Review Article

A Proposed Mechanism for ME/CFS Invoking Macrophage FcγRI and Interferon Gamma

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Evidence bearing on possible mechanisms for the clinical syndrome of ME/CFS is reviewed. The evidence is used to argue for a hypothesis that centres on a form of persistent, inappropriate, 'neuroimmune hypervigilance' mediated primarily by T lymphocyte-macrophage interaction but influenced by IgG antibody binding to the gamma interferon-inducible high affinity immunoglobulin receptor FcγRI. This proposed mechanism could explain why the illness resembles post-infective T cell-mediated autoinflammatory syndromes in age of onset and time course but has a female preponderance similar to autoantibody-mediated disease.

> 'A little more T cells …'
>
> *Anon*

Introduction

ME/CFS (historically from myalgic encephalomyelitis/chronic fatigue syndrome) has been widely viewed as a useful clinical syndrome category since the proposed case definition based on Canadian Consensus Criteria in 2003[1][2]. It has, however, been difficult to find biological leads allowing identification of a common element of disease mechanism to justify the syndrome concept. Some remain sceptical about a specific mechanism, despite a range of suggestive findings in cardiorespiratory physiology and immune cell function and the appearance of a similar clinical picture following Covid-19 infection (see e.g. [3][4][5][6][7][8][9][10]).

There is hope that this situation will change if the DecodeME genome-wide association study (see [11][12]) reports significant genetic links to ME/CFS. The task will then be to interpret what we already know

about the illness in terms of roles for associated genes in common elements of mechanism.

The purpose of this review is to lay out what we consider current salient knowledge and to propose a synthesis focusing on a specific hypothetical mechanism involving the IgG receptor FcγRI. This is not the only hypothesis of interest to us, or others, but has the attraction of invoking specific signalling pathways that may be critical in at least a proportion of cases and might lead to empirical testing.

Clinical Background

The absence of identified structural or biochemical pathology in ME/CFS has meant that definition is based entirely on symptoms and their dynamics over time[1]. As a result, diagnostic ascertainment is a major problem. Prevalence rates are uncertain within as much as a fivefold range[13][12]. This impacts the interpretation of all research data. Nevertheless, some basic findings are agreed upon.

Onset and Course

ME/CFS is an acquired illness, with subjects healthy prior to onset, even if, rarely, that occurs under the age of 10. Whatever the genetic predisposition, *at least one further maturational, environmental, or internal stochastic event* must be involved. The likely domains for such events in ME/CFS are generally regarded as the adaptive immune and central nervous systems (reviewed in [14]), if only on the grounds of the complexity of regulatory disturbance indicated by the illness dynamics. The link to infection points to a role for the immune response, even if replicated findings are still limited[3][6][15][8]. Psychological approaches to central nervous processes have proven unhelpful (see [16]), but neurochemical events look likely to be involved, at least in terms of pain and autonomic disturbance.

Familial clustering has been reported, suggesting one or more genetic factors[17], although the confounding effect of diagnostic ascertainment makes it difficult to be sure even of the implications of twin studies[18]. Specific gene linkage studies should clarify the situation.

The relative importance of roles for genetic predisposition and subsequent internal stochastic or environmental events in conferring lifetime incidence is likely to vary between cases. As for lupus[19], some may be destined to develop ME/CFS at an early age purely from genetic make-up, and others may acquire the disease through encountering micro-organisms or through a series of chance events, for instance within the generation of antibody or T cell receptor diversity.

ME/CFS has a variable course. Spontaneous improvement or even resolution may occur, chiefly with onset before the age of 20[20]. Otherwise, it is a long-term fluctuating illness, in some cases with progressive deterioration. Adult-onset illness mostly never fully resolves. These patterns suggest that, once initiated, processes responsible for symptoms involve a *shift in a regulatory mechanism, open to ongoing feedback effects*, both positive and negative.

Age Profile

Despite a few cases of earlier onset, the incidence of ME/CFS rises steeply in the teenage years. This suggests that maturational factors play an important role. Both musculoskeletal growth and changes at puberty have been implicated in the initiation of other chronic diseases. The steep early rise recalls both seronegative spondyloarthropathies, which are likely T cell-mediated, and systemic lupus, which is autoantibody-mediated[21][22][23]. There is, therefore, reason to think ME/CFS might be influenced by maturational events affecting *either B or T cell expansion (whether as classical adaptive responses or, for some T cell subsets, driven primarily by innate signals).* Exposure to specific infections in the late teenage years (such as chlamydia and EBV) may skew things further, but both for spondyloarthropathies and ME/CFS, these are unlikely to be the whole story.

It is also conceivable that epigenetic changes affecting innate immune cells (e.g., macrophages) are relevant[24], but so far there is no clear precedent. Maturational changes in the nervous system might also be relevant (see later section).

In women, there is evidence for a second incidence peak in the late thirties for ME/CFS[25]. The implications are unclear, but this second peak is close to the peak for multiple sclerosis[26].

Incidence of ME/CFS does not continue to climb into old age, as it does in rheumatoid disease[27], which suggests that the time of onset does not simply reflect a life-long accumulation of stochastic immunological events, which may be implicated in familiar autoantibody-mediated diseases[28].

Female Predominance

Despite problems with diagnostic ascertainment, the prevalence of ME/CFS is consistently reported as between twice and four times greater in females than in males[12]. The rise in incidence in the teenage years is seen in both sexes, but there may be no second peak for males[25].

The best-known category with a sex incidence ratio of this sort is autoantibody-mediated disease, with ratios ranging from 3:1 (rheumatoid) to 9:1 (lupus)[27][23]. Female predominance is consistently seen for antibody-mediated processes in a way not often seen outside diseases of female organ systems such as the uterus or breast. Such ratios are not seen in T cell-mediated diseases like psoriasis or ankylosing spondylitis (where the ratio is reversed)[21].

Autoantibody-associated diseases also tend to be associated with MHC Class II alleles, and seronegative inflammatory disorders with MHC Class I alleles[29]. The evidence for linkage of ME/CFS to specific autoantibodies or MHC genes has so far been inconclusive, although one study suggested linkage to both Class I and Class II alleles[30].

Female predominance might possibly be linked to neurodevelopmental differences, but the background evidence here is less clear. None of the major psychiatric illnesses show the sort of female predominance shared by ME/CFS and autoantibody-mediated diseases.

Relation to Intracellular Infection

It is widely accepted that ME/CFS onset frequently follows infection with an intracellular pathogen, including viruses such as Epstein-Barr and the atypical bacterium *Coxiella burnetii*[31]. However, the role of immediately antecedent infection may be one of a non-specific and inconsistent trigger. Relatively short-term post-viral fatigue, lasting a matter of months, is also common for a number of infections, notably EBV, and diagnostic boundaries are uncertain. There is no clear time relation between infective illness and onset of ME/CFS, which may be immediate or delayed for weeks or months in patient reports. Furthermore, the symptoms of ME/CFS overlap with those of viral infection. As a result, there is not the stereotyped history of post-infective illness seen, for instance, in Reiter's syndrome, in which new symptoms appear several days after the acquisition of infection.

Nevertheless, onset of a persistent illness following an intracellular infection is, in theory, a pointer to a *T cell-mediated immune process*. Conventional CD8 T cells arising as a result of the infection might remain elevated long-term, potentially in an activated state contributing to symptoms. Additionally, innate cytotoxic cells such as NK cells and MAIT (mucosa-associated invariant T) cells might also be implicated. Changes in MAIT cell populations have been reported in ME/CFS[6][32]. Historically, changes in NK cell numbers and function have also been reported, but in both cases being reduced rather than increased, and findings have been difficult to replicate[3][33]. CD4 helper T cells are also expanded upon infection

and may fail to undergo normal homeostatic contraction in people with ME/CFS, potentially contributing to macrophage-mediated effects[32].

Post-infective T cell-mediated illness is well recognised. Moreover, the clinical presentation of post-infective T cell-mediated inflammatory disease appears to have more to do with T cell traffic domains (skin for psoriasis, mucosae for Reiter's, gut for inflammatory bowel disease, and 'general' ($\alpha 1\beta 4$ integrin traffic domain) for spondyloarthropathy (AS)) than with the distribution of tissue-specific antigens[22]. Although T cells are traditionally considered as mediating antigen-specific adaptive responses, it is increasingly recognised that T cell subsets are responsive to a range of innate signals, such as MAIT cells which respond to riboflavin and folic acid biosynthesis intermediates, derived from bacterial metabolism. (No evidence for reactivity to specific autoantigens has been identified in these syndromes.) In contrast, evidence for post-infective autoantibody-mediated disease is minimal, with the possible exception of Guillain-Barré syndrome[34]. Moreover, ME/CFS appears much the same following a range of intracellular infections. Antibody responses to a range of microbial antigens would not be expected to manifest as the same clinical syndrome; in autoantibody-mediated disease, different antibody specificities are reflected in different clinical syndromes.

In conclusion, the implication of ME/CFS incidence following intracellular infection remains uncertain, but there is a strong case for suspecting a change in sensitivity of T cell responses. ME/CFS does not localise to a specific T cell traffic domain; symptoms relate to both locomotor tissues and the gut, as well as higher mental function. It is, however, uncertain exactly where the pathology is located. At least some of the symptomatology may reflect cell interactions within the lymphoid tissue itself. The paradox is that a central role for T cells is *at odds with the female preponderance.*

Failure of Treatment with Rituximab

Following initial promising phase II trial data[35], a phase III clinical trial of the B cell-depleting agent rituximab was set up by Fluge and Mella[36] in ME/CFS patients. The result was clearly negative, despite reports of major improvement in individuals, presumed to be for other reasons.

Rituximab has shown major efficacy in a range of diseases associated with pathological B cell clonal expansion, both in typical autoantibody-associated diseases and in multiple sclerosis[37][38]. However, benefit in autoantibody-associated diseases is seen chiefly where autoantibody levels decline significantly over a 6-month period, presumably being derived from short-lived plasma cells[39][40].

Levels of antibodies to nucleoprotein antigens, for instance, fall less consistently. A failure of response to rituximab in ME/CFS is, therefore, chiefly evidence *against symptoms being driven either by autoantibodies derived from short-lived plasma cells or by direct B cell interactions.*

Nonetheless, difficulties remain when trying to implicate classical autoantibodies in ME/CFS. The lack of any clinical correlate to a specific organism makes tissue-specific molecular mimicry implausible, and the clinical picture does not suggest immune complex disease. No autoantibodies have been found with a difference from normals consistent with a major pathogenic role. An increase in levels of antibodies to G protein-coupled receptors has been reported[41] but the difference was modest, and a recent study screening for antibodies to a range of known protein self and viral antigens found no difference from healthy controls[42]. (Although this study highlights some interesting differences in antibody levels between males and females.)

What may be important, however, is that there appear to be no *universal* sets of rules for autoimmune and autoinflammatory disease dynamics. Both B and T cells may get caught up in processes in different ways in each disease – ranging from lupus through coeliac disease to Crohn's disease[28]. There remains at least one possible way to fit the pieces together.

B cells or T cells?

Female dominance in autoimmune disease suggests that both the possession of two X chromosomes and ongoing oestrogen levels alter the rules for B cell proliferation in a way that we do not fully understand[27], but likely to be of advantage in passing antibodies to a newborn child. 'Looser' rules may lead to a wider range of antibody affinities. The downside may be a higher risk of expanding autoimmune clones. That alteration may also broaden the spectrum of B cell clones that produce not classical autoantibodies but *antibodies with relatively low affinity for available antigens*, which do not mediate typical Type 2 or Type 3 hypersensitivity responses but may yet contribute indirectly to T cell (classically, 'Type 4') responses. We will return to this idea in the Synthesis section.

It is unlikely that a shift in B cell populations assists a pathological T cell-mediated process through antigen presentation by autoreactive B cells in ME/CFS because we would then expect rituximab to have reduced symptoms during many months of B cell depletion, and it did not[35]. Antibodies could, however, assist a T cell-mediated process by facilitating the uptake of antigen by *macrophages* with subsequent antigen presentation to T cells by those macrophages (discussed further below). Antibodies to several

self-antigens occur in chronic inflammation and after trauma and viral infections, perhaps bypassing some of the checkpoints of a full adaptive immune response. Such responses may not amount to pathogenic autoimmunity but nevertheless may have significant implications for the way tissues are cleared by macrophages (see Cambridge et al.[43]).

There is some limited evidence for general shifts in B cell populations and their behaviour in ME/CFS. The expression of CD24, a maturation marker, has been found to be altered with changes in mitochondrial energy sources[5]. There is also a report of shifts in Ig heavy chain variable region gene usage and IgM levels[7]. B cell metabolism has also been reported to be shifted[5][8]. This may reflect a more general shift in cellular metabolism, consistent with a 'vigilant' or 'conserving' state induced by other ongoing immune cell interactions. Further work in this area may bear fruit. Nevertheless, all these findings tend to point to a broad shift in B cell function rather than a single antigen-specific adaptive response.

Absence of Inflammation

ME/CFS does not involve inflammation as such. No tissues show swelling, heat, or redness, even if there is pain, and magnetic resonance imaging has not shown inflammatory oedema. One study suggested microglial activation in the brain[44], but that alone does not amount to inflammation, and the findings have not been replicated. Even the most subtle inflammatory changes in blood vessels lead to tissue oedema, and modern techniques are sensitive enough to establish that this is not present.

Absence of inflammation *does not, however, imply that immune signals often associated with inflammation are not operating*. Symptomatic benefit from corticosteroids suggests that symptoms may involve pathways used in inflammation, even if steroids have wide effects on gene expression and the benefits in ME/CFS appear short-lived and modest[45]. Many autoimmune disorders are not primarily inflammatory; antibodies can cause functional disturbance in other ways. Circulating cytokines can cause fever without inflammation. A rise in C-reactive protein can follow Kupffer cell activation in the liver without inflammation as such. Every disease context is a bit different.

C-reactive protein levels in ME/CFS are normal in most cases, but a recent study indicates that a few patients have slightly elevated levels and that the mean level is higher than in healthy controls[46]. This does not establish the presence of inflammation but does suggest that other immune signalling

mechanisms may be operating, including low-level production of interleukin-6 (driving C-reactive protein).

Terminology in this area is often confused, with loose reference to not just inflammation but 'neuroinflammation' and even 'hyperinflammation'. In our view, these terms are most often unhelpful or misleading. Testable theories of chronic disease mechanism need to be couched in terms of specific signalling aberrations, which may cut across normal patterns of response to injury.

Myalgia, not Arthralgia

Pain is a common, but variable, feature of ME/CFS. Ramsay's[47] description of 'chronic ME' focused on myalgia. It is not clear exactly where pain is localised – it tends to be widespread and diffuse, as in 'fibromyalgia' – but if it localises anywhere, it is in or around muscle. People with ME/CFS may coincidentally have joint problems, but there is little indication that ME/CFS itself involves synovitis of the sort seen in rheumatoid or lupus.

Diffuse symptoms with a lack of overt inflammation may be a clue to likely mediators. TNF has a dominant role in synovial disease[48]. Interleukin-1 may similarly be a dominant signal for skin,[49] which is also not typically affected in ME/CFS. Myalgia without inflammation is consistent with roles for factors such as eicosanoids or *interferons*, typical of the response to viral infection, which similarly includes myalgia without inflammation.

Such mediators may be released locally in muscle but may also act systemically, being produced elsewhere. It is tempting to invoke T cell interaction with macrophages within muscle, but as already noted, the focus on muscle may be something of a distraction. Even if generated locally, interferons on their own may be adapted to mediating a 'tidy' process of removing defective or infected cells by apoptosis, with minimal inflammatory signs. Cytokines such as TNF may be more relevant to the killing of bacteria in a purulent or granulomatous response. Reports of systemic cytokine levels in ME/CFS have been inconsistent, but one relatively recent study found raised serum levels of gamma interferon and transforming growth factor beta but not TNF, IL-6, or IL-1[15].

Pathological changes have been reported in skeletal muscle biopsies following exercise in patients with Long Covid[50] with a clinical picture similar to ME/CFS. It would be valuable to have confirmation of these findings, perhaps using non-invasive methods such as magnetic resonance imaging or creatine kinase levels. It may be that muscle does develop overt inflammatory change after exercise, at least in

Long Covid, although historic studies of ME/CFS failed to show significant inflammatory change, and Nacul et al.[51] reported low creatine kinase levels in ME/CFS.

The cytokine most consistently found to be elevated in ME/CFS is transforming growth factor beta[15], although even here, findings are variable. TGFβ binds to fibrils in connective tissues throughout the body, including synovium, ligament, and perimysium in muscle[52]. Other immunomodulatory proteins are also found adsorbed on to fibrillar proteins, including complement decay acceleration factor and a form of FcγRIII, in different combinations in different tissues[53]. One possibility is that the process responsible for generalised symptoms in ME/CFS involves signals that are facilitated in muscle, and/or associated fibrous tissue, by matrix-bound regulatory proteins, with sensitisation of nerve fibres involved in the perception of pain and 'fatigue' without other overt features of inflammation.

Inasmuch as such characterisations are helpful, TGF-beta is regarded as largely anti-inflammatory[54]. In the context of ME/CFS, TGF-beta seems most likely to be a systemic modulating influence responding to local activation events. Systemic levels might explain reports of low natural killer cell activity[3]. *TGFβ may play a role in ensuring that local signalling does not activate overt inflammatory pathways. GDF15, another member of the TGF beta family, has also been reported as raised in ME/CFS and may be similarly relevant*[55].

Evidence for Nervous System Involvement

All the clinical features of ME/CFS could be due to signals coming from non-neural tissues affected by immune processes. No consistent macroscopic or microscopic structural changes have been found in the brain, and despite problems with mental tasks known as 'brain fog', there is no evidence for deterioration in intelligence, or sensory or motor abilities attributable to brain damage, of the sort seen in stroke, multiple sclerosis, or dementia. Nevertheless, there are several possible pointers to involvement of neurons in the underlying mechanism of the illness. Plasticity in neuronal synaptic connections over time might contribute to persistent symptoms and would probably not be detectable with current imaging methods.

An ME/CFS-like illness has been reported after exposure to acetylcholinesterase inhibitors. Acetylcholine is an important neurotransmitter both for the brain and peripheral nerves. Antibodies to muscarinic acetylcholine receptors have been reported in ME/CFS, although probably not at a level to suggest they cause symptoms[41]. ME/CFS is associated with symptoms such as orthostatic intolerance suggestive of

autonomic nervous changes. All these findings are suggestive of cholinergic nerve involvement, but inconclusive.

The brain is largely isolated from immune cell interactions by the blood-brain barrier. Yet, people with ME/CFS often report a deterioration in symptoms, which is typically delayed and often prolonged, following mental as well as physical exertion (post-exertional malaise). It is not known exactly how neuronal activity in the brain could trigger immune signalling, even if there was an increase in metabolic activity. On the other hand, aggravation of symptoms following mental effort may equally be part of the symptom picture of infections like influenza, and it may be that no additional neural signalling problem needs to be invoked. Mental activity may amplify adverse afferent autonomic or cytokine signals through purely central neural pathways.

Another factor that might suggest a problem with neural 'housekeeping' is the common occurrence of disturbances in sleep patterns in ME/CFS, with sleep typically being described as 'unrefreshing'[1]. Sleep may play an important role in updating synaptic connections in a useful way from day to day. A possible hint that there may be a shift in 'synaptic housekeeping' in ME/CFS is the shift seen in certain complement factors in a cohort of ME/CFS patients[46], complement being implicated in synaptic plasticity.

The evidence for long-term epigenetic or 'learnt' neuroplastic change in ME/CFS remains at present inconclusive, but it is possible that it could contribute to the difference between the common resolving 'post-viral fatigue syndrome' seen after infections like EBV and the persistent disabling illness of ME/CFS, perhaps because of genetic susceptibility. This might also be relevant to the finding that cytokine and lymphocyte population shifts in ME/CFS appear to be more pronounced in the first 3-5 years after onset compared to the longer-term situation[56][5].

A recent preliminary communication on whole genome sequencing in ME/CFS[57] notes that genes flagged up for this condition have also been linked to autism spectrum disorder. The age of onset and sex ratio (M:F 2-4:1) for autism differ from ME/CFS, but it is conceivable that the same pathways might be caught up in different regulatory errors.

The synthesis below suggests that ME/CFS is one of a range of 'immune hypervigilance' states. In this context, we cannot rule out the possibility that the higher rate of diagnosis of ME/CFS in women is in part due to a greater 'health vigilance' in women – of central nervous origin. Nevertheless, it is hard to argue

that this alters arguments about pathogenesis significantly, and there are many aspects that it would not explain.

Synthesis

There follows a speculative proposal for how the information reviewed above might fit into a plausible mechanism for ME/CFS. One option would be simply to say that the clues all point to T cells and neurons, perhaps mediated by T cell cytokines such as gamma interferon. However, we think that the female predominance deserves careful thought and may be a clue to a more complex story.

The easiest explanation for the female predominance in ME/CFS is that, as with autoimmune diseases, it reflects a 'looser' control over B cell clonal expansion and the generation of antibody diversity in females, with risks in terms of disease. In classical autoimmune diseases, specific autoantibodies undergo affinity maturation and can cause symptoms directly by, e.g., forming immune complexes capable of ligating receptors for IgG Fc or binding to tissue-specific antigens or blood cells.

Different IgG allotypes selectively interact with different Fc receptors, which fall into three classes: FcγRI, -RII, and -RIII, each expressed on different subsets of leucocytes. FcγRII and -RIII only bind IgG when complexed with antigen. Both activating and inhibitory forms exist, signalling either directly or through G-protein coupling. In the case of the gamma-interferon inducible FcγRI, however, un-complexed IgG can bind and mediate endocytosis or cytotoxicity against virus-infected cells.

Two of us have previously suggested[28] that in rheumatoid arthritis, certain IgG antibodies have a pathogenic effector role through binding interactions that can evade complement activation yet cross-link FcγRIIIa. FcγRIIIa appears to act as an 'early warning alarm system' present in specific tissues such as synovium and serosa, adapted to picking up small immune complexes. We suggest here, for ME/CFS, that there may be another subset of IgG antibodies that can contribute to inappropriate T cell activation through interactions that occur in the context of binding to FcγRI, but not in other contexts that mediate tissue damage, or deletion, or further affinity maturation of their parent B cell clones. The suggestion is that FcγRI may fulfil (amongst other things) something more like a 'nightwatchman's round' role once an immune response has been triggered, designed to maintain a focus of attention on sites where residual pathogen needs to be eradicated for what may be an extended period, perhaps especially relevant to viruses with an ability to persist, such as the *Herpes* family.

We suggest that in ME/CFS, antibodies with relatively low affinity for antigens available on an ongoing basis *contribute to disease indirectly by being taken up, together with such antigens, by high-affinity FcγRI on gamma interferon-primed macrophages and thereby facilitating presentation of antigen to T cells*[58]. Both CD4 and CD8 T cells might thus be activated, the latter via cross-presentation of antigen on MHC Class I. These antibodies may have high affinity for previously encountered microbes and may have undergone affinity maturation in some past immune response but are relevant because they bind with relatively low affinity to what might be called 'everyday junk' antigens that may include antigens derived from gut flora, low-level persistent viruses such as *Herpes*, partially degraded self proteins with post-translational modifications, or possibly normal host signal pathway proteins, such as heat shock proteins and proteasome components, upregulated during immune responses.

B cell clones producing these antibodies may be debarred from progressing to full affinity maturation with respect to ongoing available antigen but may be produced by long-lived plasma cells that generate a persistent background antibody level over years. Generation of these 'unhelpful' antibodies may in some cases reflect atypical supplementary survival signals, perhaps from VH framework region interactions, invariant T cell receptor interactions, or Toll-like receptor interactions. For instance, there has been a report of raised levels of antibodies to bacterial flagellar proteins in ME/CFS, and many flagellar proteins bind TLR-5[59]. Some of these antibodies might fulfil a 'broadly neutralising' role, with the capacity to bind a range of variants of dominant microbial antigens, and which might arise more extensively in a female repertoire.

It could be argued that high-affinity antibodies would fit the suggested role just as well or better. However, for antigens to which high-affinity antibody is present, soluble antibody should bind and mediate cytotoxicity or clearance through complement and complement receptor 1 or FcγRIIIa binding. Similarly, if antibodies showed high-affinity autoreactivity, either their parent B cell clones should be deleted by regulatory cytotoxic cells, or their specificity should be clinically apparent. A caveat to this argument would be that high-affinity antibodies to persistent viruses, such as *Herpes* , might mediate local control of residual infection through FcγRI-dependent macrophage-T cell interaction, but the case for female predominance might be harder to make. Certainly, the evidence for high-affinity autoantibodies seems weak, but antibodies with high affinity for a virus might have a low affinity for self-components that is only apparent in the context of binding to FcγRI.

T cell responses to peptide antigens are very dependent on contextual signals, and T cells will show apparent 'autoreactivity' even in the absence of autoimmune disease. The relevant T cells may, therefore,

also be recognising peptides from similar common 'junk' antigens or perhaps with invariant receptors, as for MAIT cells. They would respond to macrophages that had internalised antigen via FcγRI and presented it together with MHC Class II (or MR1 in the case of MAIT cells) by generating gamma interferon, providing a positive feedback loop with further Fc-gamma-RI expression. Such a loop might normally serve as a localising, more than an amplification, function – concentrating interacting macrophages and T cells to certain tissue domains – but become persistent in the context of a particular combination of risk factors. Of interest, a recent study of 'Long Covid' cases found increased interferon gamma production from peripheral blood CD8 T cells, dependent on antigen presentation by macrophages[60].

Gamma interferon might not be the only candidate T cell signal, but its relation to FcγRI expression would make it attractive. Gamma interferon also contributes both to MHC Class II expression and to B cell follicle development and maintenance, which might also be relevant to continued antibody production. Further, gamma interferon directly affects the metabolic function of a wide variety of cells, including bystander macrophages and immune cells, as well as skeletal and smooth muscle cells, altering their function and likely contributing to the widespread symptoms in ME/CFS.

As in acute viral infections such as influenza, this immune cell activation would sensitise nerves to pain and fatigue sensations without producing overt inflammation. Nerve sensitisation might be mediated by soluble circulating signals but might be amplified in muscle after exertion by macrophages and CD8 T cells recruited as part of normal tissue patrolling events involved in the repair of daily microdamage. Such an amplification would provide an explanation for at least some forms of post-exertional malaise, typically delayed by several hours after active exertion. In the absence of any specific new foreign antigen, further cell interactions in lymphoid tissue, such as new clonal expansions, might not occur (as explained above). Cell populations in circulation might, in this context, show an 'exhausted' phenotype[61] but this need not imply the persistence of a triggering micro-organism or autoimmune response.

The key question in the above scenario is why this process should produce seriously disabling symptoms in ~0.5% of people – those with ME/CFS - and not everyone else. Recent activation of the immune system by an infection, including anamnestic responses, might be enough to trigger the process - especially with EBV, which leads to generalised B cell activation for a period of days or weeks. Triggering might be temporary, as in the short-lived 'post-viral fatigue syndrome'. Susceptibility alleles in genes coding for relevant signalling proteins might raise the lifetime risk of the process persisting to quite a high level in

some individuals. Nevertheless, something more specific to differentiate those who develop persistent ME/CFS from the healthy population would make the story more plausible. Viral infection is a common occurrence, but the onset of ME/CFS is not. Looser control of B cell clonal selection might explain a female predominance, but the early age of onset in ME/CFS as compared to most autoimmune diseases suggests that antibody diversity may play a background 'permissive' role rather than specific clonal expansions determining disease onset. The onset looks more in keeping with a shift in T cell clonality.

(An interesting caveat to the implication of antibody diversity in female predominance is the possibility that this diversity reflects a more general sensitivity of certain cell types to gamma interferon (which is involved in B cell follicle development) in women. This would allow a model to be built entirely on T cell mechanisms! There is no obvious pointer to this in other diseases, but it cannot be ruled out[62].)

The conditions that might be most closely analogous are the seronegative autoinflammatory diseases, including psoriasis, Reiter's syndrome, ankylosing spondylitis, other MHC Class-I associated seronegative arthropathies[21] and Crohn's disease. Detailed mechanisms are not known for any of these, but it seems likely that the expansion of memory T cell clones is important, although with different relations to infection, growth, and maturation, and perhaps diet. There might also be an analogy with the familial fevers in which inflammatory control mechanisms are defective, but the long-term persistence of ME/CFS on the background of previous good health would fit most easily with an acquired T cell clonal shift that might arise from a chance combination of B and T cell receptor selection that allowed evasion of normal control signals. The relatively early age of peak incidence suggests that T cell receptor selection may be crucial since the thymus involutes in later years.

The proposed model suggests that ME/CFS, along with seronegative autoinflammatory states like psoriasis and familial febrile syndromes, can be seen as 'hypervigilance' immune states that may be precipitated by specific infections but probably persist through mechanisms that have little to do with adaptive immune responses to any single foreign or self antigen. In the case of ME/CFS, the hypervigilance presents as exhaustion and pain rather than inflammation, probably because of different signals being involved, perhaps predominantly gamma interferon interacting with nerve endings. This signalling remains 'hidden' either because it fails to produce vascular responses in target tissues in one or other T cell trafficking domain or because it remains confined to the lymphoid tissue itself.

On a broader front, it may be legitimate to see all these chronic disease states – autoimmunity, autoinflammatory states, familial fever syndromes, and ME/CFS – as each feeding off built-in risks associated with positive feedback (as in B cell clonal expansion), autocatalytic (as in coagulation and

complement cascades), or 'focussing' (as in leucocyte chemotaxis) mechanisms that can get out of control but are still ultimately sensitive to some overriding homeostatic controls. In each case, different genetic, maturational, environmental, or internal stochastic factors may trigger illness, each with rather different rules of engagement depending on the dynamics of different immune pathways, each with different 'Achilles' heels'. Phair[63] has suggested a not dissimilar model for ME/CFS based on a positive feedback loop involving the itaconate shunt pathway and alpha interferon.

When exploring tissue effector mechanisms in chronic inflammatory disease in the 1990s[28][22] it became clear how much was not known about the roles of tissue domain-specific immune microenvironments and how important they might be. ME/CFS highlights the fact that we still do not know that much about the mechanism of the 'malaise' of acute infection, mimicked by symptoms in ME/CFS. What signals generate myalgia, and where are they produced? Although evidence for shifts in energy metabolism pathways has accumulated, this is unlikely to be directly responsible for reduced muscle power through the unavailability of energy-dependent pathways[42]. It may, nevertheless, via associated inhibitory sensory signals, make an important contribution to disability.

Moreover, it has become clear in the last few decades that the simple division between 'innate' immunity and the B and CD4/CD8 T cell 'adaptive' arms no longer holds. Not only do 'innate' natural killer cells make use of antibodies, but there are also a range of T and related lymphocyte populations such as MAIT cells, NKT cells, and innate lymphoid cells, each with slightly different but overlapping roles for different contexts in different tissues. Each cell type has a different signal output in terms of cytokines. Different interactions may suit early warning, cell lysis, antigen eradication, systemic behavioural shifts (myalgia), and repair. Some lymphocytes traffic to specific tissues. Others may normally spend their lives entirely within lymphoid organs, having no local role in inflammation (including B cells).

ME/CFS may have wrong-footed us because it does not follow the textbook account of inflammatory disease. Signalling mechanisms operate invisibly in unknown compartments. In the past, that led people to abandon interest in immune mechanisms in ME/CFS, but we now know enough to see that it may not be so surprising.

In at least a proportion of cases, ME/CFS may involve further acquired hypervigilance signalling within the nervous system itself. Persistent fatigue, including perhaps that seen for several months after EBV infection, may involve shifts in synaptic connections that amplify warning signals as part of a 'convalescence' defence mechanism. Whether or not shifts in neural signalling can also feed back on to

the immune cell interactions as described above is much more speculative but not impossible. T cells can carry both muscarinic acetylcholine receptors and beta1 adrenergic receptors[64].

A neural hypervigilance state of this sort might provide the basis for what is often called 'dysautonomia', with features such as postural tachycardia[1] in people with ME/CFS. Unlike other forms of dysautonomia, there is no indication of a failure of autonomic neuronal capacities, but rather an apparent over-readiness to respond, as for tachycardia on standing in the presence of a maintained systolic blood pressure.

Implications for Treatment

The proposed mechanism for ME/CFS raises several possible options for treatment. All present potential risks in terms of blocking important immune vigilance mechanisms but probably no more than many immunomodulatory treatments currently in use. The main targets implicated are persistent low-affinity IgG antibody populations, FcγRI expression on macrophages, local gamma interferon release (perhaps other cytokines without direct inflammatory actions), and T cell activation or clonal expansion.

B cell depletion with rituximab or more recent B cell-targeting monoclonals has proved useful in reducing levels of antibodies produced by short-lived plasma cells. The disappointment has been that in almost all autoimmune diseases, the return of B cells is followed, immediately or after a delay, by re-engagement of B cell lineage expansion and the return of autoantibodies. Reducing levels of low-affinity antibodies produced by long-term plasma cells presents a rather different task and may be best achieved using plasma cell-targeting monoclonals such as anti-CD38, perhaps in combination with small molecule agents capable of reducing IgG levels such as mycophenolate or bortezomib. To date, the effectiveness and safety of such a strategy for IgG reduction remain uncertain. On the other hand, if the antibodies being targeted are not the result of the sort of positive feedback loop seen in the production of a typical high-affinity antibody response, there may be reasons to be more optimistic that similar antibody populations will not immediately return. It is conceivable that the improvements in ME/CFS anecdotally reported following intensive chemotherapy that motivated the trial of rituximab[35] reflected a useful reduction of IgG populations capable of contributing to ME/CFS.

Displacement of endogenous IgG from binding FcγRI, particularly on an easily reversible basis with a competitive inhibitor with a short half-life, might be an interesting strategy to investigate. Intravenous immunoglobulin therapy might produce some benefit in this way but is cumbersome and expensive. We are not aware of other available agents as yet. Blockade of the production or interaction of gamma

interferon from T cells might similarly be a practical strategy. Monoclonal antibody-based agents are likely to have the disadvantage of having relatively long half-lives, with effects not being easily reversible should concern about infection arise.

Targeting T cell populations, particularly those expected to provide protection from viral infection, has been met with little enthusiasm in the context of other T cell-mediated conditions. Long-term T cell depletion with anti-CD52 proved to be associated with relatively little morbidity in trials for rheumatoid disease, but a more subtle approach targeting T cell signalling probably remains a more attractive option, perhaps through the JAK/STAT pathway.

Until recently, treatment for ME/CFS has tended to focus on rehabilitative programs that encourage patients to undertake physical exertion of the sort that triggers symptoms. It is now clear that this approach not only has no valid theoretical basis but produces no useful benefit and often leaves patients more unwell[16][65]. If activity triggers non-specific immune signals that fuel further macrophage-T cell interaction, this is hardly surprising.

Conclusion

We suggest that the available evidence relating to ME/CFS points to a role for both antibodies and T cells in a form of 'hypervigilant' immune activation in which both FcγRI and gamma interferon may have a central place. This may be compounded by changes in neural signalling patterns, although this is less clear. The involvement of specific B or T cell receptor species or affinities for particular antigens may vary from individual to individual, as may the relative importance of genetic susceptibility and acquired events. As yet, there is probably not enough evidence to justify therapeutic studies with potentially toxic agents, but the strength of the evidence may change with new data from genetic studies. Anecdotal evidence of improvement in ME/CFS following the use of relevant therapeutic agents for other co-incidental conditions might also provide useful motivation for specific clinical trials.

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