

UNIVERSITY OF BERGEN, DEPARTMENT OF BIOMEDICINE

The International ME/CFS Conference 2025
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ME/CFS:
**Mapping the changed patterns of blood metabolites and
proteins to extract pathomechanistic insights**

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Research - measurable findings in the bodies of ME patients

- Changes in autonomic functions
- Changes in the immune system
- Neuroinflammation
- Changes in cellular energy metabolism
- Changes in blood/oxygen supply
- Possible disease-causing factors in the blood
- Possible risk genes
- Possible changes in gut flora

Research - current hypotheses for the mechanism behind ME

- Viruses that remain in the body
 - Persistent inflammation in the body
 - Metabolic disturbances
 - Immune system errors - autoimmunity
- *Perhaps multiple, or other, mechanisms may be relevant*

Conceptual model for mechanism - ME/CFS

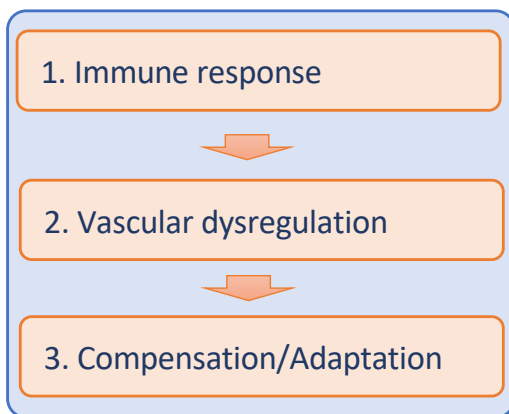
The Journal of Clinical Investigation

VIEWPOINT

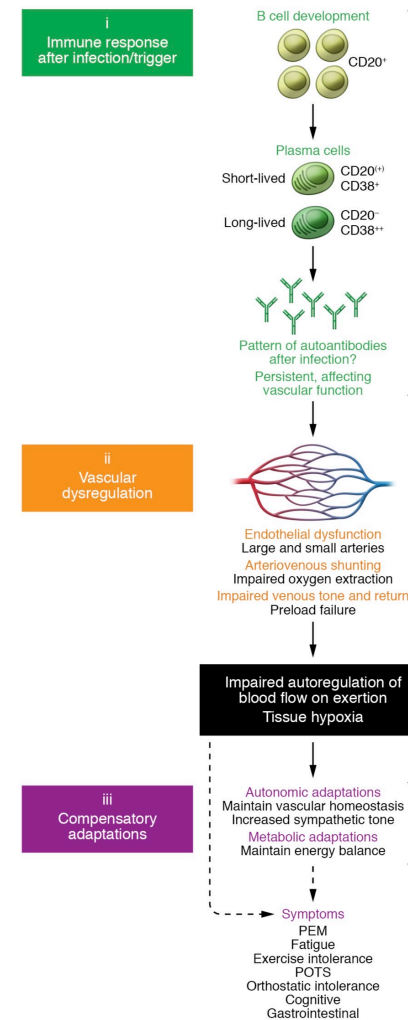
Pathomechanisms and possible interventions in myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)

Øystein Fluge,^{1,2} Karl J. Tronstad,³ and Olav Mella^{1,2}

¹Department of Oncology and Medical Physics, Haukeland University Hospital, Bergen, Norway. ²Department of Clinical Science and ³Department of Biomedicine, University of Bergen, Bergen, Norway.



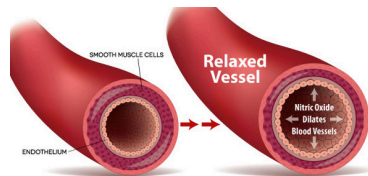
“In conclusion, we suggest that ME/CFS in a subgroup of patients is a variant of an autoimmune disease, with a role for B cells/plasma cells and a pattern of autoantibodies emerging after infection and persisting over time. Key symptoms may result from the consequent functional disturbance in blood flow autoregulation causing tissue hypoxia on exertion and associated autonomic and metabolic responses to maintain energy homeostasis.”



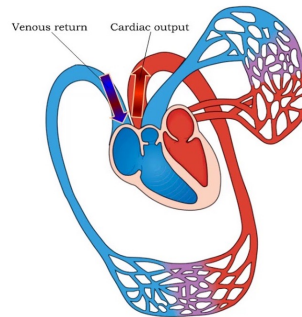
Research - Impaired blood supply/perfusion

- Dysfunction in small arteries – vessel wall (endothelial cells) (e.g., Sørland et al, 2021, Front Med)
- Impaired circulation and reduced oxygen uptake during activity (e.g., Joseph et al, 2021, Chest)
- Less blood to the brain (e.g., van Campen et al, 2021, J Transl Med)

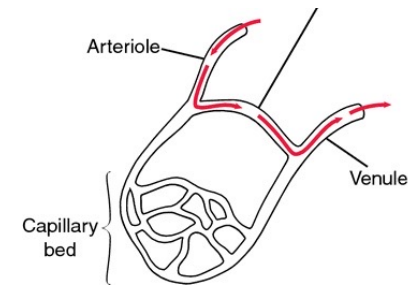
Endothelial dysfunction



Impaired circulation



«Shunting»



Research – Metabolic changes in ME

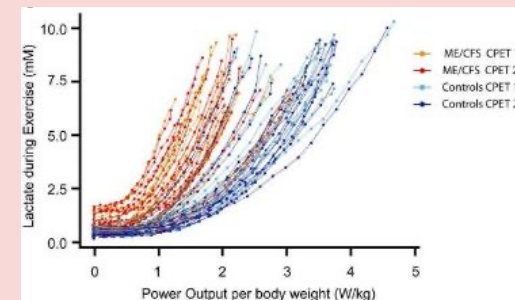
Exertion-triggered changes:

- Overproduction of lactic acid during activity (lactate) (e.g., Lien K et al, Physiological Reports, 2019)

Persistent changes:

(Fluge et al, JCI Insight, 2016; Hoel et al, JCI Insight, 2021; +)

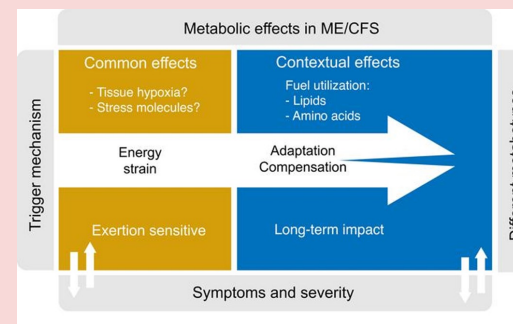
- Alternative use of energy sources
- Changes in key enzymes/proteins
- Changes related to metabolic hormones



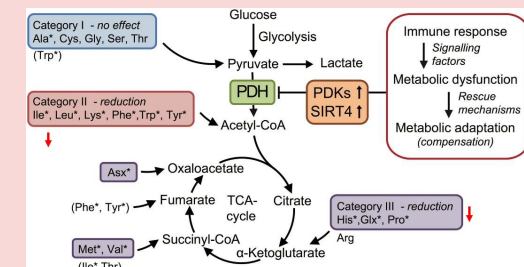
Lien K et al, Physiological Reports, 2019

Metabolic adaptations – stress responses:

- Exercise
- Starvation, fasting, caloric restriction
- Hypoxia, metabolic stress
- Aging, cancer, neurodegeneration, diabetes, CVD +++

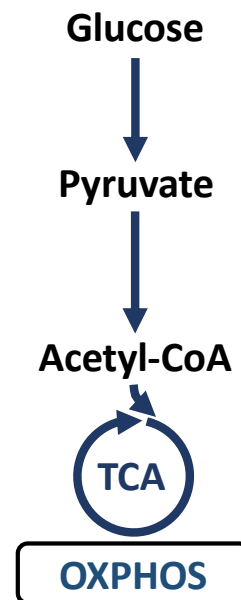


Hoel et al, JCI Insight, 2021



Fluge et al, JCI Insight, 2016

A possible cause of metabolic energy stress in ME/CFS - Hypoxia



A possible cause of metabolic energy stress in ME/CFS - Hypoxia

Amplified hypoxia effects

Cause a metabolic shift towards increased glycolysis and reduced OXPHOS

Lack of O₂

Possible causes

- reduced oxygen supply to cells (blood/vascular effects)
- mitochondrial dysfunction
- metabolic diseases

Consequences:

- Metabolic compromises
- More lactate
- Struggle for ATP
- Amplified during activity

Negative physiological impact

- lowered anaerobic threshold
- exercise intolerance
- post-exertional malaise (PEM)?



Metabolic adaptations to energy stress

Persistent metabolic adaptations through inherent regulatory frameworks

Purpose: To secure and maintain energy supply

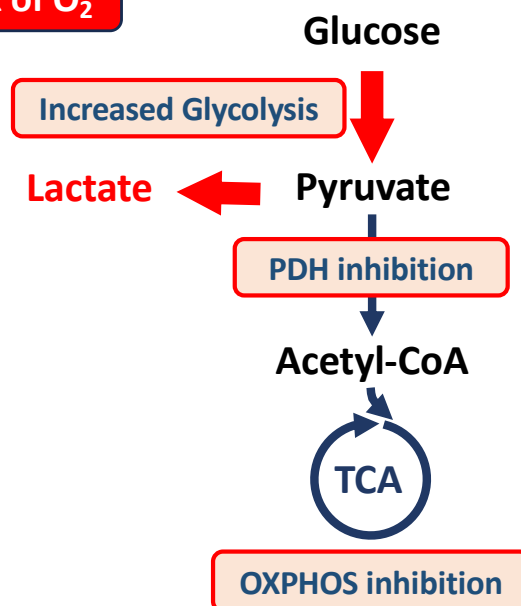
- context dependent programs (starvation, exercise, etc)
- fuel switching (metabolic flexibility)
- systemic impact

Protection effects

- counteract the effects of hypoxia/energy stress
- alternative pathways

Positive physiological impact

- may have mitigating influence on symptoms
- influenced by genetics, diet, lifestyle, exercise, disease, medication, supplements, etc



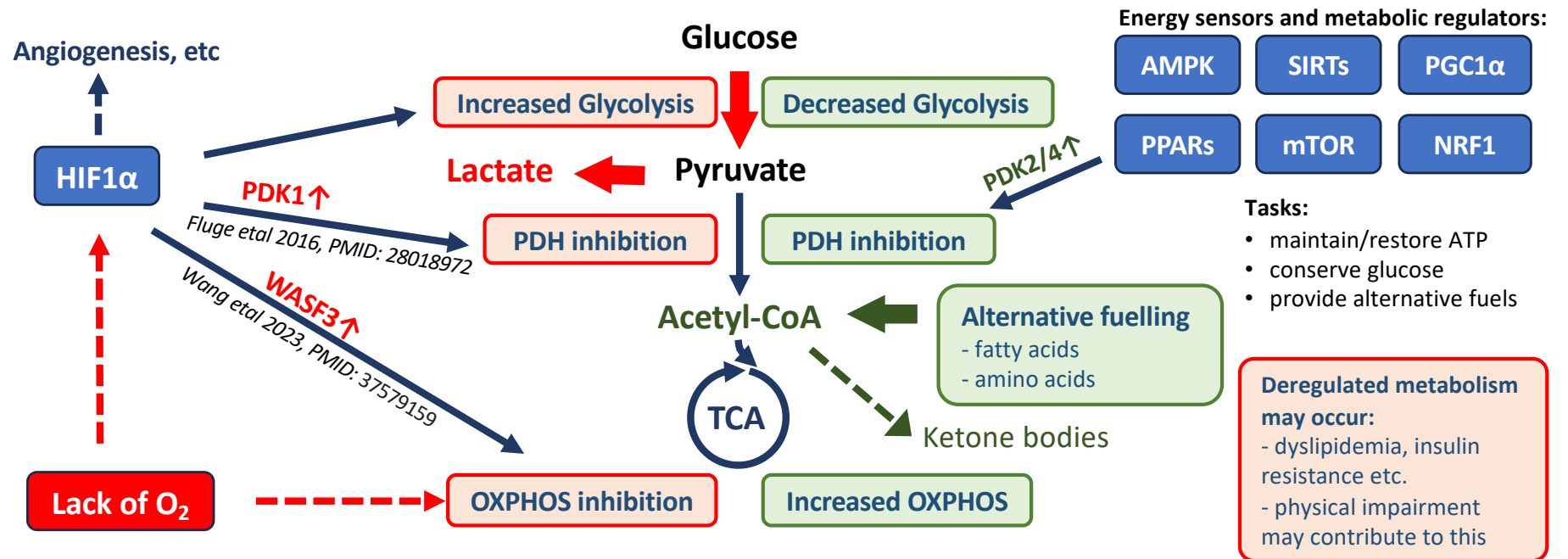
Hypoxia and metabolic adaptations in ME/CFS

Amplified hypoxia effects

Cause a metabolic shift towards increased glycolysis and reduced OXPHOS

Metabolic adaptations to energy stress

Persistent metabolic adaptations through inherent regulatory frameworks



Metabolic changes in ME/CFS - impact and treatments?

Amplified hypoxia effects

Cause a metabolic shift towards increased glycolysis and reduced OXPHOS



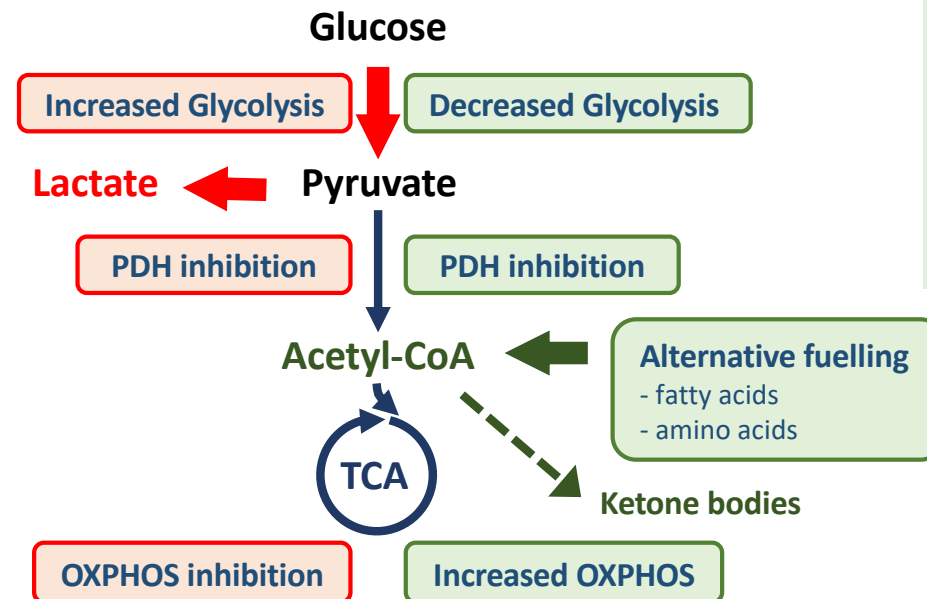
Metabolic adaptations to energy stress

Persistent metabolic adaptations through inherent regulatory frameworks

May be improved by?

- supplements
- drugs
- O₂, HBO

- physical activity



May be improved by?

- diet
- supplements
- drugs

- physical activity

Metabolic effects in ME/CFS – a key to understand the disease

1. Common features of energy strain
- possibly due to tissue hypoxia

2. Contextual metabolic differences :

Metabotype 1 (M1):

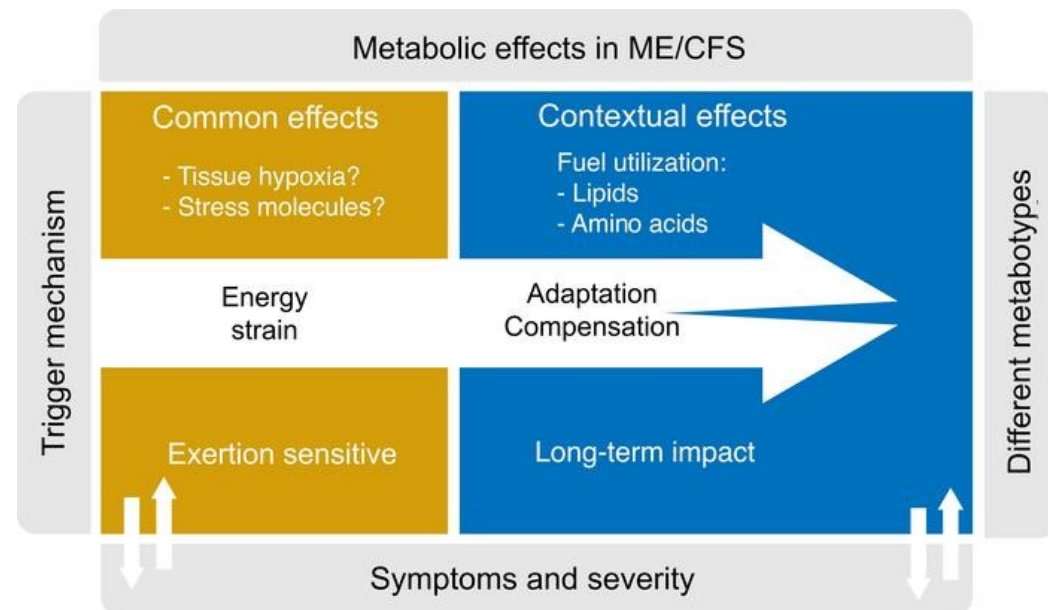
- Similarity to fasting (or endurance activity)
- increased NEFAs and ketone bodies, low TAG

Metabotype 2 (M2)

- Similarity to dyslipidemia
- High TAG, low NEFAs

Metabotype 3 (M3)

- less effects
- overlap with both M1 and M2



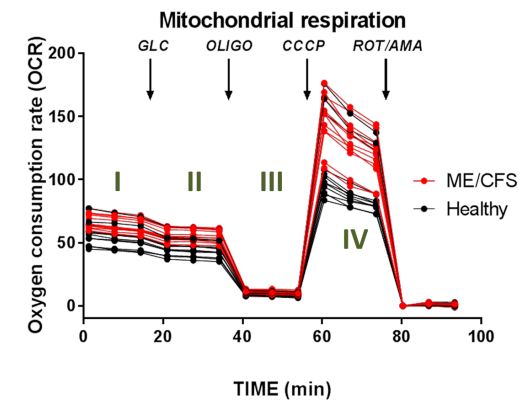
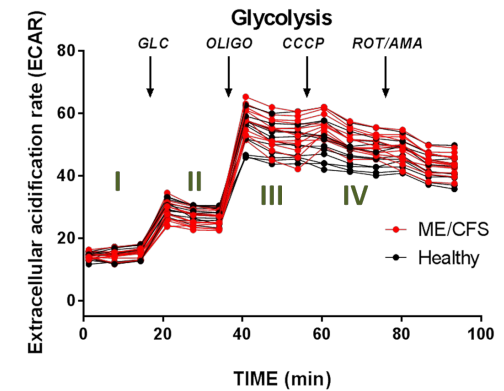
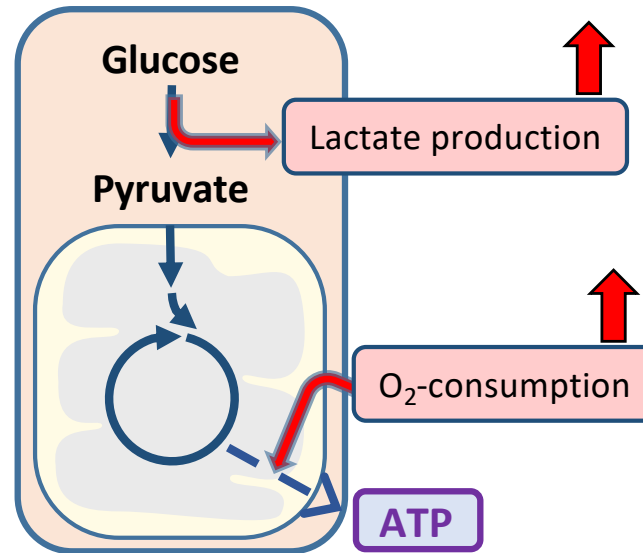
Laboratory studies:

- something in ME/CFS blood stresses cellular energy metabolism

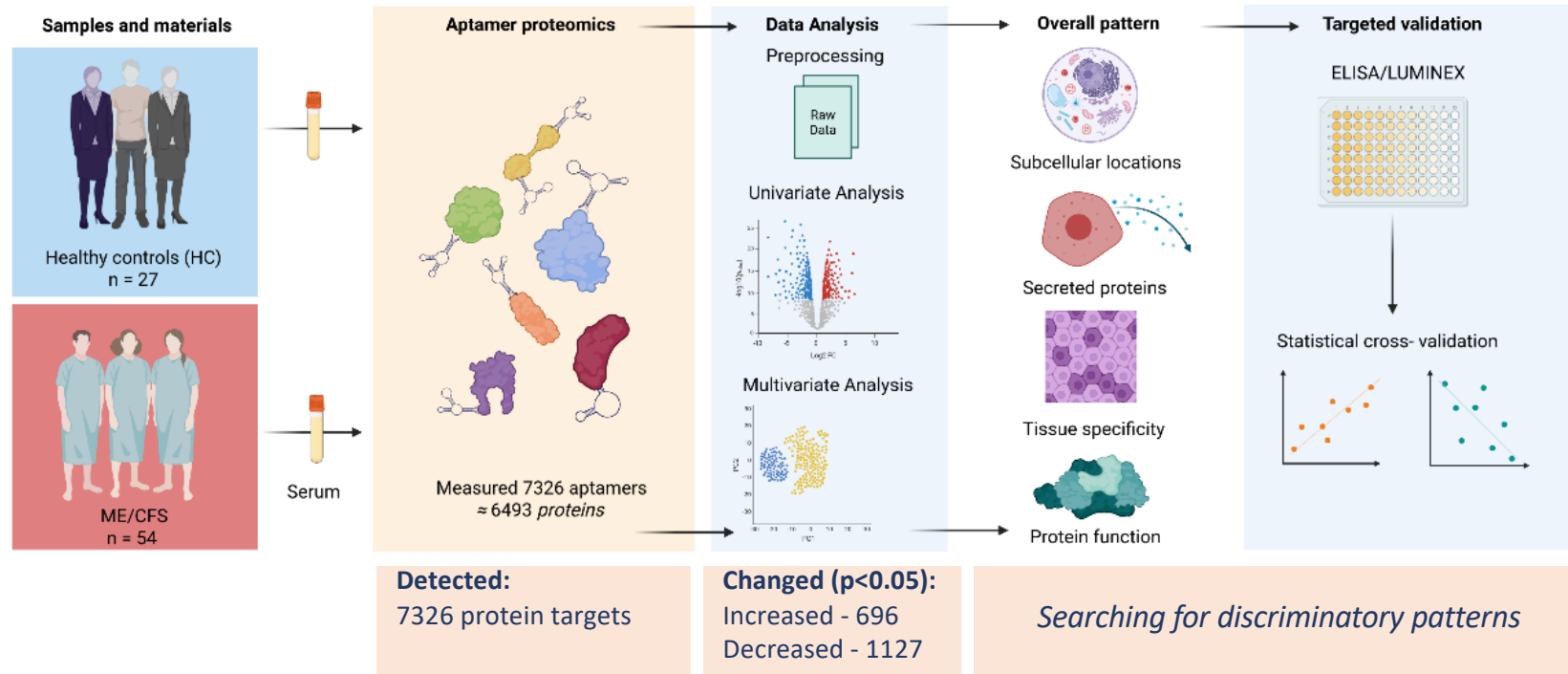
ME/CFS serum affects healthy muscle cells:

- Increased oxygen consumption
- Increased "exertion-triggered" lactate production

Healthy muscle cells cultured in the presence of ME/CFS serum



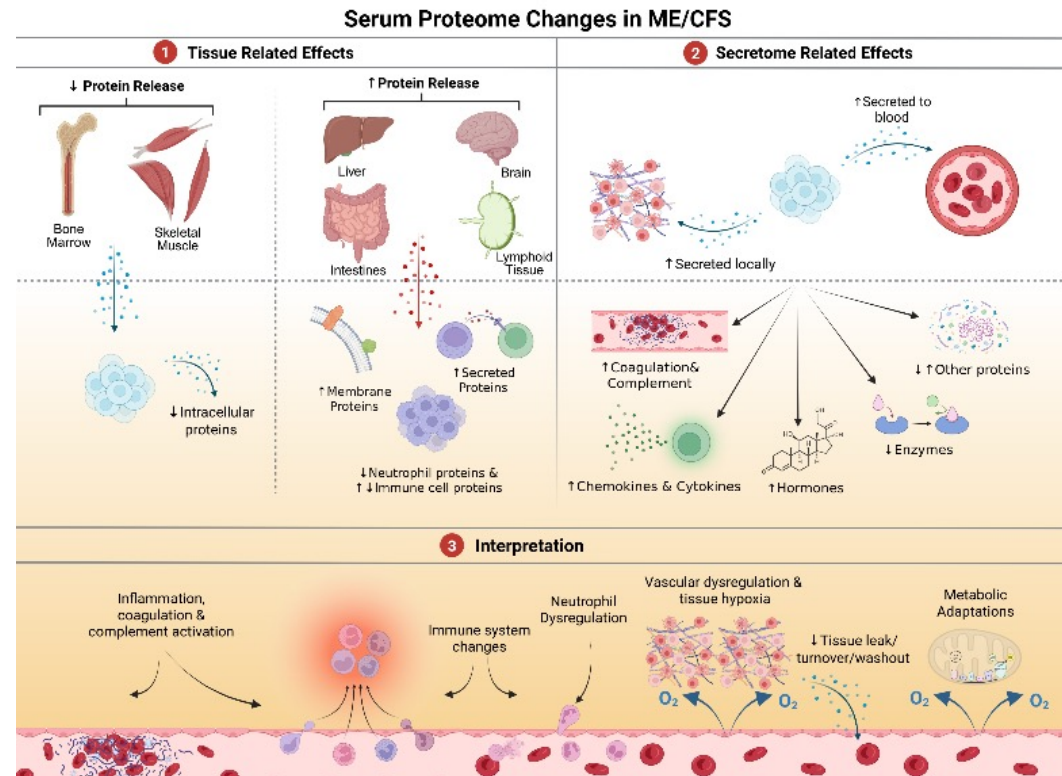
A new ME/CFS serum proteome study



Findings:

- Multiorgan impact
- Immune dysregulation
- Secretome: systems-level impact
- Metabolic adaptations

The multiscale patterns converge toward a mechanism involving immune, vascular, and metabolic dysregulation



Acknowledgements



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THANK YOU!



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