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REPORT OF PROGRESS ME/CFS: OCT 2016

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FORGIVE AND FORGET…
US FEDERAL AGENCIES ARE RAMPING UP SUPPORT

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- **CDC. MCAM** http://www.cdc.gov/cfs/programs/clinical-assessment

  Multi-site Clinical Assessment of ME/CFS. 2012-current yearly follow up

  Enrolling from 7 ME/CFS clinics—470 patients and 2013 HC

  Questionnaires. (MFI-20, SF-36, CDC-SI, PROMIS)

  Physical exam. 10 min NASA Lean test and Rhomberg testing

  Biological sample collection

  Adding: pediatric/adolescent, early onset, homebound cases, chronic illness controls

  Exercise [CPET] and cognition for a subset

  NKC function/cytotoxicity

- An increasingly valuable resource for following patients longitudinally and facilitating future research

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- **CFSAC** (CFS Advisory Committee to the Secretary of Health, HHS)
  - Functioning more like it was originally intended
  - 13 members: seven shall be biomedical research scientists with demonstrated expertise in biomedical research applicable to ME/CFS; three shall be individuals with expertise in health care delivery, private health care services or insurers, or voluntary organizations concerned with the problems of individuals with ME/CFS, and at least three shall be patients or caregivers affected by ME/CFS. All voting members of this Committee are classified as special government employees (SGEs) and are subject to government ethics rules.
  - 8 non-voting *ex officio* members. The *ex-officio* membership will comprise representation from the Agency for Healthcare Research and Quality, Centers for Disease Control and Prevention, Food and Drug Administration, Health Resources and Services Administration, National Institutes of Health, Social Security Administration, U.S. Department of Veteran Affairs and the Department of Defense.
  - https://www.hhs.gov/ash/advisory-committees/cfsac/index.html

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IOM report: Clinical Diagnostic Criteria for ME/CFS to improve rate of diagnosis

- http://www.nationalacademies.org/hmd/Activities/Disease/DiagnosisMyalgicEncephalomyelitisChronicFatigueSyndrome.aspx (the plan)
- http://nationalacademies.org/HMD/Reports/2015/ME-CFS.aspx (the reports)
- https://www.ncbi.nlm.nih.gov/pubmed/25695122 (the published report)

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P2P Pathways to Prevention Report

- https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/me-cfs
- https://prevention.nih.gov/programs-events/pathways-to-prevention/workshops/me-cfs/workshop-resources#finalreport

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News Release by director of NIH Francis Collins PhD, Thursday Oct 29, 2015

- https://www.nih.gov/news-events/news-releases/nih-takes-action-bolster-research-myalgic-encephalomyelitis/chronic-fatigue-syndrome
- **National Institutes of Health:** NIH, the nation's medical research agency, includes 27 Institutes and Centers and is a component of the U.S. Department of Health and Human Services. NIH is the primary federal agency conducting and supporting basic, clinical, and translational medical research, and is investigating the causes, treatments, and cures for both common and rare diseases. For more information about NIH and its programs, visit www.nih.gov

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- Interagency ME/CFS collaborative: HRSA, FDA, AHRQ, CDC, NIH, SSA, DoD, VA
- Trans-NIH Working Group:
  - https://www.nih.gov/research-training/medical-research-initiatives/mecfs
- Goals:
  - Advance research on the cause, prevention, diagnosis, pathophysiology and treatment of ME/CFS
  - Encourage biomedical research investigators and organizations to study ME/CFS
  - Communicate ME/CFS research information with NIH Institutes and Centers

- Chair: Walter Koroshetz MD
  - Director NINDS

Vicki Whittemore PhD
NIH rep CFSAC

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- **NIH Intramural study---** researchers from NINDS, the NIAID , NINR, National Heart, Lung, and Blood Institute. Explore the clinical and biological characteristics of ME/CFS following a probable infection to improve understanding of the disease's cause and progression. https://www.nih.gov/mecfs/nih-me-cfs-clinical-study or http://mecfs.ctss.nih.gov/
- **NIH is increasing funding** for extramural research, facilitated by all of the above
  - Notices of Intent to Publish a Funding Opportunity….
  - NOT-NS-17-003 **ME/CFS Collaborative Research Centers** (CRCs) (U54)
    - https://grants.nih.gov/grants/guide/notice-files/NOT-NS-17-003.html
  - NOT-NS-17-004 **ME/CFS Data Management and Coordinating Center** (DMCC) (U01)
    - https://grants.nih.gov/grants/guide/notice-files/NOT-NS-17-004.html

THINGS WE ALREADY KNOW ABOUT ME/CFS

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- **Function is impaired** and the illness is a **global, systemic** process (IOM/SEID)
  - SF36 evidence. Low anerobic threshold during exercise testing (CPET)
- **PEM**: Illness symptoms worsen with exertion of any type (physical, cognitive, orthostatic)
  - Gene expression. CPET, especially if tested on day 1 and 2
- **Central nervous system and autonomic nervous system** involvement supported by disturbed sleep, cognitive impairment, widespread pain, orthostatic intolerance.
  - Neuroimaging: PET, qEEG, fMRI. Abnormal spinal fluid.
  - Tilt Table testing. 10 minute NASA Lean Test (bedside testing for OI)
- **Immune disturbances**, but not clear, although Natural Killer Cell (NKC) cytotoxicity/function and cytokine patterns are supportive.
- Phases of illness may present differently. Early onset versus later chronic illness cytokines

THINGS WE ALREADY KNOW ABOUT ME/CFS

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- No one has been able to decide on a "new name". We just argue.
- Our many ME, ME/CFS, ME case definitions are problematic, to put it mildly. We argue.
- There is an equally problematic overlap of fibromyalgia (FM), POTS, MCS, and many other case definitions. We are not able to be precise in diagnosis.
- We have not been able to produce objective biomarkers to improve diagnosis and direct treatment using the current diagnostic criteria and approaches
- People with ME/CFS are suffering and have not received good medical care or social support

WHAT DID I LEARN IN OCTOBER 2016?

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Scientific research clearly supports that ME/CFS is a biological disease.

We are never going back. Everything has changed.

Research advances will become exponential

Clinical medicine is totally unprepared for what is happening.

NEUROLOGIC ABNORMALITIES ARE MEASURABLE IN THE CLINICAL SETTING

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- Rhomberg balance testing abnormalities are associated with abnormal 10 min stand test (Miwa, Japan)
- The 10 min NASA Lean test can be used in place of Tilt Table Testing (BHC poster, Wall)
- Cognitive Testing more suited to ME/CFS should be coming soon
  - CogState screening battery may pave the way (CDC MCAM, Lang)
- Small fiber poly neuropathy (SFPN) can be diagnosed by a combination of physical exam findings and skin biopsy. May contribute to widespread pain and autonomic dysfunction

WE HAVE A FEW TREATMENT TOOLS AND MAY SOON HAVE MORE

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- LDN works better than opioids in FMS (Younger, Univ of Alabama)
- Treatments for orthostatic intolerance, including orthostatic hypotension and POTS are available (Rowe, Johns Hopkins)
- Methylphenidate, and/or methylphenidate with micronutrients, helps some patients
  - Synergy Trial, KPAX Pharmaceuticals
- Rituximab, a monoclonal antibody drug that targets, kills and depletes B-cells with CD20 receptors, seems to treat the whole disease process in some ME/CFS patients. Why?
- N-acetylcysteine alleviates the glutathione deficit seen in the brain using proton magnetic resonance spectroscopy (MRS). (Shungu, Weill Cornell Medicine) *Glutathione is a critical molecule for many cellular pathways, and N-acetylcysteine is a precursor to the formation of glutathione*

HOPE FOR OTHER OBJECTIVE DIAGNOSTIC TESTS

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- Post-exercise cytokines differ between ME/CFS and Healthy Controls (Montoya, Stanford)
- Circulating cytokines in ME/CFS are associated with disease severity (Montoya, Stanford)
- Genomics reveals a systemic inflammatory response in ME/CFS (Montoya, Stanford)
- The microbiome of ME/CFS is different than HC. Bacterial and viral communities. Less diversity. "Leaky gut" may lead to inflammatory state (Giloteaux, M Hansen, S Levine, et al)
- Metabolomics may show a signature of illness subsets, but also provide important clues to the cause and physiology of the illness (Naviaux, Hansen, others coming soon)
- Mitochondria? Electron micrograph images of muscle biopsies show mitochondrial degeneration. Oxidative damage and increased activity of antioxidant enzymes in muscle.
- Blood lactate rises more quickly in the second CPET test in ME/CFS (Lein, Univ of Oslo)

ME/CFS IS A HYPOMETABOLIC STATE (LOW ENERGY)

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- Low anaerobic threshold during CPET (Snell, Vermuelen, Keller in past publications)
- Metabolomics, in one published study, suggest a very low or hypometabolic state (Naviaux, PNAS, 2016) due to abnormal metabolite levels, especially sphingolipids, phospholipids, purines, riboflavin and branched amino acids…

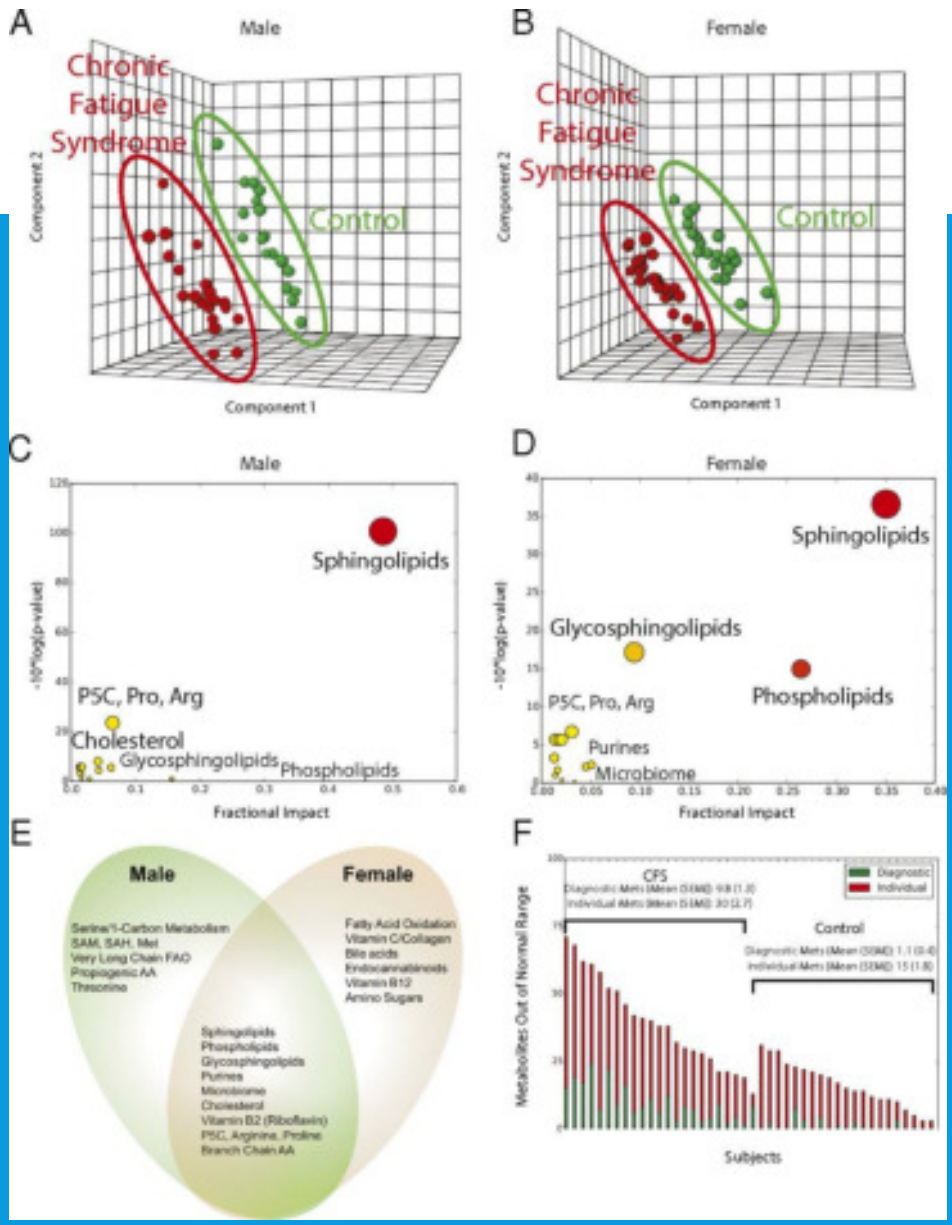
Metabolomics is the scientific study of chemical processes involving metabolites. Specifically, metabolomics is the "systematic study of the unique chemical fingerprints that specific cellular processes leave behind", the study of their small-molecule metabolite profiles.

- New metabolomics data presented by Maureen Hansen, publication pending. The metabolic signature of ME/CFS is very similar to "over training syndrome" in athletes.

Metabolomic diagnosis of CFS. (A) Males. (B) Females

Robert K. Naviaux et al. PNAS doi:10.1073/pnas.1607571113
Metabolic features of chronic fatigue syndrome.

- The products of several metabolic pathways distinguish ME/CFS from HC
- Male and Female ME/CFS share common pathways, but also have sex-specific pathways
- Sphingolipids stand out



SPHINGOLIPIDS ARE ASSOCIATED WITH BRAIN CELL MEMBRANES

- Sphingolipids are commonly believed to protect the cell surface against harmful environmental factors by forming a mechanically stable and chemically resistant outer leaflet of the plasma membrane lipid bilayer [Wikipedia]
- "A highly conserved lipid component of cell membranes involved in the formation of lipid raft domains that house many of the receptors and cell-to-cell signaling factors involved in regulating cell division, maturation, and terminal differentiation". (Cutler RG et al. Mech Ageing Dev. 2011)

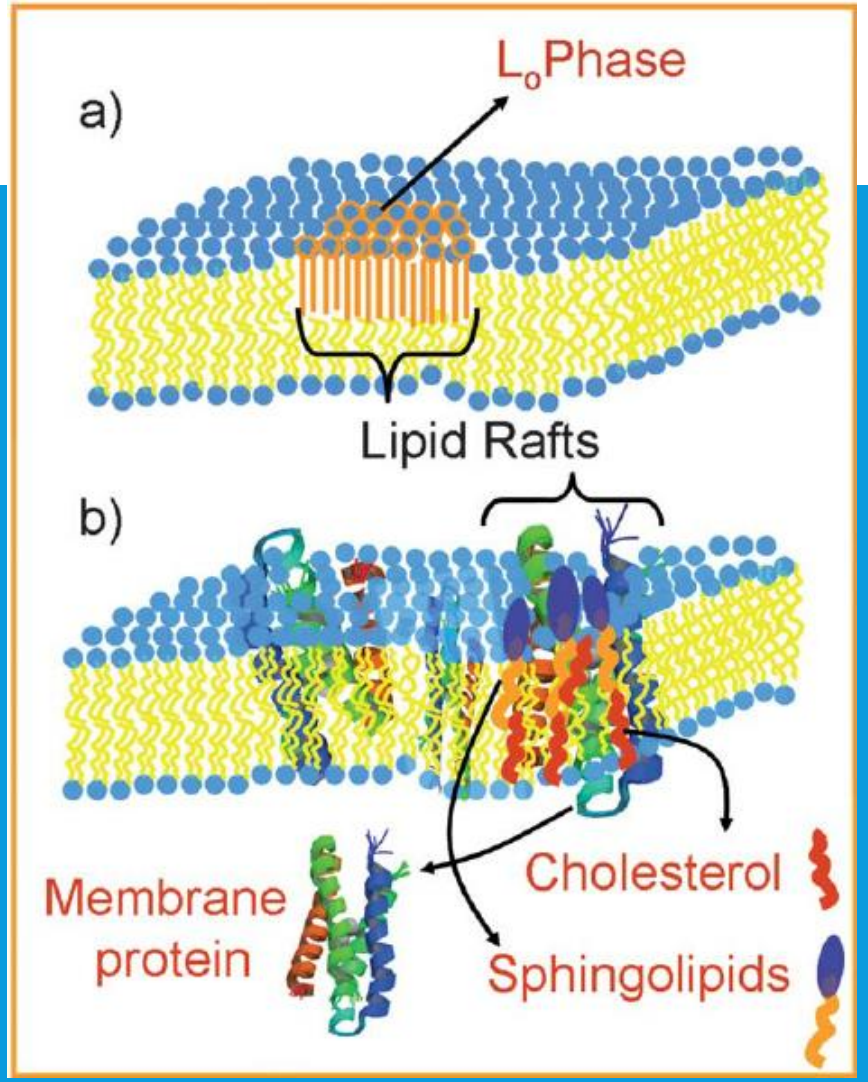


Diagram from: Nanoscale 4(19):5779-91 · August 2012 DOI: 10.1039/c2nr31465g
Chandrashekhar V. Kulkarni. University of Central Lancashire

SWEDEN AND THE CASE FOR AUTOIMMUNE UNDERPINNINGS OF ME/CFS

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- **Jonas Blomberg**, professor emeritus in Clinical virology, University of Uppsala and
- **Anders Rosén**, professor in Clinical and experimental medicine, University of Linköping. Shared insights about the metabolomics paper.
- **Geraldine (Jo) Cambridge**, PhD, Dep. Medicine, University College, London, UK, and **Oystein Fluge**, oncologist from Norway
- **Rituximab for ME/CFS: Revealing immunological cues to underlying disease mechanisms**. B-cell specialist. Lab showed the benefit of using rituximab for autoimmune disease RA
- **Per Julin, MD** Neurological Rehabilitation Clinic. ME/CFS clinic and clinical research using neuroradiologic studies in ME/CFS

SWEDEN

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Jonas Blomberg is developing a hypothesis paper that will tie together much of the evidence. He notes--

- Microbes in the gut help train our immune system, from within, how to recognize and react correctly to microbes from outside.
- Certain B-cells are involved with auto-immunity and produce auto-antibodies
- He notes that Primary Biliary Cirrhosis is an autoimmune disease characterized by antibodies to mitochondria . Patients with PBC have PEM. We might be able to learn from this disease.

SWEDEN

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Anders Rosen stated the following in his lecture on metabolomics:

- **Viruses** exploit membranes and their components, such as **sphingolipids,** in all steps of their life cycle, including attachment and membrane fusion, intracellular transport, replication, protein sorting and budding.
  - For example: HIV, rhinovirus, measles, Ebola, Hep C, influenza A
  - EBV LMP1 modulates lipid raft microdomains and the vimentin cytoskeleton for signal transduction and transformation. (Meckes DG Jr, Menaker NF, Raab-Traub N. J Virol 2013)

ME/CFS IS A HYPOMETABOLIC STATE: REMEMBER BIOLOGY CLASS?

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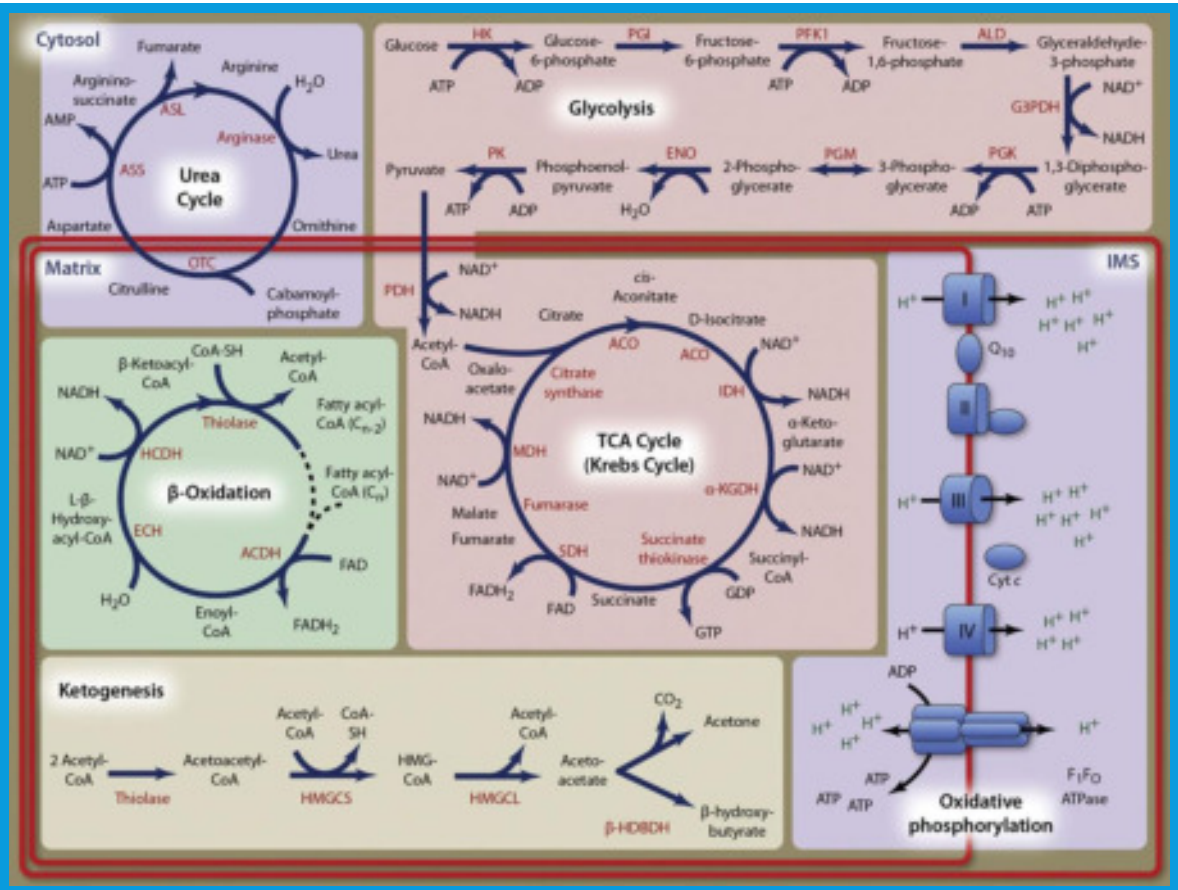
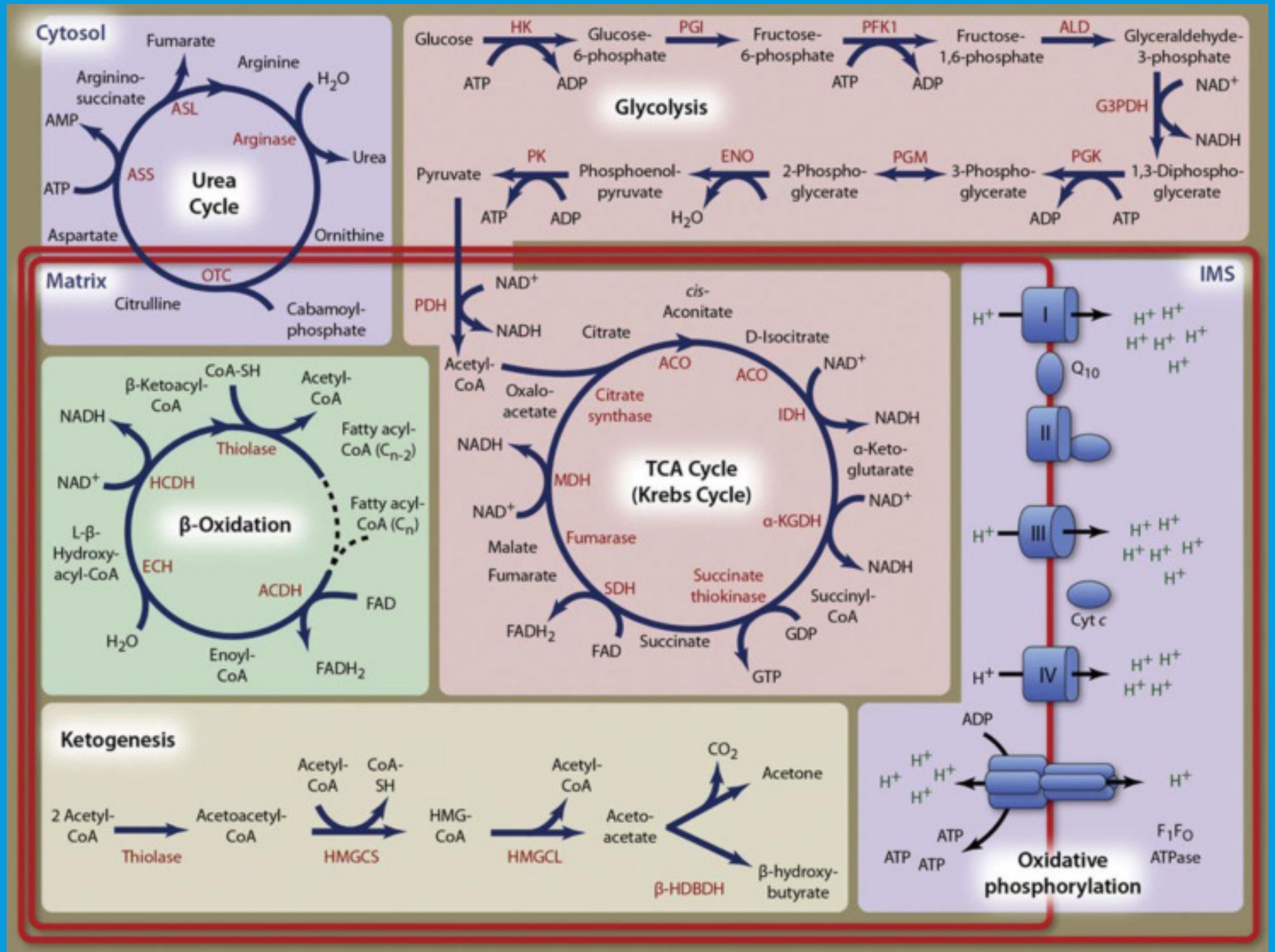
- **TCA cycle and urea cycle** are abnormal in MECFS compared to HC based on metabolite concentrations.

(Sci Rep. 2016; 6: 34990. Published online 2016 Oct 11. Index markers of chronic fatigue syndrome with dysfunction of TCA and urea cycles. Emi Yamano, et al.) Suzanne Vernon interprets this paper in the BHC blog.

- Fluge and Mella also found clues of abnormal cellular respiration (a series of chemical reactions that lead to energy---ATP---within each cell) based on abnormal metabolites. *They suggest reduced ATP production at the level of the PDH complex*.
- Patients with ME/CFS may not be able to make ATP normally!!



Mitochondrial Control of Cellular Life, Stress, and Death. Lorenzo Galluzzi et al. Circulation Research. 2012;111:1198-1207



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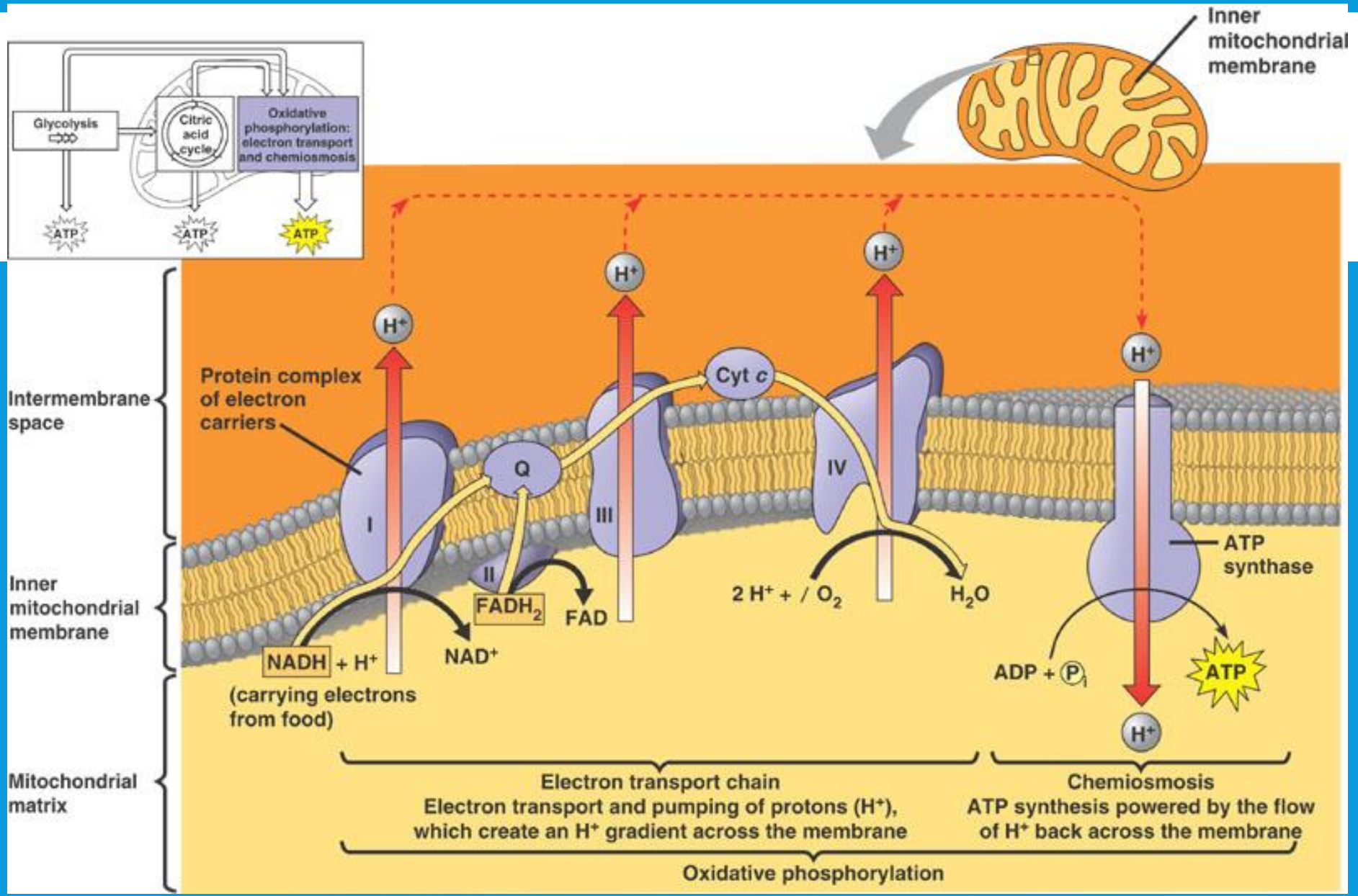

From Wordpress blog: Science Policy

WHY DOES B-CELL DEPLETION IMPROVE ME/CFS?

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Fluge and Mella are awaiting completion of the 3 year ME/CFS rituximab trial, but they have been busy evaluating other scientific data. Jo Cambridge is studying their B-cells.

Anders Rosen also stated "mitochondria are regulating hubs and emit signals to nucleus and circulation" His hypothesis: *initial agents [virus or bacteria] trigger innate B-cells to produce antibodies. These B-cells are then continuously fueled/activated at a low level by altered self-antigens (antigenic mimicry) to produce antibodies that react with self-structures (like myelin in MS). The activated regulatory B cells release mitochondrial proinflammatory signals that result in the hypometabolic state.*

A WORD ABOUT ALLERGIES

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- Evaluation of the CFI data supports higher rate of allergies and allergic disease and association with pain and GI issues. (Levine)
- Mast cell dysregulation syndrome may explain some of the severe "allergic" reactions and many symptoms, such as POTS.

WHAT'S NEXT?

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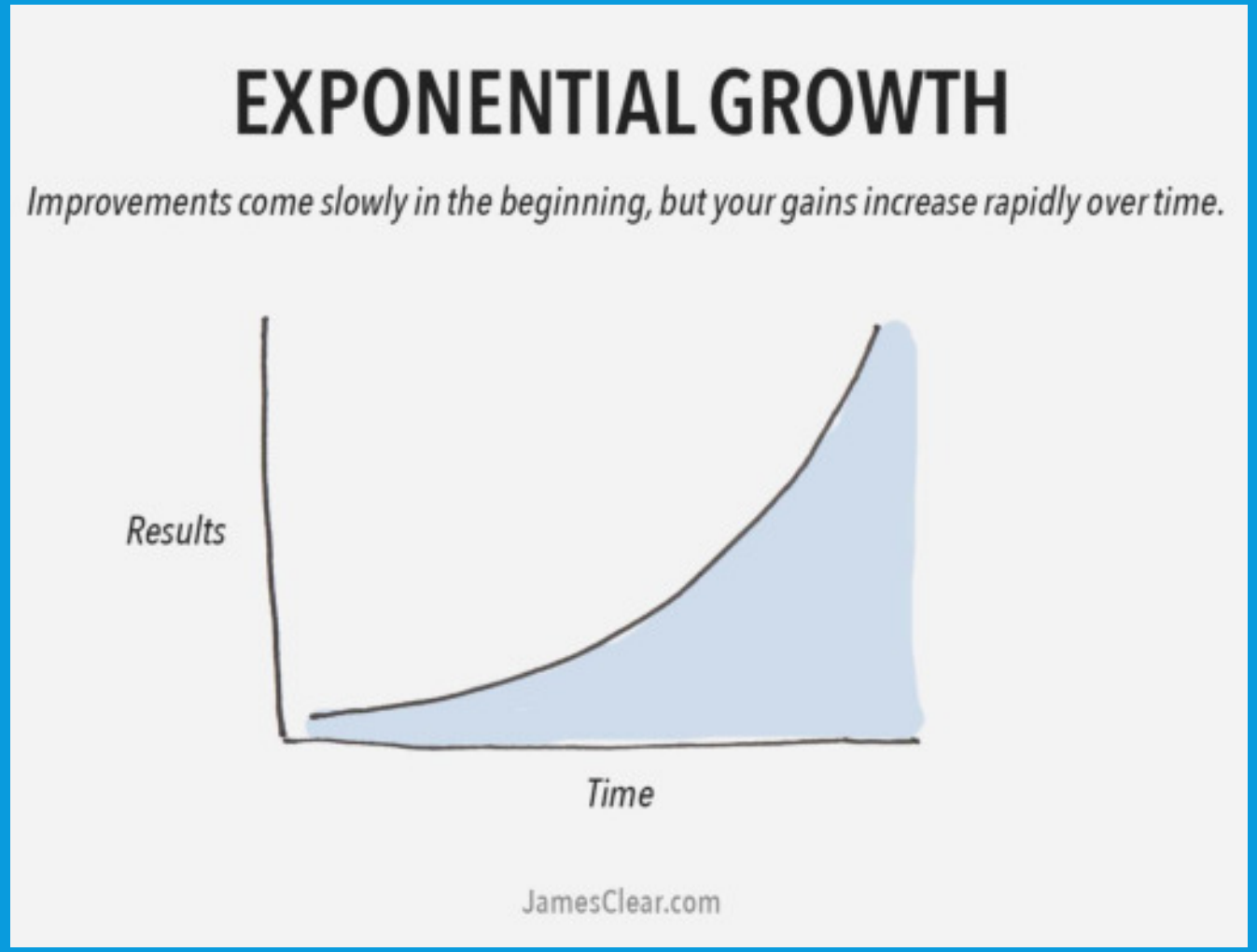

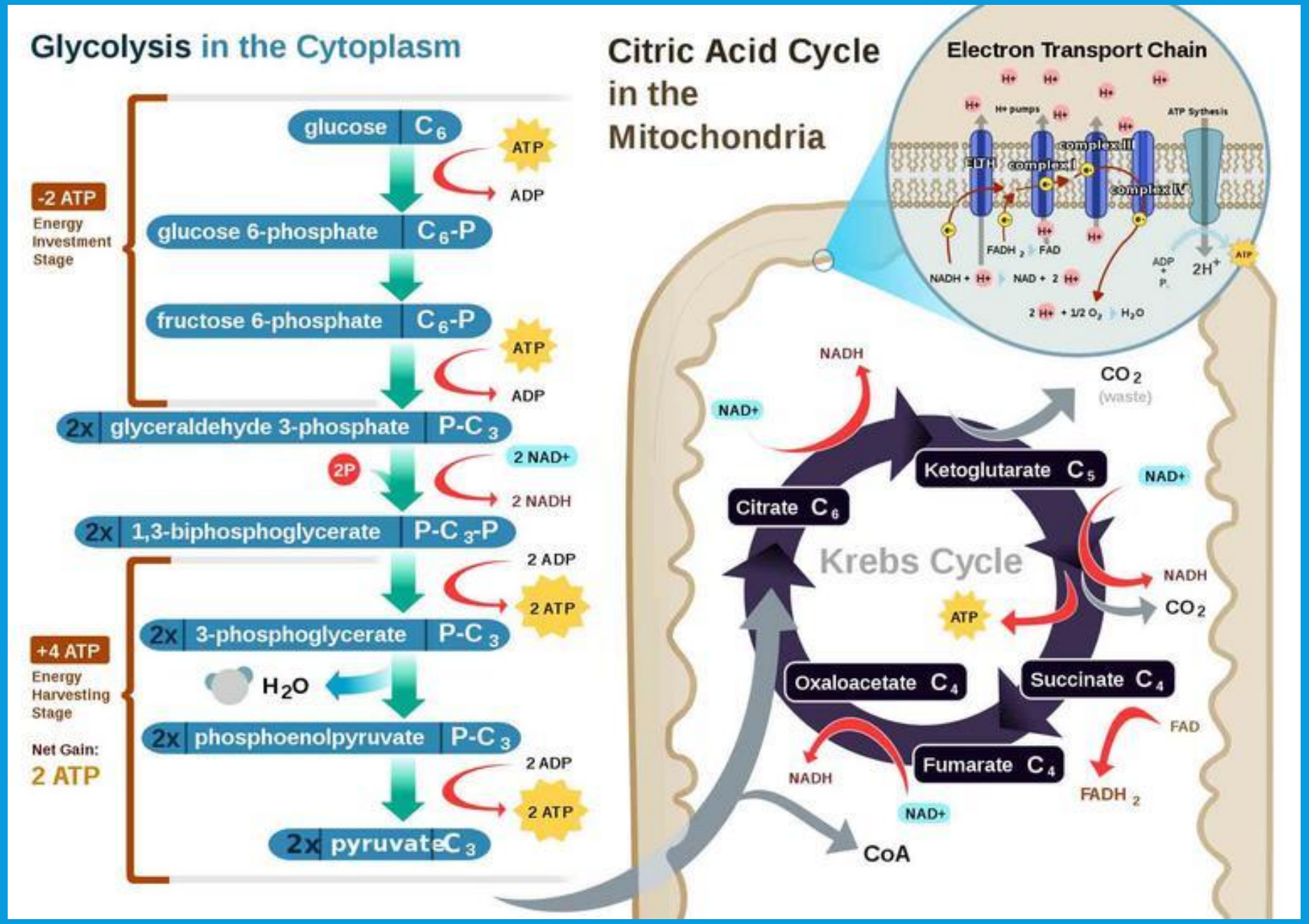

http://www.scienceprofonline.com/metabolism/electron-transport-chain-cellular-respiration.html