Summary of recent significant findings in M.E./cfs research – updated May 2016

Immune System & Cytokine studies.

Author(s)	Title	Journal & Link	Description of findings
Fluge et. al. 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 http://journals.plos.org/plosone/article?id=10.1371/journal.pone.0026358	The delayed responses starting from 2–7 months after Rituximab treatment, in spite of rapid B-cell depletion, suggests that M.E/cfs is an autoimmune disease and may be consistent with the gradual elimination of autoantibodies preceding clinical responses. http://www.meassociation.org.uk/2011/10/rituximab-clinical-trial-questions-and-answers/
Elfaitouri A, et. al. 2013 Lead investigator: Jonas Blomberg	Epitopes of microbial and human heat shock protein 60 and their recognition in myalgic encephalomyelitis	Plos One http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3842916/	Levels of antibodies to specific parts of HSP60 were relatively high, both in ME/CFS patients and in control samples. However, significant levels of antibodies to Chlamydia pneumoniae-derived HSP60 were present in around a quarter (24.6%) of ME/CFS patients – a far higher proportion than in the patients with other illnesses (0.003%). http://tinyurl.com/kmmdyq2
Horning et. al. 2015	Distinct plasma immune signatures in ME/CFS are present early in the course of illness.	Science Advances http://advances.sciencemag.org/content/1/1/e1400121 Author comment: http://cii.columbia.edu/blog.aspx?cid=yEsoKU	This is the first study to demonstrate altered plasma immune signatures early in the course of ME/CFS that are not present in subjects with longer duration of illness. Analyses based on disease duration revealed that early ME/CFS cases had a prominent activation of both pro- and anti-inflammatory cytokines as well as dissociation of intercytokine regulatory networks. We found a stronger correlation of cytokine alterations with illness duration than with measures of illness severity, suggesting that the immunopathology of ME/CFS is not static.
Huth et. al. 2014 Sonya Marshall-Gradisnik	Characterization of Natural Killer Cell Phenotypes in Chronic Fatigue Syndrome/Myalgic Encephalomyelitis	Clinical & Cellular Immunology http://tinyurl.com/kaelzrx	The data suggests that a combination of impairments in $CD56^{dim}CD56+$ NK cells from CFS/ME patients may contribute to reduced cytotoxic activity of this phenotype.
Curriu et. al. 2014 Julia Blanco	Screening NK-, B- and T-cell phenotype and function in patients suffering from Chronic Fatigue Syndrome	Journal of Translational Medicine. http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3614537/	Findings suggest that alterations in T-cell phenotype and proliferative response along with the specific signature of NK cell phenotype may be useful to identify CFS individuals. The striking down modulation of T cell mediated immunity may help to understand inter-current viral infections in CFS.

Author(s)	Title	Journal & Link	Description of findings
Loebl et. al. 2013 Carmen Scheibenbogen	Deficient EBV-Specific B- and T-Cell Response in Patients with Chronic Fatigue Syndrome	Plos One http://tinyurl.com/okexay9	Taken together, these findings give evidence for a deficient EBV-specific B- and T-cell memory response in CFS patients and suggest an impaired ability to control early steps of EBV reactivation.
Bradley et. al. 2013 Lead Investigator: Amolak Bansal	Altered functional B cell subset populations in patients with chronic fatigue syndrome compared to healthy controls	Clinical & Experimental Immunology. http://tinyurl.com/q3njllt	CFS patients had greater numbers of naive B cells as a percentage of lymphocytes: 6·3 versus 3·9% in HC (P = 0·034), greater numbers of naive B cells as a percentage of B cells: 65 versus 47% in controls (P = 0·003), greater numbers of transitional B cells: 1·8 versus 0·8% in controls (P = 0·025) and reduced numbers of plasmablasts: 0·5 versus 0·9% in controls (P = 0·013). While the cause of these changes is unclear, we speculate whether they may suggest a subtle tendency to autoimmunity.
Brenu et. al. 2014	The Role of Adaptive and Innate Immune Cells in Chronic Fatigue Syndrome/ Myalgic Encephalomyelitis	International Immunology. http://tinyurl.com/kxblzpf	Alterations in B cells, Tregs, NK cells and neutrophils suggest significant impairments in immune regulation in CFS/ME and these may have similarities to a number of autoimmune disorders.
Hardcastle et. al. 2014	Analysis of the Relationship between Immune Dysfunction and Symptom Severity in Patients with Chronic Fatigue Syndrome/Myalgic Encephalomyelitis (CFS/ME)	Journal of Clinical & Cellular Immunology http://tinyurl.com/la862or	This study is the first to determine alterations in NK, iNKT, B, DC and γδ T cell phenotypes in both moderate and severe CFS/ME patients. Immunological alterations are present in innate and adaptive immune cells and sometimes, immune deregulation appears worse in CFS/ME patients with more severe symptoms.
Huth et. al. 2016	ERK1/2, MEK1/2 and p38 downstream signalling molecules impaired in CD56 dim CD16+ and CD56 bright CD16 dim/− natural killer cells in ME/cfs	Journal of Translational Medicine. http://bit.ly/1T4o15r	This is the first study to report significant differences in MAPK intracellular signalling molecules in CD56 dim CD16+ and CD56 bright CD16dim/− Natural Killer cells from CFS/ME patients. In CFS/ME patients, dysfunctional MAPK signalling may contribute to reduced Natural Killer cell cytotoxic activity.
Hornig et al. 2015	Cytokine network analysis of cerebrospinal fluid in M.E./cfs	Nature: Molecular Psychiatry http://bit.ly/1T69ZwN	The results indicate a markedly disturbed immune signature in the cerebrospinal fluid of M.E./cfs patients that is consistent with immune activation in the central nervous system, and a shift toward an allergic or T helper type-2 pattern associated with autoimmunity. Simmaron Research explanation of findings: http://bit.ly/24OgpeH
Wong et al. 2015	A Comparison of Cytokine Profiles of Chronic Fatigue Syndrome/Myalgic Encephalomyelitis and Multiple Sclerosis Patients	International Journal of Clinical Medicine http://bit.ly/27dYi0u	ME/cfs and MS patients both displayed abnormal cytokine levels, with dual expression of Th1 and Th2 cytokines. Interferon-γ, Interleukin-10 and IL-5 were significantly higher in the serum of both ME/cfs and MS patients compared to the healthy controls.

Muscular, Exercise & Metabolic studies.

Author(s)	Title	Journal & Link	Description
Brown et. al. 2015 Lead Investigator: Julia Newton	Abnormalities of AMPK Activation and Glucose Uptake in Cultured Skeletal Muscle Cells from Individuals with Chronic Fatigue Syndrome	Plos One http://tinyurl.com/poqbecu For a detailed explanation: http://bit.ly/1Gq2Nbf	Overall, the evidence from this important study points to an exercise-related primary abnormality in the muscle tissues of ME/CFS patients which, because it was observed in cultured isolated muscle cells, (and therefore not subject to external influencing factors, such as emotional stress or clinical depression) may well have a genetic or epigenetic basis.
Keller et. al. 2014	Inability of myalgic encephalomyelitis /chronic fatigue syndrome patients to reproduce VO2 peak indicates functional impairment	Journal of Translational Medicine http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4004422/	ME/CFS patients exhibited significant post-exertional declines in VO2, work, minute ventilation and O2 pulse at both maximal and ventilatory threshold intensities. Consequently, classification of functional impairment based on VO2peak and VO2 at ventilatory threshold over-estimated the functional ability of 50% of ME/CFS in this sample when based on only one CPET.
Jones et. al. 2011	Loss of capacity to recover from acidosis on repeat exercise in chronic fatigue syndrome: a case–control study	European Journal of Clinical Investigation. http://tinyurl.com/p2vomfn	When exercising to comparable levels to normal controls, CFS patients exhibit profound abnormality in bioenergetic function and response to it.
Arroll et. al. 2014	The delayed fatigue effect in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)	Fatigue: Biomedicine, Health & Behaviour http://tinyurl.com/nhn5vnk	These findings are suggestive of post-exertional symptom exacerbation following mental effort. This may have implications for working environments that present cognitive demands to individuals with ME/CFS.
Twisk & Geraghty 2015	Deviant Cellular and Physiological Responses to Exercise in M.E./ cfs	Jacobs Journal of Physiology http://bit.ly/1kDXkq7	This article reviews observations which support the position that post-exertional “malaise” in ME/CFS may be linked to a number of observable deviant physiological responses to exercise, including muscle weakness and myalgia, a substantial fall of oxygen uptake after exercise, an increase in metabolite-detecting (pain) receptors, increased acidosis, abnormal immune responses, and orthostatic intolerance.
Rutherford at al 2016	Understanding Muscle Dysfunction in Chronic Fatigue Syndrome	Journal of Aging Research http://bit.ly/22UyR4C	There is increasing evidence to suggest that muscular biochemical abnormality may play a major role in CFS/ME associated fatigue. The literature suggests patients exhibit profound intramuscular dysfunction regarding acid generation and clearance, with a tendency towards an over-utilisation of the lactate dehydrogenase pathway following relatively low-level activity.

Brain & Neurological studies.

Author(s)	Title	Journal & Link	Description of findings
Barnden et. al. 2015	Evidence in chronic fatigue syndrome for severity-dependent up-regulation of prefrontal myelination that is independent of anxiety and depression	NMR in Biomedicine http://tinyurl.com/lvt2l33	The severity-dependent elevation of myelination in the internal capsule and prefrontal White Matter reported here, together with midbrain volume loss and midbrain neuroinflammation in CFS reported elsewhere (4,5), suggest that these midbrain changes are associated with impaired midbrain nerve conduction. Impaired brain–body and brain–brain communication through the midbrain could explain many of the autonomic and cognitive symptoms of CFS.
Puri et. al. 2014	Regional grey and white matter volumetric changes in myalgic encephalomyelitis (chronic fatigue syndrome): a voxel-based morphometry 3-T MRI study.	British Journal of Radiology. http://www.birpublications.org/doi/full/10.1259/bjr/93889091	These data support the hypothesis that significant neuroanatomical changes occur in CFS, and are consistent with the complaint of impaired memory that is common in this illness; they also suggest that subtle abnormalities in visual processing, and discrepancies between intended actions and consequent movements, may occur in CFS. http://tinyurl.com/mov8n2x
Nakatomi et. al. 2014	Neuroinflammation in Patients with Chronic Fatigue Syndrome / Myalgic Encephalomyelitis: An 11C-(R)-PK11195 PET Study	Journal of Nuclear Medicine http://tinyurl.com/p8druw7	Neuroinflammation was shown to be present in widespread brain areas in CFS/ME patients and was associated with the severity of neuropsychologic symptoms. Evaluation of neuroinflammation in CFS/ME patients may be essential for understanding the core pathophysiology and for developing objective diagnostic criteria and effective medical treatments.
Barnden et. al. 2011	A brain MRI study of chronic fatigue syndrome: evidence of brainstem dysfunction and altered homeostasis		The study observed MR changes in CFS consistent with accelerated volume loss in the midbrain and disrupted homeostasis in the brainstem, cerebellum, prefrontal WM and hypothalamus. In addition, we found indirect evidence for impaired regulation of the cerebral microvasculature. We suggest that at least some of these changes could be a result of astrocyte dysfunction.
Shan et al. 2016	Progressive brain changes in patients with chronic fatigue syndrome: A longitudinal MRI study	Journal of Magnetic Resonance Imaging http://bit.ly/1TkVJQa	The results suggested that CFS is associated with left inferior fronto-occipital fasciculus (IFOF) White Matter deficits which continue to deteriorate at an abnormal rate.
Barnden et. al. 2016	Autonomic correlations with MRI are abnormal in the brainstem vasomotor centre in Chronic Fatigue Syndrome	NeuroImage: Clinical http://bit.ly/1OhZk5p	Vasomotor centre, midbrain and hypothalamus correlations were abnormal in CFS. MRI group comparisons between CFS and controls detected no differences. Regulatory nuclei and peripheral effectors/sensors appear to function correctly. Signalling between brainstem/midbrain regulatory nuclei appears to be impaired.

Author(s)	Title	Journal & Link	Description of findings
Puri et al. 2012	Regional grey and white matter volumetric changes in M.E./cfs: a voxel-based morphometry 3 T MRI study.	British Journal of Radiology http://bit.ly/27dZOj7	These data support the hypothesis that significant neuroanatomical changes occur in M.E./cfs, and are consistent with the complaint of impaired memory that is common in this illness; they also suggest that subtle abnormalities in visual processing, and discrepancies between intended actions and consequent movements, may occur in M.E/cfs.

Mitochondrial Dysfunction Studies:

Author(s)	Title	Journal & Link	Description of findings
Morris & Maes 2014	Mitochondrial dysfunctions in Myalgic Encephalomyelitis / chronic fatigue syndrome explained by activated immuno-inflammatory, oxidative and nitrosative stress pathways	Metabolic Brain Disease http://bit.ly/1TQDmVY	Evidence suggests that immuno-inflammatory and Oxidative & Nitrosative pathways may play a role in the mitochondrial dysfunctions and consequently the bio-energetic abnormalities seen in patients with ME/cfs. Defects in ATP production and the electron transport complex, in turn, are associated with an elevated production of superoxide and hydrogen peroxide in mitochondria creating adaptive and synergistic damage. It is argued that mitochondrial dysfunctions, e.g. lowered ATP production, may play a role in the onset of ME/cfs symptoms, e.g. fatigue and post exertional malaise, and may explain in part the central metabolic abnormalities observed in ME/cfs, e.g. glucose hypo-metabolism and cerebral hypo-perfusion.
Myhill et al. 2009	Chronic fatigue syndrome and mitochondrial dysfunction	International Journal of Clinical Experimental Medicine. http://www.ijcem.com/files/IJCEM812001.pdf	The power and usefulness of the "ATP profile" test in confirming and pin-pointing biochemical dysfunctions in people with CFS is discussed. Observations strongly implicate mitochondrial dysfunction as the immediate cause of CFS symptoms. However, it isn't yet clear whether the damage to mitochondrial function is a primary effect, or a secondary effect to one or more of a number of primary conditions, for example cellular hypoxia [30], or oxidative stress including excessive peroxynitrite
Booth et al. 2012	Mitochondrial dysfunction and the pathophysiology of Myalgic Encephalomyelitis/Chronic Fatigue Syndrome (ME/CFS)	International Journal of Clinical Experimental Medicine. http://www.ijcem.com/files/IJCEM1204005.pdf http://bit.ly/1XlwjaW	Measurements of Cell-free DNA show that ME/CFS patients have abnormally high levels of damaged and necrotic cells and that there is strong correlation with the measured mitochondrial dysfunction. The ATP Profile is an objective test of ME/CFS and clearly shows that this illness has a physical basis. Individually and collectively the biomedical quantities select patients whose symptoms are the direct result of mitochondrial dysfunction. These quantities also reflect the severity of the illness and, together with one or more additional tests such as Cell-free DNA they demonstrate that it is not just neutrophils that are dysfunctional but also other biological systems.

Cardio-vascular studies.

Author(s)	Title	Journal & Link	Description
Witham et. al. 2014 Lead Investigator: Faisal Khan	Association between vitamin D status and markers of vascular health in patients with chronic fatigue syndrome/myalgic encephalomyelitis.	Intl. Journal of Cardiology http://tinyurl.com/le44d7f	There were significant correlations between 25(OH)D levels and markers of inflammation, oxidative stress, endothelial function and arterial stiffness. http://tinyurl.com/qxgwa6x
Baumont et. al. 2012	Reduced Cardiac Vagal Modulation Impacts on Cognitive Performance in Chronic Fatigue Syndrome	Plos One http://tinyurl.com/mf97jzk	A role for heart rate variability (HRV) in cognitive flexibility has been demonstrated in healthy individuals, but this relationship has not as yet been examined in CFS. These findings reveal for the first time an association between reduced cardiac vagal tone and cognitive impairment in CFS and confirm previous reports of diminished vagal activity.
Newton D et. al. 2011	Large and small artery endothelial dysfunction in chronic fatigue syndrome.	International Journal of Cardiology http://tinyurl.com/pc5e2d7	These findings provide direct evidence of endothelial dysfunction in both the large and small vessels of patients with ME/CFS, which may warrant a large prospective trial of cardiovascular outcomes in the disease. This evidence collectively points to increased cardiovascular risk in ME/CFS patients, which is borne out epidemiologically by their high mortality due to heart disease
Hollingsworth et al. 2012	Impaired cardiac function in chronic fatigue syndrome measured using magnetic resonance cardiac tagging.	Journal of Internal Medicine http://bit.ly/1rGvYnf	Patients with CFS have markedly reduced cardiac mass and blood pool volumes, particularly end-diastolic volume: this results in significant impairments in stroke volume and cardiac output compared to controls. The CFS group appeared to have a delay in the release of torsion.
Naschitz et al. 2006	Shortened QT interval: a distinctive feature of the dysautonomia of chronic fatigue syndrome.	Journal of Electrocardiology http://bit.ly/1NqJWDy	the average supine & tilted QTc intervals in CFS were significantly shorter than in healthy controls. Relatively short QTc intervals are features of the CFS-related dysautonomia.

Genetics & Single Nucleotide Polymorphism (genetic mutation) studies.

Author(s)	Title	Journal & Link	Description
Shimosako N, Kerr JR 2014	Use of single-nucleotide polymorphisms (SNPs) to distinguish gene expression subtypes of chronic fatigue syndrome/myalgic encephalomyelitis	Journal of Clinical Pathology http://tinyurl.com/pqmrysd http://www.ncbi.nlm.nih.gov/pubmed/25240059	The headline result was that 21 SNP alleles had significantly different 'frequency distributions' in ME/CFS patients than in depression control or healthy control subjects – seven of these SNPs were within the BMP2K gene and two were within the IL6ST gene. http://tinyurl.com/k3d88tt
Sonya Marshall-Gradisnik 2015	Examination of Single Nucleotide Polymorphisms (SNPs) in Transient Receptor Potential (TRP) Ion Channels in Chronic Fatigue Syndrome Patients	Immunology & Immunogenetics Insights. http://tinyurl.com/m9erktl	The data from this pilot study suggest an association between TRP ion channels, predominantly TRPM3 and CFS. This and other TRPs identified may contribute to the etiology and patho-mechanism of CFS.
Sonya Marshall-Gradisnik 2016	Natural killer cells and single nucleotide polymorphisms of specific ion channels and receptor genes in M.E/cfs	The Application of Clinical Genetics - Dove Press http://bit.ly/1NquqaO	Detected a number of Single Nucleotide Polymorphisms and genotypes for Transient Receptor Potential ion channels and Acetylcholine Receptors from isolated Natural Killer cells in patients with ME/CFS, suggesting these SNPs and genotypes may be involved in changes in NK cell function and the development of ME/CFS pathology. These anomalies suggest a role for dysregulation of Ca2+ in AChR and TRP ion channel signaling in the pathomechanism of ME/CFS.
Billing-Ross et. al. 2016	Mitochondrial DNA variants correlate with symptoms in M.E./cfs	Journal of Translational Medicine. http://bit.ly/1TzZd1l Layman's explanation: http://bit.ly/1sdqe4O	Analysis of mitochondrial genomes in ME/CFS cases indicates that individuals of a certain haplogroup or carrying specific SNPs are more likely to exhibit certain neurological, inflammatory, and/or gastrointestinal symptoms. No increase in susceptibility to ME/CFS of individuals carrying particular mitochondrial genomes or SNPs was observed.
Unger et al. 2016	Telomere Length Analysis in Chronic Fatigue Syndrome	FASEB Journal http://bit.ly/1rVNALx	These results indicate that CFS should be included in the list of conditions associated with telomere shortening. Consequently, people with this illness are likely to have a reduced life-expectancy. M.E. Research U.K. explanation: http://bit.ly/24oZVpQ
De Vega et al. 2014	DNA Methylation Modifications Associated with Chronic Fatigue Syndrome.	PLOS One	An increased abundance of differentially methylated genes related to the immune response, cellular metabolism, and kinase activity were found. Genes associated with immune cell regulation, the largest coordinated enrichment of differentially methylated pathways, showed hypomethylation within promoters and other gene regulatory elements in CFS. These data are consistent with evidence of multisystem dysregulation in CFS and implicate the involvement of DNA modifications in CFS pathology.

Gastro-intestinal studies.

Author(s)	Title	Journal & Link	Description
Chia et. al. 2015	Functional Dyspepsia and Chronic Gastritis Associated with Enteroviruses	Open Journal of gastroenterology. http://tinyurl.com/op5q65j	In this research by Dr. Chia on enteroviral involvement in ME/CFS, he shows that the upset stomach, nausea, bloating and other stomach symptoms common in ME/CFS patients as well as in healthy patients without H. Pylori infection are due to enteroviral infection.
Chia J & Chia A 2008	Chronic fatigue syndrome is associated with chronic enterovirus infection of the stomach	Journal of Clinical Pathology http://jcp.bmjjournals.com/content/61/1/43.abstract	Enterovirus VP1, RNA and non-cytopathic viruses were detected in the stomach biopsy specimens of CFS patients with chronic abdominal complaints. A significant subset of CFS patients may have a chronic, disseminated, non-cytolytic form of enteroviral infection, which could be diagnosed by stomach biopsy.
De Merleir et.al. 2013	Plasmacytoid Dendritic Cells in the Duodenum of Individuals Diagnosed with Myalgic Encephalomyelitis Are Uniquely Immunoreactive to Antibodies to Human Endogenous Retroviral Proteins	In Vivo http://iv.iiarjournals.org/content/27/2/177.full	In eight out of 12 individuals with ME, immunoreactivity to HERV proteins was observed in duodenal biopsies. In contrast, no immunoreactivity was detected in any of the eight controls. Although the significance of HERVs present in the pDCs of individuals with ME has yet to be determined, these data raise the possibility of an involvment of pDCs and HERVs in ME pathology.
Fremont et. al. 2009	Detection of Herpesviruses and Parvovirus B19 in Gastric and Intestinal Mucosa of Chronic Fatigue Syndrome Patients	In Vivo http://iv.iiarjournals.org/content/23/2/209.full	A most important finding is the higher frequency of parvovirus B19 positive biopsies in the CFS population, compared to the controls (38-40% in CFS duodenum and stomach biopsies, versus less than 14% in the controls). This difference suggests that parvovirus B19 may be involved in the development and maintenance of CFS, at least for a subset of patients.

Potential Diagnostic Biomarkers:

Author(s)	Title	Journal & Link	Description
Petty et.al. 2016	MicroRNAs hsa-miR-99b, hsa-miR-330, hsa-miR-126 and hsa-miR-30c: Potential Diagnostic Biomarkers in Natural Killer (NK) Cells of Patients with M.E./cfs	PLOS One http://bit.ly/1WpA6oH M.E. Research U.K. http://bit.ly/1REftQO	This study demonstrates altered microRNA expression in the peripheral blood mononuclear cells of CFS/ME patients, which are potential diagnostic biomarkers. The greatest degree of miRNA deregulation was identified in NK cells with targets consistent with cellular activation and altered effector function.
Sun et. al. 2016	Orosomucoid as a potential Biomarker for the diagnosis of Chronic Fatigue Syndrome.	CNS Neuroscience & Therapeutics http://bit.ly/1TzWXY0	Compared with a healthy control group, Orosomucoid (ORM) levels were dramatically elevated in blood serum in Fukuda-defined CFS patients. See M.E. Research U.K. explanation: http://bit.ly/1KHfOC9

Definitions and Models of Illness causation.

Author(s)	Title	Journal & Link	Description of findings
Ellen Wright-Clayton. 2015	Beyond Myalgic Encephalomyelitis / Chronic Fatigue Syndrome: Redefining an Illness. An IOM report on redefining an illness	National Academy of Science Institute of Medicine http://bit.ly/24oZVpQ	ME/CFS is a multisystem and often long-lasting disorder, with manifestations that can cause substantial morbidity and can severely impair patients' health and well-being. Patients with ME/CFS are typically unable to perform their normal activities, and as many as one-fourth are homebound or bedridden, sometimes for extended periods. This report describes efforts to develop diagnostic criteria for clinical use and recommend new terminology for the disorder.
Edwards et. al. 2016	The biological challenge of M.E./cfs: A solvable problem	Fatigue: Biomedicine, Health & Behaviour. http://bit.ly/1QDv5A5	See comments below:
Suggests that three major categories of causal model appear of most interest for future M.E./cfs research: 1. The brain is responding normally and symptoms are due to persistent signal input from peripheral tissues, such as cytokines or metabolites, based on persistent immune dysregulation (as in autoimmunity, for example, or, conceivably, low-grade infection). 2. There is a persistent abnormality of 'housekeeping' processes in the brain, such as an increase in activation of microglia following an initial insult, which leads to distorted processing of peripheral signals including autonomic pathway activation. 3. There is a persistent abnormality in neural signalling in sensory pathways. This may be quantitative (comparable to dopamine depletion in Parkinson's disease) or qualitative (comparable to post-concussion amnesia or post-traumatic stress disorder) due to CNS structural or regulatory changes following an initial insult.			
Morris et. al. 2013	The Emerging Role of Autoimmunity in ME/cfs	Molecular neurobiology http://tinyurl.com/l6sycph	See comments below.
Low Natural Killer Cell function is a source of disrupted homeostasis and prolonged effector T cell survival. Low ATP production and mitochondrial dysfunction is a source of autoimmunity by inhibiting apoptotic and stimulating necrotic cell death pathways and hence decreasing immunosuppression at the termination of the immune response and increasing inflammation. Elevated levels of pro-inflammatory and other cytokine species conspire together to impair the normal homeostatic mechanisms which govern T and B cell activation differentiation and survival. This leads to an imbalance of regulatory and effector lymphocytes. Elevated O&NS damage lipids and proteins leading to the formation of neo-epitopes which become immunogenic leading to the disruption of many essential cellular processes. Elevated levels of NF-κB not only contribute to prolonged lymphocyte survival but also increase the generation of autoreactive B cells. Elevated levels of pro-inflammatory cytokines result in elevated levels of NO and leptin. Both entities lead to disruption of homeostatic mechanisms via interaction of mTOR. Elevated levels of NO lead to blockade of the methionine cycle and hypomethylation of DNA. Finally, increased levels of pro-inflammatory cytokines and NF-κB conspire to disrupt epithelial tight junctions in the intestine allowing the potential translocation of bacterial LPS into the general circulation.			