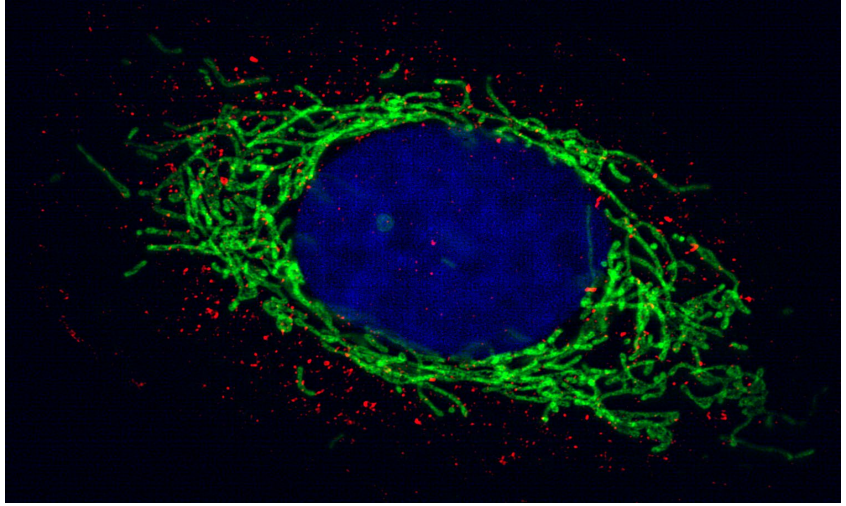


Understanding the Infectious Origin of ME/CFS

through the recent pandemic

Prof Dr. Bhupesh K Prusty
Institute for Virology and Immunobiology, JMU Würzburg

Julius-Maximilians-
UNIVERSITÄT
WÜRZBURG

PrustyLab

Understanding early stages of disease development is key to treatment

Initiation of the disease
possibly due to an infection

12-18 months

Chronic Illness

Biomarker search

Yeh….You have ME/CFS

SARS-CoV-2: an opportunity to learn post-viral illness

GEFÖRDERT VOM
Bundesministerium für Bildung und Forschung

NAPKON
NATIONALES PANDEMIE KOHORTEN NETZ

STAAB
Forschung für starke Herzen!

Immune Mechanisms of ME

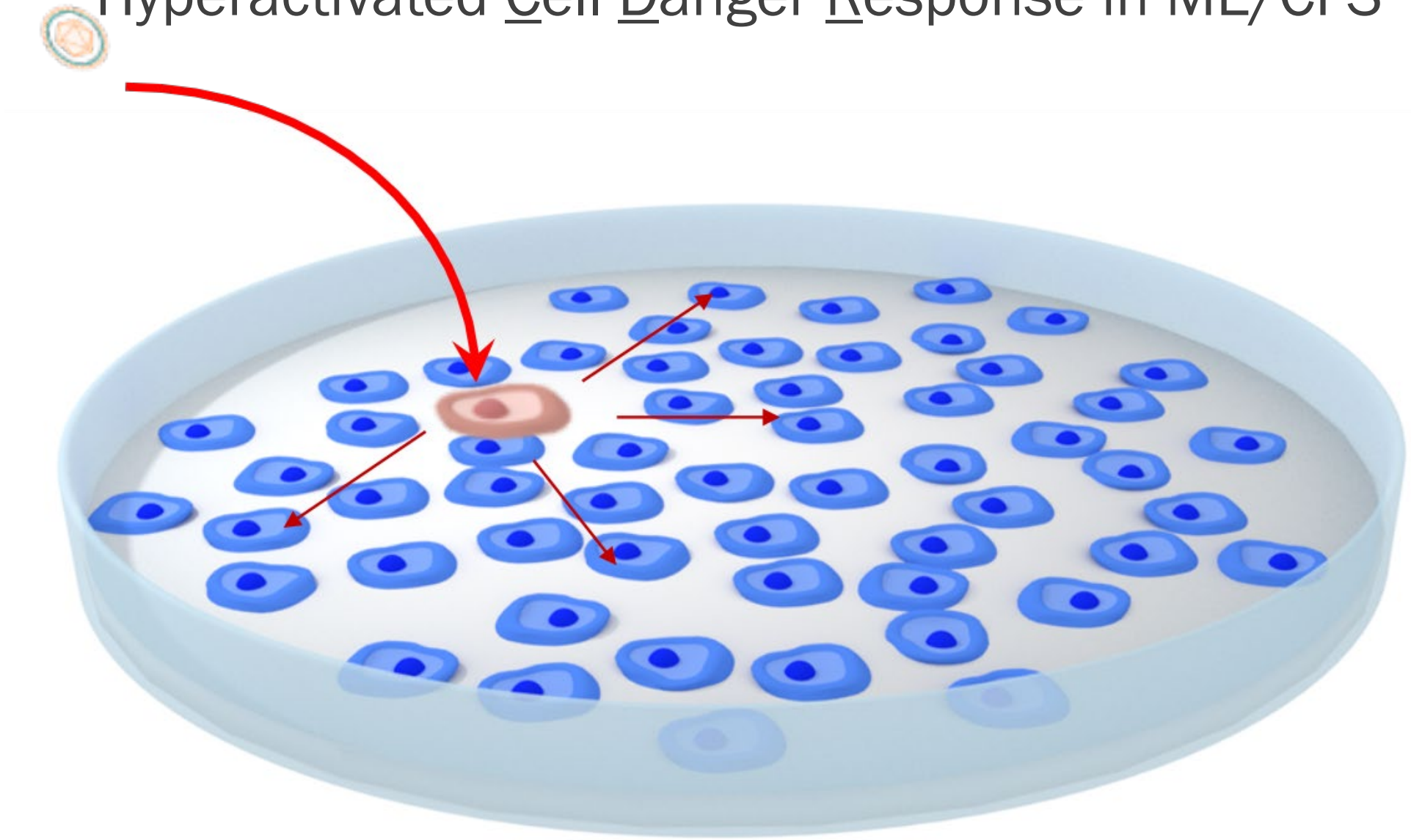
6-12 months after being SARS-CoV-2 positive

COVIDOM
Würzburg cohort

Healthy controls	ME/CFS	No LC	Mild LC	Severe LC
n = 83	n = 106	n = 149	n = 107	n = 23
male = 32 female = 51	male = 33 female = 73	male = 67 female = 82	male = 39 female = 68	male = 8 female = 15

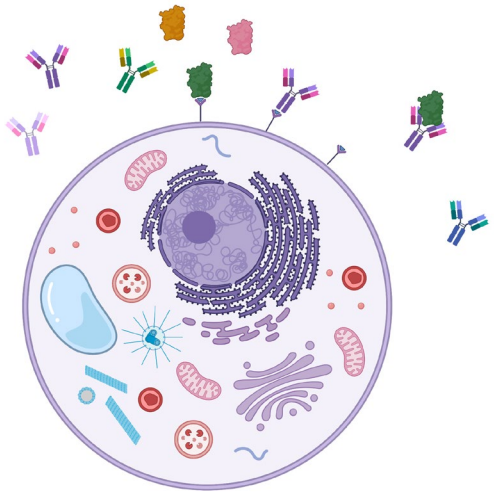
Zheng et al., 2023, MedRxiv

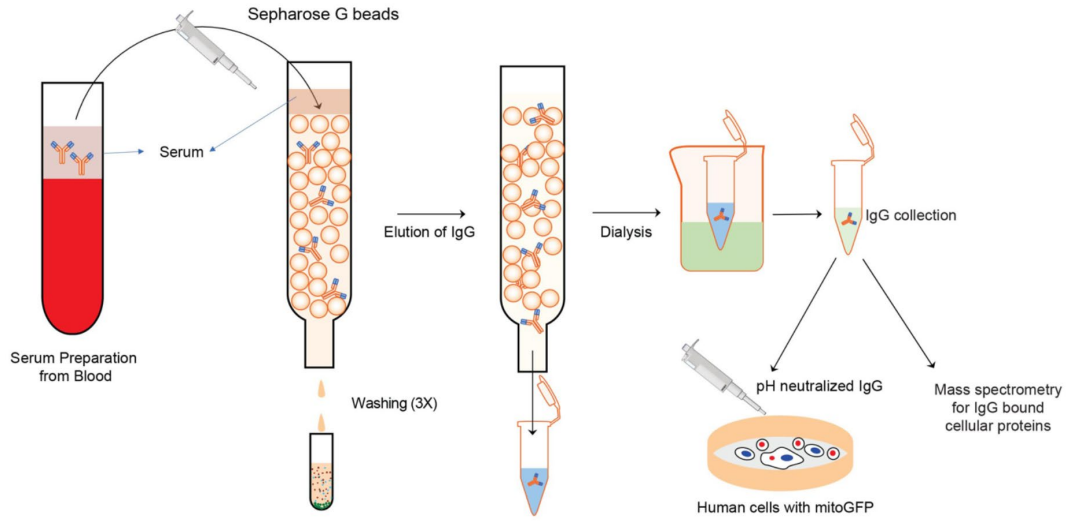
Hyperactivated Cell Danger Response in ME/CFS



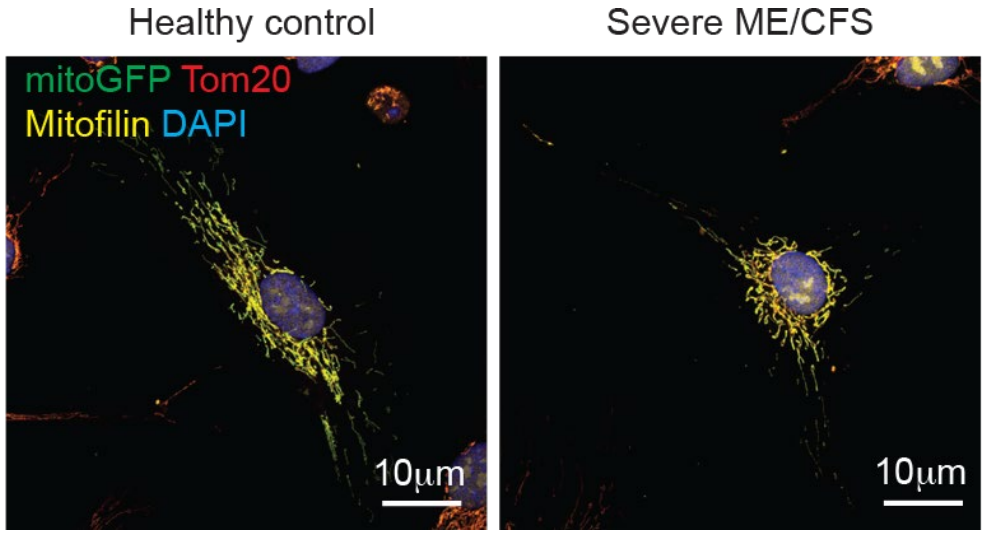
The Mosaic Disease
(Searching for a needle in a haystack)

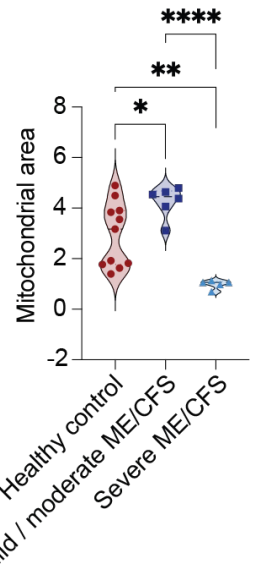
Serum-transferrable phenotype via Immunoglubulins

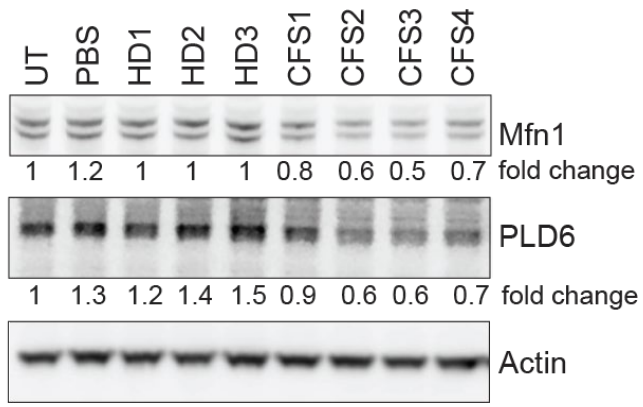




Immunoglobulin purification from patient serum

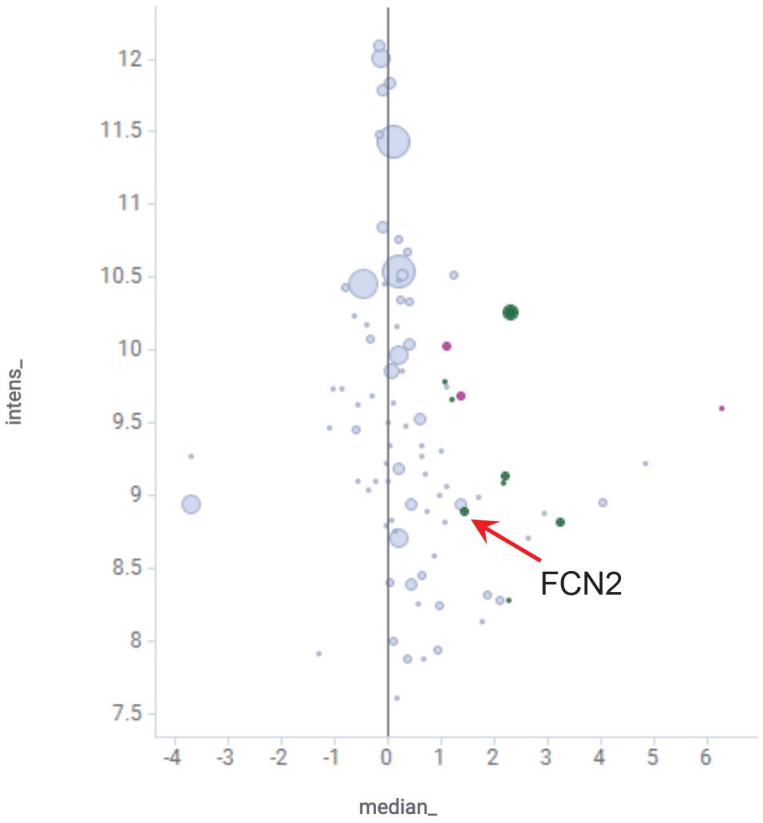




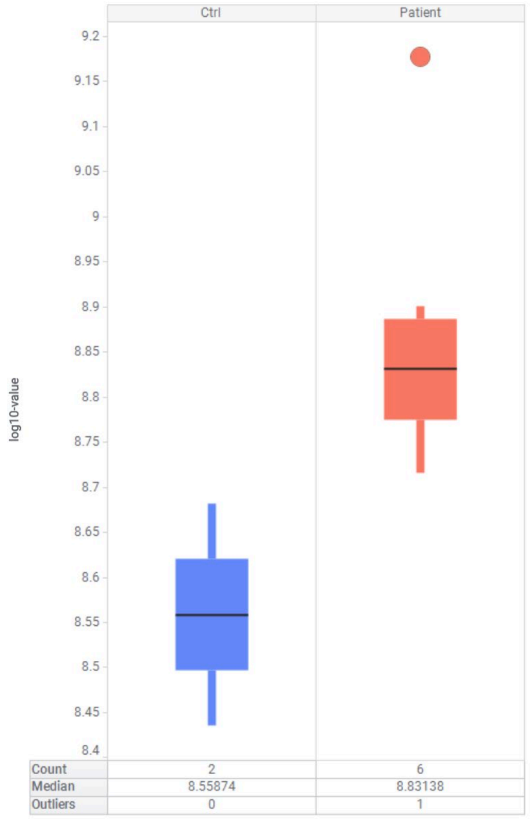


Immunoglobulins from severe ME/CFS patients can induce mitochondrial fragmentation in primary human endothelial cells

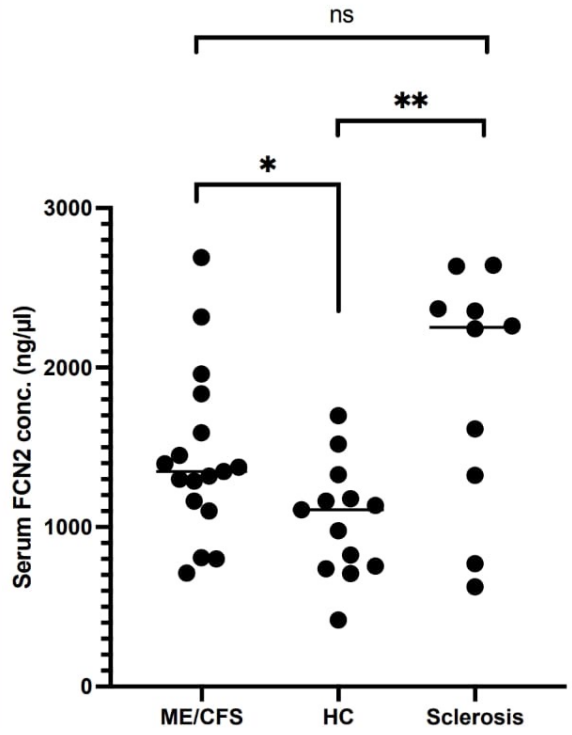
FCN2 is increased within immune complexes of some of the ME/CFS patients



Normalized fold changes in protein levels in a ME/CFS patient vs a paired control



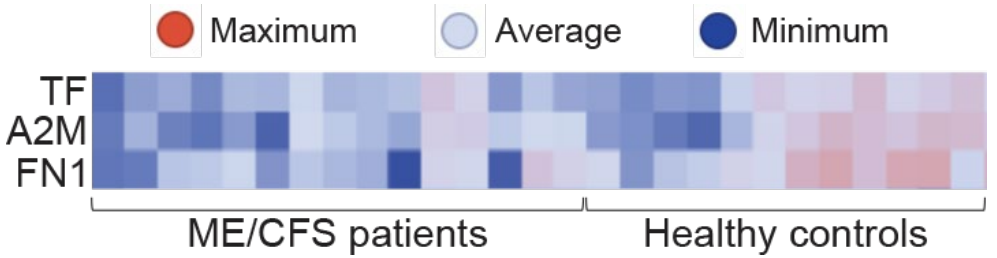
Normalized fold changes in protein levels in all ME/CFS patients vs all controls



ELISA-based quantification of total serum FCN2 levels

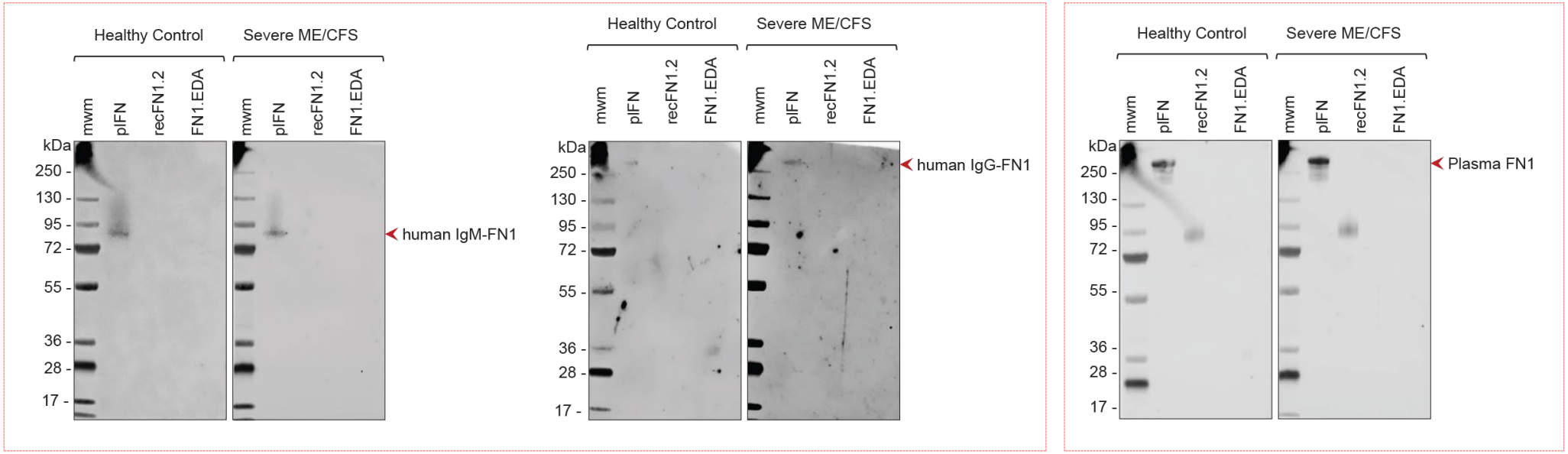
- FCN2 (Ficolin 2) is associated with Adenoiditis and Rheumatic Fever.
- Initial triggering of Complement cascade, involved in calcium ion binding.
- May function in innate immunity through activation of the lectin complement pathway.

Specific Functions of Fibronectin is altered in ME/CFS



Amounts of proteins within the circulating immune complex
as determined by mass-spectrometry analysis of purified Immunoglobulins

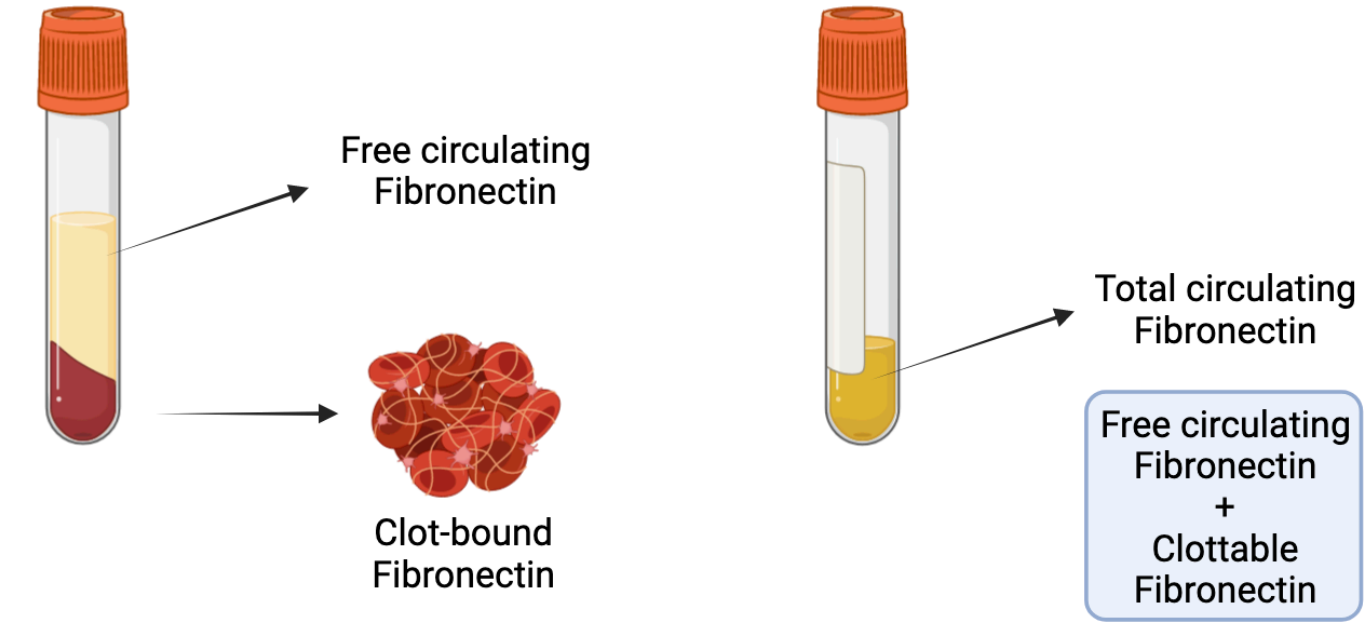
IgM and IgG against FN1 within purified immune complexes

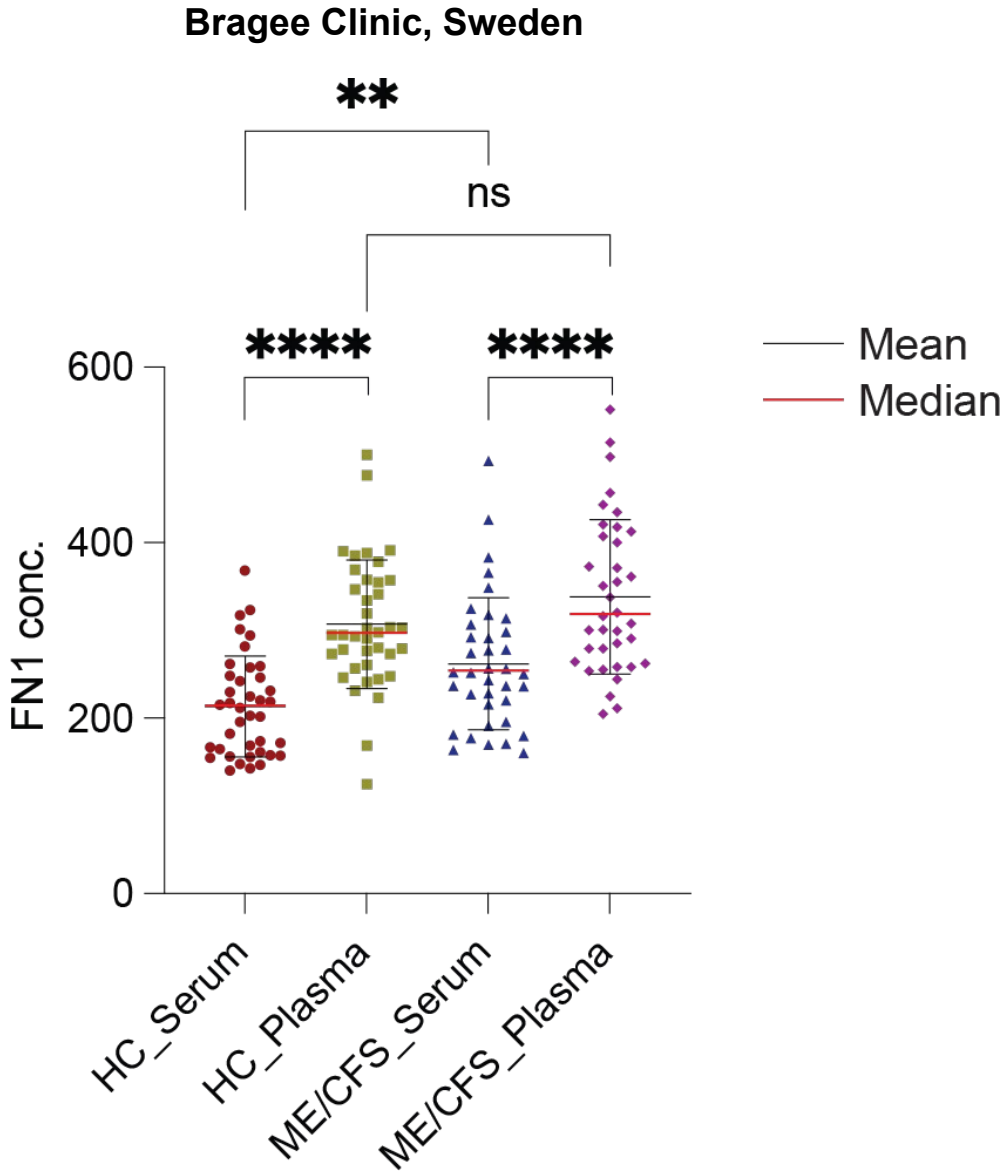


Antibody levels against Fibronectin are not altered. Only the antigenic Fibronectin is altered.

Possibility of protein modifications.

Serum vs Plasma Fibronectin levels

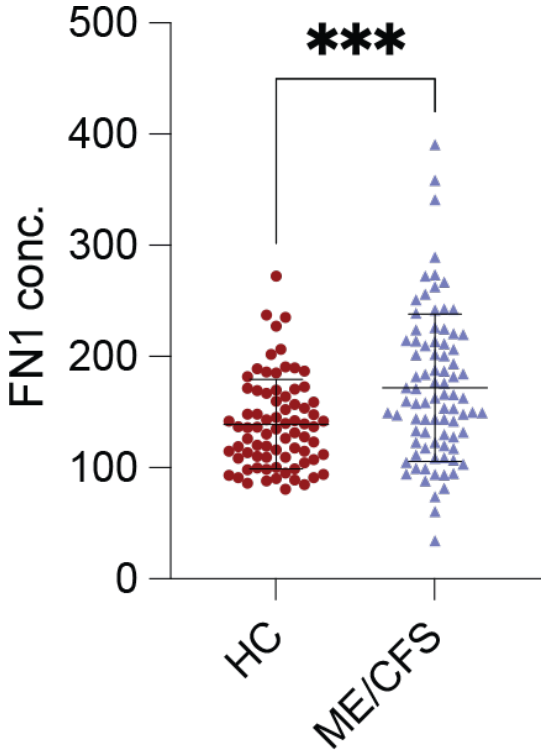


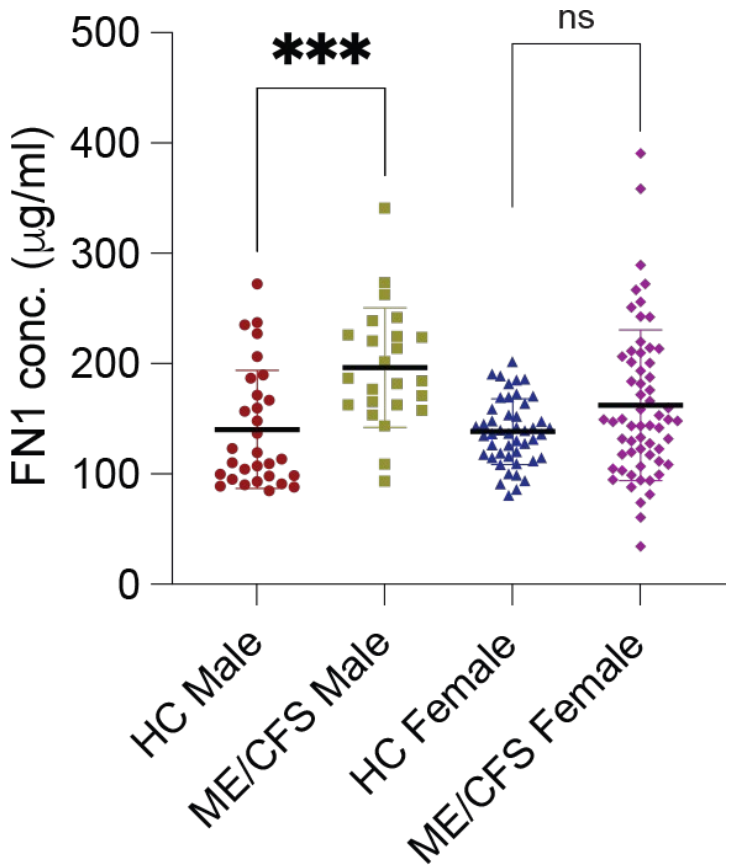


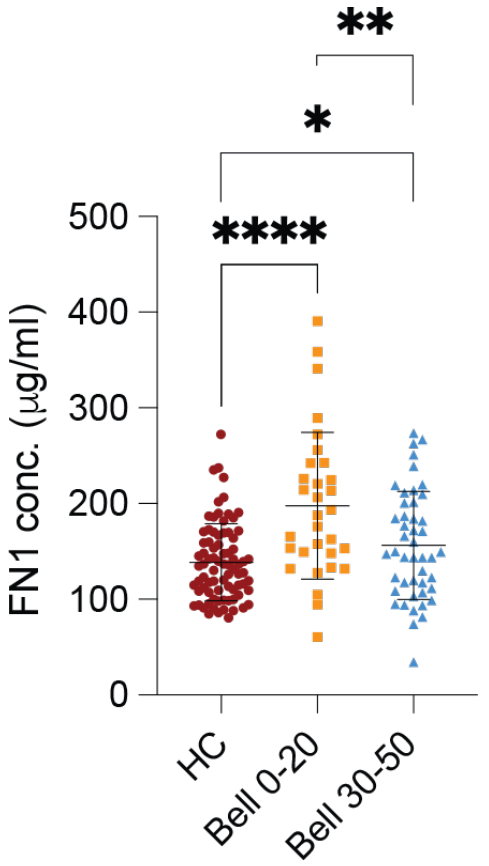
Fibronectin is possibly not efficiently incorporated into the clotting process in ME/CFS

Serum Fibronectin levels in ME/CFS

Total ME/CFS cohort (Germany)

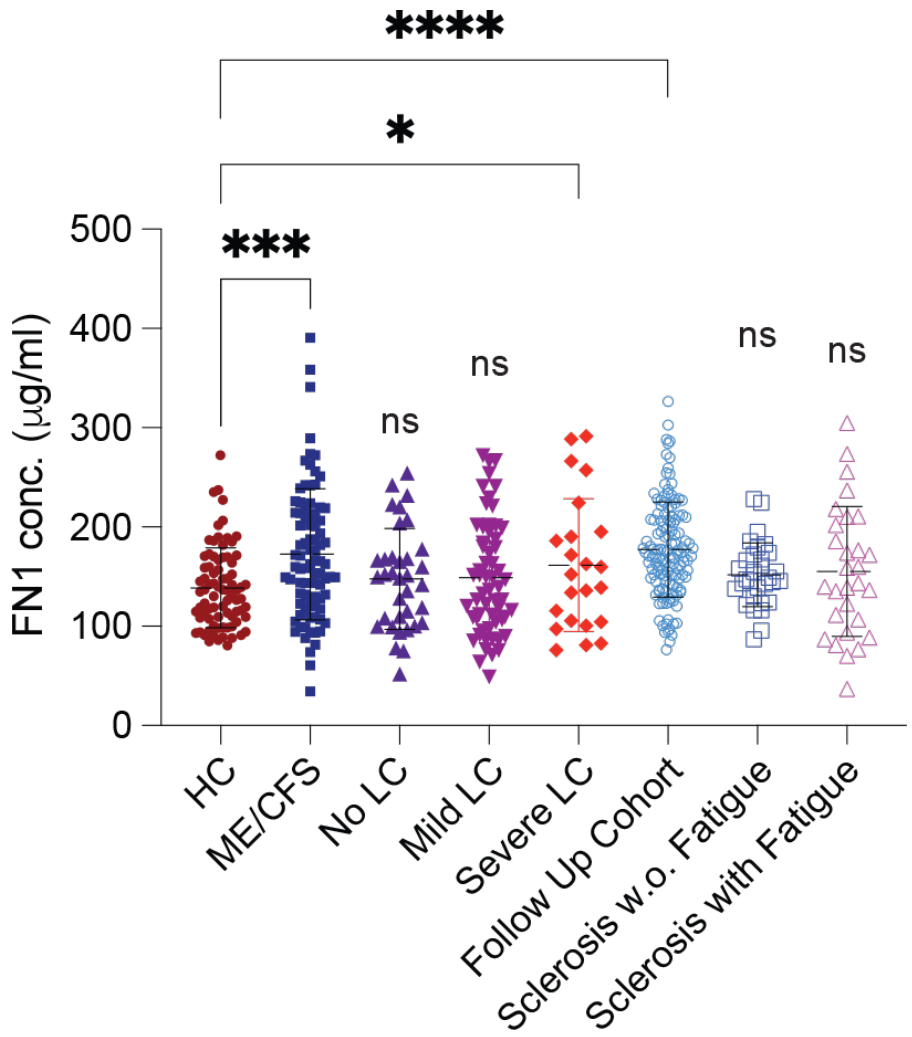






ELISA-based quantification of Fibronectin levels in Serum

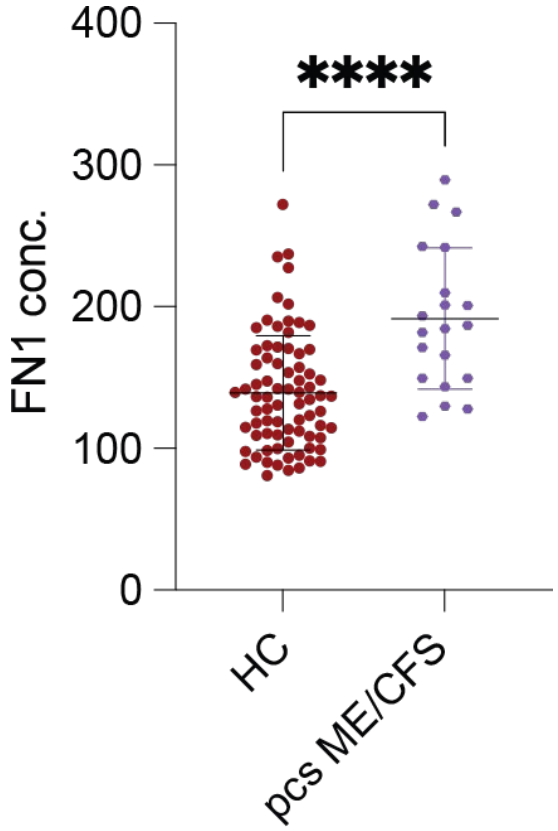
Circulating Fibronectin levels in serum after SARS-CoV-2 infection

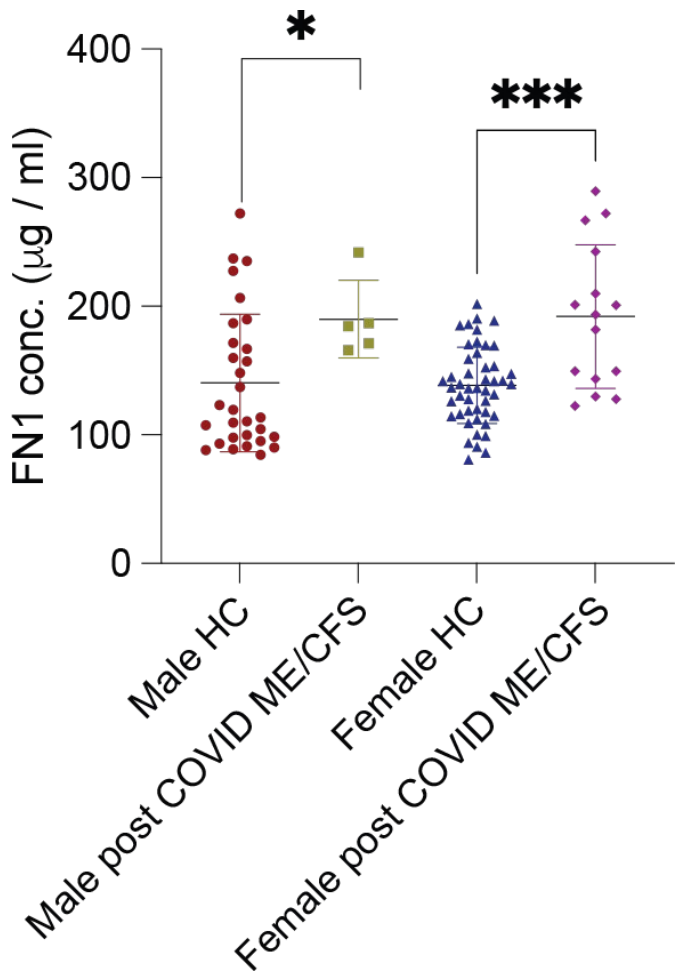


In Collaboration with
Prof. Gabriela Riemakasten, Lübeck

ELISA-based quantification of Fibronectin levels in Serum

Serum Fibronectin levels in Covid-induced ME/CFS



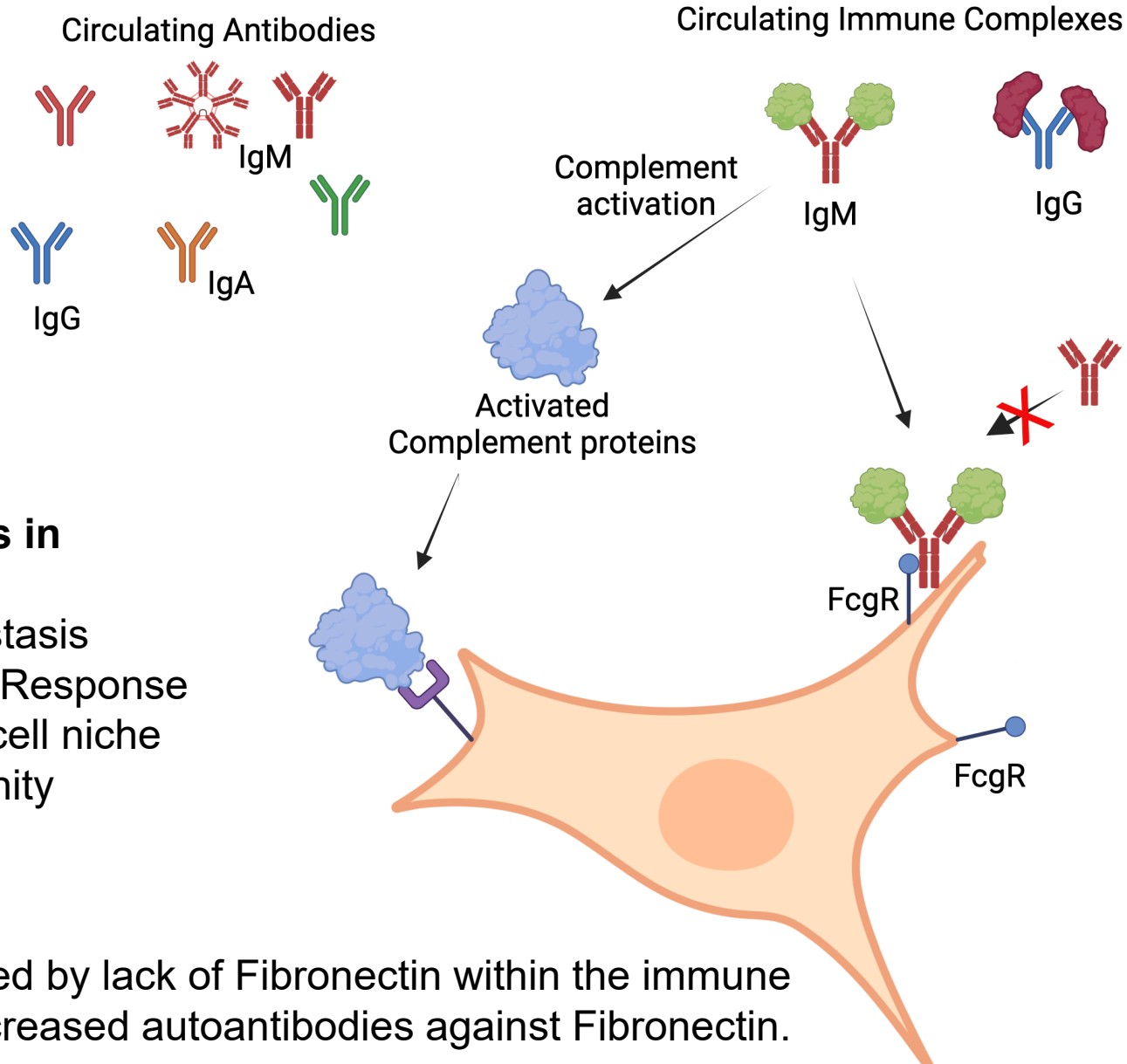


COVID-induced ME/CFS (pcs)

The best time to identify these differences is just after disease initiation

In Collaboration with
Prof. Carmen Scheibenbogen, Berlin

Possible hypothesis linking Immunoglobulin to Mitochondrial function and cell survival



Alterations in

IgM Homeostasis
Humoral Immune Response
Alterations in B cell niche
Autoimmunity

B- cells might be altered by lack of Fibronectin within the immune complex producing increased autoantibodies against Fibronectin.

Ouchida R et al., PNAS (2012)

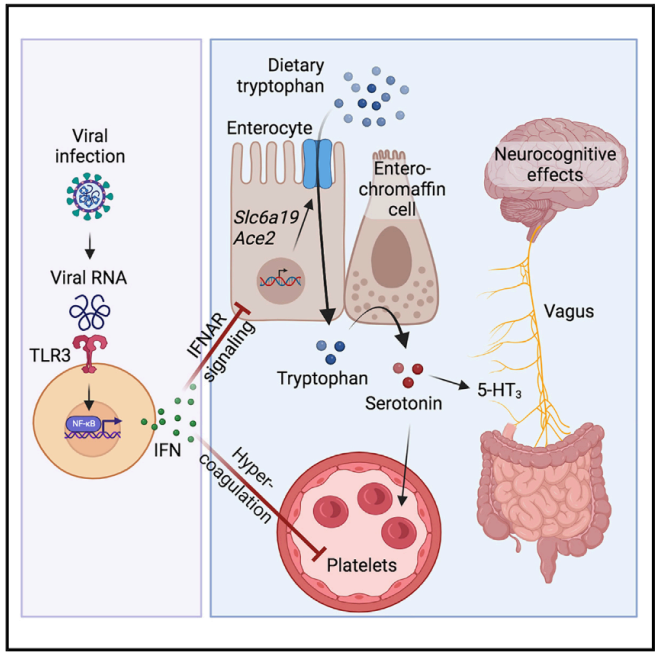
Potential association between Serotonin and Fibronectin

Article

Cell

Serotonin reduction in post-acute sequelae of viral infection

Graphical abstract



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In brief

Post-viral syndromes are associated with serotonin reduction, which may contribute to the neurological and cognitive symptoms seen in individuals with Long COVID.

AMERICAN JOURNAL OF PHYSIOLOGY
american physiological society
LUNG CELLULAR AND MOLECULAR PHYSIOLOGY

Am J Physiol Lung Cell Mol Physiol. 2012 Jun 15; 302(12): L1273–L1279. PMCID: PMC3379044
Published online 2012 Apr 20. doi: 10.1152/ajplung.00082.2012 PMID: 22523280

Serotonylated fibronectin is elevated in pulmonary hypertension

Lin Wei,[1] Rod R. Warburton,[1] Ioana R. Preston,[1] Kari E. Roberts,[1] Suzy A. A. Comhair,[2] Serpil C. Erzurum,[2] Nicholas S. Hill,[1] and Barry L. Fanburg[1]

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Abstract

Go to:

Serotonin (5-HT) and fibronectin (FN) have been associated with pulmonary hypertension (PH). We previously reported that FN is posttranslationally modified by tissue transglutaminase (TGase) to form serotonylated FN (s-FN) in pulmonary artery smooth muscle cells and that serotonylation stimulates their proliferation and migration, hallmarks of PH. We hypothesized that s-FN and its

Fibronectin is possibly not incorporated into the active immune complex in ME/CFS

Collaborative Partners and Funders

Prof. Carmen Scheibenbogen, Charite, Berlin

Prof. Uta Behrends, Helmholtz Zentrum, Munich

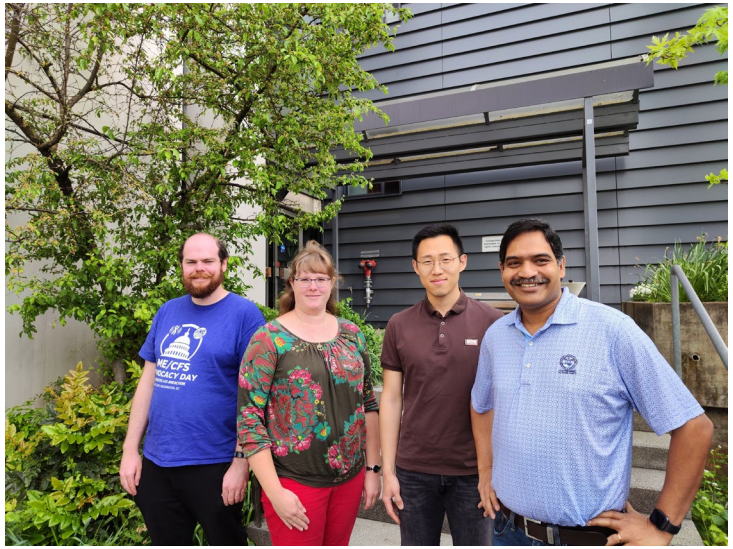
Dr. Franziska Sotzny, Charite, Berlin

Prof. Robert K Naviaux, UCSD, USA

Prof. Marshall V. Williams, Ohio State University, USA

Prof. Maria Ariza, Ohio State University, USA

Bragee Clinic, Sweden



Sam, Claudia and Stefan

TEMPI Stiftung

HHV-6 FOUNDATION

ME RESEARCH UK

AMAR FOUNDATION California, USA

immme Immune Mechanisms of ME

GEFÖRDERT VOM Bundesministerium für Bildung und Forschung

COVIDOM

NAPKON NATIONALES PANDEMIE KOHORTEN NETZ

Fatigatio e.V. Bundesverband ME/CFS

Bragée kliniker Trodd och trygg

ME/CFS DEUTSCHE GESELLSCHAFT FÜR ME/CFS E.V.

The ME/CFS Patient Community

TEXAS TECH UNIVERSITY
HEALTH SCIENCES CENTER™

SEC Call

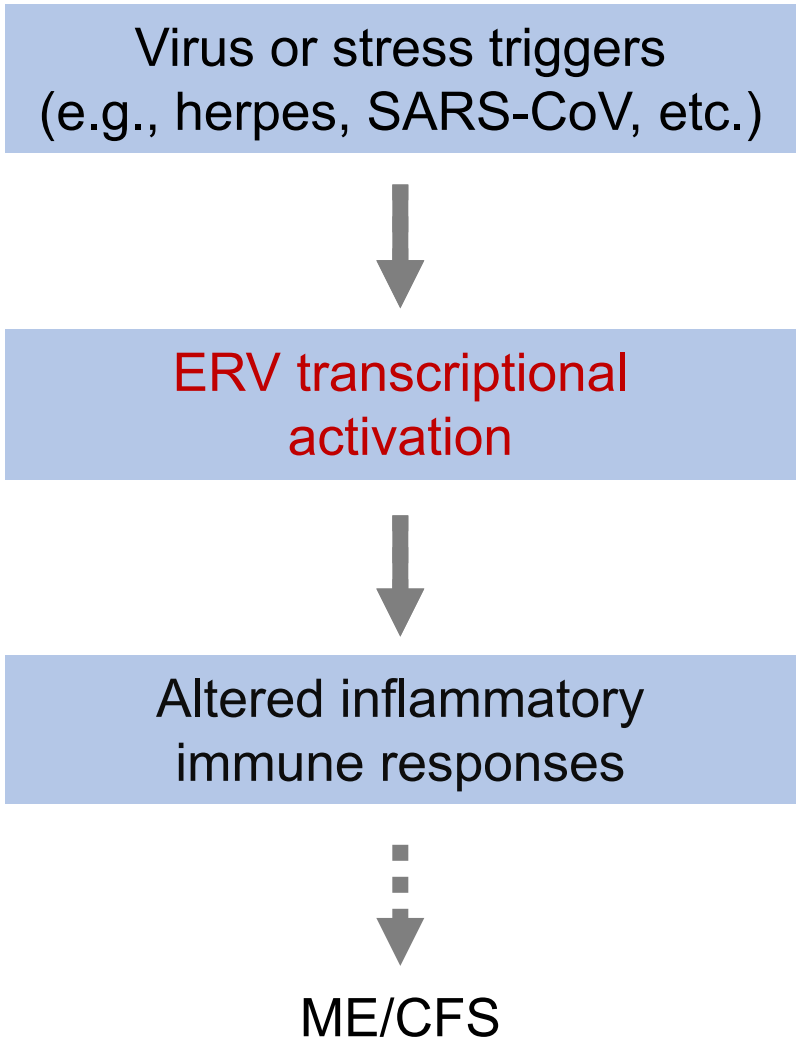
Endogenous retroviruses and ME/CFS

Dawei Li, Ph.D.

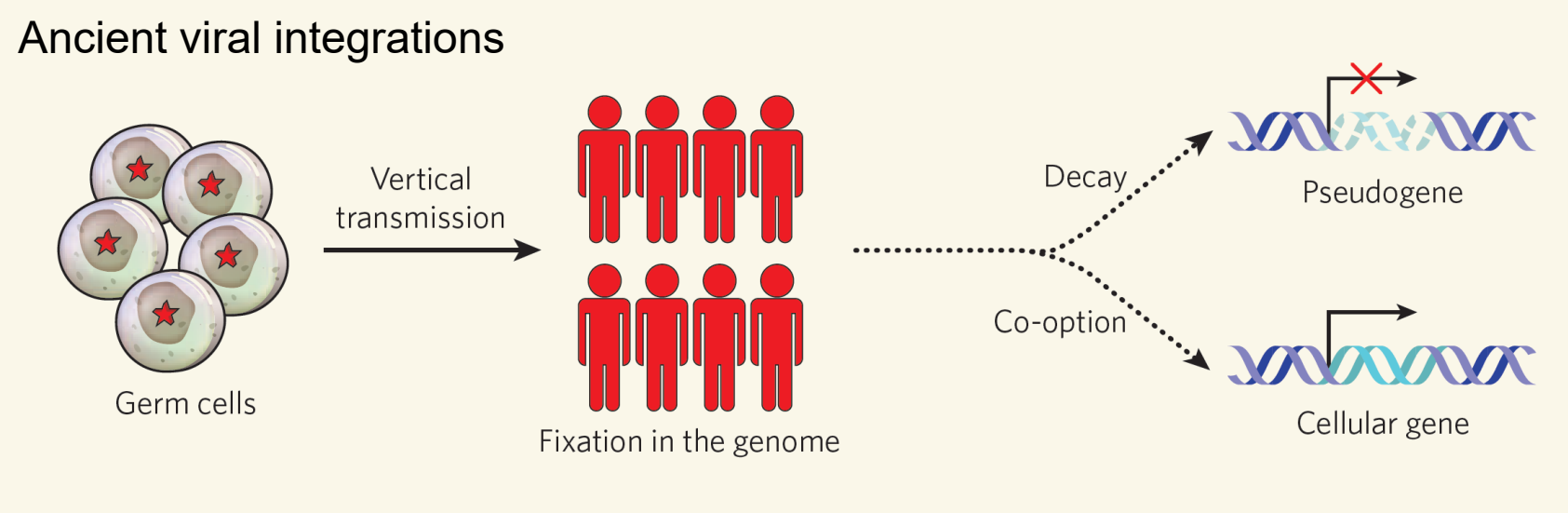
Associate Professor
Department of Immunology & Molecular Microbiology
Texas Tech University Health Sciences Center

December 18, 2023

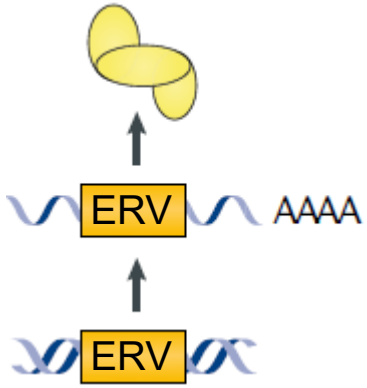
Possible endogenous retrovirus–ME/CFS link



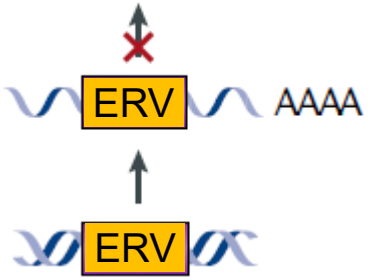
Endogenous retroviruses (ERVs): 8% of the human genome



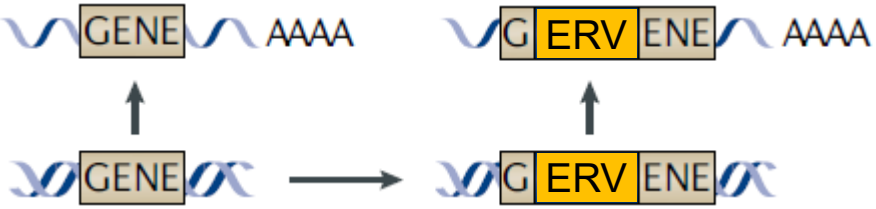
ERV functions



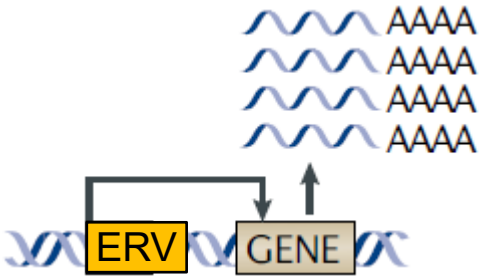
Protein-coding



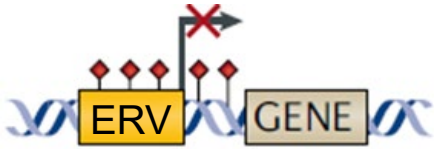
Non-coding



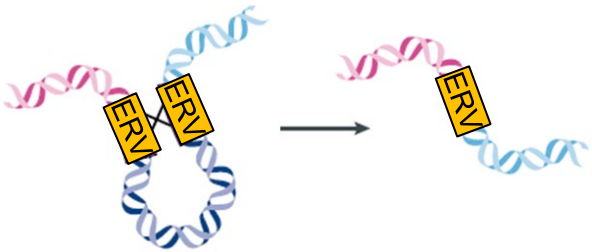
Fusion transcripts



Cis-upregulate

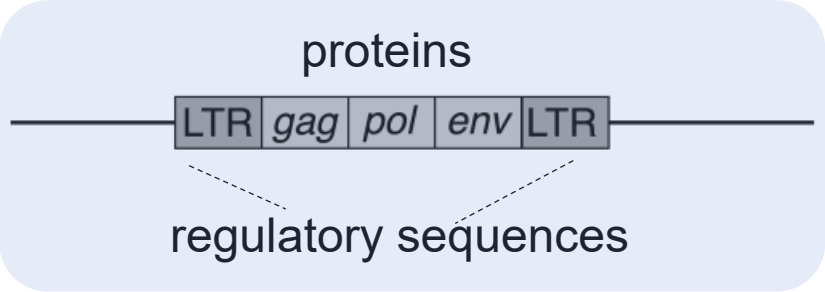


Silence

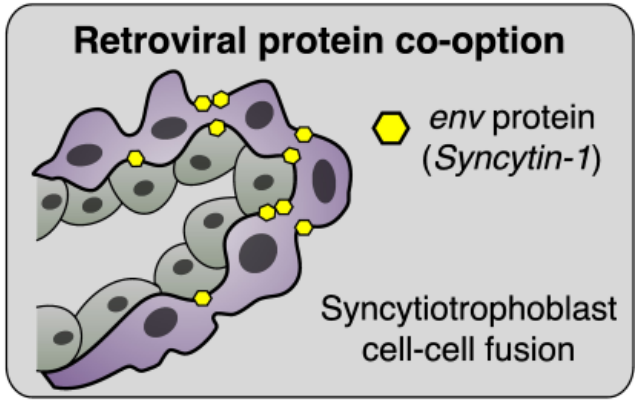


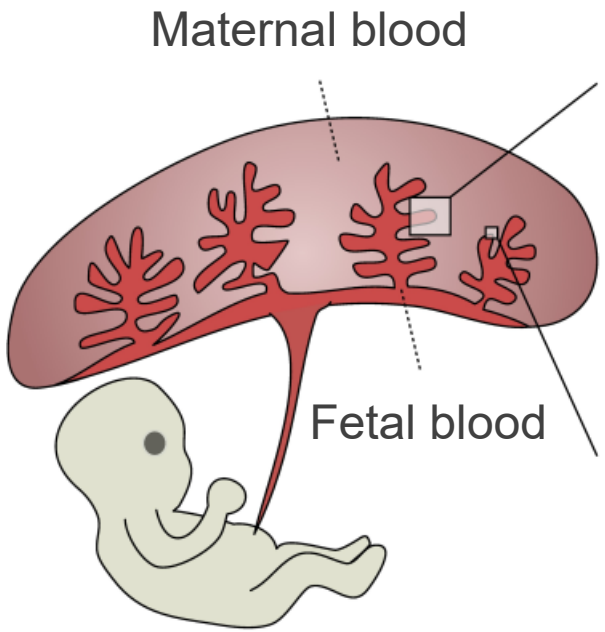
Copy number variations

ERV proteins and regulatory sequences co-option in the placenta

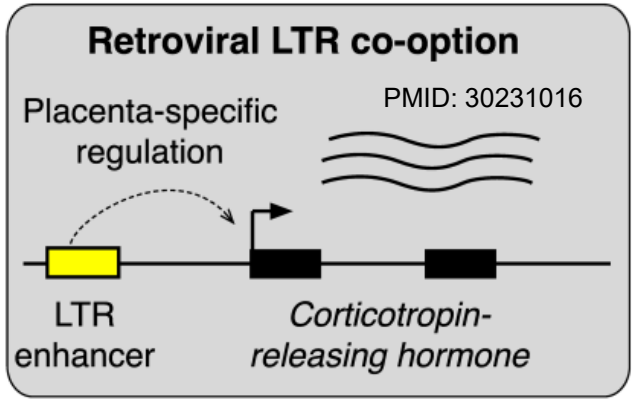


Cell–cell fusion and immune modulation of the placenta



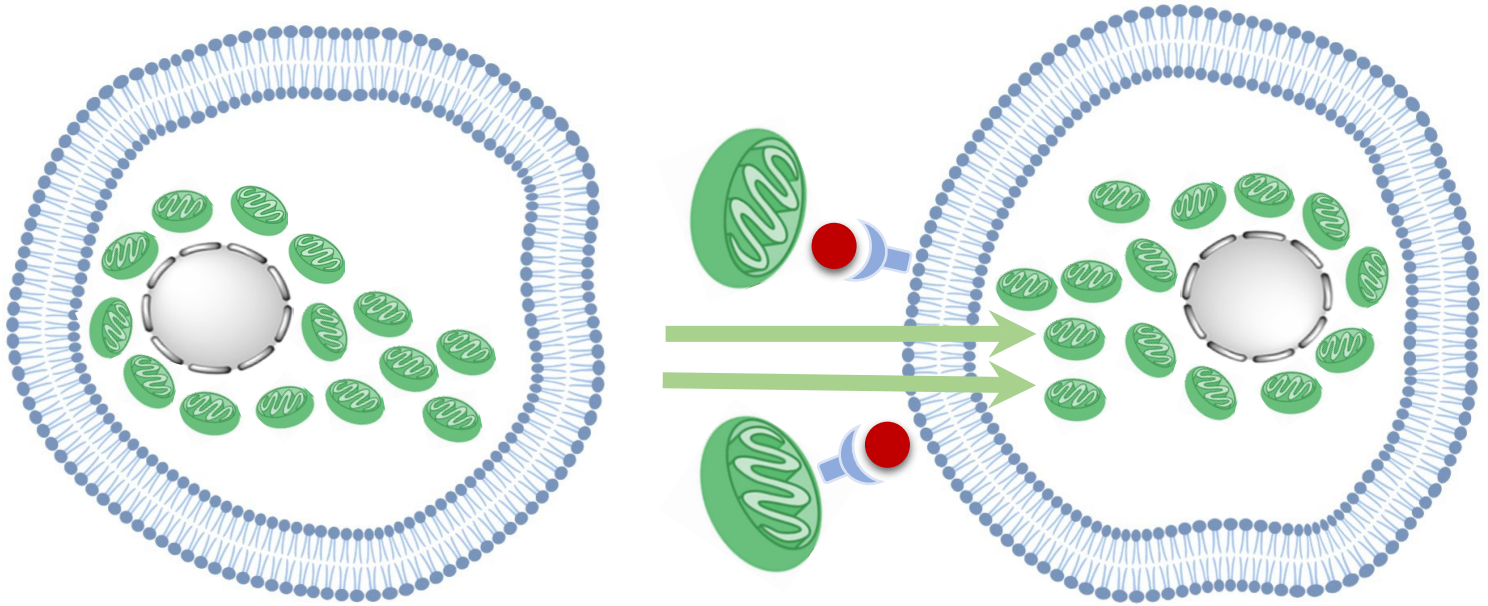


Regulation of gene (*CRH*) important for pregnancy



ERV proteins can control energy production

ERV proteins mediate cell-to-cell transfer of mitochondria

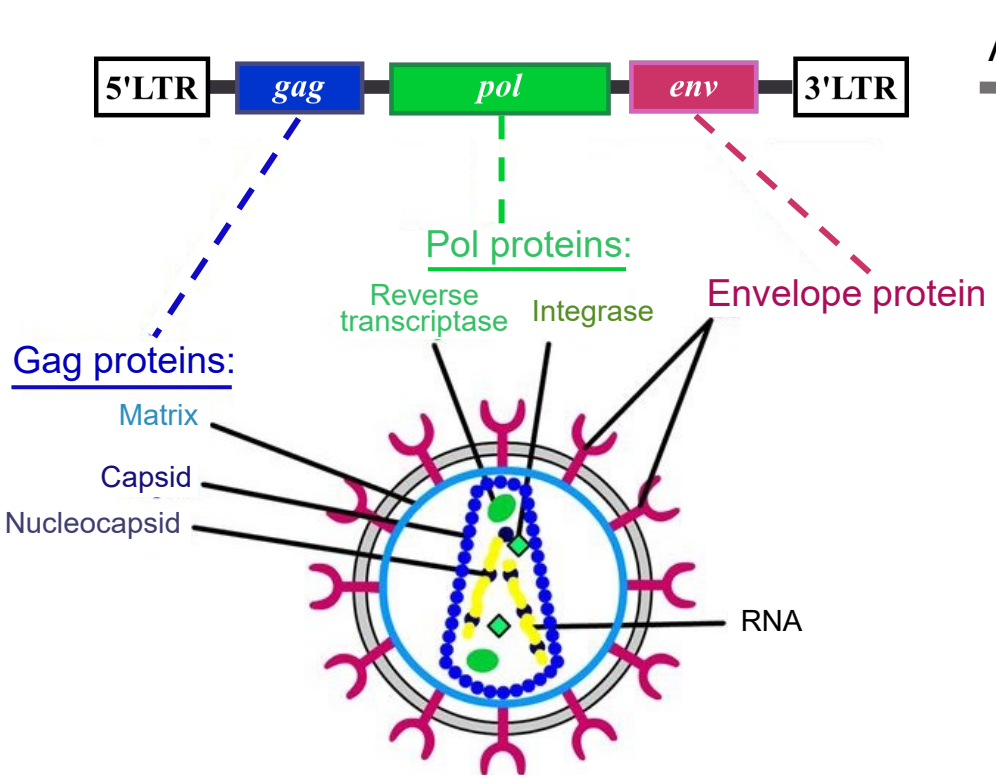


ERV protein (ligand)

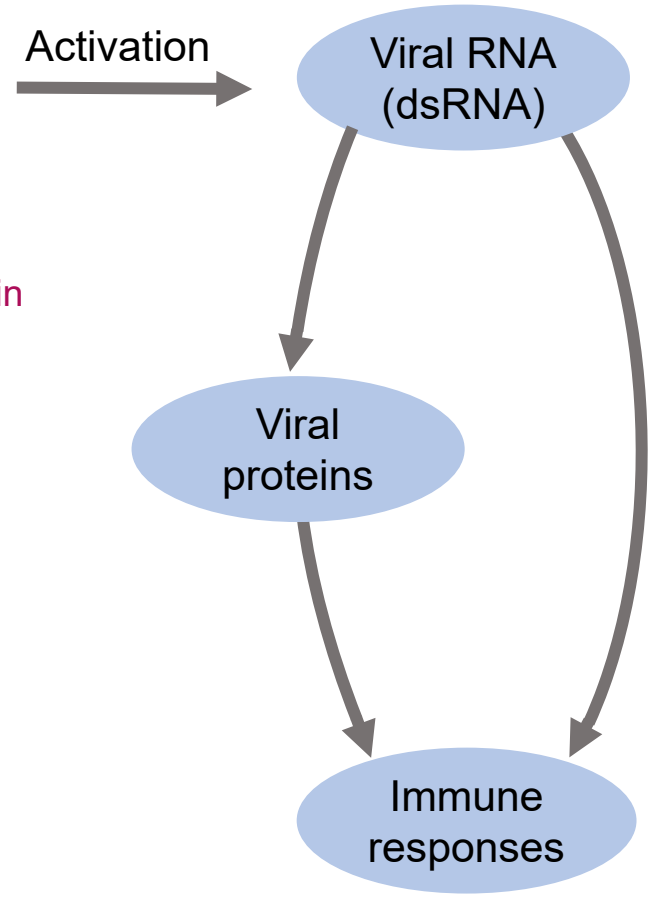
Receptor

Energy (ATP) production wrong in ME/CFS

ERV genomes and activation

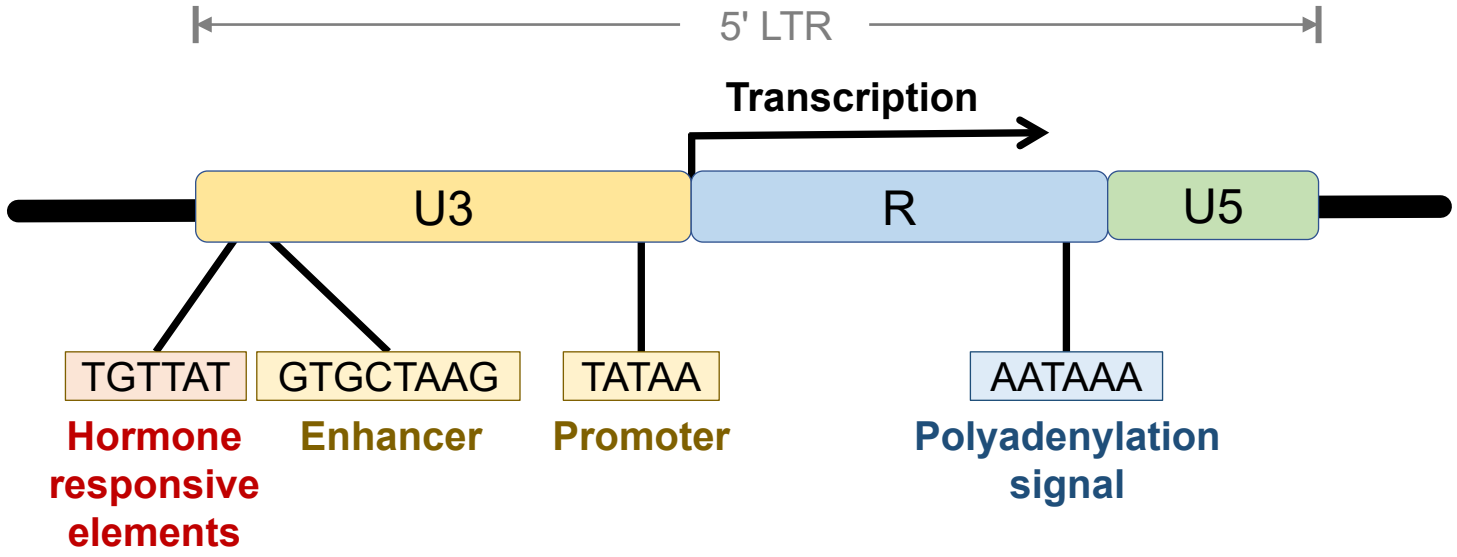


ERV genomes (n>600,000)



ERV activation additionally enhanced by female sex hormones

ERV has hormone responsive elements



3 in 4 ME/CFS patients are women

ERV detection challenges

ERV variants are:

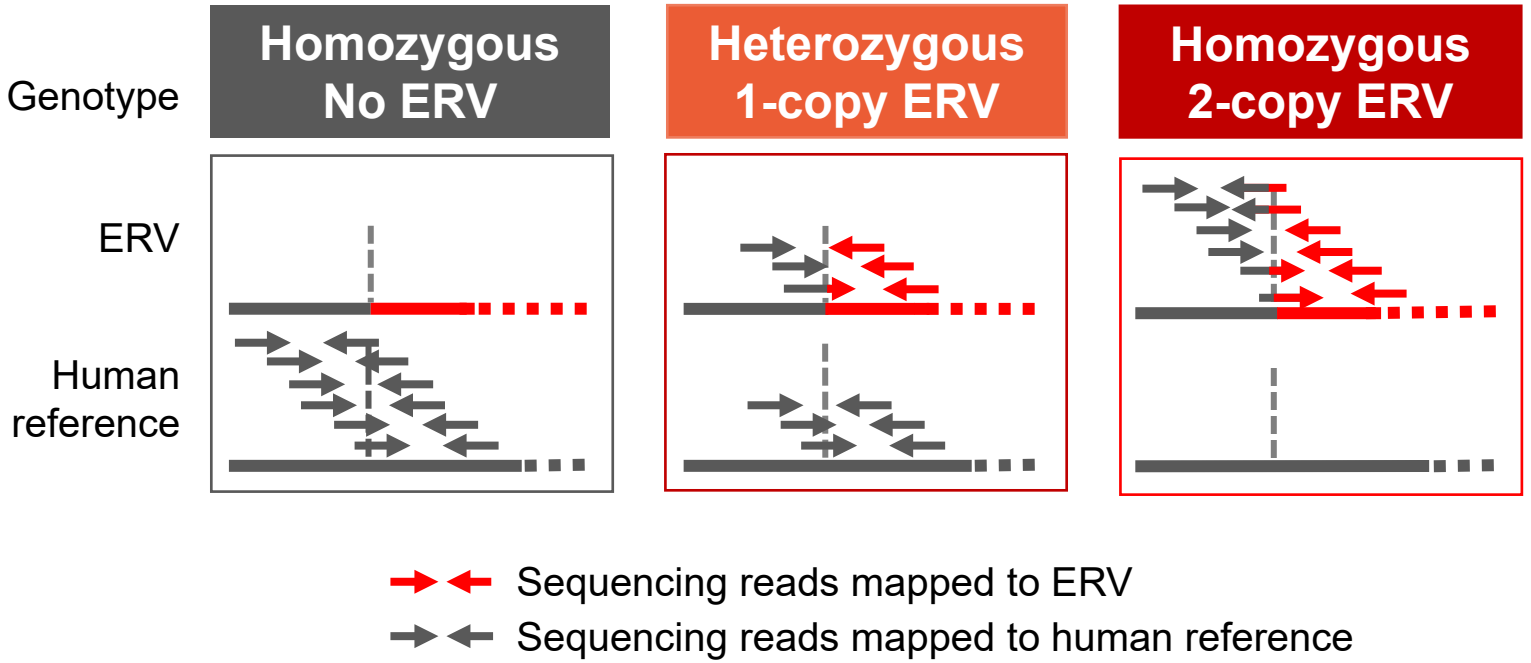
- NOT captured by SNP genotyping arrays
- NOT in GWAS imputation databases
- NOT in standard NGS pipelines (e.g., GATK)
- NOT in dbSNP or dbVar

ERV expression is:

- NOT in standard RNA-Seq pipelines
- NOT in RefSeq

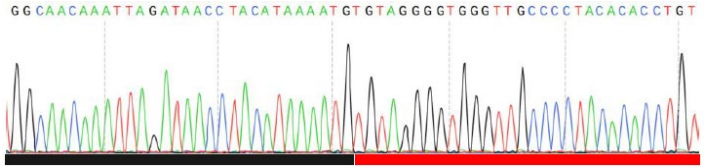
Existing ERV detection methods very limited

ERVcaller: accurately genotype each distinct individual ERV



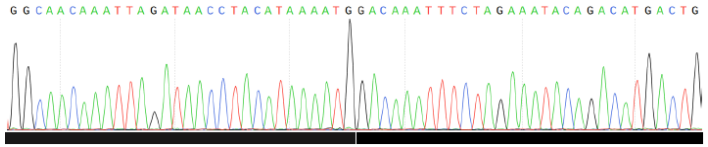
PCR/Sanger sequencing verification of ERVs

Allele with ERV insertion



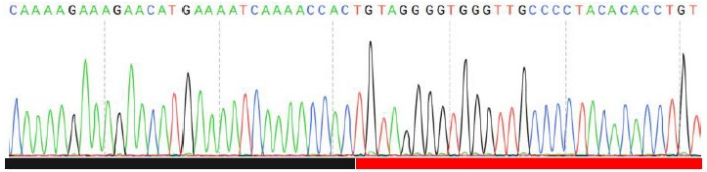
Chr11:60449895 (+) ERV-K: 969 (-)

Allele without ERV insertion



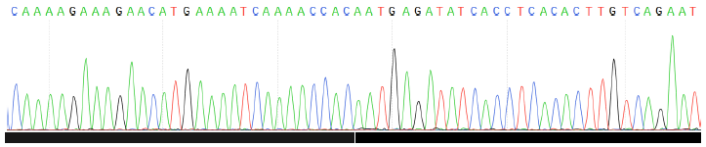
Subject
HG00731

Allele with ERV insertion



Chr12:44313657 (-) ERV-K: 969 (-)

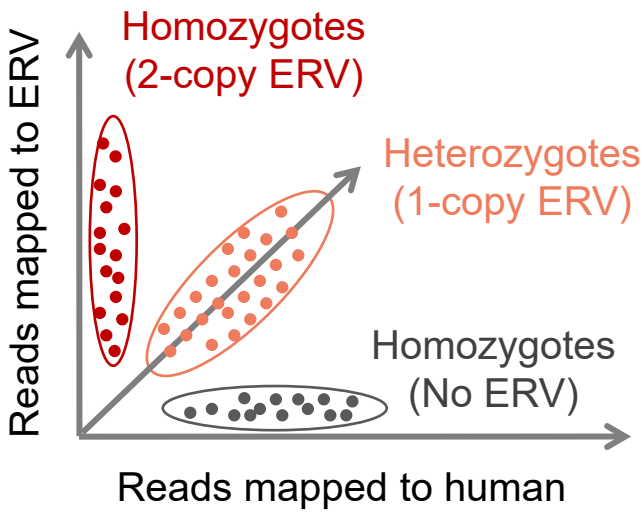
Allele without ERV insertion



Subject
HG00273

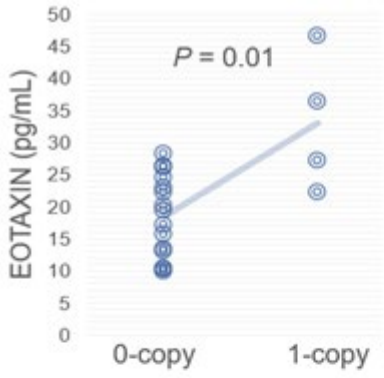
Human reference genome
ERV insertion

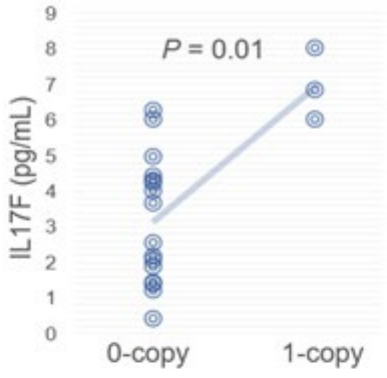
ERV-Wide Association Study (EWAS)

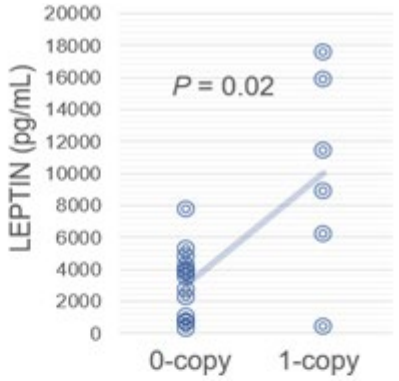


ERVcaller generates standard VCF and PLINK format of ERV genotypes
ready for genome-wide association study

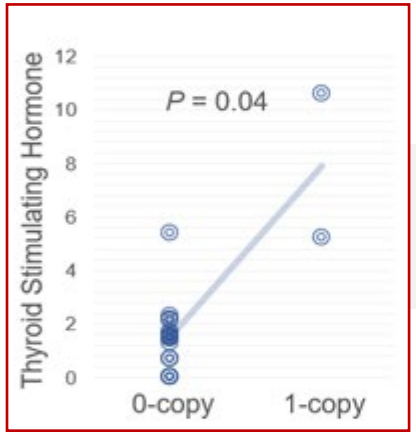
ERV genotypes associated with cytokines/blood measures in ME/CFS



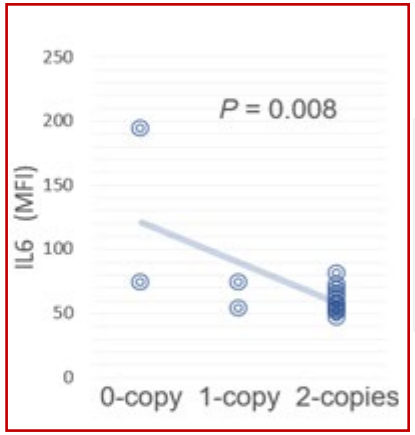




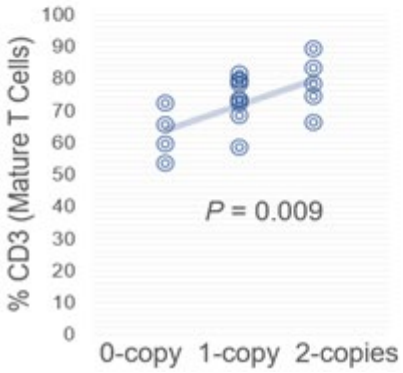
Positively correlated with ME/CFS severity (PMID: 28760971)

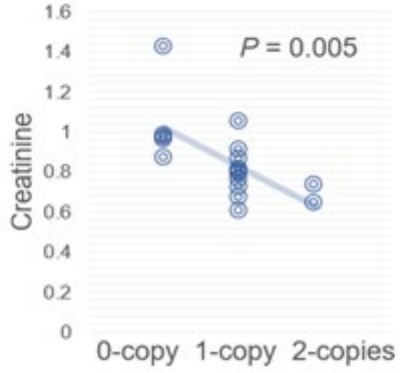


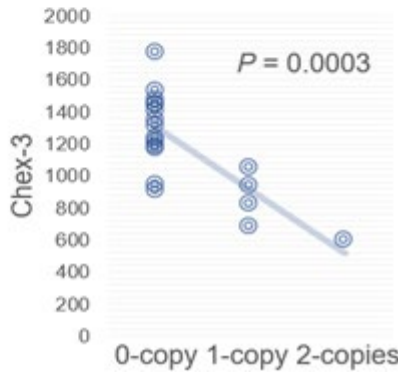
Predictor of poststroke fatigue (PMID: 30366976)



Regulator of mitochondria function in T cells (PMID: 27407249)





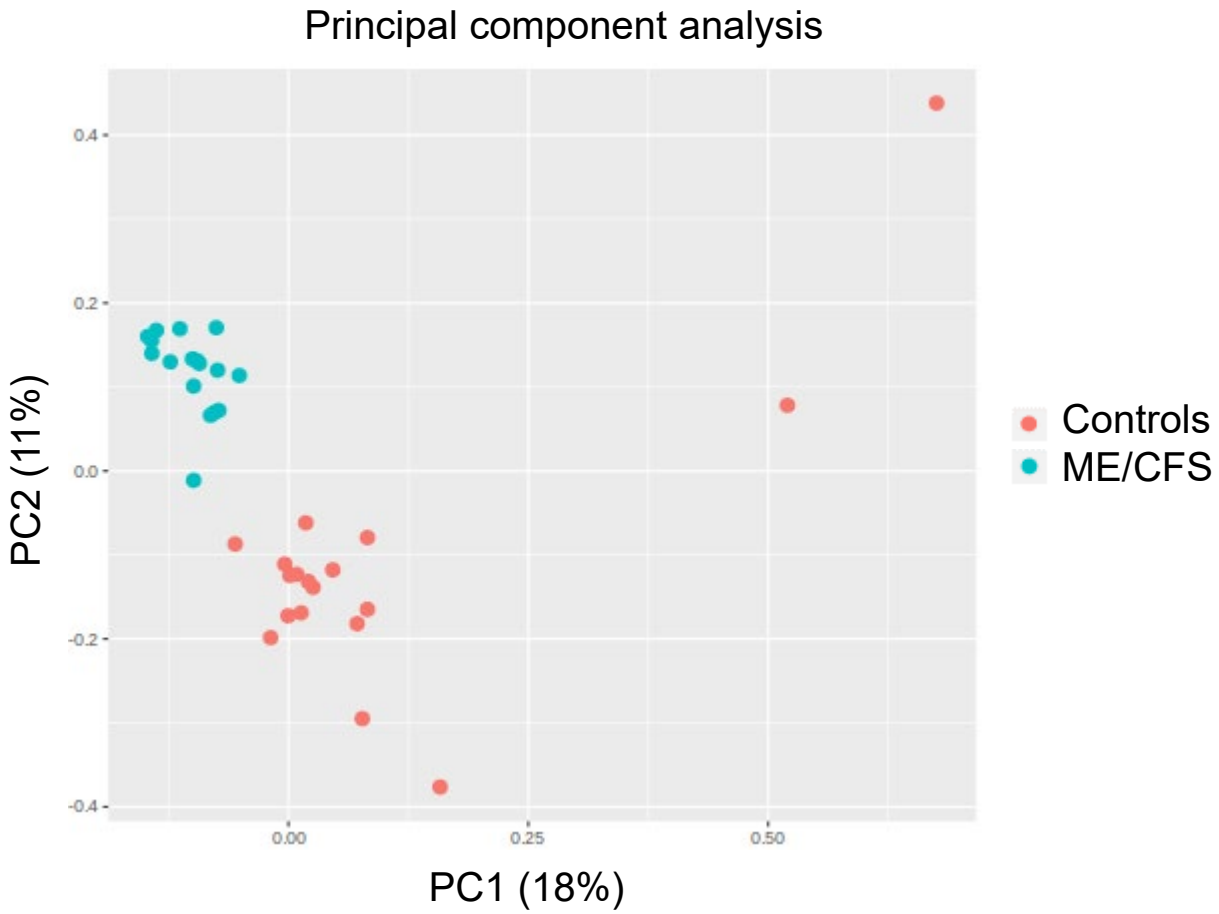


WGS from 20 bed-bound patients

8 individual ERVs (Mann-Whitney test)

Unpublished

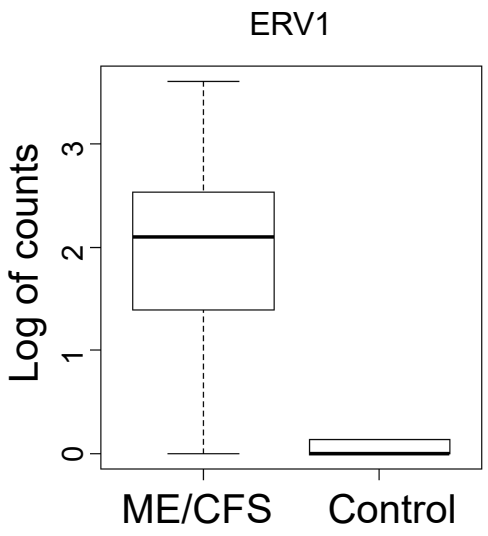
ERV transcripts separate ME/CFS

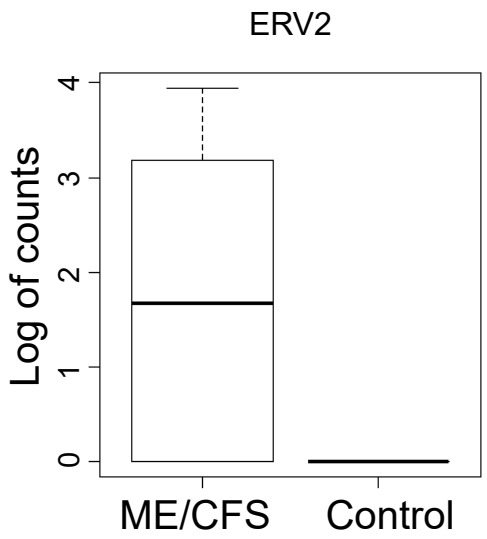


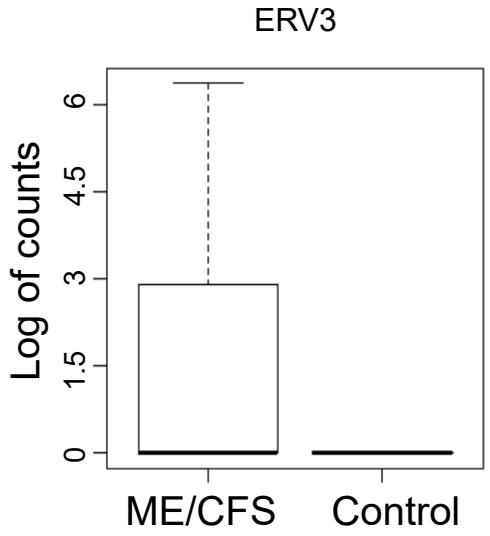
ERVs from RNA-Seq of ME/CFS-controls

Unpublished

ERV transcripts unique to ME/CFS







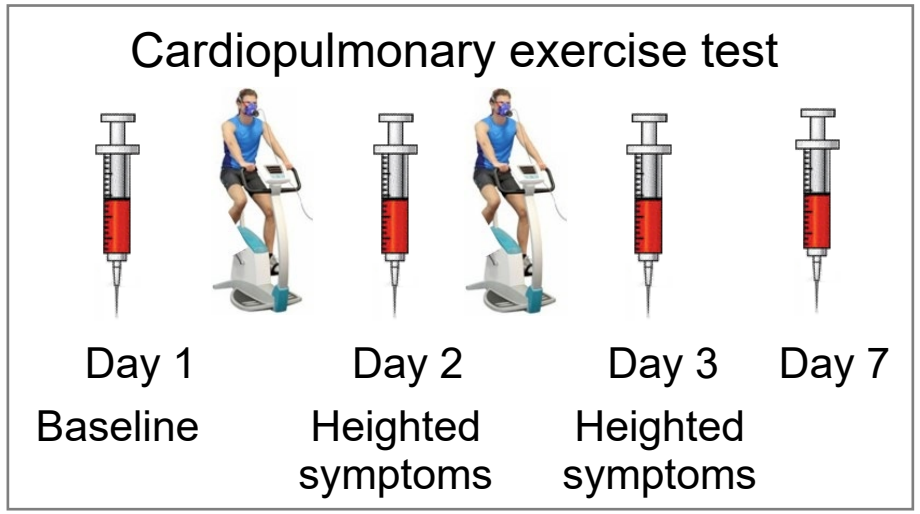
e.g., this ERV is located in *PLD5*

- Inflammatory immune response;
- Expresses in brain/ovary;
- PLD5 protein in mitochondria

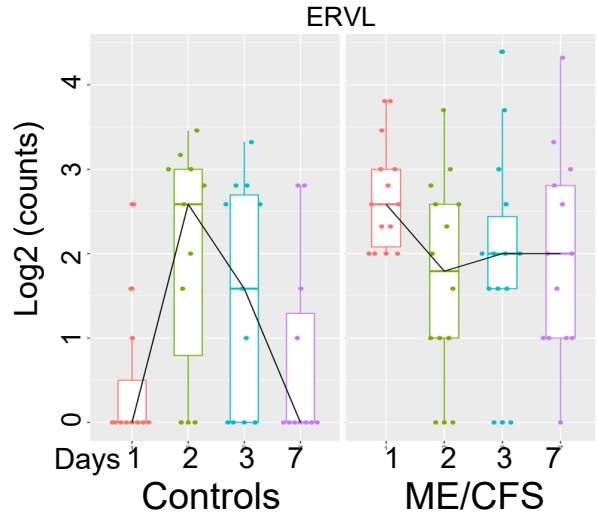
ME/CFS-specific ERVs distinguish diagnosis.

Unpublished

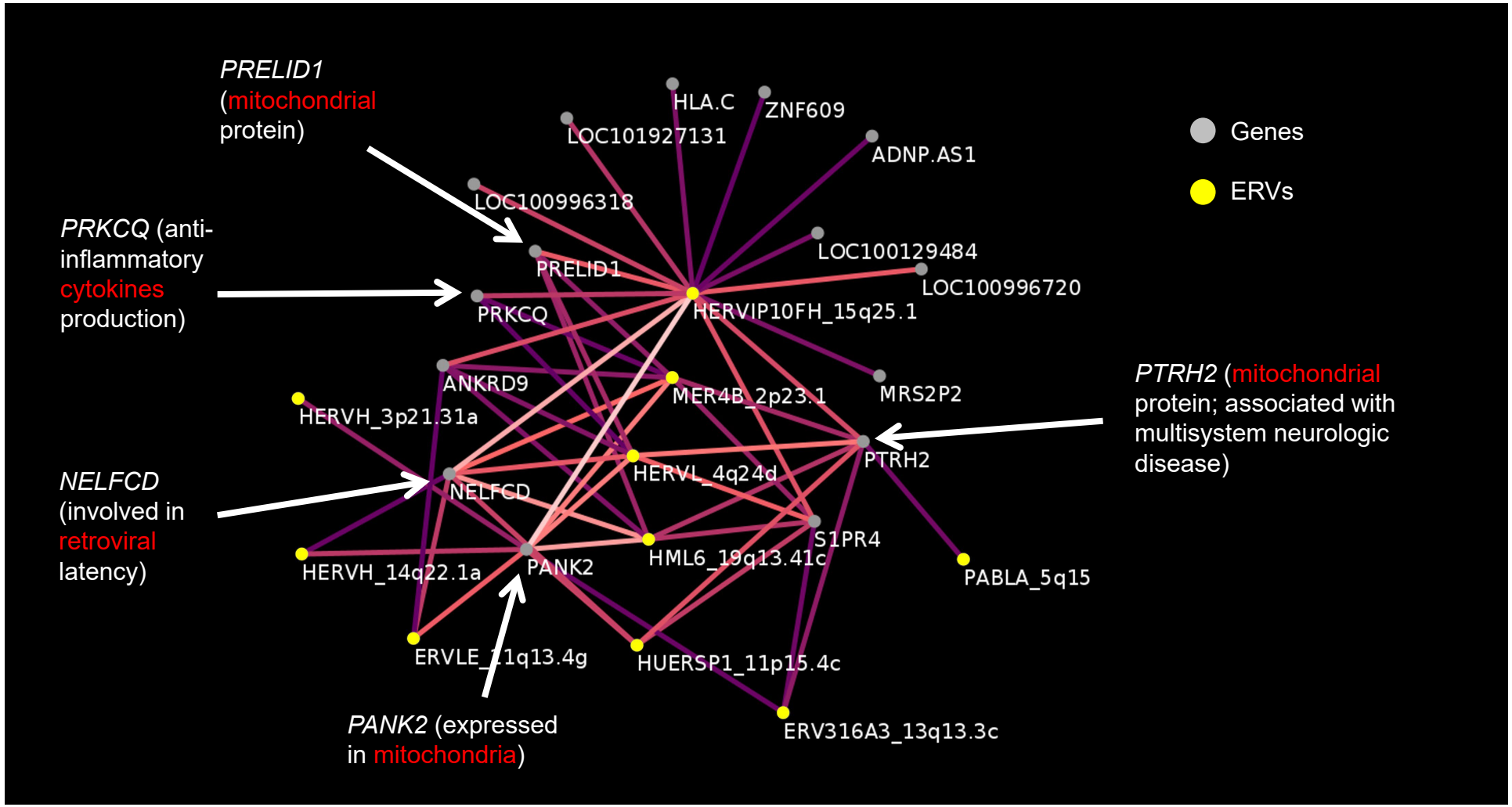
Exercise/stress to stimulate ME/CFS hallmark: post-exertional malaise (PEM)



RNA-Seq from 14 ME/CFS vs. 11 sedentary healthy controls before and after exercise



ERV-gene co-expression networks

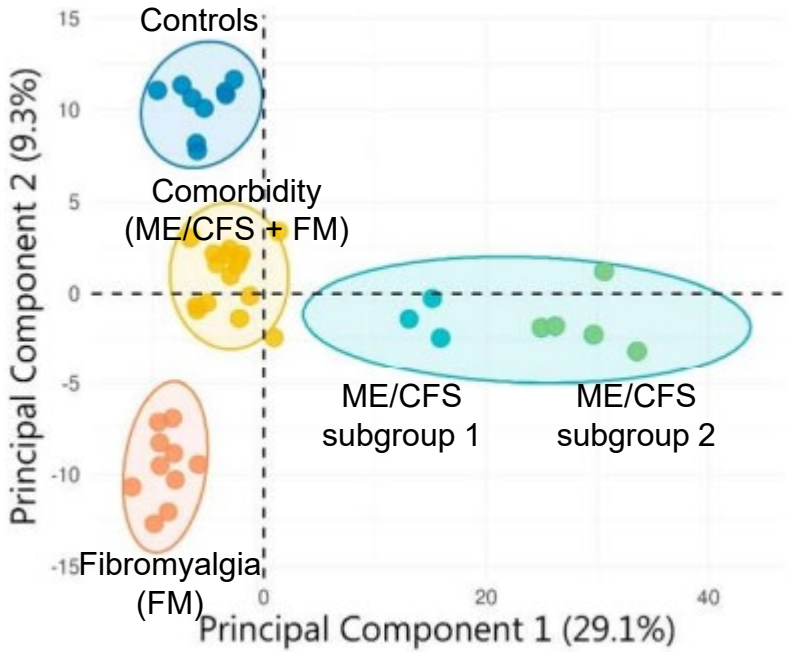


Light purple: stronger correlation. Only one module shown.

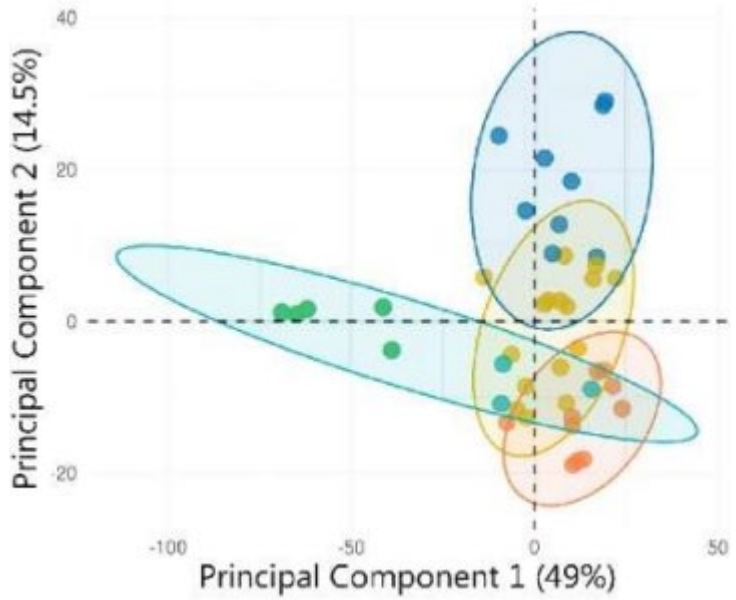
Unpublished

ERVs separate ME/CFS

ERVs



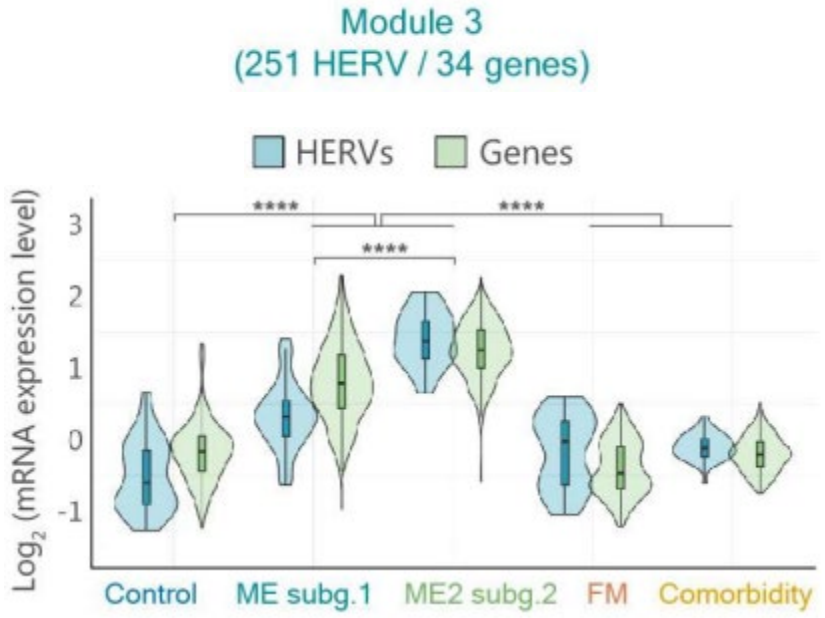
Genes



Affy HERV-V3 microarray

bioRxiv preprint doi:10.1101/2023.10.05.561025

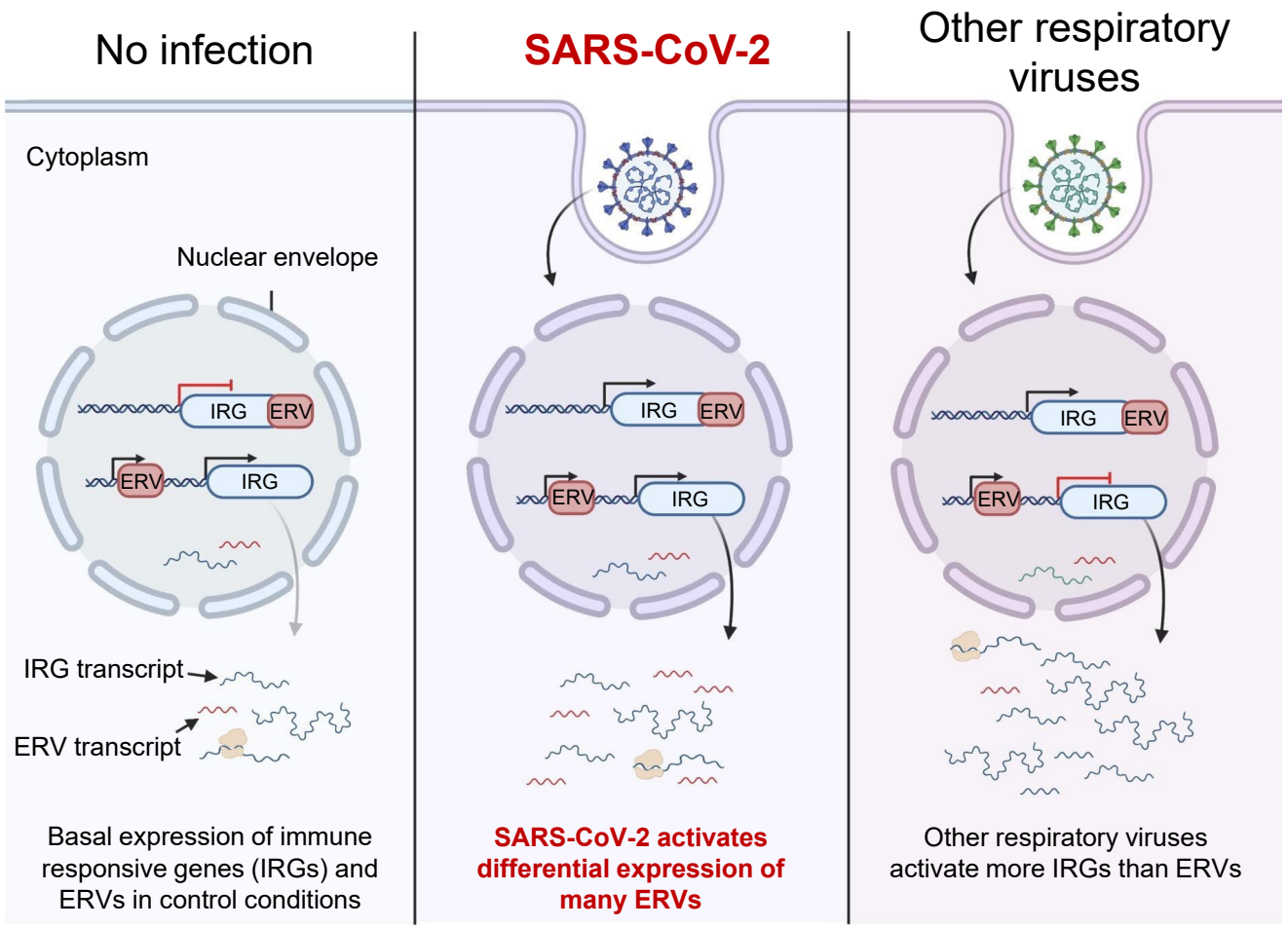
ERV expression correlates with immune response genes



ERVs-correlated genes involved in: Alpha-beta T cell activation, and Thelper 17 cell commitment

bioRxiv preprint doi:10.1101/2023.10.05.561025

SARS-CoV-2 can activate ERVs



Epstein-Barr virus

EBV can activate ERVs

PMID: 34731091

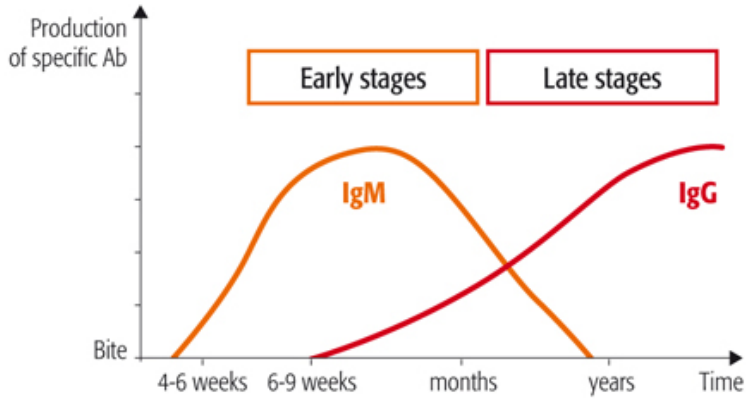
COVID

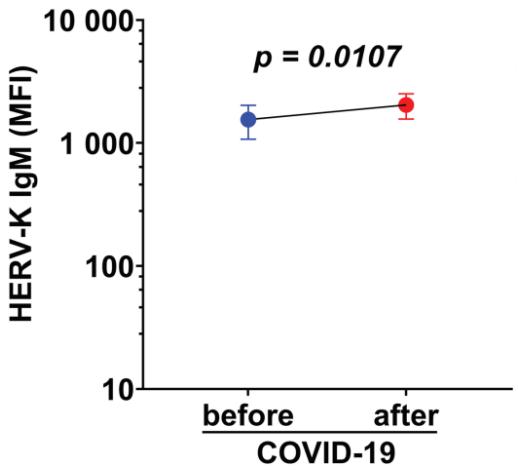
Long COVID

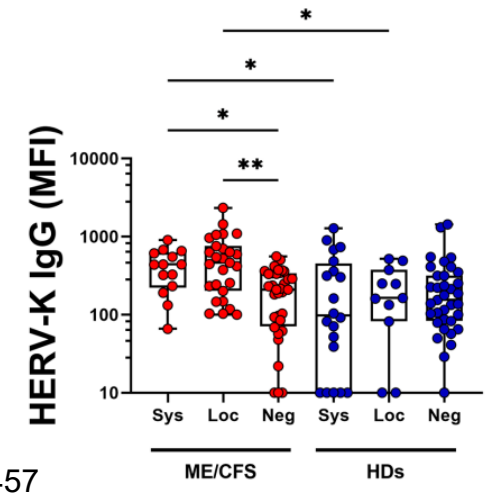
Flu

~~Long Flu~~

SARS-CoV-2: trigger of ERV reactivation

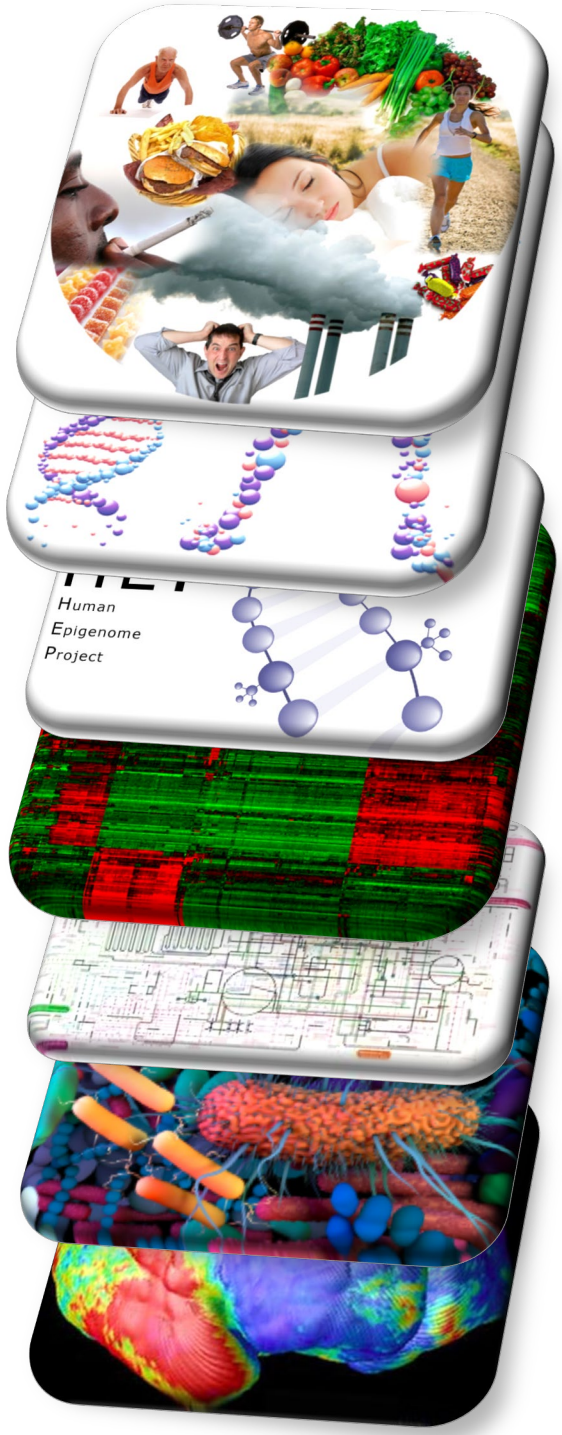






PMID: 36341457

SARS-CoV-2, even in its mild or asymptomatic form, is a potent trigger for ERV reactivation.



Exposome (virome, etc.)

Genome

Epigenome

Transcriptome

Metabolome/Proteome

Microbiome

Imaging

Innovative methods

Causes

Diagnostic biomarkers

Treatment

Approaches to prevent

Acknowledgements

Thanks to patients and care givers

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Ronald Davis / Wenzhong Xiao (Stanford / Harvard)

Maureen Hanson (Cornell)

Alain Moreau (Université de Montréal)

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HOPE

OpenMedicine Foundation

NIH NIAID

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