Chapter 10

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

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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 being described in CFS/ME. Hence, the purpose of this chapter is to describe the findings related to the above mentioned cells in

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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)-1α and β, IL-6, interferon (IFN)-α and tumour necrosis factor (TNF)-α 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 in to cluster differentiation (CD)4^+ and $CD8^+$T cells as they recognise peptides with MHCII and MHCI molecules respectively. $CD4^+$T cells can be further subdivided into the T helper (Th) 1, 2, 17 and regulatory T cells (Tregs). $CD8^+$T cells are the main cytotoxic cells in the adaptive immune system while $CD4^+$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 $CD8^+$T cells (Brenu et al., 2011), direct investigations of $CD4^+$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 $CD4^+$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

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degranulatioin 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-1β 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 FcγR 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-α and neutrophils are among the key mediators of immune dysfunction in SLE patients. IFN-α 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-α (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 β 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 TGFβ1 (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 (FcγRIII)) surface molecules (Farag et al., 2002). Thus NK cells can be classified into two main subtypes, $CD56^{dim}CD16^{positive}$ and $CD56^{bright}CD16^{negative}$ 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-γ 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 ($2DS2^{+}$/2DL2- and $2DS1^{+}$/2DS2-) and SLE ($2DS^{+}$/2DS2-) (Momot et al., 2004; Pellett et al., 2007). Similarly, polymorphism in the FcγRIIIa 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

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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 KIRS3DS1 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-α, IFN-γ 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 $CD4^+$T cells (Carter et al., 2011). In humans Bregs can be distinguished from other cells via the expression of $CD19^+CD24^{hi}CD38^{hi}$ with high levels of CD1d, $CD5^+$ 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 $CD27^{+}$B cells and CD27-/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-α, TNF-α alters the predominance of naïve and memory B cells however, following anti-TNF-α 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 $CD19^{+}CD27^{+}$CD38-CD138- and $CD19^{+}CD38^{+}CD138^{+}$ (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 $CD19^{+}CD27^{-}$ 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 β cells thus their deletion prolongs the life of the β cells (Xiu et al.,

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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 $CD8^+$ Tregs or $CD4^+$Tregs. However, for the purposes of this chapter the focus will be on the $CD4^+$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-β 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 $CD4^+CD25^+$Tregs while others have shown no difference in $CD4^+CD25^+$, $CD4^+CD25^{hi}$, $CD4^+FOXP3^+CD45RO^+$, $CD4^+FOXP3^+CD45RA^+$ 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-β normalized the Tregs levels as it caused an increase in the number of $CD4^+CD25^+$Foxp3 Tregs (Chen et al., 2012). Similarly, $CD39^+$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-γ 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 $CD4^+CD25^{hi}$ 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 $CD127^+FOXP3^+$ 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 $CD4^+CD25^{hi}$ 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-α producing APCs, CD95 apoptosis and diminishing levels of IL-2 (Katsiari and Tsokos, 2006). Similarly, the observation of defective $CD4^+CD25^+$ 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-β is necessary for the peripheral generation of $CD4^+CD25^+$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).

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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-γ and TNF-α (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-α, 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. $CD4^+$T cells are the predominant producers of both anti and pro-inflammatory cytokines. Th1 cells produce IL-2 and IFN-γ 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-α, IL-1β, 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).

Insulitis 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 β and α cells occurs in the presence of cytokines such as IL-1, IFN-γ, TNF-α and TNF-β (Mandrup-Poulsen et al., 1990; Rabinovitch et al., 1993). β cells may indirectly stimulate autoreactive T cells via the production of IFN-α during stress while T cells may stimulate IFN-γ which in turn penetrate the islets and cause their destruction (Chakrabarti et al., 1996; Stewart et al., 1993). Similarly increase in the expression of MHCI and Fas increases the likelihood for the destruction of β cells by $CD8^+$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-γ which is elevated both in MS and in the experimental condition, EAE (Ferber et al., 1996). In EAE mice IFN-γ 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-γ, EAE is not obliterated as there is evidence to suggest an increase in severity in mice depleted of IFN-γ (Hassani et al., 1999). Although, IFN-γ may have a deleterious role in EAE it may be necessary for the regulation of other inflammatory activities, deletion of certain components of IFN-γ 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-γ and IL-10 are elevated in RP and SP but not in PP MS patients (Balashov et al., 2000). The presence of TNF-α 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-α, IFN-γ, 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-γ 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

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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 factory 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-γ and TNF-α. 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 being 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 being 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 being 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-

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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 validatory 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[1,2], Lotti Tajouri[3], Kevin J. Ashton[3], Donald R. Staines[1,4] and Sonya M. Marshall-Gradisnik[1,2]

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

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