ME/CFS

Immunological Abnormalities

Metabolic Disturbances

Sex-specific Differences

Prior Infections

Epstein-Barr virus 11% develop ME/CFS symptoms
Ross River virus
Coxiella burnetti

SARS 50% develop ME/CFS symptoms
MERS

Human herpesvirus 6
Enterovirus
Rubella
Candida albicans
Bornaviruses
Mycoplasma
Human immunodeficiency
XMRV

Infections studied but not found to be a cause of ME/CFS
High Profile Reports of “Pathogens” Linked to ME/CFS that Led to Spurious Treatments

**Demonstration of Borna disease virus RNA in peripheral blood mononuclear cells derived from Japanese patients with chronic fatigue syndrome**

Takaaki Nakaya, Hirokazu Takahashi, Yuhe Nakamura, Sayumi Asahi, Minoru Tobiume, Hirohiko Kuratsune, Teruo Kitani, Koochi Yamanishi, Kazuyoshi Ikuta


**Detection of an Infectious Retrovirus, XMRV, in Blood Cells of Patients with Chronic Fatigue Syndrome**


23 Oct 2009

Retraction


**Detection of MLV-related virus gene sequences in blood of patients with chronic fatigue syndrome and healthy blood donors**

Shyh-Ching Lo, Natalia Pripuzova, Bingjie Li, Anthony L. Komaroff, Guo-Chiuan Hung, Richard Wang, and Harvey J. Alter

August 23, 2010

Retraction


**The role of enterovirus in chronic fatigue syndrome**

J K S Chia

Center Aims

**Microbiome**
Inventory of bacteria, viruses, fungi in blood, orpharynx, and feces
Surveil microbial exposures through antibody surveys

**Immune responses**
Profile plasma cytokines and proteins; PBMC and mRNA

**Metabolism**
Profile plasma metabolome

**Investigate impact of exercise stress on immune function and metabolism**
Microbiology

Blood and oropharynx unremarkable
Virome unremarkable
qPCR Quantitation of Fecal Butyrate Producing Bacteria: *Faecalibacterium prausnitzii* and *Roseburia-Eubacterium* spp.

Controls (n=91) vs. ME/CFS (n=106)

 Controls (-) sr-IBS (n=88) vs. ME/CFS (-) sr-IBS (n=71) vs. ME/CFS (+) sr-IBS (n=35)
Fecal Short Chain Fatty Acids:
ME/CFS Patients Have Deficient Acetate and Butyrate Compared to Controls

Controls (n=91)
ME/CFS (n=106)

Controls (-) sr-IBS (n=88)
ME/CFS (-) sr-IBS (n=71)
ME/CFS (+) sr-IBS (n=35)
Why is Bacterially-derived Butyrate Important?

Gut Effects

- Energy source for colon cells
- Mucus production
- Mineral absorption
- Anti-inflammatory
- Intestinal cell life cycle
- Control of barrier function
- Pathogen control
- Promotes malignant cell death

Peripheral Effects

- Learning & Memory
- Depression-like behaviour
- Social behaviour
- Addiction
- Neuroinflammation?

Functions of butyrate

- Supports gut motility
- Ext. application into periphery (p.)
- Butyrate producers
- Dietary fibre
- Gut epithelium

Brain
- Neuron
- Microglia
- Astrocyte

Liver
- MCT/SMCT
- S-HT receptor 3
- GP1A1/FA3R
- GP1B3/FA3R
- GP1A9/CAR2
- SF/FA3R

Neutrophil
- Neutrophil
- Neutrophil

BUTYRATE

Stilling et al., 2016 Neurochemistry International 99: 110-132
Polyclonal B cell Activation in ME/CFS

Our findings in Swedish CFS patients differ from reports of BDV infection in Japanese CFS patients (Nakaya et al., 1996; Kitani et al., 1996) where similar methods were employed for serology and RT–PCR detection of P-gene transcripts in PBMC. This could be due to geographic distinctions between the two groups with respect to diagnosis, clinical course, or differential exposure to infectious agents. Although serum immunoreactivity to BDV proteins observed in Swedish CFS patients by ELISA may reflect infection with related microbial agents that induce cross-reactivity with conformational determinants on BDV proteins (Kliche et al., 1996) and β-galactosidase, the serologic findings are also consistent with nonspecific polyclonal B-cell activation. Indeed, increased levels of antibodies against different microbial agents and other viruses, such as EBV, have previously been shown in sera from CFS patients (Jones et al., 1985; Straus et al., 1985) and interpreted as evidence of polyclonal activation.
Distinct plasma immune signatures in ME/CFS are present early in the course of illness

Mady Hornig, José G. Montoya, Nancy G. Klimas, Susan Levine, Donna Felsenstein, Lucinda Bateman, Daniel L. Peterson, C. Gunnar Gottschalk, Andrew F. Schultz, Xiaoyu Che, Meredith L. Edby, Anthony L. Komaroff, and W. Ian Lipkin
Antigen-Driven Clonal B cell Expansion in ME/CFS (Plasma Proteomics)

ME/CFS is associated with alterations in plasma levels of specific immunoglobulins
- IGHV3-23/30: OR = 4.439; p-value = 0.0182
- IGKV3(D)-11: OR = 4.527; p-value = 0.032
- IGHV3-23/30: OR = 4.545; p-value = 0.019

IGHV3-23/30
- Associations to lymphomas, anti-myelin associated glycoprotein neuropathy
- Induction: chronic stimulation from either microbial or auto-antigens
- Therapeutic implications: identify and remove stimulant, use kinase inhibitors
- ME/CFS patients are at an increased risk for lymphoma

Predictive modeling through biomarker analysis
- Altered levels: CAMP, IGLV1-47, LRG1, IGF1, GSN, IGFALS, FCRL3, SERPINA3
“Recently, an association between IGHV3-23/30 and ME/CFS has been shown using a plasma proteomic approach (Milivojevic et al., 2020). Despite differences in methodology, the fact that the expression of the same IGHV region was significantly increased in ME/CFS patients provides further evidence of the importance of IGHV3-30.”
Impact of Exercise Stress

Exercise Tolerance Test (ETT) - TruCulture
ME/CFS ETT TruCulture

Tubes collected at each blood draw
1. Null/no stimulant
2. LPS (gram neg bacteria)
3. Poly I:C (viruses)
4. Staphylococcal enterotoxin B (gram pos bacteria)
5. C. albicans (fungi)

Same analytical strategy as in ME/CFS ETT metabolomics analysis

Key inferences:
• Baseline ME/CFS v. control
• Cross-over in the trajectory of the repeated measures between ME/CFS and control groups

Incubation at 37°C for 48 hours
• Supernatant for biochemical analyses
• Cell pellet for nucleic acid analyses
Higher GM-CSF Responses to the Superantigen SEB in Women with ME/CFS

Highest response in women >45Y

**pre-ETT Case**
**post-ETT Case**
**pre-ETT Control**
**post-ETT Control**

* adj. p value < 0.1
** adj. p value < 0.05
*** adj. p value < 0.01
Higher IL6 Responses to the Superantigen SEB in Women with ME/CFS

*Highest response in women >45Y*

![Graph showing IL6 responses to SEB for different age groups and genders.](image-url)
No Significant Differences in IL10 Responses to SEB
ME/CFS ETT Metabolomics

* Bayes Factor > 3
Cytokine Summary

HKCA
IFNγ, IL1β, IL23 and TNFα levels are increased in ME/CFS at baseline (before ETT)
GM-CSF, IFNγ, IL1β, IL6, IL10 and TNFα levels decrease in ME/CFS after exercise with most dramatic decreases in women

SEB
CXCL5, GM-CSF, IFNγ, IL1β, IL2, IL6, IL8, IL13, IL17, IL23, and TNFα levels are increased in ME/CFS cases at baseline and after exercise with most dramatic decreases in women <45 years old
GM-CSF levels are increased in controls after exercise.
Symptom Overlap in ME/CFS, GWI, and Post-COVID

ME/CFS: symptoms persist for at least 6 months

GWI: symptoms persist for at least 6 months, appeared during active duty in Southeast Asia military operations by 12/31/21, and be at least 10% disabling. *Attributing illnesses include: Chronic Fatigue Syndrome, Fibromyalgia, functional gastrointestinal disorders, undiagnosed illnesses

Post-COVID: symptoms persist more than 4 weeks after initial infection and include asymptomatic cases
Acute Flaccid Myelitis

Immunoreactivity to EV VP1 in Serum

Granular Serosurveillance Using Peptide Arrays
Acute Flaccid Myelitis

Immunoreactivity to an EV-D68 Specific Peptide in CSF and Serum
Summary

ME/CFS is an immunological disorder characterized by cytokine dysregulation, B cell activation, and metabolomic disturbances.

The spectrum of agents implicated in triggering ME/CFS is more likely to be identified through seroepidemiology than through sequencing.

Reductions in butyrate-producing bacteria may contribute to immunological and metabolomic dysfunction; however, we do not know whether our findings represent a primary defect or a function of reduced physical activity.

Similarities in clinical manifestations in ME/CFS and other disorders suggest potential for similarities in pathophysiology and opportunities for insight.