GENIE Primer – Using GENIE to Understand CIRS Symptoms

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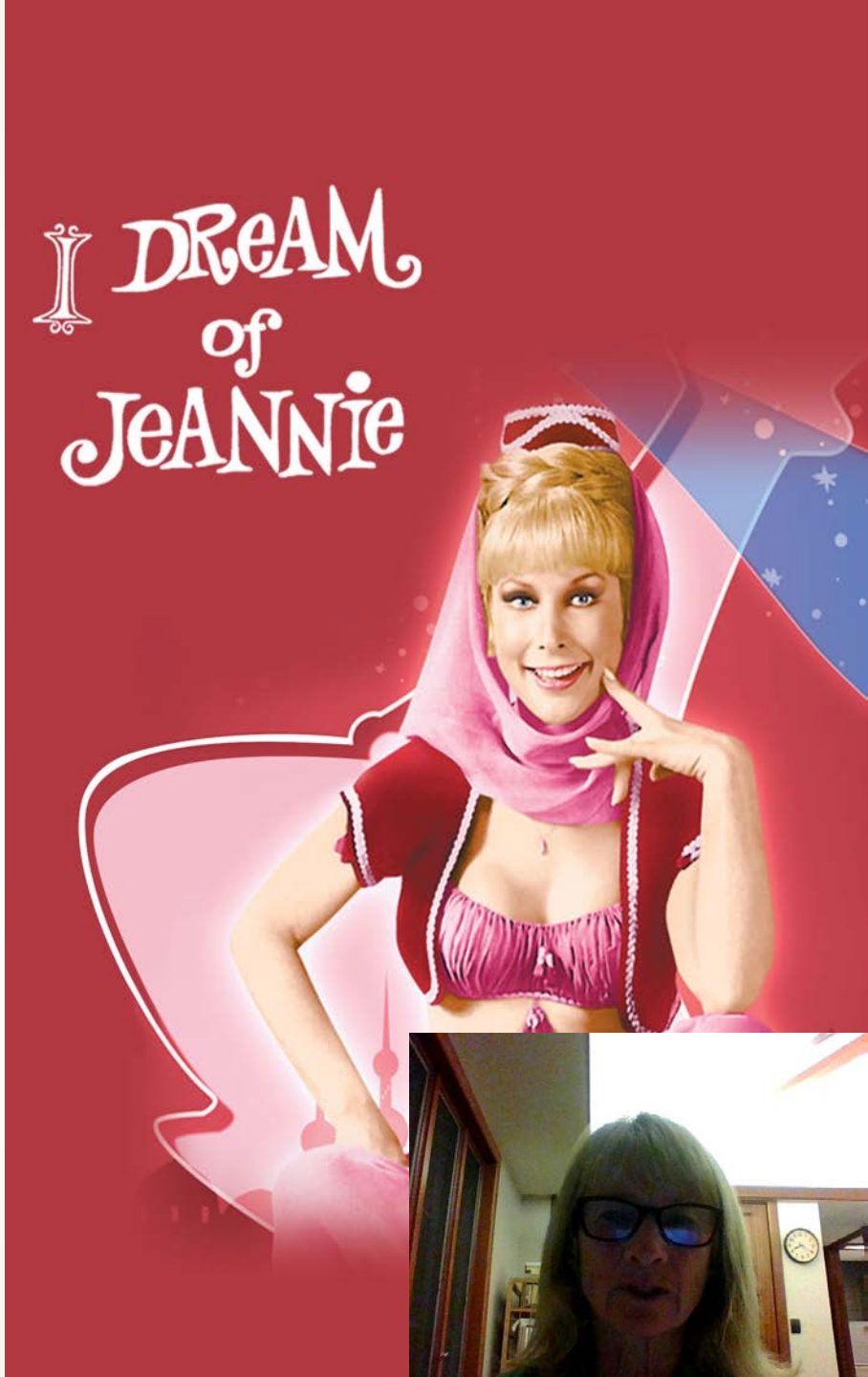
SurvivingMold/CIRSx Joint Web Conference

June 4, 2021-

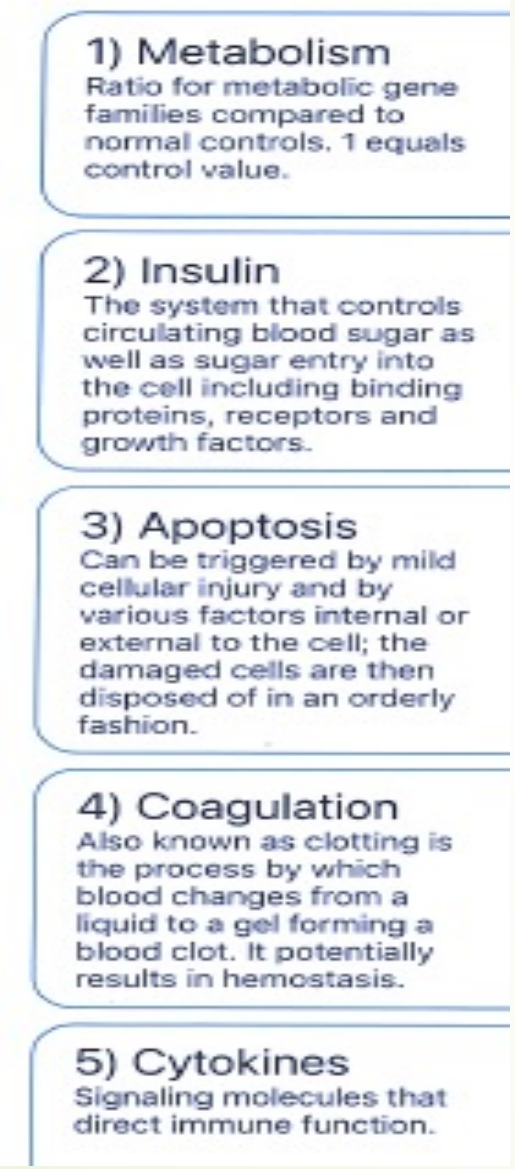
I Dream of Genie



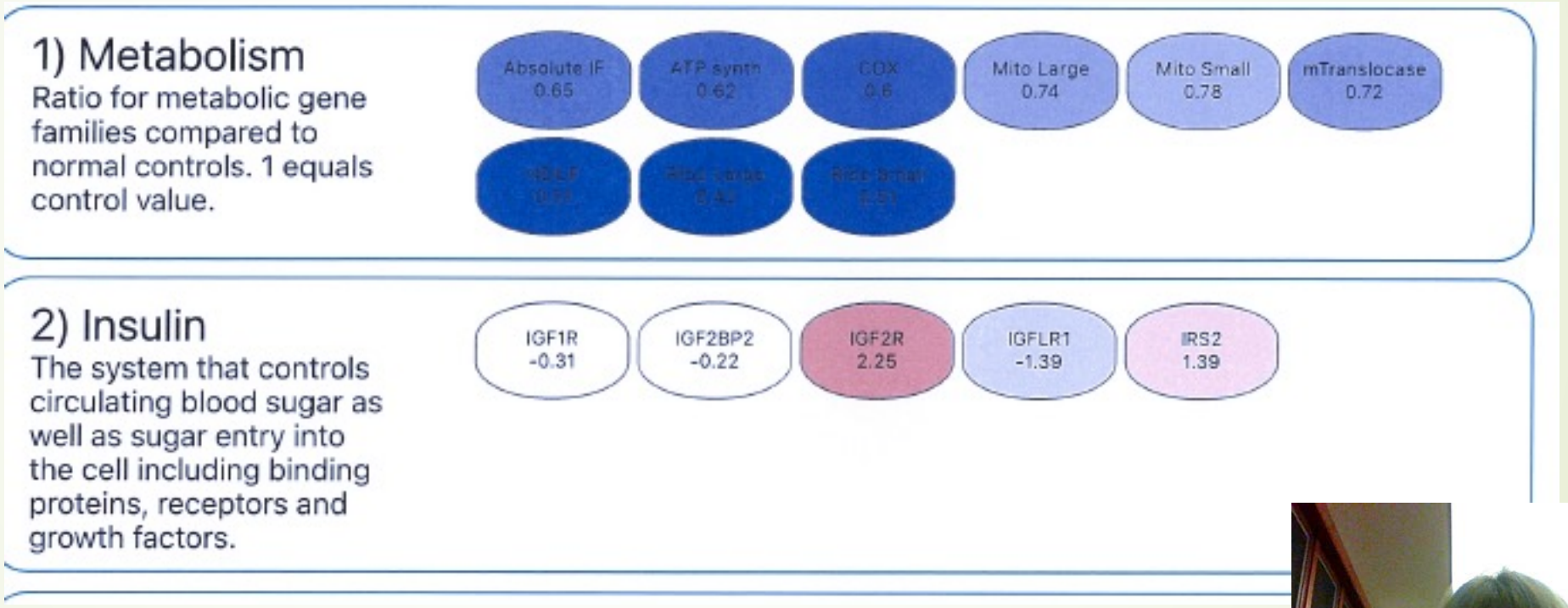
I have no disclosures

OBJECTIVE:

- To define the key actionable areas from GENIE by adding perspective to each of the 20 report categories, shown are examples of the first five.



Gene expression is compared to age matched controls. Coloration of the oval indicates the degree of expression. The darker the red, the greater the upregulation. The darker the blue, the greater the down regulation.



Item #1 & 2

- Identify Molecular Hypometabolism (MHM) and Proliferative Physiology.
- MHM is the reduction in the expression of ribosomal and nuclear encoded mitochondrial genes.
- Proliferative Physiology is the use of aerobic glycolysis rather than oxidative phosphorylation for ATP production.
- IRS 2 and translocase are the 2 principal markers for MHM and Proliferative physiology.
- IRS 2 tells about glycolysis and translocase tells about delivery of mitochondrial gene products across the outer mitochondrial membrane pore

HYPOMETABOLISM

- Translocase downregulation or suppression causes closure of Voltage Dependent Anion Channels (VDAC) on outer mitochondrial membrane resulting in suppression of nuclear encoded mitochondrial gene products. Messenger RNA suppression disrupts ribosomal protein synthesis resulting in hypometabolism.
- Disruption of nuclear encoded mitochondrial RNA impacts multiple mitochondrial functions including production of ATP Synthases (ATP synth) interfering with ATP production and further reducing metabolism
- Additional contributors to MHM include downregulation of IRS2 and Actinomycetes which reduces release of endosomal insulin and glucose.
- NADH dehydrogenase (NDUF) if downregulated impairs the transfer of electrons to CoenzymeQ disrupting Complex 1 & 3 of the ETC.

Translocase & IRS 2

- Due to translocase suppression causing closure of Voltage Dependent Anion Channels (VDAC) on outer mitochondrial membrane, pyruvate cannot enter the mitochondria. If at the same time Glut 1 & 4 are open as a result of IRS2 upregulation, glucose builds up in the cytoplasm increasing glycolysis.
- Aerobic cytosolic glycolysis impacts energy production since pyruvate cannot enter the mitochondria. Pyruvate is either converted into lactic acid, increasing the anion gap, or shunted into biosynthetic pathways in preparation for cell division.
- Lactic acidosis is a by product of aerobic glycolysis since pyruvate is converted into lactic acid.
- IRS2 downregulation impairs both glycolysis and oxidative phosphorylation which can lead to unprogrammed cell death.

Proliferative Physiology

- This is due to increased substrate production from aerobic glycolysis as a result of positive IRS2 and downregulated translocase.
- Lipids and nucleotide substrates produced by the first 3 steps of aerobic glycolysis contribute to proliferative physiology.
- Associated with pulmonary hypertension which can be further exacerbated by pulmonary fibrosis due to elevation of TGF beta
- Associated with deficient T reg cells and neuronal injury with grey matter nuclear atrophy. Elevated beta tubulin also contributes to this. The greatest degree of atrophy is seen with positive MHM and IRS2.

3. APOPTOSIS

- RIPK1 is the most important marker in this section. Upregulation results in the most dramatic suppression of apoptosis.
- BCL2 not infrequently associated with COVID-19
- CASP10, CASP3 & CASP8 sequential activation involved in execution phase of apoptosis
- CLU clears cellular debris and aids in protein folding
- FAS apoptosis signaling receptor
- FOXO3 upregulates genes necessary for cell death
- MAP3K5 implicated in neurodegenerative and oxidative stress related diseases
- CD48 modulate NK cell function

4. COAGULATION

- Impacted if 3 or more genes are positive leading to microvascular clots and increasing risk of vascular dementia. Atrophic nuclei are seen with coag gene abnormalities.
- F13A1 associated with discordant protein and fibril formation especially if CLU and TUBB1 are elevated. CLU is involved in aiding protein folding. Misfolded proteins are associated with neurodegenerative diseases.
- F5 is Factor 5 Leiden
- ITGA2B & ITGB3 are involved in formation of a fibrinogen receptor on platelets. Cognitive impairment increases with over expression.
- GP6 is involved with collagen induced activation and aggregation of platelets.
- PF4 promotes coagulation

4. COAGULATION-continued

- GP9 forms a non-covalent complex with glycoprotein 1B and is a receptor for von Willebrand factor.
- SELP produces a cell adhesion molecule
- THBS1 plays a role in platelet aggregation
- TREML1 facilitates platelet aggregation by binding to fibrinogen

5. CYTOKINES

- The most significant are IL1B, TGF beta-1 and TGFBR1, 2 & 3.
- IL1B mediates inflammation and is involved in cell proliferation, differentiation and apoptosis
- TGF beta-1 and TGFBR1, 2 & 3 are markers for specific exposure to actinomycetes along with MAPK.

6. LYME

- All are significant and can rule in or out Lyme with GENIE
- Lyme scores can indicate untreated Lyme or Lyme treated in the past 6 months. If Z score of TGF beta, tumor necrosis factor (TNF), Interleukin 1 beta (IL1B) and CD4 are added, the sum is divided by 4 and if the result is greater than 1.37 it is suggestive of untreated Lyme. If all the Lyme scores on GENIE are added except EIF4g2, divided by 7 and if the number is greater than 1.37, then it is suggestive of Lyme treated in the past 6 months

7. GRANZYMES & DEFENSINS

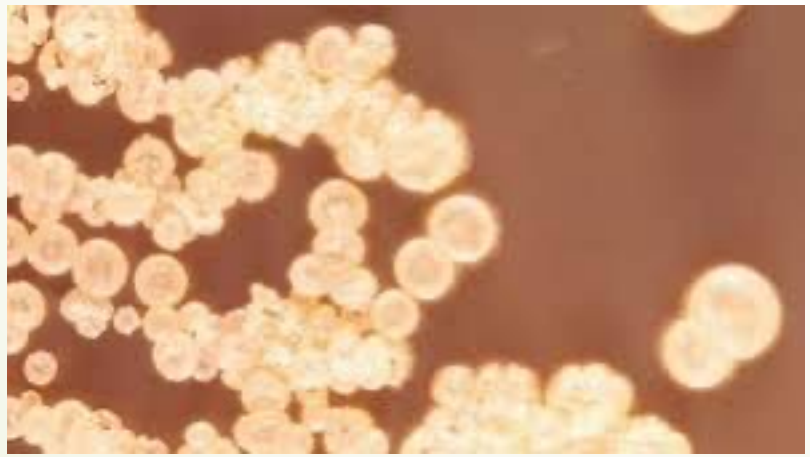
- A1B and A4 are most significant
- Positive with viral activation and often with Bartonella

8. IKAROS ZINC FINGER PROTEIN

- IKFZ1 associated with chromatin remodeling and IKZF2 regulates lymphocyte development
- If 3 Ikaros are +ve and VIPR1 –ve, MCS is likely in 85% of cases
- If VIPR is upregulated with hypometabolism, VIP can cause an untoward response.
- Use caution advancing VIP dosing if VIPR1 and all 3 Ikaros genes are downregulated
- More severe CNS injury is seen when VIPR1 is +ve and Ikaros is –ve.

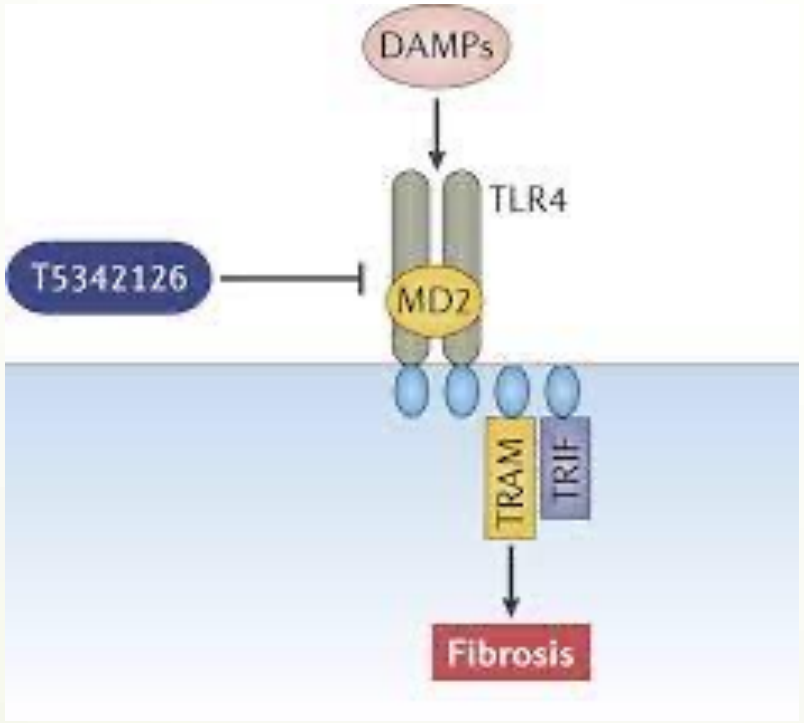
9. MAP kinase

- All are important
- Elevated MAPK along with elevation of either TGFBR1 or 2 is seen with actinomycetes exposure, explaining CIRS symptoms with a negative HERTSMI-2
- Mycotoxins typically elevate MAPK to a greater degree than actinomycetes, however in this case HERTSMI-2 is abnormal.



10. TOLL RECEPTORS

- Upregulation of CD14 and TLR4 greater than 1.37 is associated with endotoxin exposure.

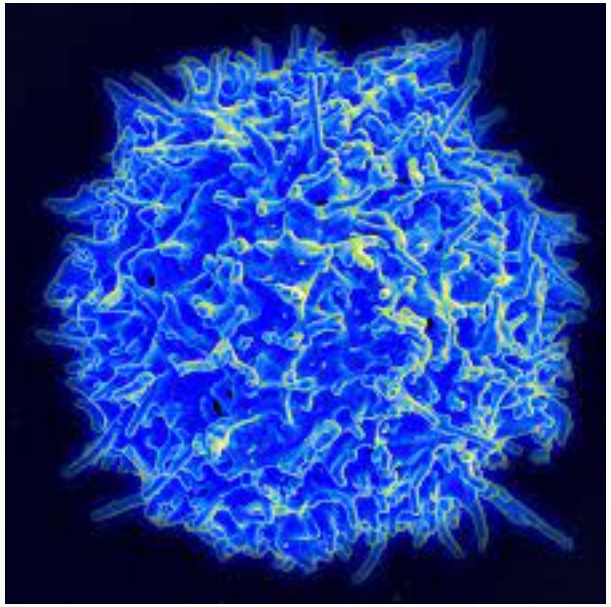


11. B CELLS

- Uncertain how these genes factor into CIRS

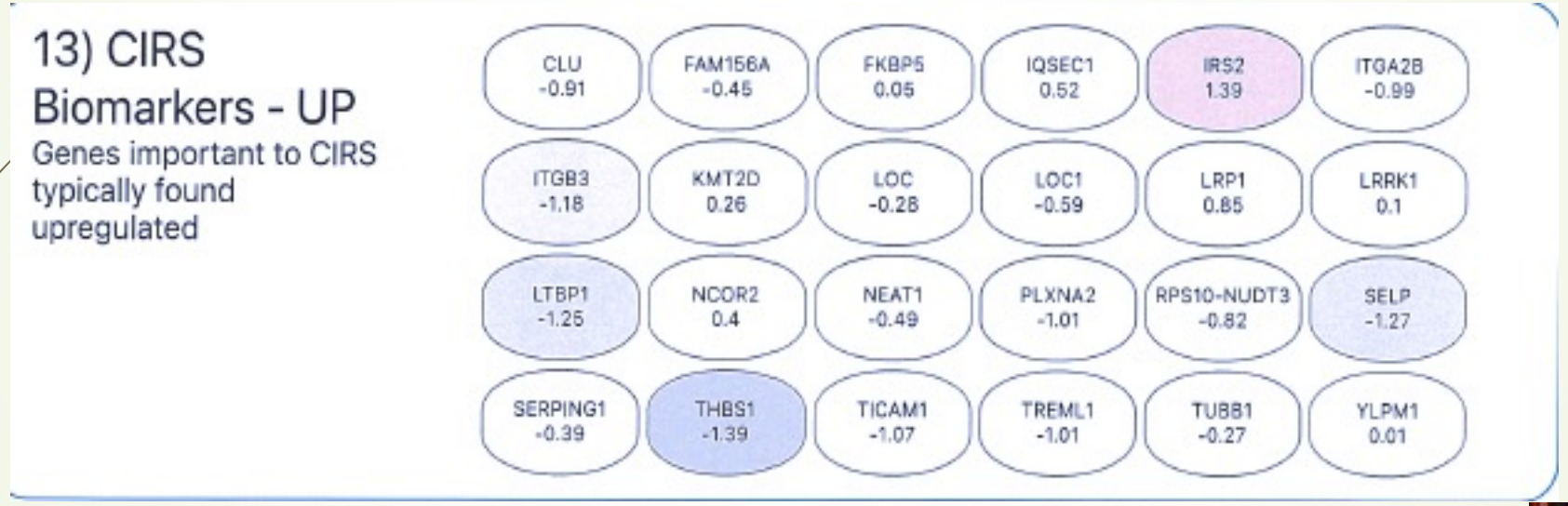
12. T CELLS

- Defective antigen presentation is seen in CIRS Stage 1 or 2 with downregulation of CD3D and CD48.



13. CIRS BIOMARKERS

- Are significant if 4 or more are upregulated.



14. CIRS BIOMARKERS

- TRPV2 upregulation is associated with ciguatera toxicity

15. PROSTAGLANDINS

- ALOX15 and PTGS1
- If upregulated NSAIDS may be beneficial

16. PTSD

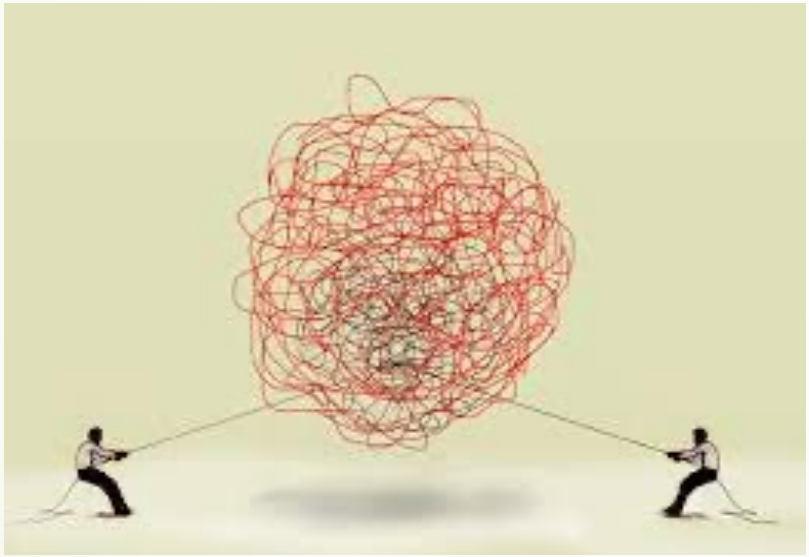
- Indicative if FKBP5 is upregulated since it is an important modulator of stress responses

17. HISTAMINE

- CCL5 is chemotactic for T cells, eosinophils and basophils
- HDC converts L-histidine to histamine
- MCAS cannot be diagnosed if either are elevated

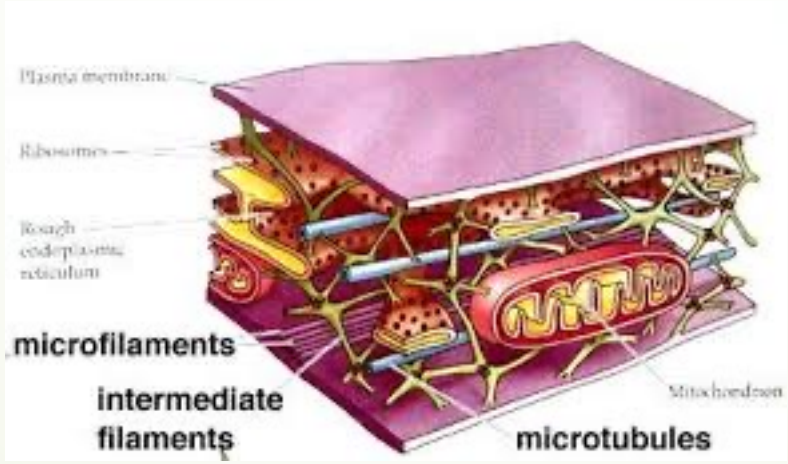
18. ECM

- MMP-9 and TIMP-2 act in opposition



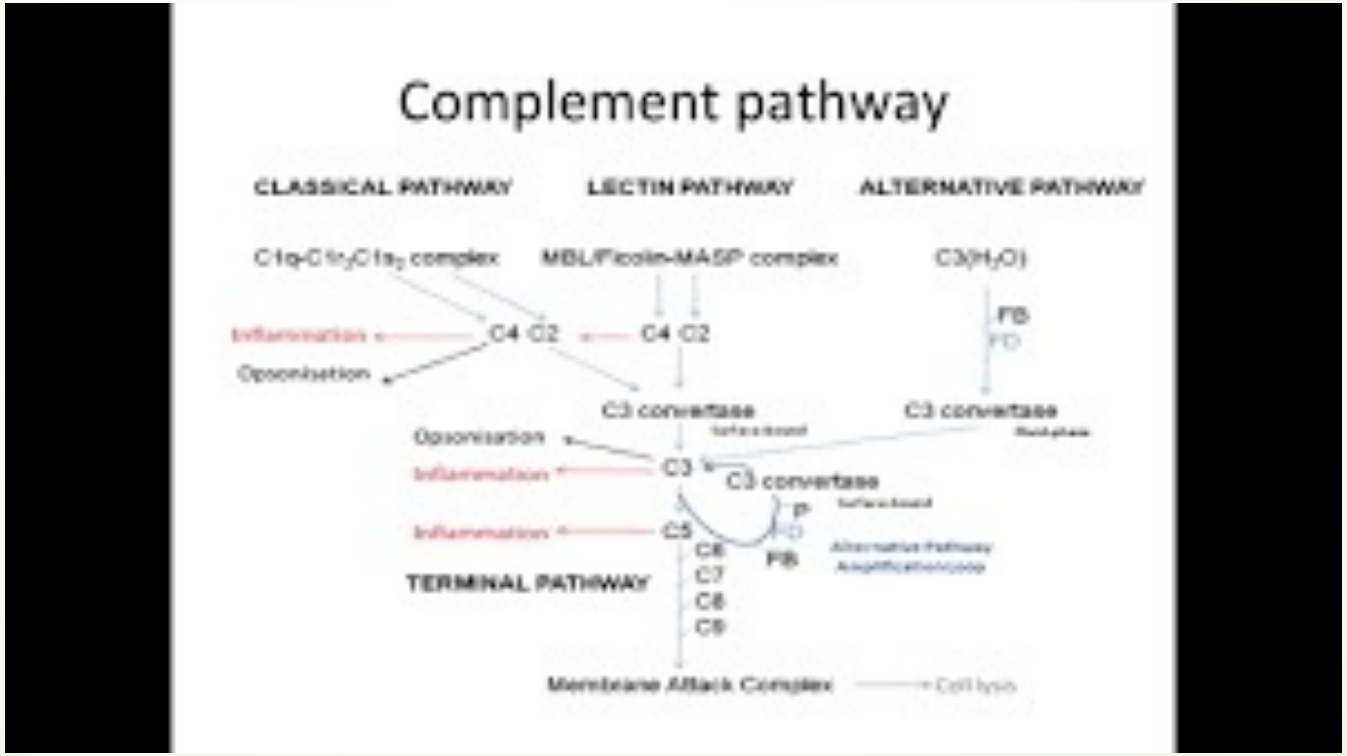
19. CYTOSKELETON

- Tubulins, TUBB1 & TUBA4A are involved in intracellular transport
- Upregulation results in closure of pores on outer mitochondrial membrane or VDAC which can lead to cell death
- The greater the upregulation of TUBA4A, the greater the grey matter nuclear atrophy on MRI.



20. COMPLEMENT

- Elevation of SERPING1 is associated with elevation of C4a



THANK YOU

- To Drs. Shoemaker and Ryan for making GENIE possible and to Dr. Shoemaker for his guidance and input on this presentation.
- Thank you to Marcia Cash for technical assistance in the presentation.

HAWAIIAN SUNSET

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