

Immune System Gone Haywire?

Some of the most vigorous research efforts to date have been dedicated to studying immune dysfunction in CFS patients. While researchers increasingly question



a disease model for chronic fatigue syndrome that focuses exclusively on the immune system, there are numerous findings to implicate immune abnormalities in the pathogenesis or maintenance of CFS.

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The immune system has been a source of interest and study in CFS since the illness was first defined in 1988. Early studies demonstrated activation of certain parts of the immune system, suggesting the body's response to an acute intruder. Other studies showed parts of the immune system were depressed. The literature presents a complex and often confusing picture. Patterns of immune dysregulation are neither dramatic nor consistent between CFS patients, or even within the same patient over time.

Dr. Komaroff has mentioned some immune abnormalities in CFS in the previous article, so here we'll cover only six prominent findings from the past 18 years of research:

- 1 impaired function of natural killer cells¹
- 2 increased numbers of destructive T cells and increased percentage of T cells expressing activation markers²
- 3 activation of several proinflammatory cytokines³
- 4 dysregulation of the 2'5'A RNase L antiviral pathway⁴
- 5 predominance of Th-2 cellular immunity²
- 6 differential expression of gene markers whose products cause T cell activation⁵

Exploring key findings

We don't yet know whether these six characteristics represent cause or effect and what the role of the immune system is in the pathogenesis of CFS. However, the findings are both important and intriguing, and we'll explore them further here.

1 Natural killer (NK) cells mount a primary defense against foreign invaders. Multiple studies have shown that in chronic fatigue syndrome, NK cells are in short supply and are weakened in their response to infection or cancerous cells. One study showed that intracellular perforin, an NK-cell lytic protein, is reduced in CFS patients.⁶ Reactivation of Epstein-Barr and other herpesviruses seen in CFS may be secondary to the reduced cytotoxicity of NK cells.⁷ NK cell function has been used as an outcome measure in treatment studies of Imunovir, Ampligen and interferon-alpha with some positive changes measured.



ON THE FRONTIER

Some Infections Trigger CFS in 10% of Cases

One of the central questions in CFS research over the past two decades has been whether or not CFS is caused by an infectious agent or trigger. The question arose because a substantial proportion of individuals with chronic fatigue syndrome report that the illness began suddenly, often in conjunction with a likely infection since the onset was associated with fever and constitutional symptoms.

Postinfective fatigue states have a long history in medicine and have been linked to a diverse spectrum of infections in retrospective studies (those looking at outcomes well after the initial infection). For example, protracted fatigue has been reported in retrospective studies associated with brucellosis (a bacterial infection acquired from livestock), infectious mononucleosis (caused by Epstein-Barr virus), Lyme disease (due to infection with the tick-borne bacterium *Borrelia burgdorferi*), Q fever (caused by a bacterium caught from livestock, *Coxiella burnetii*), parvovirus (a common cause of rash and fever in childhood), Ross River virus (a mosquito-borne infection found in countries around the Pacific rim) and viral meningitis (most commonly caused by enteroviral infection). Although such reports may well be valid and imply that the infection was the trigger for the subsequent fatiguing illness, this attribution should be made with caution because, unless well-documented, the recollection of the initial symptom complex is subject to recall bias, with the details clouded by the subsequent illness experience.

The ideal scientific approach is to collect information prospectively, that is from the time of onset of acute infection. Data available from such prospective cohort studies gathered over the last decade indicate that certain infections do indeed act as a trigger for CFS, whereas common nonspecific viral infections don't. A large prospective cohort study conducted in general practice in the UK by Simon Wessely found that people presenting with minor symptomatic infections such as common colds weren't more likely to subsequently report chronic fatigue than those presenting to the general practice for reasons unrelated to apparent infection. By contrast, prospective cohort studies (conducted by Peter White in the UK, by Dedra Buchwald in the United States and by me in Australia) following individuals with confirmed Epstein-Barr virus infection have documented the development of CFS in approximately one in 10 individuals when assessed six months after onset. In addition, the Australian study has confirmed that both Q fever and Ross River virus infections also trigger CFS at the same 10% rate.

Both the UK and Australian studies have shown that the development of CFS is independent of psychiatric disorder, and that severity of the acute illness is a key predictor of the subsequent development of CFS. The Australian study also found that neither ongoing infection nor ongoing production of cytokines—immunological hormones—are associated with CFS following infection.

Further longitudinal studies in such cohorts will provide the best opportunity to unravel the complex disease mechanisms underlying CFS.



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2 Destructive T cells that directly attack tumor cells, viruses and other invaders are present in increased numbers in the immune system of CFS patients, most consistently those who report an acute onset of the syndrome. Another finding consistent with immune activation is the increased expression of cell surface markers CD38, CD28, CD26 and HLA-DR in CFS patients compared to healthy controls. The reports of several groups who measured such abnormalities suggest that among CFS patients, the degree of cellular immune activation is associated with the severity of CFS-related physical symptoms, cognitive complaints and perceived illness burden.⁸

3 Numerous research groups have measured elevations of multiple cytokines including tumor necrosis factor-alpha (TNF-a), interleukin-1 alpha (IL-1a), interleukin-1 beta (IL-1b), IL-2, IL-4, IL-5, IL-6, IL-10 and tumor necrosis factor-beta (TNF-b). Although studies have demonstrated widely varying levels of these cytokines in CFS patients compared to healthy controls, it's difficult to directly compare results because of differing study methods and case selection criteria. Regardless, elevated levels of these cytokines are known to produce fatigue, muscle pain, fever, sleep disturbance and slowed cognition in other illness states, all of which are characteristic of CFS. Certain of these cytokines have powerful inflammatory effects and act on the endocrine system as well. A preliminary report of a pilot study of etanercept, an agent that blocks the action of TNF-b, showed promise in decreasing the occurrence and severity of fatigue, muscle pain, headache and lymph node pain in CFS.⁹

4 Three independent groups studying the interferon-inducible antiviral RNase L pathway have documented activation of this pathway in CFS.^{10,11} Two of these groups have reported finding a lower molecular weight form of the RNase L protein in CFS patients compared to healthy controls or patients with either fibromyalgia or depression. Further, the higher the level of the smaller form of RNase L, the more severe the patient's overall disability, cognitive impairment and exercise intolerance. In fact, the most severely ill CFS patients have almost none of the normal form of RNase L.¹²

5 Healthy immune systems are balanced by two ongoing processes: cellular immunity and humoral immunity. Cellular immune processes are based on the action of T-helper-2 (Th-2) cells that produce

Does Chronic Inflammation Cause Disease?

Inflammation has suddenly become one of the hottest areas of medical research. That's because there's mounting evidence that chronic inflammation may play a huge role in the development of some cancers, heart disease, Alzheimer's and other diseases.

Usually, inflammation is the body's way of fending off disease-causing viruses and bacteria and of healing damaged tissue at the site of an injury. But when the process goes awry and the immune system doesn't subside, inflammation can become chronic, and permanent damage can occur. It now appears that this breakdown in the body's complex checks and balances regulating the immune system can trigger a host of diseases.

For instance, doctors once believed heart attacks were primarily a plumbing problem, with fatty deposits called plaques building up on the inside of major coronary arteries until they shut off the blood supply to part of the heart. High LDL levels ("bad" cholesterol) were cited as the biggest risk factor for heart attacks because they cause these plaques. Then, in the 1990s, Dr. Paul Ridker, a cardiologist at Brigham and Women's Hospital, came up with a groundbreaking new theory. Because half of all heart attacks occur in people with normal cholesterol levels, and many of the plaques found weren't very large, he speculated that something else—an inflammatory reaction—was causing those plaque deposits to burst, triggering a heart attack. Turns out he was right. Even slightly elevated inflammatory levels, as measured by C-reactive protein levels, can triple your risk of heart disease.

Autoimmune disorders like rheumatoid arthritis, multiple sclerosis and lupus, in which the body's immunological defenses mistakenly attack healthy cells, are being studied to determine the precise link with chronic inflammation. Illnesses like CFS and FM, with their documented immune irregularities, also merit further study to determine what role chronic inflammation may play.

antibodies and certain cytokines to fight infections. Humoral immunity, a Th-1-based process, activates the killing power of macrophages and natural killer cells to control viruses, bacteria and other foreign invaders. In CFS, there is a shift toward Th-2 predominance, as evidenced by the elevated levels of Th-2 cytokines described earlier. In CFS there is also frequent reactivation of latent viruses, another sign of dysfunction of humoral immunity. Based on an immunotherapy effective in patients with a similar immunity shift due to HIV infection, investigators conducted a pilot study of CFS patients with acute illness onset and evidence of immune dysfunction. Lymph nodes were extracted and cells from them were expanded in culture using anti-CD3

Stress Activates Inflammation in CFS

Patients suffering with chronic fatigue syndrome have reason to draw hope from recent advances in our knowledge of ways in which stress and immune system interactions may be relevant to managing this disabling condition. We have known for many years that stress, especially when chronic, can make people sick, tired and depressed. But only in the last decade has it become clear that stress does this, at least in part, by activating the same inflammatory pathways that protect us against bacteria and viruses, but that also contribute to a number of particularly modern maladies, including cardiovascular disease, obesity, stroke and Alzheimer's disease.

Inflammatory molecules, known as cytokines, are potent inducers of fatigue. Not surprisingly, some studies find that inflammatory cytokines are elevated in CFS. While the sources of inflammatory activity in CFS are unclear, we would do well to abandon old mind-body dichotomies, given overwhelming recent evidence that psychological stress activates inflammation. Indeed, increased proinflammatory cytokines have been seen in a variety of stressful situations ranging from participation in a laboratory speaking task to taking final examinations to caring for a loved one with dementia. And many people with major depression, a condition characterized by stress system hyperactivity, also appear to be mildly to moderately inflamed, even when otherwise medically healthy. Other factors that contribute to increased inflammation in the modern world include sleep loss, diets low in omega-3 fatty acids and obesity.

These findings suggest that lifestyle choices aimed at reducing inflammatory activity might well be of benefit for symptom management in CFS.



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and IL-2 to improve cytotoxicity. The cells were then reinfused to the donor. Of 11 test patients, nine showed demonstrable shift to Th-1 predominance and experienced significant lasting improvements in cognition and other CFS symptoms.¹³ One of the most exciting observations in the recent past has been one group's report of aberrant cytotoxic activity among 25 CFS subjects who demonstrate a differential expression of at least 35 gene sequences compared to matched normal controls.⁵ The identity of the protein products of these genes—one a neuropeptide target esterase and the other a eukaryotic translator initiating factor—suggests links to organophosphate exposure and a defect in combating viral infections, respectively.

This study is currently being expanded to 1,000 subjects, and other groups, including the CDC, are pursuing similar methods to identify unique patterns of gene and protein expression in CFS. (See page 26.)

A multidisciplinary approach

In assessing the role of the immune system in CFS, it's important to consider that the immune system is in constant communication with other body systems also shown to be impaired in CFS. Feedback between these body systems adds further complexity to understanding the pathophysiology of CFS.

For instance, low levels of corticotrophin-releasing hormone (CRH) observed among a subset of CFS patients in turn allow for a heightened cytotoxic T cell response that promotes the uncontrolled production of autoimmune markers. Levels of IL-1 are often high, and together with diminished amounts of CRH, may contribute to abnormal sleep patterns. The impact of low circulating levels of glucocorticoids may diminish production of IL-10 and IL-12, robbing the body of beneficial immunomodulatory effects.

Stress is known to affect both immune activity and neuroendocrine response in CFS. A 1995 study of CFS patients living in the area affected by Hurricane Andrew showed persisting alterations in NK cell cytotoxicity, elevated levels of circulating cytokines (compared to prestorm values) and significantly greater symptom levels compared to CFS patients living in an adjacent area not affected by the hurricane.^{14,15} Stress has also been shown to reactivate latent herpesviruses in CFS patients.⁷ The effect of depression and other mood disorders on immune and neuroendocrine function in CFS must be considered as well. Cognitive behavioral therapy has been shown to improve CFS patients' coping mechanisms and is proposed to have a modulating effect on the immune system as well.¹⁶ Optimism and positive social support were associated with less elevation in TNF- α levels among victims of Hurricane Andrew.¹⁵

The immune system serves many important functions in helping the body adapt to its environment and maintain homeostasis. As research sorts out the nature and ultimate impact of immune system dysfunction in CFS, we are sure to gain a greater appreciation for the dynamic immune responses and actions that occur at the molecular, cellular and global level in human physiology. ■

Can Lyme Disease Lead to CFS?

Researchers have discovered that some infections, like Epstein Barr virus and Ross River virus, lead to CFS in 10% of people who contract these illnesses (see page 29). Recent studies suggest that Lyme disease, caused by a spiral-shaped bacteria called *Borrelia burgdorferi*, is among the infections that can trigger CFS in a small percentage of patients, and clinicians on the front lines are seeing cases of Lyme that become chronic and lead to CFS-like symptoms.

The symptoms of chronic Lyme disease are remarkably similar to CFS and FM. These overlapping symptoms—crushing fatigue, flu-like illness, muscle and joint aches, severe headaches, pain or weakness in the limbs and cognitive dysfunction—make it difficult to distinguish between the illnesses.

According to Dr. Joseph Jemsek, an infectious disease and Lyme specialist, the existence of chronic Lyme, and the notion that Lyme infection may trigger CFS in some patients, are still very controversial. "We're at a primitive state as far as the clinical science is concerned," he says. "It's a matter of having scientific evidence to prove chronic Lyme's existence, but unfortunately we don't have that right now."

In spite of skepticism in some circles, Jemsek says, "I am convinced that the *Borrelia burgdorferi* bacteria that cause Lyme disease can persist and cause chronic or recurrent symptoms. I also believe that chronic Lyme is the ringleader in many other illnesses, especially when symptoms of immune dysregulation exist."



CFS or CFIDS?

Abnormalities found in the immune system in the late 1980s, although subtle and inconsistent, were sufficient to spark debate about renaming chronic fatigue syndrome (CFS) chronic fatigue and immune dysfunction syndrome (CFIDS) or chronic immune activation syndrome. While the scientific and medical community continued to use the label CFS, many patient-based organizations adopted the term CFIDS to reflect a condition more complex and serious than the fatigue label alone suggested.

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