Immunometabolism in CIRS

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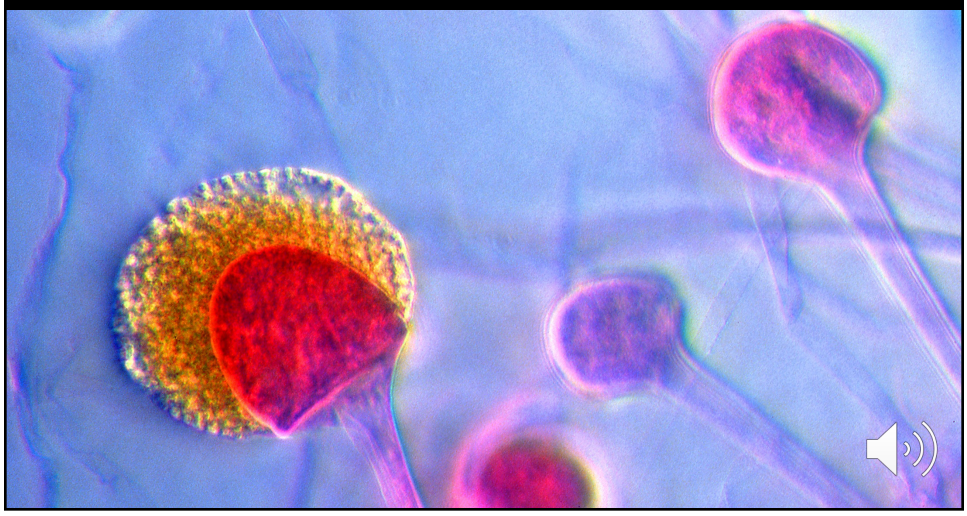

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Disclosures

James Ryan is a principal in Progene DX, a company that sells the transcriptomic test called GENIE

Gene ExpressioN: Inflammation Explained

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Metabolism - Energy Production and Use

- Glycolysis – Cytoplasm
- Krebs Cycle (TCA) – Mitochondria
- OxPhos (ETC) - Mitochondria

- Returns chemical energy in the forms of Adenosine triphosphate (ATP) and nicotinamide adenine dinucleotide (NADH) using oxygen

- ATP is the finished product while NADH is used in the Electron Transport Chain

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ImmunoMetabolism

The cellular adaptation of metabolic pathways (metabolic rewiring) to best suit the immune functions required by the cell, as determined by immunogen and microenvironment.

"Cells in the innate and adaptive immune systems are characterized by rapid transition between the quiescent and activated states, marked heterogeneity of cell fate choices, and context-specific tissue adaptation. Associated with such temporospatial regulation of immune reactions is the dynamic reprogramming of cell metabolism and the crosstalk with signal transduction, including the signaling roles mediated by metabolites and nutrients."

Chi, H. Immunometabolism at the intersection of metabolic signaling, cell fate, and systems immunology. *Cell Mol Immunol* **19**, 299–302 (2022).

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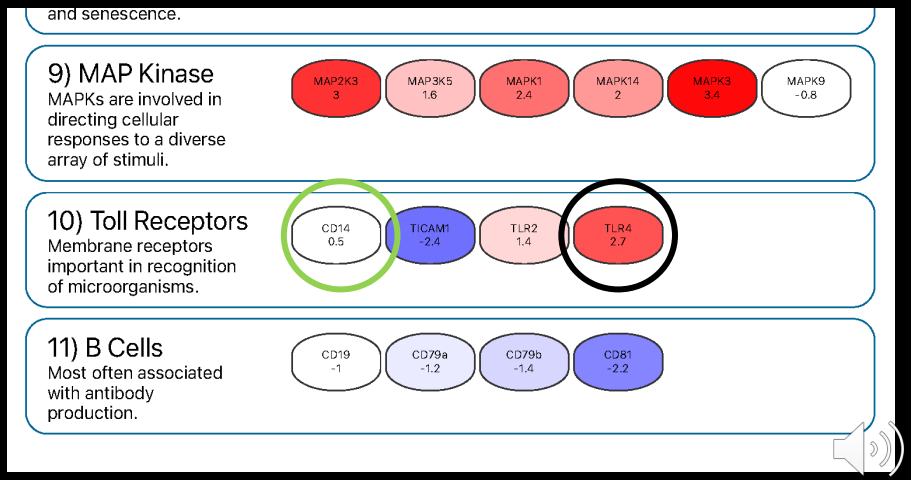
TLR4



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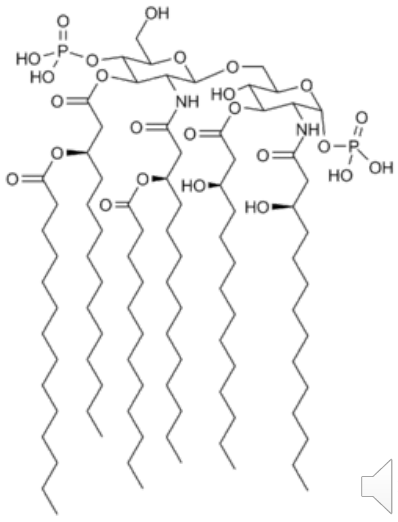
Wikipedia - Chemical structure of lipid A as found in *E. coli*

Lipid A is a lipid component of an endotoxin and held responsible for the toxicity of gram-negative bacteria. Fatty acid chains of 10-16 carbons are typical



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Saturated fatty acids trigger TLR4-mediated inflammatory response

D.M. Roch et al, Atherosclerosis November 20,2015
2015DOI:https://doi.org/10.1016/j.atherosclerosis.2015.11.015

Highlights

- SFA can trigger inflammatory pathways similarly to LPS.
- SFA leads to gut microbiota modification and LPS overproduction.
- Metabolic endotoxaemia induced by SFA raise the oxLDL and oxPL production.
- Also, SFA increases the lipemia and the oxLDL and mmLDL production.
- Those molecules generated from SFA can induce the TLR4 inflammatory pathways.

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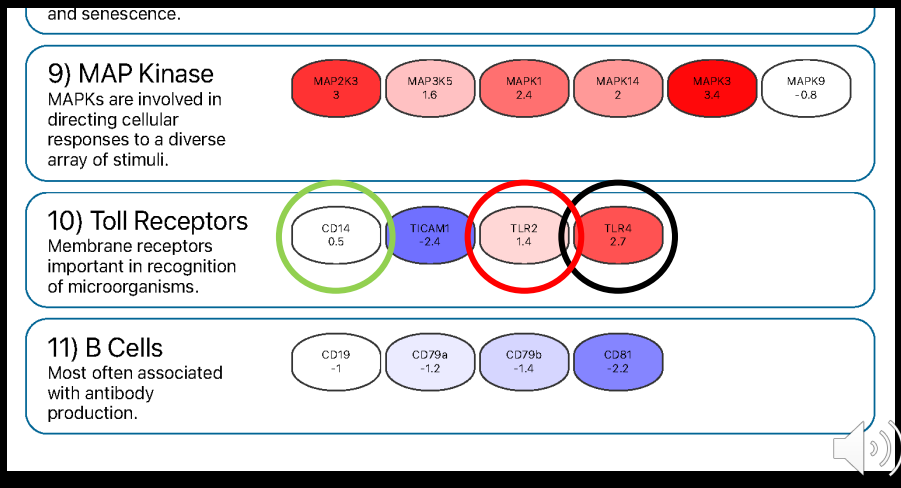
TLR4



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Mechanisms for the activation of Toll-like receptor 2/4 by saturated fatty acids and inhibition by docosahexaenoic acid

Hwang et al, Eur J Pharmacol. 2016 Aug 15; 785: 24-35.

- TLR2 recognizes a variety of microbial components derived from Gram-positive bacteria, such as lipopeptides, peptidoglycan and lipoteichoic acid
- The concentrations of SFAs to activate TLR4 exceed 100 μM in cell culture systems, whereas those for LPS are in pM ranges. Similarly, the effective concentrations of SFAs in inducing the dimerization of TLR2 with TLR1 exceed 100 μM

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Lipid infusion decreases the expression of nuclear encoded mitochondrial genes and increases the expression of extracellular matrix genes in human skeletal muscle

Dawn K Richardson [1], Sangeeta Kashyap, Mandeep Bajaj, Kenneth Cusi, Steven J Mandarino, Jean Finlayson, Ralph A DeFronzo, Christopher P Jenkinson, Lawrence J Mandarino

J Biol Chem. 2005 Mar 18;280(11):10290-7.
doi: 10.1074/jbc.M408985200.Epub 2004 Dec 14.

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Mitochondrial dysfunction and insulin resistance from the outside in: extracellular matrix, the cytoskeleton, and mitochondria

Coletta, D. and Mandarino L, Am J Physiol Endocrinol Metab. 2011 Nov; 301(5): E749-E755.

- Obese and type 2 diabetic subjects had significantly elevated TLR4 gene expression and protein content in muscle, which correlated with the severity of insulin resistance. It is not clear at this point whether inflammation precedes or merely coincides with lower insulin action, whether individuals who reside on the lower end of the insulin action curve have greater propensity for inflammatory processes, or whether inflammation itself moves an individual leftward along the insulin action curve to a state of reduced insulin action that eventually leads to disease propensity.

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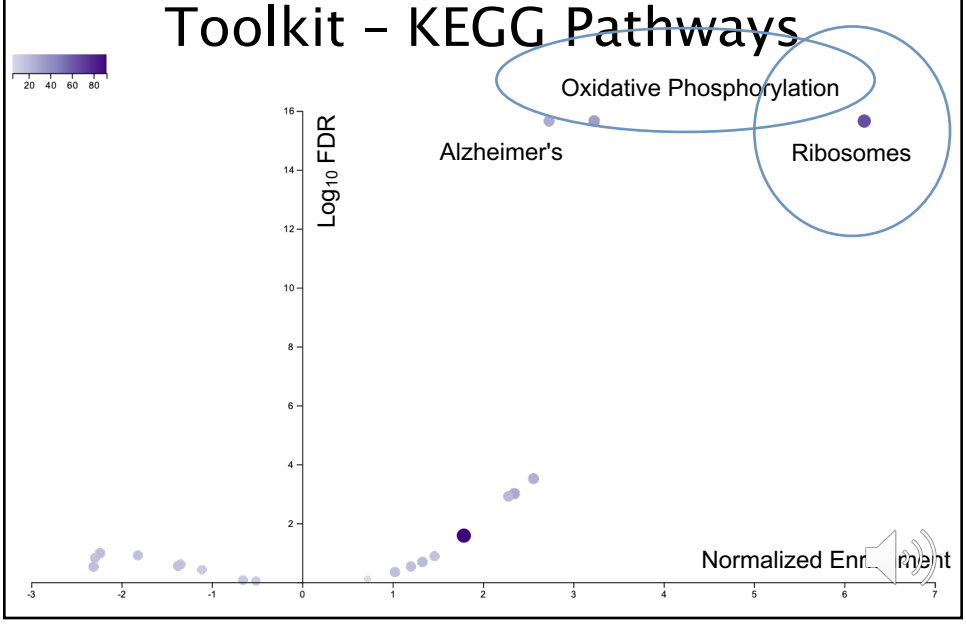
WEB-based GEne SeT AnaLysis Toolkit – KEGG Pathways



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Translation Inhibition

- Dunbar et al, C. elegans Detects Pathogen-Induced Translational Inhibition to Activate Immune Signaling. (Cell Host & Microbe *11*, 2012)
- McEwan et al, Host Translational Inhibition by Pseudomonas aeruginosa Exotoxin A Triggers an Immune Response in Caenorhabditis elegans (Cell Host & Microbe *11*, 364–374, 2012)

"Here we show that *P. aeruginosa* infection inhibits mRNA translation in the intestine via the endocytosed translation inhibitor Exotoxin A…

Thus, translational inhibition, a common pathogenic strategy, can trigger activation of an immune surveillance pathway to provide host defense"

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Whole Blood Gene Expression Profiles in Insulin Resistant Latinos with the Metabolic Syndrome

Tangen, SE, et al, PLoS ONE 8(12): e84002 December 17, 2013

KEGG Pathway	Probe Count	Up Regulated	Down Regulated	Significance
Ribosome	119	119	0	<0.0001
Oxidative Phosphorylation	32	28	4	<0.0001
Alzheimer Disease	31	22	9	<0.01
Epithelial Cell Signaling	15	1	14	<0.01
Huntington Disease	29	23	6	<0.05
Systemic Lupus Erythematosus	31	1	30	<0.05
Parkinson Disease	23	22	1	<0.05
Endocytosis	28	0	28	≤0.05
MAPK Signaling	36	0	36	0.057

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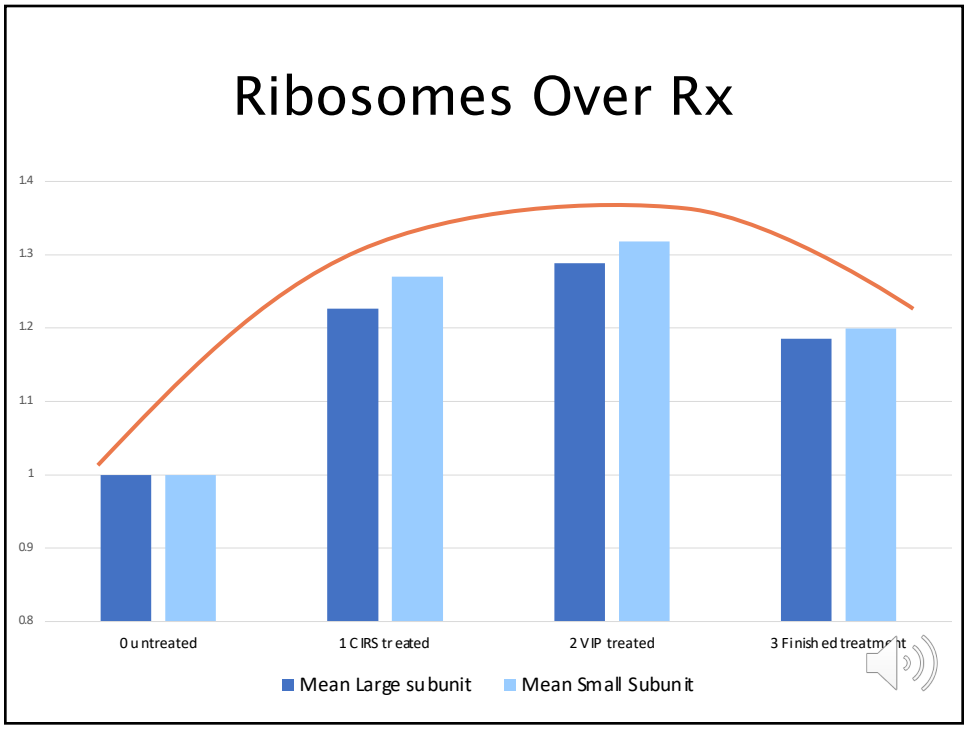
Ribosomes Over Rx
1.4
1.3
1.2
1.1
1
0.9
0.8
0 untreated
1 CIRS treated
2 VIP treated
3 Finished treatment
Mean Large subunit
Mean Small Subunit

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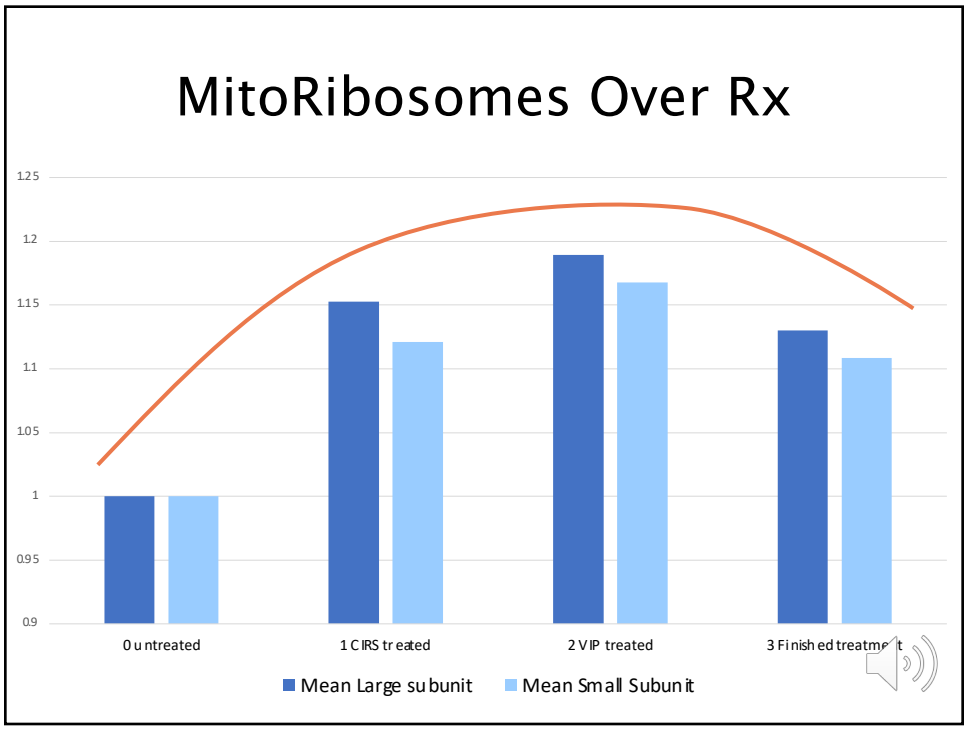
MitoRibosomes Over Rx
1.25
1.2
1.15
1.1
1.05
1
0.95
0.9
0 untreated
1 CIRS treated
2 VIP treated
3 Finished treatment
Mean Large subunit
Mean Small Subunit

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Obesity, Inflammation, Toll-Like Receptor 4 and Fatty Acids

Marcelo Macedo Rogero and Philip C. Calder Nutrients. 2018 Apr; 10(4): 432.

- CONCLUSIONS; The TLR4 signaling pathway has been recognized as one of the main triggers in increasing the obesity-induced inflammatory response. This pathway responds to the increased exposure to saturated fatty acids and to LPS. Both of these are relevant in the context of obesity, with saturated fatty acids arising from within the adipose tissue triglyceride stores and the LPS arising from increased intestinal permeability perhaps due to an altered gut microbiota. Adipose tissue driven inflammation increases insulin resistance, both locally and systemically, so contributing to the co-morbidities of obesity, like DM2. Studies indicate that omega-3 fatty acids, namely EPA and DHA, have an anti-inflammatory effect, which involves attenuating the activation of the TLR4 signaling pathway.

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Inflammatory and interferon gene expression signatures in patients with mitochondrial disease

Warren et al, J Transl Med. 2023; 21: 331.

"Increasing evidence suggests that mitochondrial dysfunction may cause chronic inflammation, which may promote hyper-responsiveness to pathogens and neurodegeneration. "

RESULTS:
"Negatively enriched gene sets included mitochondrial proteins and complexes (n = 28), ribosomes and translation (n = 30), natural killer (NK) cell (n = 9), B cell (n = 3), and major histocompatibility complex (MHC) activity (n = 8)"

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Summary

- It was demonstrated that TLR4 can be activated by free fatty acids, albeit at much lower affinity than its natural ligand, LPS. This activation has been linked to insulin resistance and causes disruptions in metabolic pathways. Can we see this on GENIE? We need some data.
- Differences of opinion exist in the literature. Study, analyze, ask for other peoples opinion if you are unsure. Don't believe everything you read, even in peer reviewed journals.

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