Solve M.E.

RESEARCHER TOOLKIT
2020

ME/CFS RESEARCH LANDSCAPE

ME/CFS is a disease characterized by central nervous system and immune system disturbances, neurological and autonomic symptoms, circulatory abnormalities, and altered metabolism. Understanding of the pathogenesis of ME/CFS has increased considerably in recent decades and a complex picture has emerged, implicating many systems and mechanisms >>>

GENETICS

- Clustering patterns are seen in families and there is need of more genome-wide association studies to identify candidate SNPs
- There is growing evidence that epigenetic patterns are different between patients and matched healthy controls and research has shown differentially methylated pathways related to immune response, glucocorticoid receptors, and metabolism.
- In-depth investigation of epigenetic mechanisms other than DNA methylation are lacking in ME/CFS, but increased HDAC expression and an upregulation of microRNA related to cell cycle and immune regulation have been described.

IMMUNOLOGY

- Research groups have found differences in ME/CFS blood cytokine signatures; some identifying patterns correlated with disease severity and others duration of illness.
- There is evidence of defective cell-mediated immunity, especially in NK cells, and increasing interest in T cell activation
- Mechanisms of autoimmunity have been explored; selective removal of autoantibodies has proved effective in small cohorts
- Altered B cell phenotypes have been uncovered
- Findings of deviations in the immune system are notably inconsistent, possibly due to patient heterogeneity and selection, the cyclical nature of the disease, and methodology

MICROBIOME

- Many patients report experiencing an infection preceding the development of ME/CFS and various pathogenic triggers have been considered, including HHV-6/7, EBV, enteroviruses, others
- Lacking evidence of chronic infection, researchers have focused on a "hit and run" hypothesis or viral reactivation
- Alterations in the gut microbiome composition of people with ME/CFS have been uncovered by different groups; it's hypothesized a "leaky gut" may trigger immune dysfunction and/or gut inflammation might disrupt bidirectional communication with the brain

NEUROLOGY

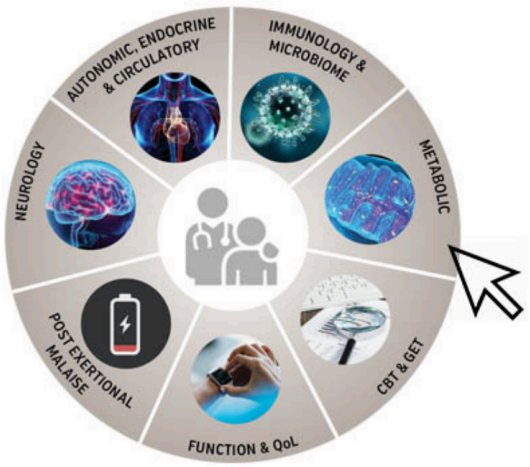
- There is considerable evidence demonstrating that ME/CFS has both structural and functional brain consequences, such as reduced functional connectivity and changes in cerebral blood flow
- Indicators of brain inflammation have been found in MRS and PET neuroimaging studies. The brainstem has been argued to be a target for future studies as it has explanatory power for autonomic dysfunction seen in patients
- Circulatory abnormalities and an association with orthostatic intolerance in ME/CFS has been described. The majority of studies in young people show a high prevalence of OI
- Neuroendocrine changes, particularly HPA axis dysfunction, have been explored

METABOLISM

- Mitochondrial dysfunction, AMPK impairment, and redox imbalance have all been associated with ME/CFS.
- The body of evidence points to irregularities in various metabolic pathways, including changes in lipid and amino acid pathways, nucleotide, nitrogen, and hormone metabolism. Overall, different groups have found evidence to support a hypometabolic state
- There has been some exploration whether metabolic dysfunction in immune cells could be driving problems with immune system functioning in ME/CFS patients

ADDITIONAL SOURCES OF INFORMATION

→ Solve ME's interactive research wheel summarizing promising original research by area of science. You can access the summaries by clicking the wheel below:



→ Check out this concise overview of ME/CFS research published in **JAMA** by Anthony L. Komaroff, MD following the NIH conference "Accelerating Research on ME/CFS". You can watch a recording of his conference talk at 06:02:00 here. *Click the icon for the full slides.*

5 DISEASE MODELS

As outlined by
Anthony L. Komaroff, MD
April '19 NIH ME/CFS conference

For Dr. Komaroff's full slides click here

Watch a recording of his talk at 06:02:00 here

1

Excessive cellular senescence with generation of fatigue-inducing molecules

2

Cell danger response/incomplete healing

3

Sickness behavior/inflammation, in which the temporary bodily response to injury and infection becomes chronic

4

Microbiome as the source of immune system activation and inflammation

5

Dauer/hibernation-torpor, in which energy-producing reactions are reduced to a minimum in response to some insult

METHODS AND RESOURCES

PATIENT SELECTION

The ME/CFS field lacks an agreed upon research or clinical case definition. Sample heterogeneity across research studies and disordered patient selection impedes replication and holds back progress in the search for biological markers and effective treatments.

We don't have the space to outline the arguments for one case definition over another in this guide, but this is unequivocal:

A well-designed study will **require the presence of post-exertional malaise (PEM)** in determining a case of ME/CFS.

RESOURCES FOR PATIENT SAMPLES

The **CureME** group has samples from 600+ donors with ME/CFS, MS and healthy controls in the UK ME/CFS Biobank. You can learn more here.

Solve M.E. maintains a biorepository in the U.S. Email biobank@solvecfs.org to inquire.

DATA COLLECTION INSTRUMENTS

NINDS COMMON DATA ELEMENTS FOR ME/CFS

Start up resources from the NINDS CDEs can be accessed here

NINDS Common Data Elements

Please note a few things:

- a method for ascertaining and recording the presence or absence of PEM as a case defining symptom is imperative
- The DePaul Symptom Questionnaire should be considered as a core instrument over the Symptom Checklist
- The use of a method to assess functional status, like the Karnofsky score, should be used along with a quality of life assessment

APPROACHES TO ME/CFS RESEARCH

- **Stratification analyses** by age, sex, severity, duration, type of onset/triggering event, symptoms, comorbid conditions, functional status
- Integrating provocation (exercise protocol) to **interrogate post-exertional malaise** (PEM), the cardinal symptom of ME/CFS
- Moving away from cross-sectional studies to the collection of information at multiple time points and **longitudinal characterization** of the disease
- Include **disease controls** along with healthy controls. Comparison with related diseases (e.g. multiple sclerosis, Gulf War Illness, fibromyalgia) will help clarify biological differences that are unique to ME/CFS
- **Cross-disciplinary research** that can dig into the multiple systems indicated in the disease
- Utilizing high-powered methodologies, including **multi-omics** and **machine-learning approaches**, and novel techniques, like examining exosomes