The Metabolic Features of Myalgic Encephalitis/Chronic Fatigue Syndrome (ME/CFS)

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Coordinated by Dr. Elizabeth Unger and Dr. Dana Brimmer
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Outline

• What is the Cell Danger Response (CDR)?
• Metabolic reflexes and the healing cycle
• Purinergic Sensory processing receptors needed for cell danger and safety detection
• Metabolic lessons from the Antiviral response
• Metabolic features of ME/CFS
• Metabolic features of Dauer Exit—clues for treatment
Mitochondria are the Cell’s “Canaries in the Coal Mine”

Their Metabolism is so Fast, They are the First to Sense Danger or Toxicity

Regulators of cell oxygen
Regulators of Cell Defense And Innate Immunity
Cellular Power Plants
Regulators of 500 Reactions in Metabolism

Self-defense is Nature’s oldest law. John Dryden (1681)
What is the Cell Danger Response (CDR)?

The CDR is a Coordinated, Multisystem, “Metabolic Reflex” Caused by an Electron Steal

0. Decrease oxygen consumption → increase dissolved O$_2$ concentration
1. Shift from polymer to monomer synthesis (ΔG; FA, AA, Dipeptides, NTs)
2. Stiffen cell membranes, lipid rafts
3. Release anti-viral and anti-microbial chemicals
4. Increase mitochondrial fission and autophagy & unfolded protein response
5. Change DNA and histone methylation—chromatin structure
6. Mobilize endogenous retroviruses, LINEs, and SVAs
7. Warn neighboring cells and call in effector cells—the “purinergic halo”
8. Alter host behavior to prevent spread of disease to kin

Starting the CDR is Universal with Every Stress or Threat

Mitochondria sense and respond to changes in the cellular environment.

Antipurinergic Therapy (APT)

Paracrine Signaling to Neighboring Cells

CD39

ATP and Other Agonists

Mitochondria

ATP

AMP

Ado

CD73

Ectonucleotides

Short Path Retrograde

Long Path Retrograde

Unstirred water layer

Chemical Gradient of Extracellular Nucleotides

dNTPs

DNA

ATP

ADP

UDP

UDP-Gal

Suramin and Other Antagonists

Pannexin / P2X7

Retrograde

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Short Path Retrograde

Long Path Retrograde

Unstirred water layer

Chemical Gradient of Extracellular Nucleotides
How do cells “smell” safety and danger in the world?
(Hint: It’s all about metabolism.)

Vertebrate Chemosensory Receptor Evolution

7 Transmembrane GPCRs

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<th>Sight</th>
<th>Smell</th>
<th>Pheremones</th>
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<td>1,037(354)</td>
<td>165(165)</td>
<td>61(148)</td>
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<td>Human</td>
<td>Opsin 4</td>
<td>388(414)</td>
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Formyl-Peptides
Chemokines
ATP, UTP
SCFAs
LPAs
Nicotine
Bradykinin

Shi/Zhang. Results Probl Cell Diff, 2009. PMID 19145414
Q: What causes chronic disease?
H: Failure to complete the healing cycle.

Chronic Disease (30% of Children in US)
The Healing Cycle and its Regulation

Healing

CDR Stages

Antipurinergic Therapy (APT, eg Suramin)

Injury and Chronic Diseases

Dangers & Stress

Injury, infection, trauma, toxins,
Radiation, pollution, solvents,
Mutagens, heavy/trace metals,
Food chain degradation, ecosystem disruption
Fatigue in ME/CFS

• Fatigue is the result of two main factors:
  – Dissipative losses of ATP through channels in the cell membrane, and
  – Reallocation of cellular resources away from mitochondrial energy production (oxphos)
    • This is the result of mitochondria following “new orders” from the nucleus, ie, “regulated mitochondrial dysfunction”
    • This is not from an intrinsic “defect” in mitochondria themselves or a specific genetic mutation, ie, recovery is possible

• “It takes more energy to relax than to react.”
  – Anxiety, restlessness, irritability, fear of change, OCD behaviors, sensory & chemical hypersensitivities, meltdowns, and bouts of hyperactivity, and even seizures, are hallmarks of a low energy state
Metabolomics—A Drop of Blood is Like a Sample of Water from a River or Ocean Ecosystem
Metabolomics Permits Diagnosis of ME/CFS

Pathway Abnormalities—Defining the Metabolic Reflex of the CDR

Chronic Fatigue Syndrome

- Sphingolipids
- Phospholipids
- Sterols/Cholesterol
- Purines
- Methionine/Cysteine
- Propionate
- Krebs cycle
- Folate/B12
- Ascorbate


Post-Zostavax Vaccination

- Krebs cycle
- Purines
- Sphingolipids
- Sterols/Cholesterol
- Methionine/Cysteine
- Propionate
- Inositol lipids
- Porphyrin/Heme/Glycine
- Amino/Sialic acid sugars


1 PBMC transcription and metabolism. Mixed male and female responses.
Metabolic Pathway Abnormalities in Males and Females with ME/CFS

Male
- Serine/1-Carbon Metabolism
- SAM, SAH, Met
- Very Long Chain FAO
- Propiogenic AA
- Threonine

Female
- Fatty Acid Oxidation
- Vitamin C/Collagen
- Bile acids
- Endocannabinoids
- Vitamin B12
- Amino Sugars

50% Shared
- Sphingolipids
- Phospholipids
- Glycosphingolipids
- Purines
- Microbiome
- Cholesterol
- Vitamin B2 (Riboflavin)
- P5C, Arginine, Proline
- Branch Chain AA
ROC Curve Accuracy Analysis—Metabolomic Diagnosis of ME/CFS

A

Males
AUC = 0.94
95% CI: 0.84-1.0

B

Females
AUC = 0.96
95% CI: 0.86-1.0
Hypometabolic Persistence and Survival States in Nature

- Persister Cells
  - Lyme
  - Tuberculosis
- Embryonic Diapause
- Hibernation
- Torpor
- Estivation
- Tun
- Dauer
- Caloric restriction/Longevity research
Reproductive Cycle
= 3 days
Menopause After
6 days
Normal life span
= 14 days

C. elegans

Dauer Shifts
- Stop eating → caloric restriction
- Mitochondrial oxphos declines
- Oxygen consumption declines
- Lipid droplets accumulate
- Glycolysis increases
- Glyoxylate shunt increases to increase OAA and gluconeogenesis

Lipid Droplets

www.wormatlas.org
Metabolic Changes Associated with Recovery/Exit from Dauer

L1
Stress
Early dauer (3-4 days)
Late dauer (10 weeks)
Recovery
Adults

20x
Choreographed Metabolic Features of Dauer Exit

The sequence (timing) of changes is important
Dauer Exit—Clues for CFS Treatment
Treatment Strategy for ME/CFS

• Remove the **CDR trigger** if it is still present
• Refill the metabolic tank—raw materials for exit from winter and return to “spring and summer metabolism”
  – Normalize calorie intake and nutrition
    • Restore depleted metabolic reserves as guided by metabolomics
• Use **antipurinergic therapy (APT)**, e.g., low-dose suramin, to reprogram metabolism and to progress through the *healing cycle*
  – Pilot study of low-dose suramin in CFS is seeking funding to launch later this year.
  – See: [http://naviauxlab.ucsd.edu/support/](http://naviauxlab.ucsd.edu/support/)
Research Support

- Dan Wright Family Foundation
- The UCSD Christini Fund
- Autism Research Institute
- The Gupta Family and Satya Fund
- N of One: Autism Research Foundation
- The Rodakis Family
- Lennox Foundation
- The UCSD Mito Walk n’ Roll 5K
- It Takes Guts Foundation
- Jane Botsford Johnson Foundation (the essential preclinical studies)
- Open Medicine Foundation (OMF)

Thank You