategies such as cognitive behavioural therapies have been used in CFS/ME. The present immune dysfunction in CFS/ME shares similarities with certain disorders where significant improvement has been observed following administration of certain drugs. Hence, CFS/ME patients may benefit to some extent from similar therapies.

Glatiramer acetate has been shown to be effective in dampening the atypical immune response in MS (Arnon et al., 2009). Significant improvement in NK cell cytotoxic activity and cytokine secretion occur following glatiramer acetate intake in MS patients (Schrempf et al., 2007). Similarly, the use of phosphodiesterase inhibitors may be important in modulating Treg function in CFS/ME patients. These inhibitors are known to enhance the presence of cAMP resulting in the induction of cytokines that regulate the immune response (Folcik et al., 1999). B cell depletion therapies in CFS/ME may likely be essential as patients administered with substances such as Rituximab demonstrate significant improvement in health (Levesque et al., 2008). Although the cause of CFS/ME remains to be determined there are suggestions that CFS/ME may arise following viral infections. Therefore, failure to effectively clear the viral infections and subsequent infections in CFS/ME may arise as a consequence of low levels or abnormal memory cells. Rapamycin an inhibitor of mTOR may be essential in promoting the presence of memory cells in CFS/ME, in particular, the memory T cells (Araki et al., 2010).

The exact role of these drugs in CFS/ME has not been investigated and whether these treatment strategies may be useful in CFS/ME remains to be determined. It may be necessary to

administer some of these drugs in combinations to ensure effective improvement in immune related responses.

## 6. Conclusion

CFS/ME shares certain parallels with a number of autoimmune diseases as described above, these similarities include decreases in oxidative phosphorylation, reduced NK cytotoxic activity, defects in B cells and equivocal levels of cytokines. NK cytotoxic activity is the most common immunological impairment in CFS/ME and the aforementioned autoimmune disorders. Although, disease presentation in each case is dissimilar to CFS/ME there are certain characteristics that seem to be present in CFS/ME and in each of the autoimmune diseases described above.

It is evident that most autoimmune diseases demonstrate equivocal levels of immune cell numbers however, in terms of the functional profile of most cells there is consistent confirmation for alterations in the activation or functional capacity of immune cells. The differences in relation to different cell numbers and phenotypes may be related to the severity or the stage of the disease, therefore, patients in the latent phases may differ in the relative numbers of immune cells in comparison to those in the early stages of the disease. Additionally, in the active state, most autoimmune diseases are characterised by high number of abnormal cells and relatively low levels of normal cells in comparison to the inactive state. Although, in CFS/ME these observations remain to be confirmed, it is thought that fluctuations in cell numbers may occur during periods of less severe symptoms that is, a substantial increase in wellness and periods of worsening symptoms. Thus, in these instances the production and generation of immune cells may differ while a substantial decrease in function still persists. Incidentally, in CFS/ME lymphocyte phenotypes have not been successfully associated with the disease presentation and this is also true of most autoimmune diseases where changes in the levels of lymphocyte phenotypes did not explain the decrease or increase in function. These findings therefore suggest that with regards to autoimmune diseases a standard assessment of leukocyte phenotypes may not necessarily explain the mechanism.

Importantly, almost all autoimmune diseases have an association with reduced cytotoxic activity and decreases in neutrophil function. Suggesting that CFS/ME may have a potential to be described as autoimmune, as this is the only consistent immunological abnormality associated with CFS/ME. A loss or a reduced function in NK cells seems to occur both in the periphery and tissues. Tissue specific NK activity has not been reported in CFS/ME however, it may be interesting to investigate NK function in other tissues and to determine whether a similar profile is observed as in other immune diseases. Nonetheless the findings from immune function in CFS/ME including reduced NK cell cytotoxic activity, low lymphocyte response to mitogenic stimulation and deficits in immunoglobulins are indicative of immune deficiency. Treg function and FOXP3 expression patterns in CFS/ME are consistent with some RA patients, however Treg suppression is more often decreased in autoimmune diseases. A plausible explanation for these differences relates to the observation that Treg func-

tion is inextricably linked to cAMP metabolism and compromise of neuropeptides such as vasoactive neuropeptide function in some tissues. This may produce impaired cAMP synthesis. Hence, Treg function may be increased to compensate, as they are known that cAMP is directly transferred from Tregs to other cells. Nonetheless, further validity studies are required to confirm these observations that we have observed in previous studies.

It is important to note that despite the inconsistencies in these autoimmune diseases mentioned above they all have a well established mechanism of action. However, in CFS/ME a mechanism for disease presentation is unknown. This is the biggest confounding factor in the study of CFS/ME, hence, it is very difficult to understand the nature of the disease and propose logical conclusions to explain the disease presentation and symptom profile.

## Author details

Ekua W. Brenu<sup>1,2</sup>, Lotti Tajouri<sup>3</sup>, Kevin J. Ashton<sup>3</sup>, Donald R. Staines<sup>1,4</sup> and Sonya M. Marshall-Gradisnik<sup>1,2</sup>

1 National Center for Neuroimmunology and Emerging Diseases, Griffith University, Gold Coast, Queensland, Australia

2 School of Medical Science, Griffith Health Institute, Griffith University, Gold Coast Campus, Gold Coast, QLD, Australia

3 Faculty of Health Science and Medicine, Bond University, Robina, Queensland, Australia

4 Queensland Health, Gold Coast Public Health Unit, Robina, Queensland, Australia

## References

- [1] Alcocer-Varela, J., Aleman-Hoey, D. and Alarcon-Segovia, D., 1992. Interleukin-1 and interleukin-6 activities are increased in the cerebrospinal fluid of patients with CNS lupus erythematosus and correlate with local late T-cell activation markers. *Lupus*. 1, 111-7.
- [2] Anolik, J.H., Ravikumar, R., Barnard, J., Owen, T., Almudevar, A., Milner, E.C., Miller, C.H., Dutcher, P.O., Hadley, J.A. and Sanz, I., 2008. Cutting edge: anti-tumor necrosis factor therapy in rheumatoid arthritis inhibits memory B lymphocytes via effects on lymphoid germinal centers and follicular dendritic cell networks. *Journal of immunology*. 180, 688-92.
- [3] Araki, K., Youngblood, B. and Ahmed, R. 2010. The role of mTOR in memory CD8 T-cell differentiation. *Immunological reviews*. 235, 234-43.



- [4] Aramaki, T., Ida, H., Izumi, Y., Fujikawa, K., Huang, M., Arima, K., Tamai, M., Kamachi, M., Nakamura, H., Kawakami, A., Origuchi, T., Matsuoka, N. and Eguchi, K., 2009. A significantly impaired natural killer cell activity due to a low activity on a per-cell basis in rheumatoid arthritis. *Modern rheumatology / the Japan Rheumatism Association*. 19, 245-52.
- [5] Arend, W.P., 2001. Physiology of cytokine pathways in rheumatoid arthritis. *Arthritis and rheumatism*. 45, 101-6.
- [6] Arnon, R., Aharoni, R. 2009. Neuroprotection and neurogeneration in MS and its animal model EAE effected by glatiramer acetate. *Journal of Neural Transmission*. 116, 1443-1449.
- [7] Astier, A.L., Meiffren, G., Freeman, S. and Hafler, D.A., 2006. Alterations in CD46-mediated Tr1 regulatory T cells in patients with multiple sclerosis. *The Journal of clinical investigation*. 116, 3252-7.
- [8] Baek, S.H., Lee, S.G., Park, Y.E., Kim, G.T., Kim, C.D. and Park, S.Y., 2012. Increased synovial expression of IL-27 by IL-17 in rheumatoid arthritis. *Inflammation research : official journal of the European Histamine Research Society ... [et al.]*.
- [9] Balashov, K.E., Comabella, M., Ohashi, T., Khoury, S.J. and Weiner, H.L., 2000. Defective regulation of IFN $\gamma$  and IL-12 by endogenous IL-10 in progressive MS. *Neurology*. 55, 192-8.
- [10] Barone, F., Bombardieri, M., Rosado, M.M., Morgan, P.R., Challacombe, S.J., De Vita, S., Carsetti, R., Spencer, J., Valesini, G. and Pitzalis, C., 2008. CXCL13, CCL21, and CXCL12 expression in salivary glands of patients with Sjogren's syndrome and MALT lymphoma: association with reactive and malignant areas of lymphoid organization. *Journal of immunology*. 180, 5130-40.
- [11] Begolka, W.S., Vanderlugt, C.L., Rahbe, S.M. and Miller, S.D., 1998. Differential expression of inflammatory cytokines parallels progression of central nervous system pathology in two clinically distinct models of multiple sclerosis. *Journal of immunology*. 161, 4437-46.
- [12] Benczur, M., Petranyl, G.G., Palfy, G., Varga, M., Talas, M., Kotsy, B., Foldes, I. and Hollan, S.R., 1980. Dysfunction of natural killer cells in multiple sclerosis: a possible pathogenetic factor. *Clinical and experimental immunology*. 39, 657-62.
- [13] Binstadt, B.A., Patel, P.R., Alencar, H., Nigrovic, P.A., Lee, D.M., Mahmood, U., Weissleder, R., Mathis, D. and Benoist, C., 2006. Particularities of the vasculature can promote the organ specificity of autoimmune attack. *Nature immunology*. 7, 284-92.
- [14] Bjartmar, C. and Trapp, B.D., 2003. Axonal degeneration and progressive neurologic disability in multiple sclerosis. *Neurotox Res*. 5, 157-64.
- [15] Bjartmar, C., Wujek, J.R. and Trapp, B.D., 2003. Axonal loss in the pathology of MS: consequences for understanding the progressive phase of the disease. *Journal of the neurological sciences*. 206, 165-71.

- [16] Blair, P.A., Norena, L.Y., Flores-Borja, F., Rawlings, D.J., Isenberg, D.A., Ehrenstein, M.R. and Mauri, C., 2010. CD19(+)CD24(hi)CD38(hi) B cells exhibit regulatory capacity in healthy individuals but are functionally impaired in systemic Lupus Erythematosus patients. *Immunity*. 32, 129-40.
- [17] Bluestone, J.A., Tang, Q. and Sedwick, C.E., 2008. T regulatory cells in autoimmune diabetes: past challenges, future prospects. *Journal of clinical immunology*. 28, 677-84.
- [18] Boissier, M.C., Assier, E., Biton, J., Denys, A., Falgarone, G. and Bessis, N., 2009. Regulatory T cells (Treg) in rheumatoid arthritis. *Joint Bone Spine*. 76, 10-4.
- [19] Bonelli, M., von Dalwigk, K., Savitskaya, A., Smolen, J.S. and Scheinecker, C., 2008. Foxp3 expression in CD4+ T cells of patients with systemic lupus erythematosus: a comparative phenotypic analysis. *Annals of the rheumatic diseases*. 67, 664-71.
- [20] Borish, L.C. and Steinke, J.W., 2003. 2. Cytokines and chemokines. *The Journal of allergy and clinical immunology*. 111, S460-75.
- [21] Borsellino, G., Kleinewietfeld, M., Di Mitri, D., Sternjak, A., Diamantini, A., Giometto, R., Hopner, S., Centonze, D., Bernardi, G., Dell'Acqua, M.L., Rossini, P.M., Battistini, L., Rotzschke, O. and Falk, K., 2007. Expression of ectonucleotidase CD39 by Foxp3+ Treg cells: hydrolysis of extracellular ATP and immune suppression. *Blood*. 110, 1225-32.
- [22] Bosch, X., 2011. Systemic lupus erythematosus and the neutrophil. *The New England journal of medicine*. 365, 758-60.
- [23] Brandenburg, S., Takahashi, T., de la Rosa, M., Janke, M., Karsten, G., Muzzulini, T., Orinska, Z., Bulfone-Paus, S. and Scheffold, A., 2008. IL-2 induces in vivo suppression by CD4(+)CD25(+)Foxp3(+) regulatory T cells. *European journal of immunology*. 38, 1643-53.
- [24] Brenu, E.W., Staines, D.R., Baskurt, O.K., Ashton, K.J., Ramos, S.B., Christy, R.M. and Marshall-Gradisnik, S.M., 2010. Immune and hemorheological changes in chronic fatigue syndrome. *Journal of translational medicine*. 8, 1.
- [25] Brenu, E.W., van Driel, M.L., Staines, D.R., Ashton, K.J., Ramos, S.B., Keane, J., Klimas, N.G. and Marshall-Gradisnik, S.M., 2011. Immunological abnormalities as potential biomarkers in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis. *Journal of translational medicine*. 9, 81.
- [26] Bryceson, Y.T., March, M.E., Ljunggren, H.G. and Long, E.O., 2006. Activation, coactivation, and costimulation of resting human natural killer cells. *Immunological reviews*. 214, 73-91.
- [27] Buckner, J.H., 2010. Mechanisms of impaired regulation by CD4(+)CD25(+)FOXP3(+) regulatory T cells in human autoimmune diseases. *Nature reviews. Immunology*. 10, 849-59.

- [28] Buljevac, D., van Doornum, G.J., Flach, H.Z., Groen, J., Osterhaus, A.D., Hop, W., van Doorn, P.A., van der Meche, F.G. and Hintzen, R.Q., 2005. Epstein-Barr virus and disease activity in multiple sclerosis. *Journal of neurology, neurosurgery, and psychiatry*. 76, 1377-81.
- [29] Caligiuri, M.A., 2008. Human natural killer cells. *Blood*. 112, 461-9.
- [30] Cao, D., Malmstrom, V., Baecher-Allan, C., Hafler, D., Klareskog, L. and Trollmo, C., 2003. Isolation and functional characterization of regulatory CD25<sup>bright</sup>CD4<sup>+</sup> T cells from the target organ of patients with rheumatoid arthritis. *European journal of immunology*. 33, 215-23.
- [31] Cappione, A., 3rd, Anolik, J.H., Pugh-Bernard, A., Barnard, J., Dutcher, P., Silverman, G. and Sanz, I., 2005. Germinal center exclusion of autoreactive B cells is defective in human systemic lupus erythematosus. *The Journal of clinical investigation*. 115, 3205-16.
- [32] Carter, N.A., Vasconcellos, R., Rosser, E.C., Tulone, C., Munoz-Suano, A., Kamanaka, M., Ehrenstein, M.R., Flavell, R.A. and Mauri, C., 2011. Mice lacking endogenous IL-10-producing regulatory B cells develop exacerbated disease and present with an increased frequency of Th1/Th17 but a decrease in regulatory T cells. *Journal of immunology*. 186, 5569-79.
- [33] Cedergren, J., Forslund, T., Sundqvist, T. and Skogh, T., 2007. Intracellular oxidative activation in synovial fluid neutrophils from patients with rheumatoid arthritis but not from other arthritis patients. *The Journal of rheumatology*. 34, 2162-70.
- [34] Cepok, S., Jacobsen, M., Schock, S., Omer, B., Jaekel, S., Boddeker, I., Oertel, W.H., Sommer, N. and Hemmer, B., 2001. Patterns of cerebrospinal fluid pathology correlate with disease progression in multiple sclerosis. *Brain : a journal of neurology*. 124, 2169-76.
- [35] Cepok, S., Rosche, B., Grummel, V., Vogel, F., Zhou, D., Sayn, J., Sommer, N., Hartung, H.P. and Hemmer, B., 2005. Short-lived plasma blasts are the main B cell effector subset during the course of multiple sclerosis. *Brain : a journal of neurology*. 128, 1667-76.
- [36] Chakrabarti, D., Huang, X., Beck, J., Henrich, J., McFarland, N., James, R.F. and Stewart, T.A., 1996. Control of islet intercellular adhesion molecule-1 expression by interferon-alpha and hypoxia. *Diabetes*. 45, 1336-43.
- [37] Chen, J., Gusdon, A.M., Thayer, T.C. and Mathews, C.E., 2008. Role of increased ROS dissipation in prevention of T1D. *Annals of the New York Academy of Sciences*. 1150, 157-66.
- [38] Chen, M., Chen, G., Deng, S., Liu, X., Hutton, G.J. and Hong, J., 2012. IFN-beta induces the proliferation of CD4<sup>+</sup>CD25<sup>+</sup>Foxp3<sup>+</sup> regulatory T cells through upregulation of GITRL on dendritic cells in the treatment of multiple sclerosis. *Journal of neuroimmunology*. 242, 39-46.

- [39] Chitnis, T., Najafian, N., Benou, C., Salama, A.D., Grusby, M.J., Sayegh, M.H. and Khoury, S.J., 2001. Effect of targeted disruption of STAT4 and STAT6 on the induction of experimental autoimmune encephalomyelitis. *The Journal of clinical investigation*. 108, 739-47.
- [40] Clough, L.E., Wang, C.J., Schmidt, E.M., Booth, G., Hou, T.Z., Ryan, G.A. and Walker, L.S., 2008. Release from regulatory T cell-mediated suppression during the onset of tissue-specific autoimmunity is associated with elevated IL-21. *Journal of immunology*. 180, 5393-401.
- [41] Corcione, A., Arduino, N., Ferretti, E., Raffaghello, L., Roncella, S., Rossi, D., Fedeli, F., Ottonello, L., Trentin, L., Dallegri, F., Semenzato, G. and Pistoia, V., 2004. CCL19 and CXCL12 trigger in vitro chemotaxis of human mantle cell lymphoma B cells. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 10, 964-71.
- [42] Costantino, C.M., Baecher-Allan, C. and Hafler, D.A., 2008. Multiple sclerosis and regulatory T cells. *Journal of clinical immunology*. 28, 697-706.
- [43] Crispin, J.C., Martinez, A. and Alcocer-Varela, J., 2003. Quantification of regulatory T cells in patients with systemic lupus erythematosus. *Journal of autoimmunity*. 21, 273-6.
- [44] Crispin, J.C., Oukka, M., Bayliss, G., Cohen, R.A., Van Beek, C.A., Stillman, I.E., Kytaris, V.C., Juang, Y.T. and Tsokos, G.C., 2008. Expanded double negative T cells in patients with systemic lupus erythematosus produce IL-17 and infiltrate the kidneys. *Journal of immunology*. 181, 8761-6.
- [45] Csiszar, A., Nagy, G., Gergely, P., Pozsonyi, T. and Pocsik, E., 2000. Increased interferon-gamma (IFN-gamma), IL-10 and decreased IL-4 mRNA expression in peripheral blood mononuclear cells (PBMC) from patients with systemic lupus erythematosus (SLE). *Clinical and experimental immunology*. 122, 464-70.
- [46] D'Alise, A.M., Auyeung, V., Feuerer, M., Nishio, J., Fontenot, J., Benoist, C. and Mathis, D., 2008. The defect in T-cell regulation in NOD mice is an effect on the T-cell effectors. *Proceedings of the National Academy of Sciences of the United States of America*. 105, 19857-62.
- [47] Dalbeth, N. and Callan, M.F., 2002. A subset of natural killer cells is greatly expanded within inflamed joints. *Arthritis and rheumatism*. 46, 1763-72.
- [48] Davidson, A. and Diamond, B., 2001. Autoimmune diseases. *The New England journal of medicine*. 345, 340-50.
- [49] de la Fuente, H., Richaud-Patin, Y., Jabez-Ocampo, J., Gonzalez-Amaro, R. and Llorente, L., 2001. Innate immune mechanisms in the pathogenesis of systemic lupus erythematosus (SLE). *Immunology letters*. 77, 175-80.
- [50] Decker, P., 2011. Neutrophils and interferon-alpha-producing cells: who produces interferon in lupus? *Arthritis research & therapy*. 13, 118.

- [51] Della Bella, S., Gennaro, M., Vaccari, M., Ferraris, C., Nicola, S., Riva, A., Clerici, M., Greco, M. and Villa, M.L., 2003. Altered maturation of peripheral blood dendritic cells in patients with breast cancer. *British journal of cancer*. 89, 1463-72.
- [52] Dorner, T., Jacobi, A.M. and Lipsky, P.E., 2009. B cells in autoimmunity. *Arthritis research & therapy*. 11, 247.
- [53] Edwards, J.C., Cambridge, G. and Abrahams, V.M., 1999. Do self-perpetuating B lymphocytes drive human autoimmune disease? *Immunology*. 97, 188-96.
- [54] Edwards, S.W. and Hallett, M.B., 1997. Seeing the wood for the trees: the forgotten role of neutrophils in rheumatoid arthritis. *Immunology today*. 18, 320-4.
- [55] Eizirik, D.L., Colli, M.L. and Ortis, F., 2009. The role of inflammation in insulinitis and beta-cell loss in type 1 diabetes. *Nat Rev Endocrinol*. 5, 219-26.
- [56] Eyles, J.L., Roberts, A.W., Metcalf, D. and Wicks, I.P., 2006. Granulocyte colony-stimulating factor and neutrophils--forgotten mediators of inflammatory disease. *Nature clinical practice. Rheumatology*. 2, 500-10.
- [57] Farag, S.S., Fehniger, T., Ruggeri, L., Velardi, A. and Caligiuri, M.A., 2002. Natural killer cells: biology and application in stem-cell transplantation. *Cytherapy*. 4, 445-6.
- [58] Feger, U., Luther, C., Poeschel, S., Melms, A., Tolosa, E. and Wiendl, H., 2007. Increased frequency of CD4<sup>+</sup> CD25<sup>+</sup> regulatory T cells in the cerebrospinal fluid but not in the blood of multiple sclerosis patients. *Clinical and experimental immunology*. 147, 412-8.
- [59] Ferber, I.A., Brocke, S., Taylor-Edwards, C., Ridgway, W., Dinisco, C., Steinman, L., Dalton, D. and Fathman, C.G., 1996. Mice with a disrupted IFN-gamma gene are susceptible to the induction of experimental autoimmune encephalomyelitis (EAE). *Journal of immunology*. 156, 5-7.
- [60] Ferretti, G., Bacchetti, T., DiLudovico, F., Viti, B., Angeleri, V.A., Danni, M. and Provinciali, L., 2006. Intracellular oxidative activity and respiratory burst of leukocytes isolated from multiple sclerosis patients. *Neurochemistry international*. 48, 87-92.
- [61] Fiocco, U., Sfriso, P., Oliviero, F., Pagnin, E., Scagliori, E., Campana, C., Dainese, S., Cozzi, L. and Punzi, L., 2008. Co-stimulatory modulation in rheumatoid arthritis: the role of (CTLA4-Ig) abatacept. *Autoimmunity reviews*. 8, 76-82.
- [62] Fletcher, M.A., Zeng, X.R., Barnes, Z., Levis, S. and Klimas, N.G., 2009. Plasma cytokines in women with chronic fatigue syndrome. *Journal of translational medicine*. 7, 96.
- [63] Fletcher, M.A., Zeng, X.R., Maher, K., Levis, S., Hurwitz, B., Antoni, M., Broderick, G. and Klimas, N.G., 2010. Biomarkers in chronic fatigue syndrome: evaluation of natural killer cell function and dipeptidyl peptidase IV/CD26. *PloS one*. 5, e10817.

- [64] Fluge, O., Bruland, O., Risa, K., Storstein, A., Kristoffersen, E.K., Sapkota, D., Naess, H., Dahl, O., Nyland, H. and Mella, O., 2011. Benefit from B-lymphocyte depletion using the anti-CD20 antibody rituximab in chronic fatigue syndrome. A double-blind and placebo-controlled study. *PloS one*. 6, e26358.
- [65] Fluge, O. and Mella, O., 2009. Clinical impact of B-cell depletion with the anti-CD20 antibody rituximab in chronic fatigue syndrome: a preliminary case series. *BMC neurology*. 9, 28.
- [66] Folcik, V.A., Smith, T., O'Bryant, S., Kawczak, J.A., Zhu, B., Sakurai, H., Kajiwara, A., Staddon, J.M., Glabinski, A., Chernosky, A.L., Johnson, J.M., Tuohy, V.K., Rubin, L.L. and Ransohoff, R.M. *Journal of Neuroimmunology*. 97, 119-20.
- [67] Fontenot, J.D. and Rudensky, A.Y., 2004. Molecular aspects of regulatory T cell development. *Seminars in immunology*. 16, 73-80.
- [68] Franciotta, D., Salvetti, M., Lolli, F., Serafini, B. and Aloisi, F., 2008. B cells and multiple sclerosis. *Lancet neurology*. 7, 852-8.
- [69] Fukuda, K., Straus, S.E., Hickie, I., Sharpe, M.C., Dobbins, J.G. and Komaroff, A., 1994. The chronic fatigue syndrome: a comprehensive approach to its definition and study. International Chronic Fatigue Syndrome Study Group. *Annals of internal medicine*. 121, 953-9.
- [70] Gordon, R.A., Grigoriev, G., Lee, A., Kalliolias, G.D. and Ivashkiv, L.B., 2012. The IFN signature and STAT1 expression in RA synovial fluid macrophages are induced by TNFalpha and counter-regulated by synovial fluid microenvironment. *Arthritis and rheumatism*.
- [71] Grykiel, K., Zozulinska, D., Kostrzewa, A., Wiktorowicz, K. and Wierusz-Wysocka, B., 2001. [Evaluation of expression of polymorphonuclear neutrophil surface receptors in patients with type 1 diabetes]. *Pol Arch Med Wewn*. 105, 377-81.
- [72] Harris, D.P., Haynes, L., Sayles, P.C., Duso, D.K., Eaton, S.M., Lepak, N.M., Johnson, L.L., Swain, S.L. and Lund, F.E., 2000. Reciprocal regulation of polarized cytokine production by effector B and T cells. *Nature immunology*. 1, 475-82.
- [73] Haskins, K., Bradley, B., Powers, K., Fadok, V., Flores, S., Ling, X., Pugazhenthii, S., Reusch, J. and Kench, J., 2003. Oxidative stress in type 1 diabetes. *Annals of the New York Academy of Sciences*. 1005, 43-54.
- [74] Hassani, O., Loew, D., Van Dorsselaer, A., Papandreou, M.J., Sorokine, O., Rochat, H., Sampieri, F. and Mansuelle, P., 1999. Aah VI, a novel, N-glycosylated anti-insect toxin from *Androctonus australis hector* scorpion venom: isolation, characterisation, and glycan structure determination. *FEBS letters*. 443, 175-80.
- [75] Hilliard, B., Wilmen, A., Seidel, C., Liu, T.S., Goke, R. and Chen, Y., 2001. Roles of TNF-related apoptosis-inducing ligand in experimental autoimmune encephalomyelitis. *Journal of immunology*. 166, 1314-9.

- [76] Huang, G. and Elferink, C.J., 2005. Multiple mechanisms are involved in Ah receptor-mediated cell cycle arrest. *Molecular pharmacology*. 67, 88-96.
- [77] Issazadeh, S., Ljungdahl, A., Hojeberg, B., Mustafa, M. and Olsson, T., 1995. Cytokine production in the central nervous system of Lewis rats with experimental autoimmune encephalomyelitis: dynamics of mRNA expression for interleukin-10, interleukin-12, cytolysin, tumor necrosis factor alpha and tumor necrosis factor beta. *Journal of neuroimmunology*. 61, 205-12.
- [78] Itoh, N., Hanafusa, T., Miyazaki, A., Miyagawa, J., Yamagata, K., Yamamoto, K., Waguri, M., Imagawa, A., Tamura, S., Inada, M. and et al., 1993. Mononuclear cell infiltration and its relation to the expression of major histocompatibility complex antigens and adhesion molecules in pancreas biopsy specimens from newly diagnosed insulin-dependent diabetes mellitus patients. *The Journal of clinical investigation*. 92, 2313-22.
- [79] Jacobi, A.M., Reiter, K., Mackay, M., Aranow, C., Hiepe, F., Radbruch, A., Hansen, A., Burmester, G.R., Diamond, B., Lipsky, P.E. and Dorner, T., 2008. Activated memory B cell subsets correlate with disease activity in systemic lupus erythematosus: delineation by expression of CD27, IgD, and CD95. *Arthritis and rheumatism*. 58, 1762-73.
- [80] Jonsen, A., Gunnarsson, I., Gullstrand, B., Svenungsson, E., Bengtsson, A.A., Nived, O., Lundberg, I.E., Truedsson, L. and Sturfelt, G., 2007. Association between SLE nephritis and polymorphic variants of the CRP and FcgammaRIIIa genes. *Rheumatology*. 46, 1417-21.
- [81] Josefowicz, S.Z., Lu, L.F. and Rudensky, A.Y., 2012. Regulatory T cells: mechanisms of differentiation and function. *Annual review of immunology*. 30, 531-64.
- [82] Kallmann, B.A., Huther, M., Tubes, M., Feldkamp, J., Bertrams, J., Gries, F.A., Lampeter, E.F. and Kolb, H., 1997. Systemic bias of cytokine production toward cell-mediated immune regulation in IDDM and toward humoral immunity in Graves' disease. *Diabetes*. 46, 237-43.
- [83] Kastrukoff, L.F., Morgan, N.G., Zecchini, D., White, R., Petkau, A.J., Satoh, J. and Paty, D.W., 1998. A role for natural killer cells in the immunopathogenesis of multiple sclerosis. *Journal of neuroimmunology*. 86, 123-33.
- [84] Katsiari, C.G. and Tsokos, G.C., 2006. Transcriptional repression of interleukin-2 in human systemic lupus erythematosus. *Autoimmunity reviews*. 5, 118-21.
- [85] Katsikis, P.D., Chu, C.Q., Brennan, F.M., Maini, R.N. and Feldmann, M., 1994. Immunoregulatory role of interleukin 10 in rheumatoid arthritis. *The Journal of experimental medicine*. 179, 1517-27.
- [86] Kennedy, G., Spence, V., Underwood, C. and Belch, J.J., 2004. Increased neutrophil apoptosis in chronic fatigue syndrome. *Journal of clinical pathology*. 57, 891-3.

- [87] Klimas, N.G., Broderick, G. and Fletcher, M.A., 2012. Biomarkers for chronic fatigue. Brain, behavior, and immunity.
- [88] Klimas, N.G., Salvato, F.R., Morgan, R. and Fletcher, M.A., 1990. Immunologic abnormalities in chronic fatigue syndrome. *Journal of clinical microbiology*. 28, 1403-10.
- [89] Kohm, A.P., Carpentier, P.A. and Miller, S.D., 2003. Regulation of experimental autoimmune encephalomyelitis (EAE) by CD4+CD25+ regulatory T cells. *Novartis Foundation symposium*. 252, 45-52; discussion 52-4, 106-14.
- [90] Kuenz, B., Lutterotti, A., Ehling, R., Gneiss, C., Haemmerle, M., Rainer, C., Deisenhammer, F., Schocke, M., Berger, T. and Reindl, M., 2008. Cerebrospinal fluid B cells correlate with early brain inflammation in multiple sclerosis. *PloS one*. 3, e2559.
- [91] Kunz, M. and Ibrahim, S.M., 2009. Cytokines and cytokine profiles in human autoimmune diseases and animal models of autoimmunity. *Mediators of inflammation*. 2009, 979258.
- [92] Lande, R., Ganguly, D., Facchinetti, V., Frasca, L., Conrad, C., Gregorio, J., Meller, S., Chamilos, G., Sebasigari, R., Ricciari, V., Bassett, R., Amuro, H., Fukuhara, S., Ito, T., Liu, Y.J. and Gilliet, M., 2011. Neutrophils activate plasmacytoid dendritic cells by releasing self-DNA-peptide complexes in systemic lupus erythematosus. *Science translational medicine*. 3, 73ra19.
- [93] Laurence, A., Tato, C.M., Davidson, T.S., Kanno, Y., Chen, Z., Yao, Z., Blank, R.B., Meylan, F., Siegel, R., Hennighausen, L., Shevach, E.M. and O'Shea J, J., 2007. Interleukin-2 signaling via STAT5 constrains T helper 17 cell generation. *Immunity*. 26, 371-81.
- [94] Lee, H.Y., Hong, Y.K., Yun, H.J., Kim, Y.M., Kim, J.R. and Yoo, W.H., 2008. Altered frequency and migration capacity of CD4+CD25+ regulatory T cells in systemic lupus erythematosus. *Rheumatology*. 47, 789-94.
- [95] Lee, J.H., Wang, L.C., Lin, Y.T., Yang, Y.H., Lin, D.T. and Chiang, B.L., 2006. Inverse correlation between CD4+ regulatory T-cell population and autoantibody levels in paediatric patients with systemic lupus erythematosus. *Immunology*. 117, 280-6.
- [96] Leipe, J., Skapenko, A., Lipsky, P.E. and Schulze-Koops, H., 2005. Regulatory T cells in rheumatoid arthritis. *Arthritis research & therapy*. 7, 93.
- [97] Levesque, M.C. and St Clair, E.W. B cell-directed therapies for autoimmune disease and correlates of disease response and relapse. *Journal of Allergy and Clinical Immunology*. 121, 13-21.
- [98] Lindau, D., Ronnefarth, V., Erbacher, A., Rammensee, H.G. and Decker, P., 2011. Nucleosome-induced neutrophil activation occurs independently of TLR9 and endosomal acidification: implications for systemic lupus erythematosus. *European journal of immunology*. 41, 669-81.



- [99] Linker-Israeli, M., Deans, R.J., Wallace, D.J., Prehn, J., Ozeri-Chen, T. and Klinenberg, J.R., 1991. Elevated levels of endogenous IL-6 in systemic lupus erythematosus. A putative role in pathogenesis. *Journal of immunology*. 147, 117-23.
- [100] Logters, T., Margraf, S., Altrichter, J., Cinatl, J., Mitzner, S., Windolf, J. and Scholz, M., 2009. The clinical value of neutrophil extracellular traps. *Medical microbiology and immunology*. 198, 211-9.
- [101] Lorusso, L., Mikhaylova, S.V., Capelli, E., Ferrari, D., Ngonga, G.K. and Ricevuti, G., 2009. Immunological aspects of chronic fatigue syndrome. *Autoimmunity reviews*. 8, 287-91.
- [102] Lucchinetti, C., Bruck, W., Parisi, J., Scheithauer, B., Rodriguez, M. and Lassmann, H., 2000. Heterogeneity of multiple sclerosis lesions: implications for the pathogenesis of demyelination. *Annals of neurology*. 47, 707-17.
- [103] Maher, K.J., Klimas, N.G. and Fletcher, M.A., 2005. Chronic fatigue syndrome is associated with diminished intracellular perforin. *Clinical and experimental immunology*. 142, 505-11.
- [104] Mandrup-Poulsen, T., Helqvist, S., Wogensen, L.D., Molvig, J., Pociot, F., Johannesen, J. and Nerup, J., 1990. Cytokine and free radicals as effector molecules in the destruction of pancreatic beta cells. *Curr Top Microbiol Immunol*. 164, 169-93.
- [105] Marhoffer, W., Stein, M., Schleinkofer, L. and Federlin, K., 1993. Evidence of ex vivo and in vitro impaired neutrophil oxidative burst and phagocytic capacity in type 1 diabetes mellitus. *Diabetes research and clinical practice*. 19, 183-8.
- [106] Marino, E., Batten, M., Groom, J., Walters, S., Liuwantara, D., Mackay, F. and Grey, S.T., 2008. Marginal-zone B-cells of nonobese diabetic mice expand with diabetes onset, invade the pancreatic lymph nodes, and present autoantigen to diabetogenic T-cells. *Diabetes*. 57, 395-404.
- [107] Marino, F. and Cosentino, M., 2011. Adrenergic modulation of immune cells: an update. *Amino acids*.
- [108] Martinez-Forero, I., Garcia-Munoz, R., Martinez-Pasamar, S., Inoges, S., Lopez-Diaz de Cerio, A., Palacios, R., Sepulcre, J., Moreno, B., Gonzalez, Z., Fernandez-Diez, B., Melero, I., Bendandi, M. and Villoslada, P., 2008. IL-10 suppressor activity and ex vivo Tr1 cell function are impaired in multiple sclerosis. *European journal of immunology*. 38, 576-86.
- [109] Marzocchi-Machado, C.M., Alves, C.M., Azzolini, A.E., Polizello, A.C., Carvalho, I.F. and Lucisano-Valim, Y.M., 2002. Fcγ and complement receptors: expression, role and co-operation in mediating the oxidative burst and degranulation of neutrophils of Brazilian systemic lupus erythematosus patients. *Lupus*. 11, 240-8.
- [110] Mauri, C., 2010. Regulation of immunity and autoimmunity by B cells. *Current opinion in immunology*. 22, 761-7.

- [111] McInnes, I.B. and Schett, G., 2007. Cytokines in the pathogenesis of rheumatoid arthritis. *Nature reviews. Immunology*. 7, 429-42.
- [112] Meffre, E. and Wardemann, H., 2008. B-cell tolerance checkpoints in health and autoimmunity. *Current opinion in immunology*. 20, 632-8.
- [113] Menard, L., Samuels, J., Ng, Y.S. and Meffre, E., 2011. Inflammation-independent defective early B cell tolerance checkpoints in rheumatoid arthritis. *Arthritis and rheumatism*. 63, 1237-45.
- [114] Miyara, M., Amoura, Z., Parizot, C., Badoual, C., Dorgham, K., Trad, S., Nochy, D., Debre, P., Piette, J.C. and Gorochov, G., 2005. Global natural regulatory T cell depletion in active systemic lupus erythematosus. *Journal of immunology*. 175, 8392-400.
- [115] Mohr, W., Westerhellweg, H. and Wessinghage, D., 1981. Polymorphonuclear granulocytes in rheumatic tissue destruction. III. an electron microscopic study of PMNs at the pannus-cartilage junction in rheumatoid arthritis. *Annals of the rheumatic diseases*. 40, 396-9.
- [116] Momot, T., Koch, S., Hunzelmann, N., Krieg, T., Ulbricht, K., Schmidt, R.E. and Witte, T., 2004. Association of killer cell immunoglobulin-like receptors with scleroderma. *Arthritis and rheumatism*. 50, 1561-5.
- [117] Munschauer, F.E., Hartrich, L.A., Stewart, C.C. and Jacobs, L., 1995. Circulating natural killer cells but not cytotoxic T lymphocytes are reduced in patients with active relapsing multiple sclerosis and little clinical disability as compared to controls. *Journal of neuroimmunology*. 62, 177-81.
- [118] Naegele, M., Tillack, K., Reinhardt, S., Schippling, S., Martin, R. and Sospedra, M., 2012. Neutrophils in multiple sclerosis are characterized by a primed phenotype. *Journal of neuroimmunology*. 242, 60-71.
- [119] Nathan, C., 2006. Neutrophils and immunity: challenges and opportunities. *Nature reviews. Immunology*. 6, 173-82.
- [120] Nedvetzki, S., Sowinski, S., Eagle, R.A., Harris, J., Vely, F., Pende, D., Trowsdale, J., Vivier, E., Gordon, S. and Davis, D.M., 2007. Reciprocal regulation of human natural killer cells and macrophages associated with distinct immune synapses. *Blood*. 109, 3776-85.
- [121] Nemeth, T. and Mocsai, A., 2012. The role of neutrophils in autoimmune diseases. *Immunology letters*. 143, 9-19.
- [122] Noorchashm, H., Moore, D.J., Lieu, Y.K., Noorchashm, N., Schlachterman, A., Song, H.K., Barker, C.F. and Najfi, A., 1999. Contribution of the innate immune system to autoimmune diabetes: a role for the CR1/CR2 complement receptors. *Cellular immunology*. 195, 75-9.
- [123] Odendahl, M., Mei, H., Hoyer, B.F., Jacobi, A.M., Hansen, A., Muehlinghaus, G., Berrek, C., Hiepe, F., Manz, R., Radbruch, A. and Dorner, T., 2005. Generation of migra-

tory antigen-specific plasma blasts and mobilization of resident plasma cells in a secondary immune response. *Blood*. 105, 1614-21.

- [124] Ohl, K. and Tenbrock, K., 2011. Inflammatory cytokines in systemic lupus erythematosus. *Journal of biomedicine & biotechnology*. 2011, 432595.
- [125] Okamoto, A., Fujio, K., Okamura, T. and Yamamoto, K., 2011. Regulatory T-cell-associated cytokines in systemic lupus erythematosus. *Journal of biomedicine & biotechnology*. 2011, 463412.
- [126] Opsahl, M.L. and Kennedy, P.G., 2007. An attempt to investigate the presence of Epstein Barr virus in multiple sclerosis and normal control brain tissue. *Journal of neurology*. 254, 425-30.
- [127] Park, Y.W., Kee, S.J., Cho, Y.N., Lee, E.H., Lee, H.Y., Kim, E.M., Shin, M.H., Park, J.J., Kim, T.J., Lee, S.S., Yoo, D.H. and Kang, H.S., 2009. Impaired differentiation and cytotoxicity of natural killer cells in systemic lupus erythematosus. *Arthritis and rheumatism*. 60, 1753-63.
- [128] Pasare, C. and Medzhitov, R., 2003. Toll pathway-dependent blockade of CD4+CD25+ T cell-mediated suppression by dendritic cells. *Science*. 299, 1033-6.
- [129] Pascual, M.L., Muino-Blanco, T., Cebrian-Perez, J.A. and Lopez-Perez, M.J., 1994. Acquisition of viable-like surface properties of sperm cells by adsorption of seminal plasma proteins revealed by centrifugal countercurrent distribution. *Biology of the cell / under the auspices of the European Cell Biology Organization*. 82, 75-8.
- [130] Pasi, A., Bozzini, S., Carlo-Stella, N., Martinetti, M., Bombardieri, S., De Silvestri, A., Salvaneschi, L. and Cuccia, M., 2011. Excess of activating killer cell immunoglobulin-like receptors and lack of HLA-Bw4 ligands: a twoedged weapon in chronic fatigue syndrome. *Molecular medicine reports*. 4, 535-40.
- [131] Patarca, R., 2001. Cytokines and chronic fatigue syndrome. *Annals of the New York Academy of Sciences*. 933, 185-200.
- [132] Pellett, F., Siannis, F., Vukin, I., Lee, P., Urowitz, M.B. and Gladman, D.D., 2007. KIRs and autoimmune disease: studies in systemic lupus erythematosus and scleroderma. *Tissue antigens*. 69 Suppl 1, 106-8.
- [133] Pillai, S., Mattoo, H. and Cariappa, A., 2011. B cells and autoimmunity. *Current opinion in immunology*. 23, 721-31.
- [134] Rabinovitch, A., 2003. Immunoregulation by cytokines in autoimmune diabetes. *Advances in experimental medicine and biology*. 520, 159-93.
- [135] Rabinovitch, A. and Suarez-Pinzon, W.L., 2003. Role of cytokines in the pathogenesis of autoimmune diabetes mellitus. *Rev Endocr Metab Disord*. 4, 291-9.
- [136] Rabinovitch, A., Suarez, W.L. and Power, R.F., 1993. Lazaroid antioxidant reduces incidence of diabetes and insulinitis in nonobese diabetic mice. *J Lab Clin Med*. 121, 603-7.

- [137] Rapoport, M.J., Mor, A., Vardi, P., Ramot, Y., Winker, R., Hindi, A. and Bistrizter, T., 1998. Decreased secretion of Th2 cytokines precedes Up-regulated and delayed secretion of Th1 cytokines in activated peripheral blood mononuclear cells from patients with insulin-dependent diabetes mellitus. *Journal of autoimmunity*. 11, 635-42.
- [138] Raza, K., Falciani, F., Curnow, S.J., Ross, E.J., Lee, C.Y., Akbar, A.N., Lord, J.M., Gordon, C., Buckley, C.D. and Salmon, M., 2005. Early rheumatoid arthritis is characterized by a distinct and transient synovial fluid cytokine profile of T cell and stromal cell origin. *Arthritis research & therapy*. 7, R784-95.
- [139] Sakaguchi, S., Miyara, M., Costantino, C.M. and Hafler, D.A., 2010. FOXP3+ regulatory T cells in the human immune system. *Nature reviews. Immunology*. 10, 490-500.
- [140] Salomon, B., Lenschow, D.J., Rhee, L., Ashourian, N., Singh, B., Sharpe, A. and Bluestone, J.A., 2000. B7/CD28 costimulation is essential for the homeostasis of the CD4+CD25+ immunoregulatory T cells that control autoimmune diabetes. *Immunity*. 12, 431-40.
- [141] Samuels, J., Ng, Y.S., Coupillaud, C., Paget, D. and Meffre, E., 2005a. Human B cell tolerance and its failure in rheumatoid arthritis. *Annals of the New York Academy of Sciences*. 1062, 116-26.
- [142] Samuels, J., Ng, Y.S., Coupillaud, C., Paget, D. and Meffre, E., 2005b. Impaired early B cell tolerance in patients with rheumatoid arthritis. *The Journal of experimental medicine*. 201, 1659-67.
- [143] Savinov, A.Y., Tcherepanov, A., Green, E.A., Flavell, R.A. and Chervonsky, A.V., 2003. Contribution of Fas to diabetes development. *Proceedings of the National Academy of Sciences of the United States of America*. 100, 628-32.
- [144] Sawalha, A.H., Kaufman, K.M., Kelly, J.A., Adler, A.J., Aberle, T., Kilpatrick, J., Wakeland, E.K., Li, Q.Z., Wandstrat, A.E., Karp, D.R., James, J.A., Merrill, J.T., Lipsky, P. and Harley, J.B., 2008. Genetic association of interleukin-21 polymorphisms with systemic lupus erythematosus. *Annals of the rheumatic diseases*. 67, 458-61.
- [145] Schleinitz, N., Vely, F., Harle, J.R. and Vivier, E., 2010. Natural killer cells in human autoimmune diseases. *Immunology*. 131, 451-8.
- [146] Schmetterer, K.G., Neunkirchner, A. and Pickl, W.F., 2012. Naturally occurring regulatory T cells: markers, mechanisms, and manipulation. *FASEB journal : official publication of the Federation of American Societies for Experimental Biology*. 26, 2253-76.
- [147] Schmidt, A., Oberle, N. and Krammer, P.H., 2012. Molecular mechanisms of treg-mediated T cell suppression. *Front Immunol*. 3, 51.
- [148] Schrempf, W. and Ziemssen, T. Glatiramer acetate: mechanisms of action in multiple sclerosis. *Autoimmunity Reviews*. 6, 469-475.

- [149] Selmaj, K. and Raine, C.S., 1988. Tumor necrosis factor mediates myelin damage in organotypic cultures of nervous tissue. *Annals of the New York Academy of Sciences*. 540, 568-70.
- [150] Shlomchik, M.J., Craft, J.E. and Mamula, M.J., 2001. From T to B and back again: positive feedback in systemic autoimmune disease. *Nature reviews. Immunology*. 1, 147-53.
- [151] Silverman, G.J. and Carson, D.A., 2003. Roles of B cells in rheumatoid arthritis. *Arthritis research & therapy*. 5 Suppl 4, S1-6.
- [152] Sims, G.P., Ettinger, R., Shirota, Y., Yarboro, C.H., Illei, G.G. and Lipsky, P.E., 2005. Identification and characterization of circulating human transitional B cells. *Blood*. 105, 4390-8.
- [153] Souto-Carneiro, M.M., Mahadevan, V., Takada, K., Fritsch-Stork, R., Nanki, T., Brown, M., Fleisher, T.A., Wilson, M., Goldbach-Mansky, R. and Lipsky, P.E., 2009. Alterations in peripheral blood memory B cells in patients with active rheumatoid arthritis are dependent on the action of tumour necrosis factor. *Arthritis research & therapy*. 11, R84.
- [154] Stevenson, F.K. and Natvig, J., 1999. Autoantibodies revealed: the role of B cells in autoimmune disease. *Immunology today*. 20, 296-8.
- [155] Stewart, T.A., Hultgren, B., Huang, X., Pitts-Meek, S., Hully, J. and MacLachlan, N.J., 1993. Induction of type I diabetes by interferon-alpha in transgenic mice. *Science*. 260, 1942-6.
- [156] Tackey, E., Lipsky, P.E. and Illei, G.G., 2004. Rationale for interleukin-6 blockade in systemic lupus erythematosus. *Lupus*. 13, 339-43.
- [157] Tian, J., Zekzer, D., Lu, Y., Dang, H. and Kaufman, D.L., 2006. B cells are crucial for determinant spreading of T cell autoimmunity among beta cell antigens in diabetes-prone nonobese diabetic mice. *Journal of immunology*. 176, 2654-61.
- [158] Tiller, T., Tsuiji, M., Yurasov, S., Velinzon, K., Nussenzweig, M.C. and Wardemann, H., 2007. Autoreactivity in human IgG+ memory B cells. *Immunity*. 26, 205-13.
- [159] Valencia, X., Yarboro, C., Illei, G. and Lipsky, P.E., 2007. Deficient CD4+CD25high T regulatory cell function in patients with active systemic lupus erythematosus. *Journal of immunology*. 178, 2579-88.
- [160] van der Slik, A.R., Alizadeh, B.Z., Koeleman, B.P., Roep, B.O. and Giphart, M.J., 2007. Modelling KIR-HLA genotype disparities in type 1 diabetes. *Tissue antigens*. 69 Suppl 1, 101-5.
- [161] van Vollenhoven, R.F., 2009. How to dose infliximab in rheumatoid arthritis: new data on a serious issue. *Annals of the rheumatic diseases*. 68, 1237-9.
- [162] Venken, K., Hellings, N., Broekmans, T., Hensen, K., Rummens, J.L. and Stinissen, P., 2008a. Natural naive CD4+CD25+CD127low regulatory T cell (Treg) development

and function are disturbed in multiple sclerosis patients: recovery of memory Treg homeostasis during disease progression. *Journal of immunology*. 180, 6411-20.

- [163] Venken, K., Hellings, N., Hensen, K., Rummens, J.L., Medaer, R., D'Hooghe M, B., Dubois, B., Raus, J. and Stinissen, P., 2006. Secondary progressive in contrast to relapsing-remitting multiple sclerosis patients show a normal CD4+CD25+ regulatory T-cell function and FOXP3 expression. *Journal of neuroscience research*. 83, 1432-46.
- [164] Venken, K., Hellings, N., Thewissen, M., Somers, V., Hensen, K., Rummens, J.L., Medaer, R., Hupperts, R. and Stinissen, P., 2008b. Compromised CD4+ CD25(high) regulatory T-cell function in patients with relapsing-remitting multiple sclerosis is correlated with a reduced frequency of FOXP3-positive cells and reduced FOXP3 expression at the single-cell level. *Immunology*. 123, 79-89.
- [165] Visvanathan, K. and Lewin, S.R., 2006. Immunopathogenesis: role of innate and adaptive immune responses. *Semin Liver Dis*. 26, 104-15.
- [166] Vivier, E., Tomasello, E., Baratin, M., Walzer, T. and Ugolini, S., 2008. Functions of natural killer cells. *Nature immunology*. 9, 503-10.
- [167] Warde, N., 2011. Autoimmunity: the role of neutrophils in SLE: untangling the NET. *Nature reviews. Rheumatology*. 7, 252.
- [168] Willcox, A., Richardson, S.J., Bone, A.J., Foulis, A.K. and Morgan, N.G., 2009. Analysis of islet inflammation in human type 1 diabetes. *Clinical and experimental immunology*. 155, 173-81.
- [169] Wipke, B.T., Wang, Z., Nagengast, W., Reichert, D.E. and Allen, P.M., 2004. Staging the initiation of autoantibody-induced arthritis: a critical role for immune complexes. *Journal of immunology*. 172, 7694-702.
- [170] Wong, C.K., Lit, L.C., Tam, L.S., Li, E.K., Wong, P.T. and Lam, C.W., 2008. Hyperproduction of IL-23 and IL-17 in patients with systemic lupus erythematosus: implications for Th17-mediated inflammation in auto-immunity. *Clinical immunology*. 127, 385-93.
- [171] Wong, W.M., Vakis, S.A., Ayre, K.R., Ellwood, C.N., Howell, W.M., Tutt, A.L., Cawley, M.I. and Smith, J.L., 2000. Rheumatoid arthritis T cells produce Th1 cytokines in response to stimulation with a novel trispecific antibody directed against CD2, CD3, and CD28. *Scandinavian journal of rheumatology*. 29, 282-7.
- [172] Wujek, J.R., Bjartmar, C., Richer, E., Ransohoff, R.M., Yu, M., Tuohy, V.K. and Trapp, B.D., 2002. Axon loss in the spinal cord determines permanent neurological disability in an animal model of multiple sclerosis. *Journal of neuropathology and experimental neurology*. 61, 23-32.
- [173] Xing, Q., Su, H., Cui, J. and Wang, B., 2012. Role of Treg cells and TGF-beta1 in patients with systemic lupus erythematosus: a possible relation with lupus nephritis. *Immunological investigations*. 41, 15-27.

- [174] Xiu, Y., Wong, C.P., Bouaziz, J.D., Hamaguchi, Y., Wang, Y., Pop, S.M., Tisch, R.M. and Tedder, T.F., 2008. B lymphocyte depletion by CD20 monoclonal antibody prevents diabetes in nonobese diabetic mice despite isotype-specific differences in Fc gamma R effector functions. *Journal of immunology*. 180, 2863-75.
- [175] Yabuhara, A., Yang, F.C., Nakazawa, T., Iwasaki, Y., Mori, T., Koike, K., Kawai, H. and Komiyama, A., 1996. A killing defect of natural killer cells as an underlying immunologic abnormality in childhood systemic lupus erythematosus. *The Journal of rheumatology*. 23, 171-7.
- [176] Yanaba, K., Bouaziz, J.D., Haas, K.M., Poe, J.C., Fujimoto, M. and Tedder, T.F., 2008. A regulatory B cell subset with a unique CD1dhiCD5+ phenotype controls T cell-dependent inflammatory responses. *Immunity*. 28, 639-50.
- [177] Yang, J., Chu, Y., Yang, X., Gao, D., Zhu, L., Yang, X., Wan, L. and Li, M., 2009. Th17 and natural Treg cell population dynamics in systemic lupus erythematosus. *Arthritis and rheumatism*. 60, 1472-83.
- [178] Yasutomo, K., Horiuchi, T., Kagami, S., Tsukamoto, H., Hashimura, C., Urushihara, M. and Kuroda, Y., 2001. Mutation of DNASE1 in people with systemic lupus erythematosus. *Nature genetics*. 28, 313-4.
- [179] Yilmaz, M., Kendirli, S.G., Altintas, D., Bingol, G. and Antmen, B., 2001. Cytokine levels in serum of patients with juvenile rheumatoid arthritis. *Clinical rheumatology*. 20, 30-5.
- [180] You, S., Belghith, M., Cobbold, S., Alyanakian, M.A., Gouarin, C., Barriot, S., Garcia, C., Waldmann, H., Bach, J.F. and Chatenoud, L., 2005. Autoimmune diabetes onset results from qualitative rather than quantitative age-dependent changes in pathogenic T-cells. *Diabetes*. 54, 1415-22.
- [181] Yurasov, S., Wardemann, H., Hammersen, J., Tsuiji, M., Meffre, E., Pascual, V. and Nussenzweig, M.C., 2005. Defective B cell tolerance checkpoints in systemic lupus erythematosus. *The Journal of experimental medicine*. 201, 703-11.
- [182] Zhang, A.L., Colmenero, P., Purath, U., Teixeira de Matos, C., Hueber, W., Klare-skog, L., Tarner, I.H., Engleman, E.G. and Soderstrom, K., 2007. Natural killer cells trigger differentiation of monocytes into dendritic cells. *Blood*. 110, 2484-93.
- [183] Zhang, B., Yamamura, T., Kondo, T., Fujiwara, M. and Tabira, T., 1997. Regulation of experimental autoimmune encephalomyelitis by natural killer (NK) cells. *The Journal of experimental medicine*. 186, 1677-87.
- [184] Zhang, J., Jacobi, A.M., Wang, T. and Diamond, B., 2008. Pathogenic autoantibodies in systemic lupus erythematosus are derived from both self-reactive and non-self-reactive B cells. *Molecular medicine*. 14, 675-81.
- [185] Zhou, L., Chong, M.M. and Littman, D.R., 2009. Plasticity of CD4+ T cell lineage differentiation. *Immunity*. 30, 646-55.

- [186] Ziaber, J., Tchorzewski, H., Chmielewski, H., Baj, Z., Pasnik, J. and Kaczmarek, J., 1999. [TNF-alpha binding ability as a sign of peripheral blood neutrophils preactivation in the course of multiple sclerosis]. *Neurol Neurochir Pol.* 33, 789-96.

IntechOpen

IntechOpen



