Advanced Genetics and Pathways involved in MCAS, COVID, and Cancer

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Functional Genomic Analysis Software

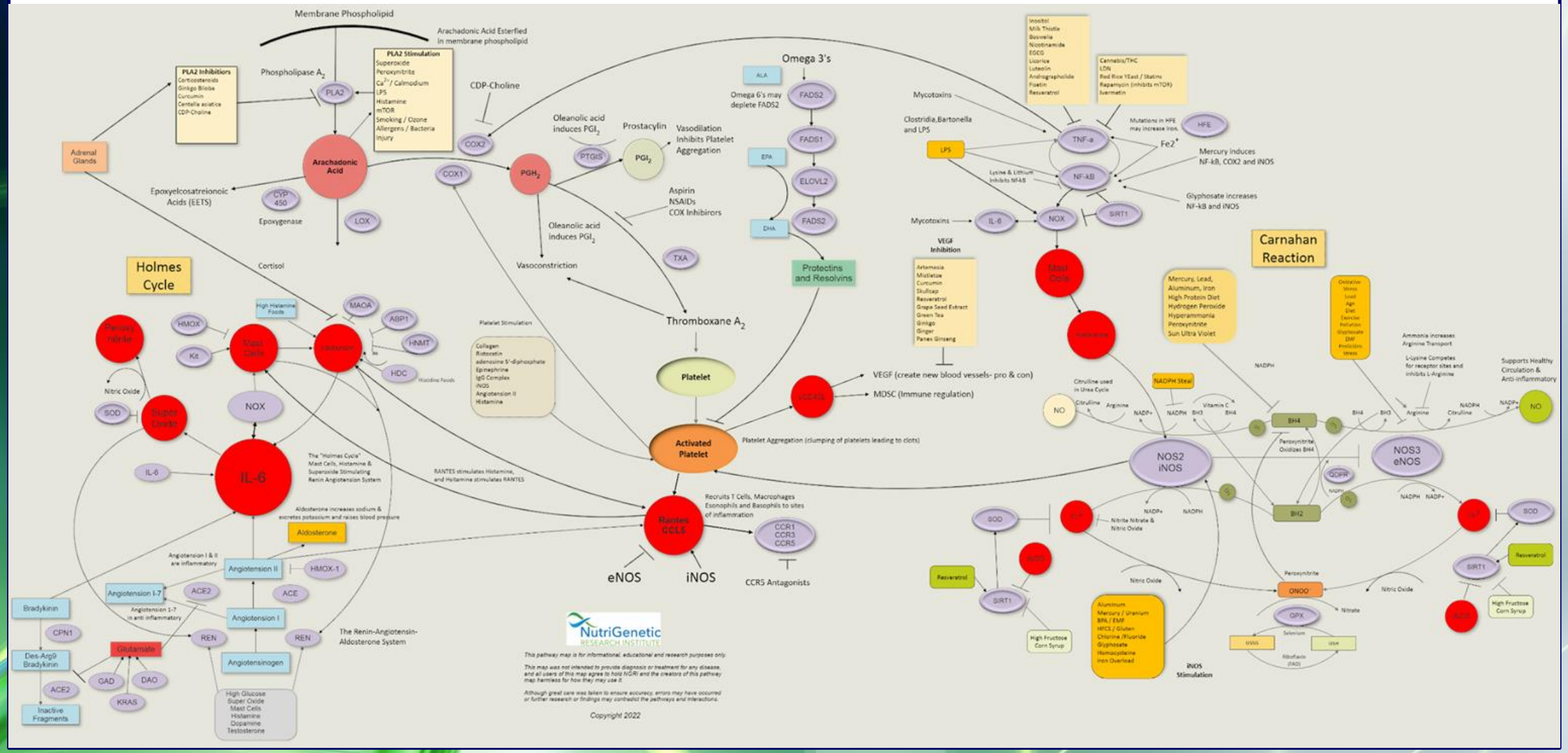
www.functionalgenomicanalysis.com
www.tolhealth.com

All of this information is for educational and informational purposes only, and is not designed to diagnose or treat any disease.

Genetics and Mast Cells

The Three-D Chess Game Played Underwater

Map is downloadable at https://www.nutrigeneticresearch.org/research



RANTES

- *RANTES (or CCL5) = Regulated upon Activation Normal T cells Expressed and Secreted*
  - A powerful pro-inflammatory mediator of the chemotactic cytokine (CC) chemokine family
  - Regulates the mobilization and survival of immune inflammatory cells from the bloodstream into tissues and other areas of injury and infection
- *Sustained production of RANTES is associated with several detrimental effects* such as atherosclerosis, liver disease, viral infection, etc.
  - *Treatments that interfere with RANTES are associated with improved outcomes*
- RANTES orchestrates its effects through binding to one of its receptors: CCR1, CCR3, and CCR5

Baturcam E, 2014

RANTES

- RANTES is produced by:
  - **Platelets**
  - Macrophages
  - Epithelial cells
  - Megakaryoblasts
  - T lymphocytes and eosinophils
- RANTES stimulates:
  - ***Histamine secretion by mast cells***
  - IgE and IgG production by lymphocytes
  - CD80 expression on antigen-presenting cells
  - *Activation and proliferation of NK cells*
- RANTES *recruits T cells, macrophages, eosinophils and basophils to sites of inflammation*

Baturcam E, 2014

Conditions Related to RANTES

RANTES and Mast Cells

- RANTES is a mediator of acute inflammatory responses
  - RANTES plays a ***fundamental role*** *in* histamine and serotonin generation and ***cell function in mast cells***
- In a study of atopic eczema, RANTES and its receptors, CCR3 and CCR5, were shown to play potentially important roles in the orchestration of eosinophil infiltration in the ongoing chronic inflammation of atopic eczema
  - Also shown to reflect the severity of disease

Castellani, 2021; Kato Y, 2006

Preprint article

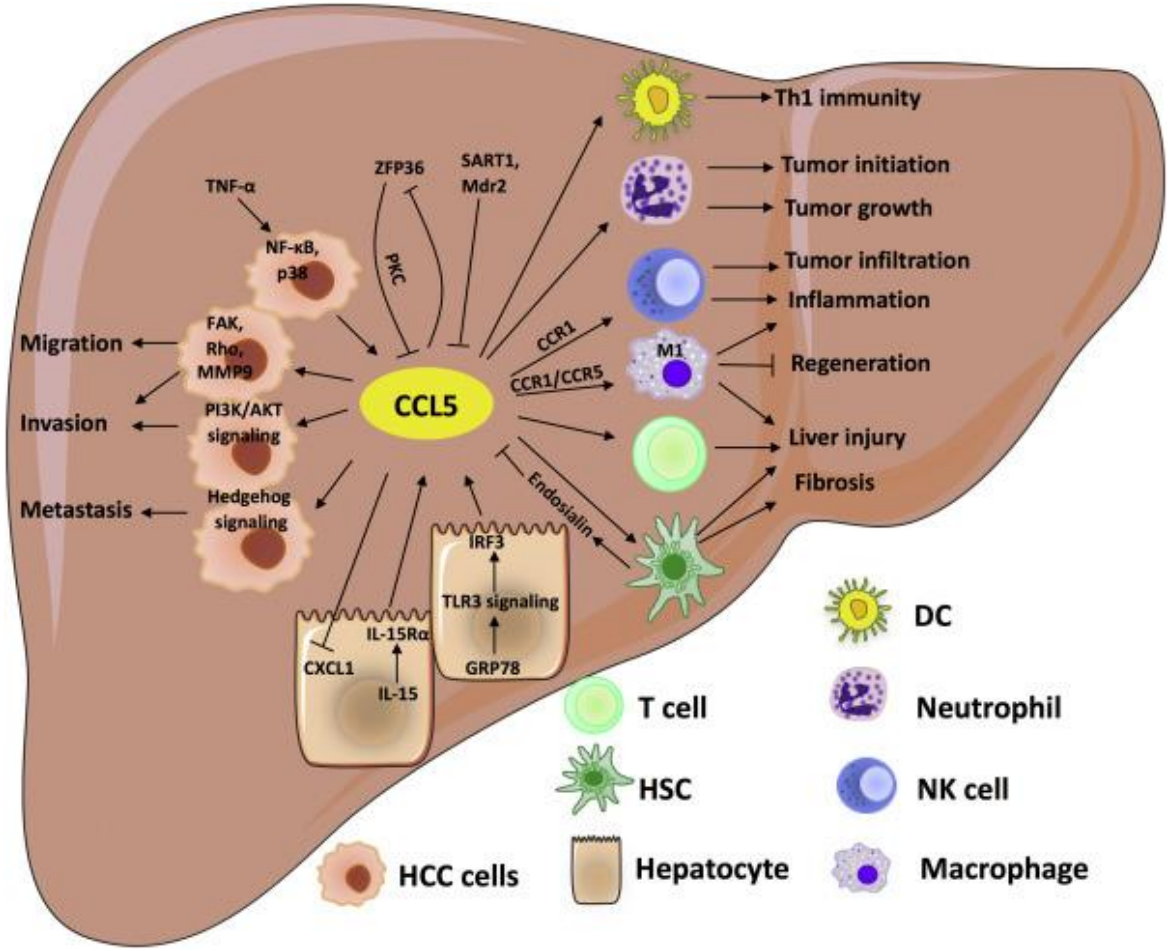
Disruption of the CCL5/RANTES-CCR5 Pathway Restores Immune Homeostasis and Reduces Plasma Viral Load in Critical COVID-19

Bruce K Patterson, Harish Seethamraju, Kush Dhody, Michael J Corley, Kazemm Kazempour, Jay P Lalezari, Alina Ps Pang, Christopher Sugai, Edgar B Francisco, Amruta Pise, Hallison Rodrigues, Matthew Ryou, Helen L Wu, Gabriela M Webb, Byung S Park, Scott Kelly, Nadar Pourhassan, Alena Lelic, Lama Kdouh, Monica Herrera, Eric Hall, Enver Aklin, Lishomwa Ndhlovu, Jonah B Sacha

PMID: 32511656 PMCID: PMC7277012 DOI: 10.1101/2020.05.02.20084673

- "Our study shows that *COVID-19 is very much a RANTES disease* demonstrating ***100 times normal levels of RANTES*** in these critically ill patients and 5 times normal levels of RANTES even in mild-moderate COVID-19 disease," said Bruce Patterson, MD, founder of IncelDx and advisor to CytoDen, in the press release.
- "When RANTES is blocked from binding to CCR5 expressed on immune cells, statistically significant increases of CD8 T-cells were seen as early as 7 days post-therapy.
- IL-6, which was less consistently elevated than RANTES in these patients was significantly decreased by Day 7."

CCL5 (RANTES) mediates hepatic injury and promotes fibrosis and HCC development by modulating hepatic inflammation.



- Under the condition of inflammation, CCL5 (RANTES) recruits immune cells (mainly T cells, macrophages, NK cells, DCs) into the inflammatory sites and promotes liver injury, tumor cells infiltration, tumor initiation and tumor growth.

Chen L, 2020

RANTES and Autism Spectrum Disorder (ASD)

- In a study of young autistic patients, RANTES and other chemokines were shown to be higher when compared with the typically developing children.
  - Supports the hypothesis that *altered chemokine levels are involved in the pathophysiology of ASD*
  - Chemokines plasma levels could be potential biomarkers for ASD

Shen Y, 2016

RANTES and Atherosclerosis

- Chemokines, like RANTES, control the recruitment of leukocytes within the vascular wall
  - Essential in development of atherosclerotic plaque formation
- Using a hypercholesterolemic mouse model, Met-RANTES (a CC chemokine antagonist) was shown to reduce progression of atherosclerosis
  - Potentially new therapeutic strategy

Veillard NR, 2004

RANTES and Inflammatory Bowel Disease (IBD)

- A study used resected colonic tissue from patients with various IBDs such as Crohn's disease
  - Frequency of chemokine-expressing cells was greatest in severely inflamed tissue
  - RANTES was expressed infrequently by T lymphocytes in normal colon lamina propria
  - Implicated various chemokines known to attract monocytes and subsets of T lymphocytes in the pathogenesis of inflammatory bowel disease
  - *Suggested significant redundancy in the generation of chemotactic signals in chronic inflammation*

Grimm MC, 2022

RANTES and Viral Lung Disease

COVID-19

- Study of 10 terminally-ill, critical COVID-19 patients
  - *Found profound elevation of plasma IL-6 and CCL5 (RANTES)*, decreased CD8+ T cell levels, and SARS-CoV-2 plasma viremia
  - Observed rapid reduction of plasma IL-6 and a significant decrease in SARS-CoV-2 plasma viremia after using leronlimab, a CCR5 blocking antibody

Respiratory Syncytial Virus (RSV)

- Infection of respiratory epithelial cells with RSV = upregulation of CCL5 secretion
- Children with RSV infections have increased CCL5 protein levels in both the upper and lower airway secretions
  - Levels of CCL5 in upper airway secretions correlate positively with disease severity

Patterson BK, 2020; Culley FJ, 2006

Research article | Open Access | Published: 19 December 2008

Genetic polymorphisms of *RANTES, IL1-A, MCP-1* and *TNF-A* genes in patients with prostate cancer

Pablo Sáenz-López, Rafael Carretero, José Manuel Cózar, José Maria Romero, Julia Canton, José Ramón Vilchez, Miguel Tallada, Federico Garrido & Francisco Ruiz-Cabello

Results

Diagnosis of prostate cancer was significantly associated with *TNF-A* GA + AA genotype (OR, 1.61; 95% CI, 1.09–2.64) and *RANTES* GA + AA genotype (OR, 1.44; 95% CI, 1.09–2.38). A alleles in *TNF-A* and *RANTES* influenced prostate cancer susceptibility and acted independently of each other in these subjects. No epistatic effect was found for the combination of different polymorphisms studied. Finally, no overall association was found between prostate cancer risk and *IL1-A* or *MCP-1* polymorphisms.

Conclusion

Our results and previously published findings on genes associated with innate immunity support the hypothesis that polymorphisms in proinflammatory genes may be important in prostate cancer development.

- Diagnosis of prostate cancer was significantly associated with RANTES GA + AA genotype (OR, 1.44; 95% CI, 1.09–2.38
- Our results and previously published findings on genes associated with innate immunity support the hypothesis that polymorphisms in proinflammatory genes may be important in prostate cancer development.

RANTES Stimulation

RANTES Stimulation

- Platelets, beside their hemostatic activity, *also function as cells that promote immunity and inflammation*
    - Occurs through multiple mechanisms, such as receptor-mediated cross-talk with and activation of different cells, or the release of potent biologically active mediators stored in their granules
        - A bidirectional interaction = the *activated cells in turn activate platelets through a number of receptor-ligand systems*

Danese S, 2004

RANTES Stimulation: Lyme Disease

- A study of human monocytes exposed to Borrelia burgdorferi = bacteria responsible for Lyme disease
  - Discovered a rapid and strong borrelia-inducible gene expression, followed by the release of chemokines with peak levels after 12 to 16 h
  - Spirochetes were effective in stimulating RANTES expression
  - B. burgdorferi appears to be a strong inducer of chemokines
    - Could contribute to the inflammation and tissue damage observed in Lyme disease through the attraction and activation of phagocytic leukocytes

Sprenger H, 1997

RANTES Stimulation: NF-kappa B

- NF-kappa B, IRF-3, and IRF-7 = important in vivo binding factors
  - Crucial for the cooperative induction of RANTES transcription after virus infection
- *The strength and kinetics of RANTES has been shown to be highly dependent on the preexistence of NF-kappa B*
  - Demonstrated in a study using fibroblastic and/or myeloid cells
- *Fe2+ has been shown to serve as a direct agonist to activate NF-kappaB, TNF-alpha promoter activity, and the release of TNF-alpha protein*
  - Showcases a molecular basis for iron-mediated accentuation of TNF-alpha-dependent liver injury

Génin P, 2000; She H, 2002

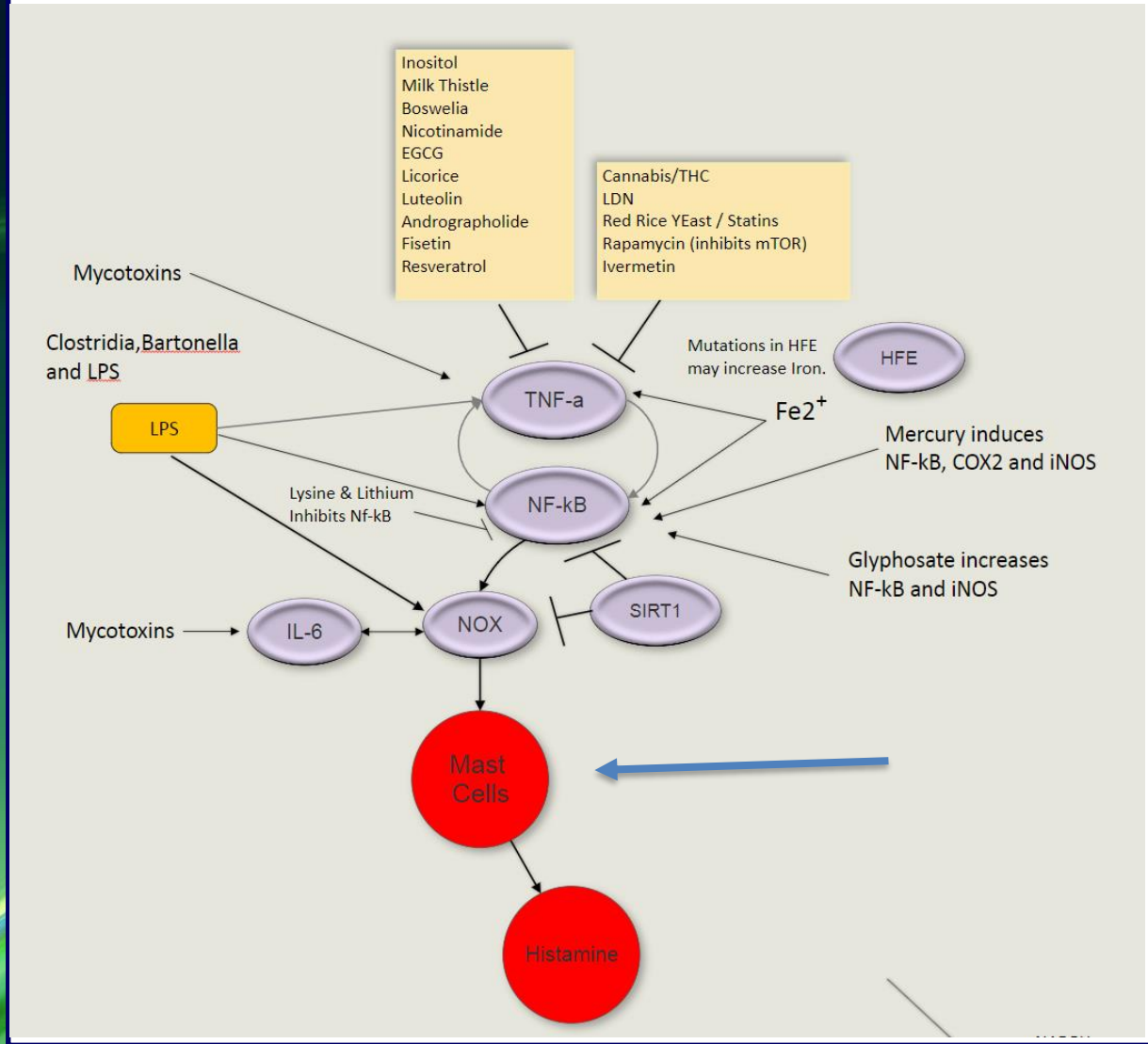
The Role of Histamine and Histamine Receptors in Mast Cell-Mediated Allergy and Inflammation: The Hunt for New Therapeutic Targets

Elden Berla Thangam[1], Ebenezer Angel Jemima[1], Himadri Singh[2], Mirza Saqib Baig[3], Mahejibin Khan[4], Clinton B. Mathias[5], Martin K. Church[6] and Rohit Saluja[2,7]*

Histamine H1 receptor is also expressed in dermal dendritic cells and keratinocytes in the skin tissue, and histamine increases the NGF production *via* H1R in human keratinocytes (66). The secretion of NGF is caused by the phosphorylation of protein kinase C, extracellular signal-regulated kinases (ERK), and the activation of AP-1 resulting from H1R stimulation. Similarly, histamine, acting *via* H1R, has also been shown to enhance the production of chemokines, such as granulocyte macrophage colony stimulating factor, regulated on activation T cell expressed and secreted (RANTES), and monocyte chemotactic protein-1 (MCP-1) in IFN-γ-stimulated keratinocytes. It also upregulates the antigen-presenting capability of dendritic cells, and leads to Th1 polarization through H1R (67).

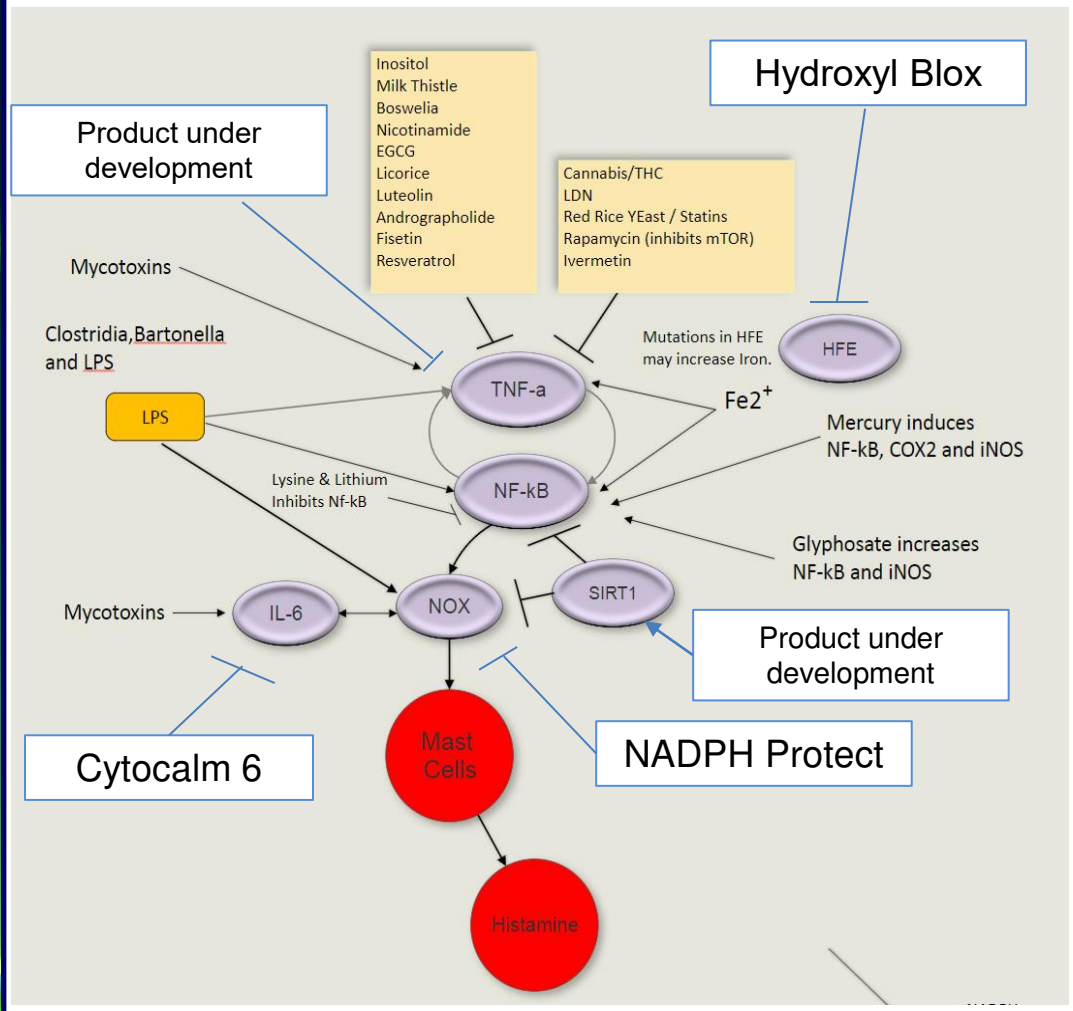
- Mast cells are the major producer of histamine in the body.
- The Histamine, from the mast cells, has also been shown to ***enhance the production*** of chemokines, such as ***RANTES***.

Pathway #1 -TNF-a



- Mycotoxins, Lyme or other sources of LPS stimulate TNF-a and begin a cascade of inflammation leading to mast cells and RANTES

Pathway #1 -TNF-a



Environmental Factors

- Clostridia
- Bartonella
- LPS
- Mercury
- Glyphosate

SNPS Impacting

- TNF-a (gain of function)
- HFE (gain of function)
- SIRT1 (lowered function)
- IL-6 (gain of function)

TNF-a / NF-kB

- Tumour Necrosis Factor alpha (TNF alpha), is an inflammatory cytokine produced by macrophages/monocytes during acute inflammation and is responsible for a diverse range of signaling events within cells, leading to necrosis or apoptosis.
- The protein is also important for resistance to infection and cancers. Increased TNF-a along with other genetic (COX2) and epigenetic factors (EMF. allergens, bacteria, injury) stimulates PLA-2 that begins a cascade resulting in increased Arachidonic Acid, Thromboxane A2, thus leading to platelet activation and increased RANTES.
- NF-κB is a family of inducible transcription factors that play a variety of evolutionarily conserved roles in the immune system. *Cytokines belonging to the TNF family induce rapid transcription of genes regulating inflammation, cell survival, proliferation and differentiation, primarily through activation of the NF-κB pathway.*
- Mutations in TNF (rs1800629) is a "Gain of Function" and will cause TNF-a to respond stronger

TNF		
Gene Name	Variants	Metrics
TNF (rs1800629) ? ▲	1	GA 24.7%

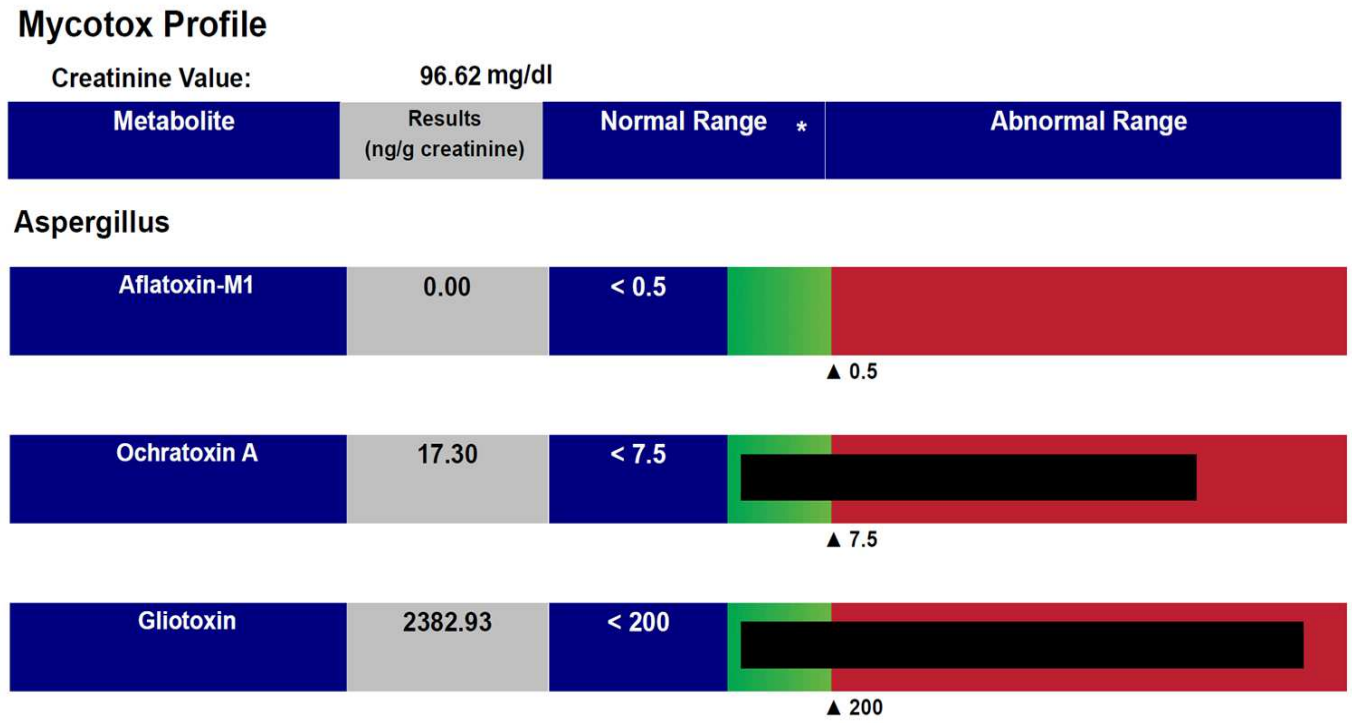
Idriss HT, 2022

TNF-a / NF-kB

- *In response to endotoxin (lipopolysaccharide [LPS])* due to gram-negative sepsis, human monocytes are triggered to produce large quantities of proinflammatory cytokines such as *tumor necrosis factor alpha (TNF-alpha)*
- Several studies have identified signal transduction pathways that are activated by LPS, *including activation of nuclear factor-kappaB (NF-kappaB)*
- The concentration of RANTES has been shown to increase due to the addition of TNF-alpha and LPS

Van der Bruggen T, 1999; Arima K, 2000

TNF-a / NF-kB



- Ochratoxin A (OTA), a natural fungal secondary metabolite, has been shown to trigger significant modulation of interleukin 2 (IL-2) and tumor necrosis factor α (TNF-α)

Darif Y, 2016

Potential
TNF-a Inhibitors

- Black Cumin (Nigella sativa)
  - During a recent meta-analysis of 10 randomized, controlled clinical trials consumption of black cumin was found to decrease serum TNFa, among other inflammatory markers
- Curcumin
- Quercetin
- Milk Thistle

Montazeri RS, 2021; Aggarwal BB, 2013; Aggarwal BB, 2013; Javadi F, 2016

SIRT1
Inhibition of NFK-b and NOX

SIRT1 (Sirtuin 1)

• SIRT1 is one of the most well-studied sirutins, and has a significant role in development, and is often considered as marker of cell senescence

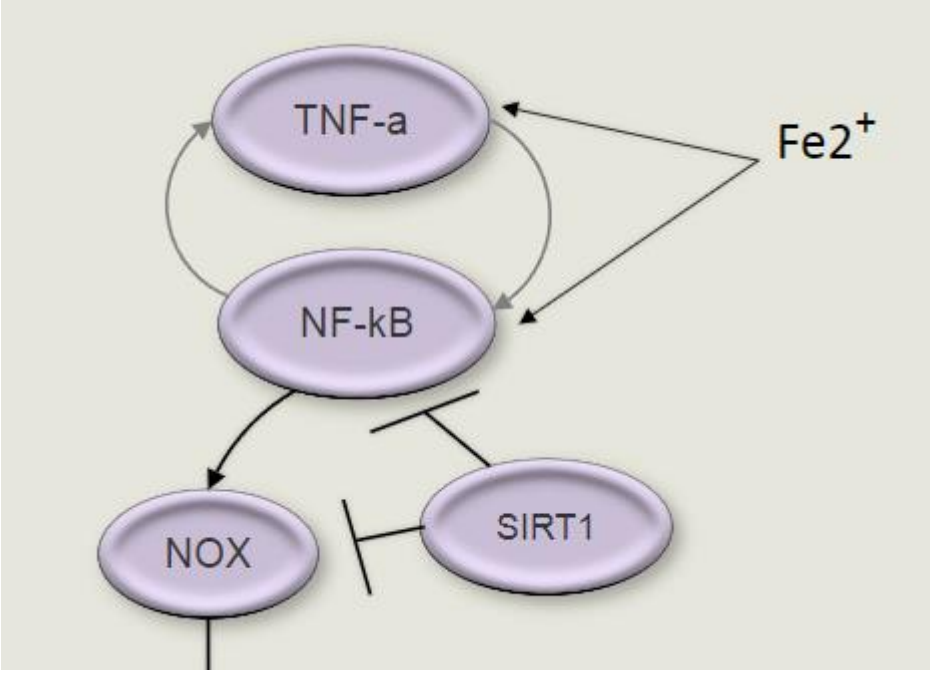
• SIRT1 activity decreases during aging, likely due to low NAD+

• Decreased levels of SIRT1 are found in the aging liver, and may be associated with decreased NAD+

• SIRT1 plays a critical role in the expression of monoamine oxidase A (MAO-A), AMPK, regulation of FOXO, SOD, NOS3 and inhibits NOX, NF-kB, IGF-1 and mTOR.

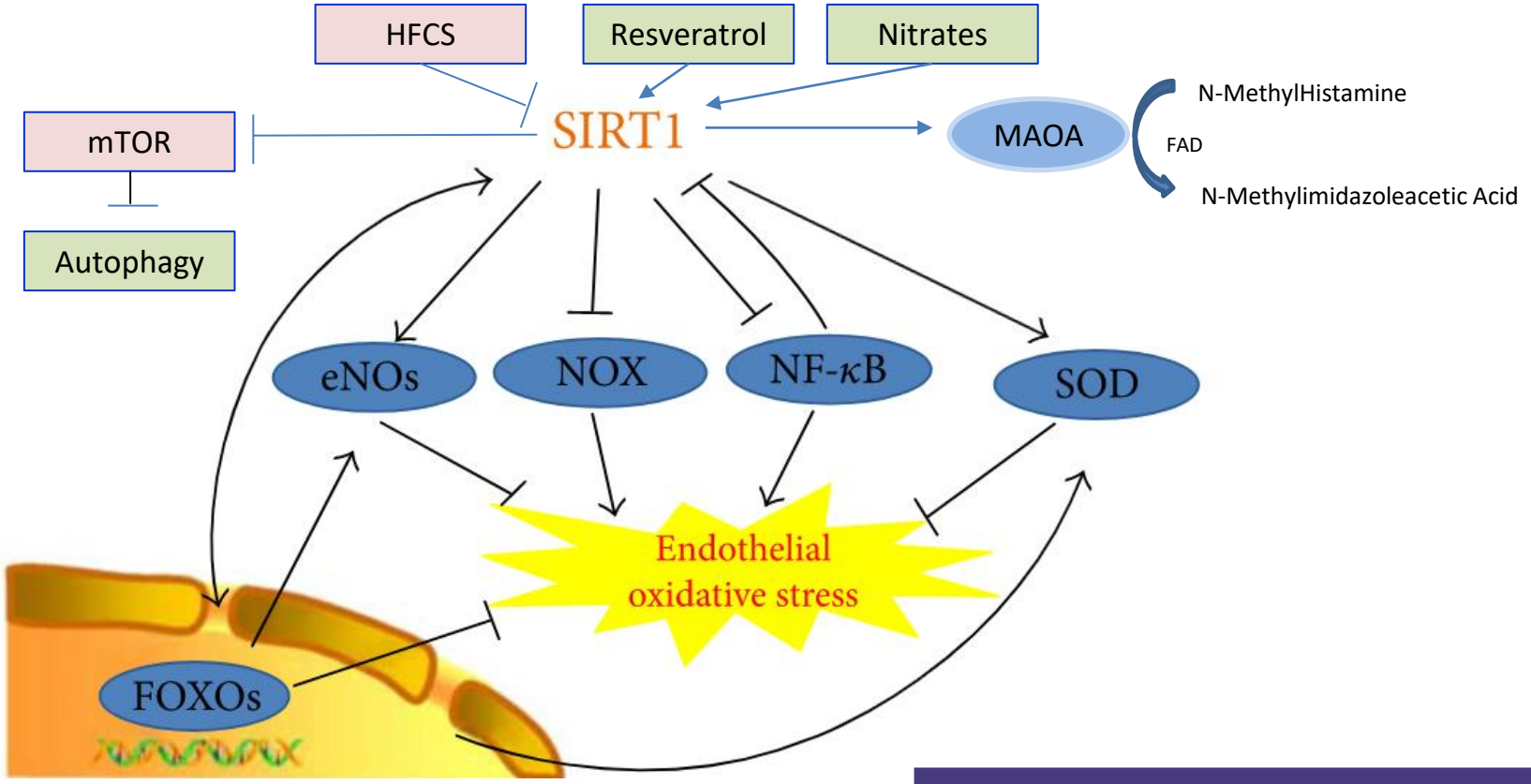
• High Fructose Corn Syrup inhibits SIRT1

• Resveratrol, quercetin and caloric restriction may activate SIRT1 activity



SIRT1


↑Rescue primary mouse embryonic fibroblast
↓Pro-apoptotic action of p53
↑Protection against Alzheimer's disease, Huntington's disease and amyotrophic lateral sclerosis
↓Onset of prion disease
↑Protection against chronic inflammation
↓Replicative life span in response to chronic genotoxic stress
↑Hormonal efficiency
↑Modulation of transcriptional repressor
Environmental stress
Cellular senescence
Neurodegenerative disease
↓Oxidative stress
↓Forkhead-dependent apoptosis
↑FoxO1 and FoxO3 induced cell cycle arrest
↓FoxO1 and FoxO3 induced cell death
Heart aging and stress
Development
Sirt1
Cell aging
↑Insulin secretion and action
↑ βcell protection
↑Fat metabolism
↓Lipid profile
Metabolic diseases
↓ Replication of ERCs (in yeast)
↑Telomere stability
↑Caloric restriction induced lifespan extension (in mice)
Placental cell survival
Cancer
Adipose tissue
↑ Cell resistance to O_2 deficiency
↑Epigenetic silencing of DNA hypermethylated TSGs
↓Transcriptional activity of p53
↑Deacetylation of β-catenin
↑DNA damage repair
↑Tumor suppression
↑Genome stability
↓c-Myc stability
↓Lipid accumulation in adipocytes
↑Lypolysis
↑Insulin sensitivity



- HFCS inhibits SIRT1
- Resveratrol supports SIRT1

SIRT1		
Gene Name	Variants	Metrics
SIRT1 (rs12778366)	1	TC 21.2%

Mast Cell Activation

- Mast cells become over-reactive and over-release inflammatory mediators
- Likely present in 9-14% of the population

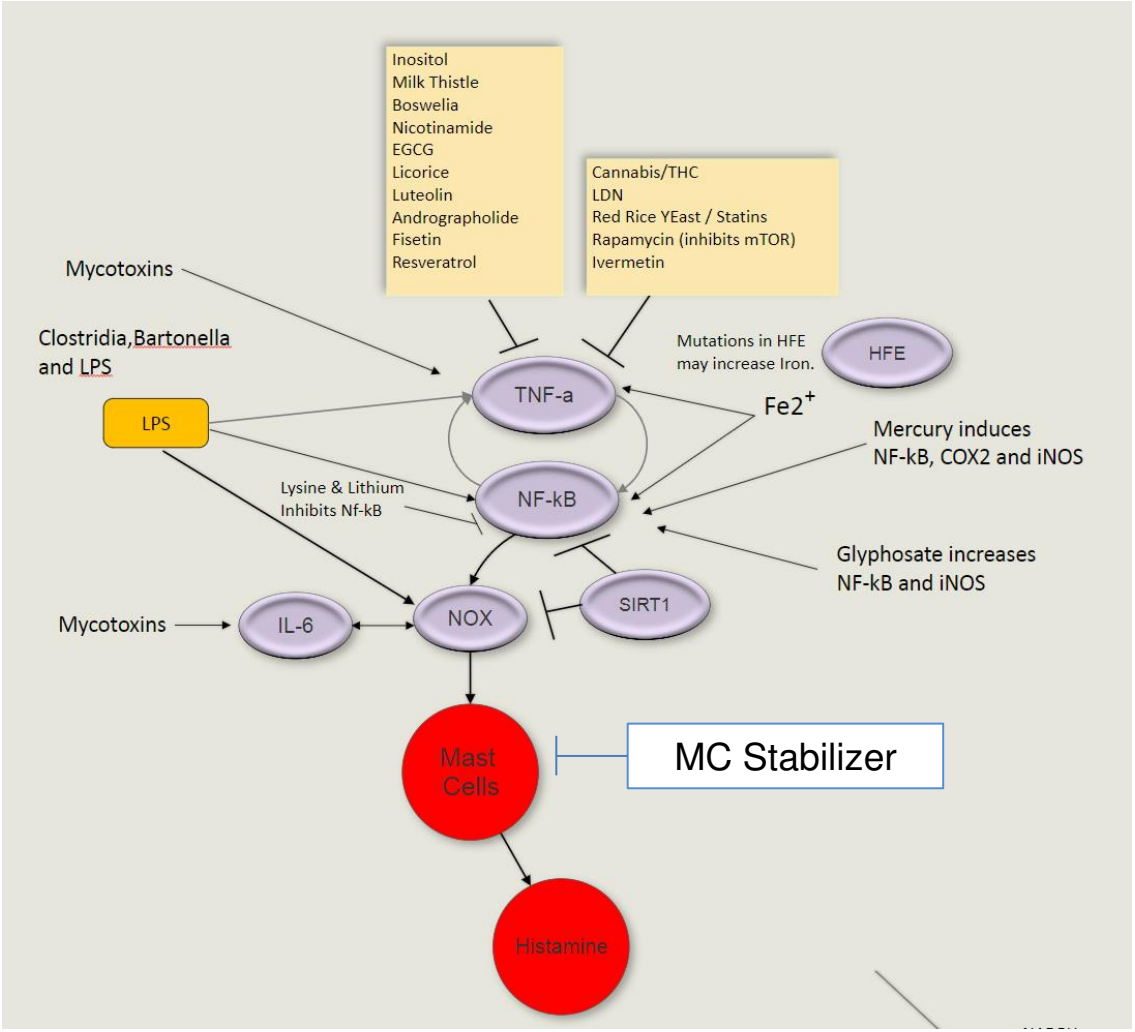
SNPS Impacting

- KIT (gain of function)

Supplements to Support *

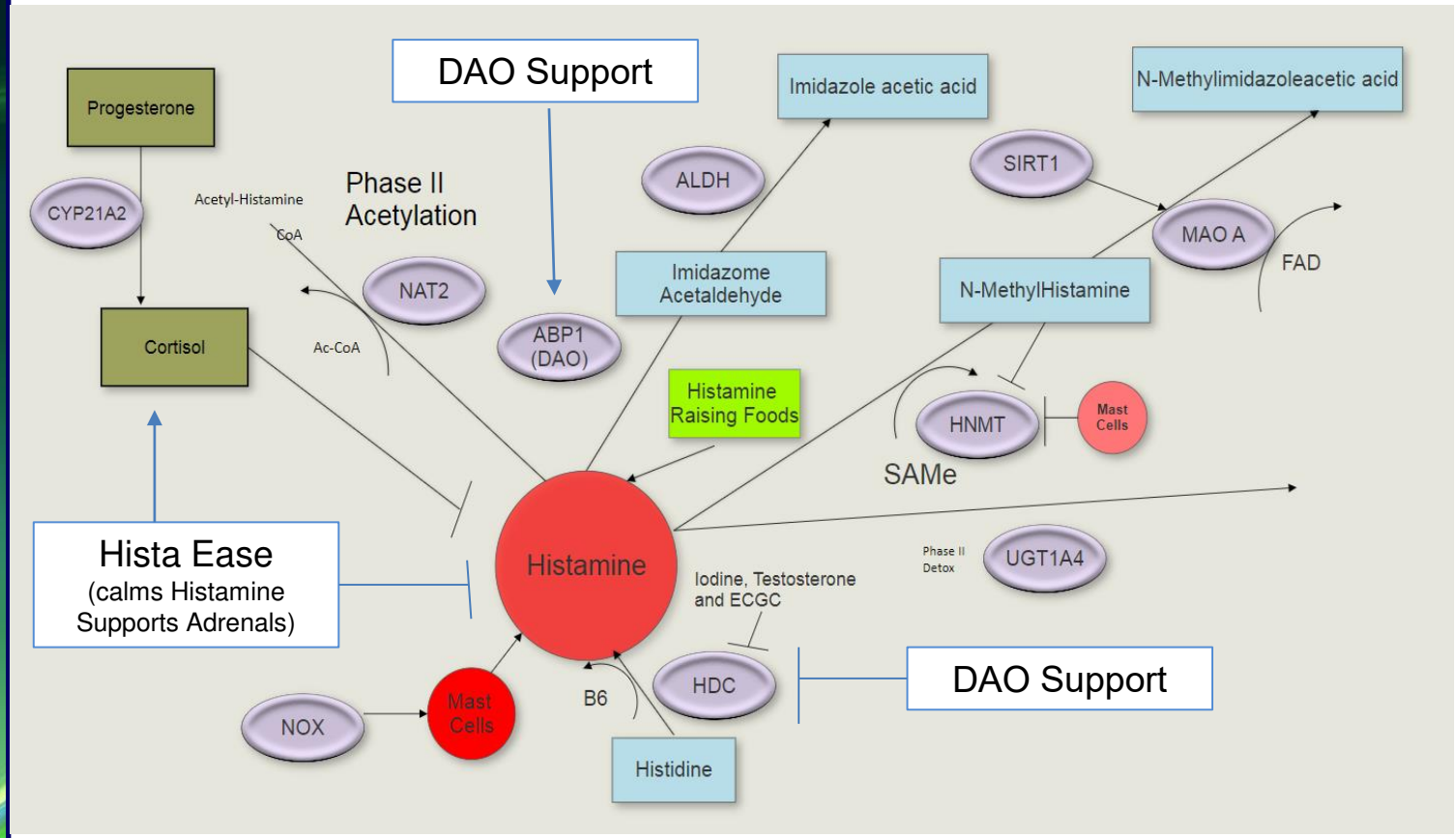
- MC Stabilizer

* See Appendix B for supplement information



See Reference Slides #1-7

Histamine



Environmental Factors

- Allergens
- High Histamine Foods

SNPS Impacting

- ABP1 (DAO production)
- MAOA
- MAOB
- UGT1A4
- CYP21A2 (progesterone to cortisol)
- HDC (histidine to histamine)

Arterioscler Thromb Vasc Biol. 2007 Jul;27(7):1556-61. doi: 10.1161/ATVBAHA.106.139089. Epub 2007 May 3.

Histamine upregulates the expression of inducible nitric oxide synthase in human intimal smooth muscle cells via histamine H1 receptor and NF-kappaB signaling pathway

Akihide Tanimoto [1], Ke-Yong Wang, Yoshitaka Murata, Satoshi Kimura, Masako Nomaguchi, Sei Nakata, Masato Tsutsui, Yasuyuki Sasaguri

Methods and results: In cultured human intimal SMCs, histamine increased NO production, iNOS expression, and NF-kappaB nuclear translocation, which were inhibited by histamine H1 blocker and NF-kappaB inhibitor. Luciferase assay using -8.3 kb upstream of human iNOS promoter region and electrophoretic mobility shift assay suggested that a NF-kappaB motif located at -3922 to -3914 would be necessary for histamine-inducible promoter activity. In addition, H1 blocker, NF-kappaB inhibitor, and dominant negative IkappaB alpha or IkappaB kinase beta downregulated the histamine-induced iNOS promoter activity. In the human aorta, histamine content was estimated to be 310+/-66 pmol/mg protein in the atherosclerotic intima, while that was to be 43+/-22 pmol/mg protein in the media ($P<0.001$).

Conclusions: Histamine stimulates intimal SMCs to increase iNOS expression via H1 receptors and NF-kappaB signaling pathway. Histamine could be one of NO-regulating factors, by inducing iNOS expression in intimal SMCs, and may be related to atherogenesis.

- Histamine stimulates iNOS expression via H1 receptors and NF-kappaB signaling pathway.

Tanimoto A, 2007

The Role of Histamine and Histamine Receptors in Mast Cell-Mediated Allergy and Inflammation: The Hunt for New Therapeutic Targets

Elden Berla Thangam[1], Ebenezer Angel Jemima[1], Himadri Singh[2], Mirza Saqib Baig[3], Mahejibin Khan[4], Clinton B. Mathias[5], Martin K. Church[6] and Rohit Saluja[2,7]*

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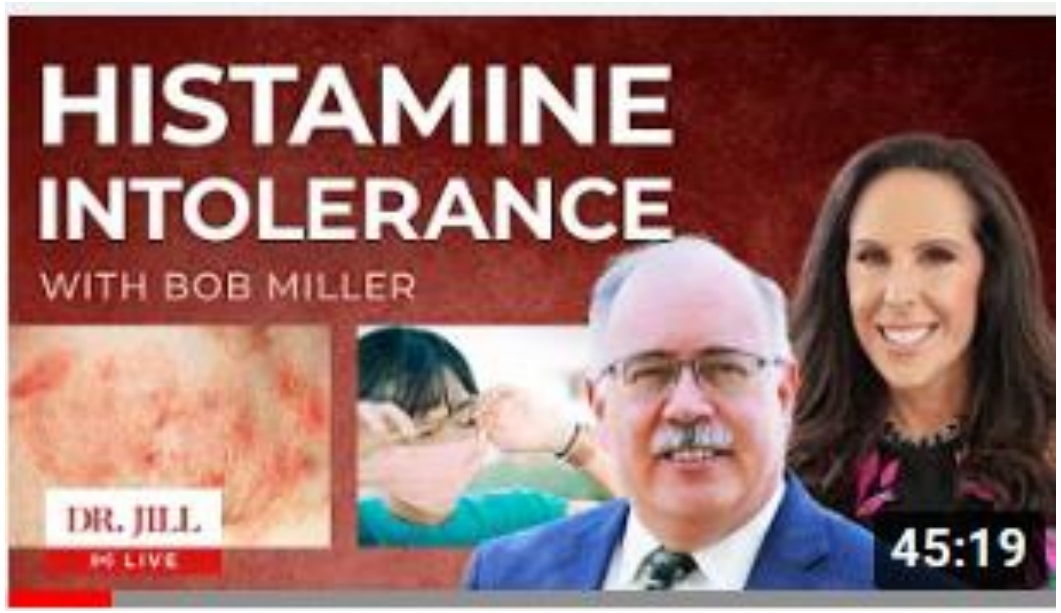
- The Histamine, from the mast cells, acting *via* H1R, has also been shown to ***enhance the production*** of chemokines, such as ***RANTES***.

Thangam EB, 2018

#34: Dr. Jill Interviews Bob Miller on Histamine Intolerance

Jill Carnahan, MD • 1.5K views • 1 year ago

In Episode #34, Dr. Jill and Bob Miller discuss implications of too much or too little histamine: The Good, The Bad, and the Ugly. Lean about histamine intolerance. Dr. Jill is your Functional...



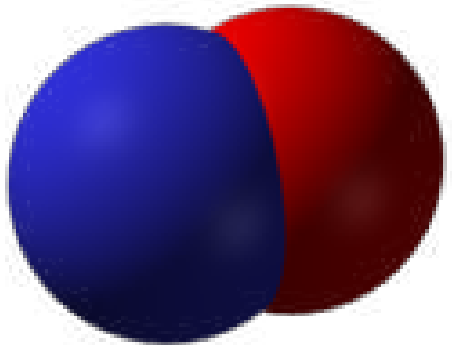
Search **Carnahan Histamine Intolerance** on YouTube

NO – The Miracle Molecule

The Benefits of Nitric Oxide

The Miracle Molecule

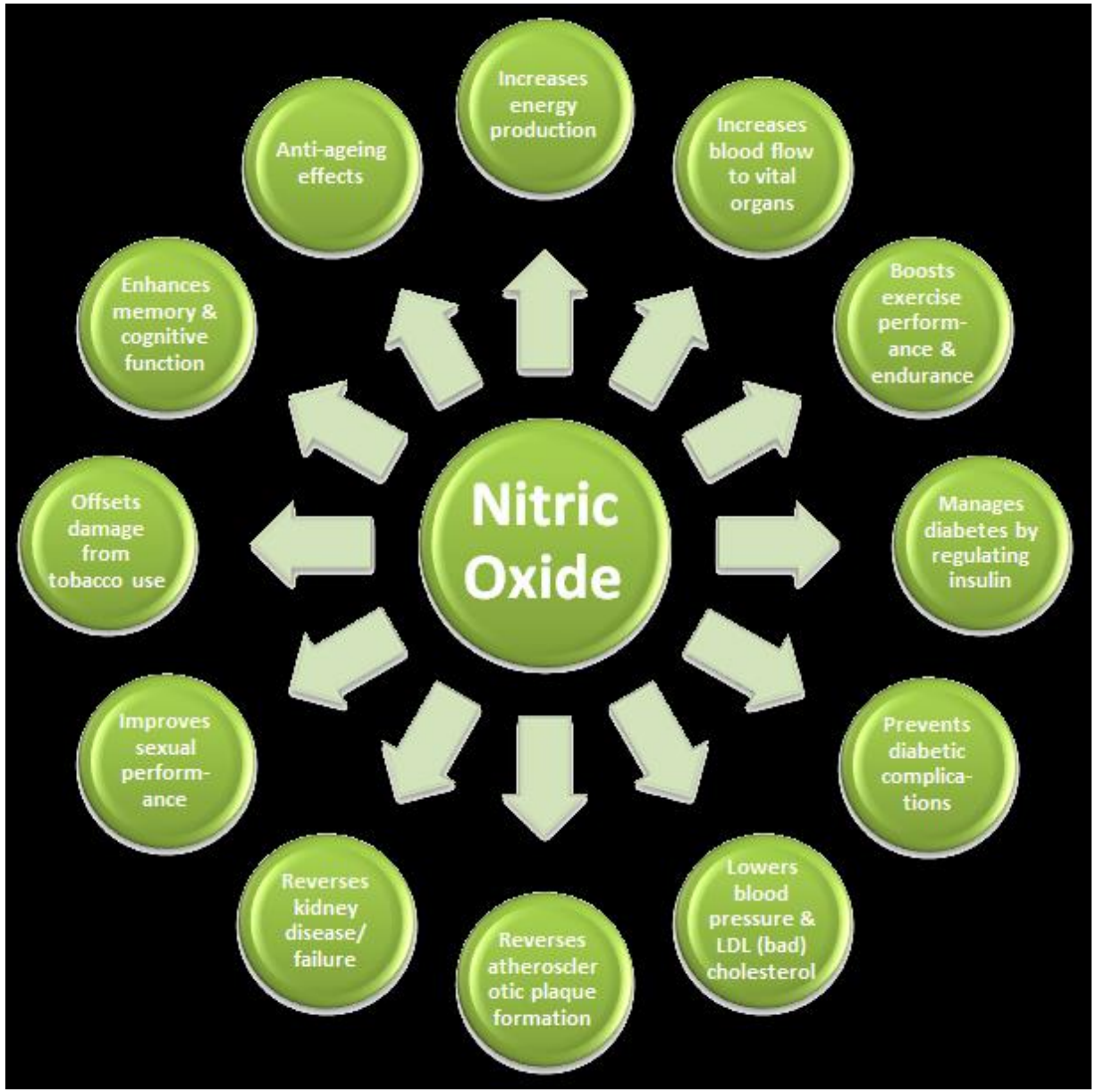
- NO is one of the simplest molecules in biology, comprised of just two atoms—one atom of nitrogen (N) and one of oxygen (O).
- Through NO's structure is simple, nitric oxide is now regarded as the most significant molecule in the body, absolutely crucial to your well-being.



Nitric Oxide molecule

NO – The Miracle Molecule

- Acts as a vasodilator, causing the blood vessels to expand. This function has obvious benefits to the circulatory system, including reducing blood pressure, increasing the flow of nutrients to the muscles and organs, and improving the efficiency with which wastes are removed from the muscles and organs.
- Stimulate the brain, help men with erectile function and impotence, increase energy, support wound healing and support the immune system.
- Nitric oxide (NO) is a powerful signaling molecule present in the cardiovascular and nervous systems as well as throughout the body, influencing the functioning of virtually every bodily organ, including the lungs, liver, kidneys, stomach, genitals, and, of course, the heart.


Nitric Oxide
Increases energy production
Increases blood flow to vital organs
Boosts exercise perform-ance & endurance
Manages diabetes by regulating insulin
Prevents diabetic complica-tions
Lowers blood pressure & LDL (bad) cholesterol
Reverses atherosclerotic plaque formation
Reverses kidney disease/ failure
Improves sexual perform-ance
Offsets damage from tobacco use
Enhances memory & cognitive function
Anti-ageing effects

iNOS – Your Bodies Defense

How iNOS in Excess (or….the Superoxide it produces) may be harmful

NOS2 or iNOS is Critical for Immune Defenses

- Our immune system is critical for protection against pathogens, and development of infections
  - iNOS (NOS2) generates very high amounts of nitric oxide to fight bacteria, virus, fungal infections and parasites.
  - Total elimination of iNOS (NOS2) in animals has shown to increase susceptibility to various infections

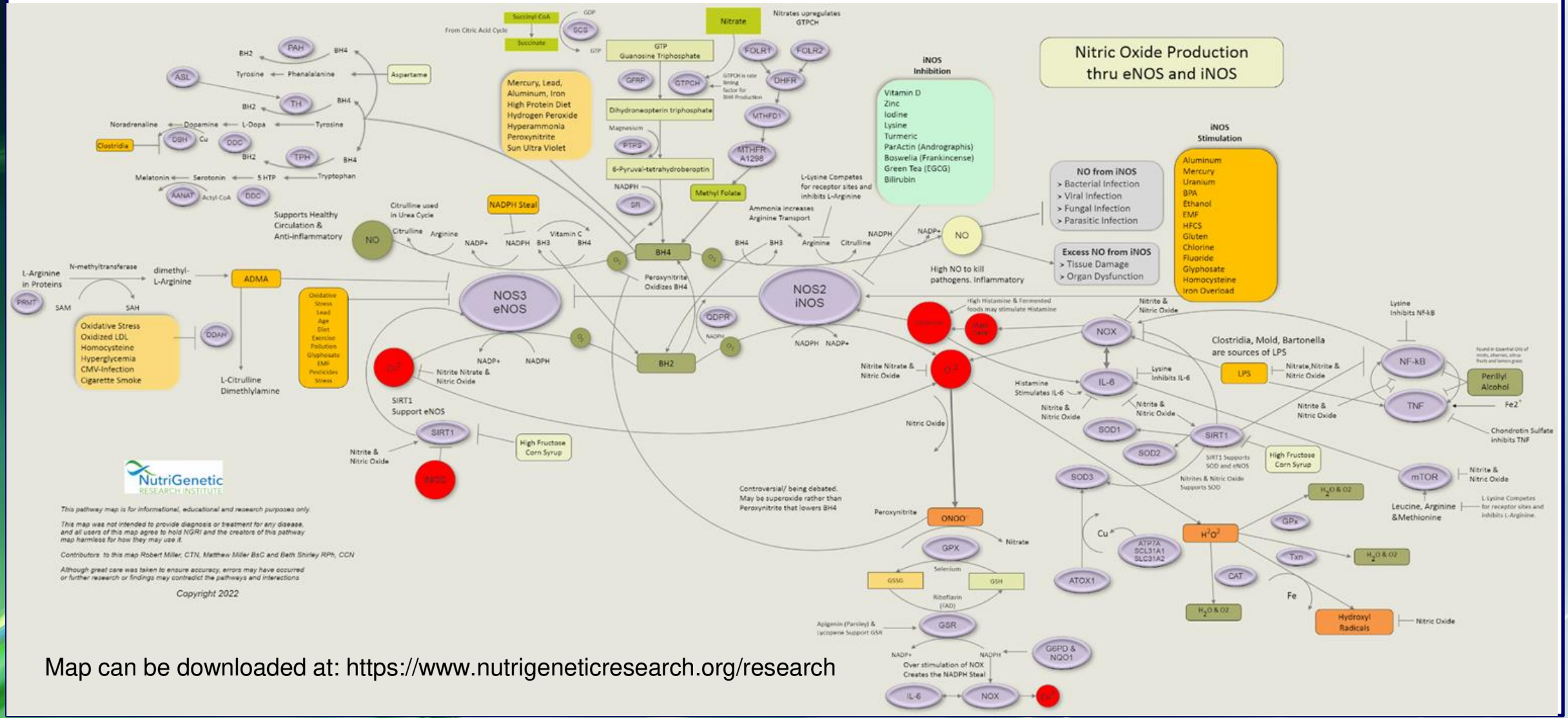
Lirk P, 2002

Potential Negative Effects of Excessive NO

- On the other hand, excessive nitric oxide from iNOS upregulation has been associated with many health concerns
    - *Excess production of NO appears to be linked to tissue damage and organ dysfunction*

Lirk P, 2002

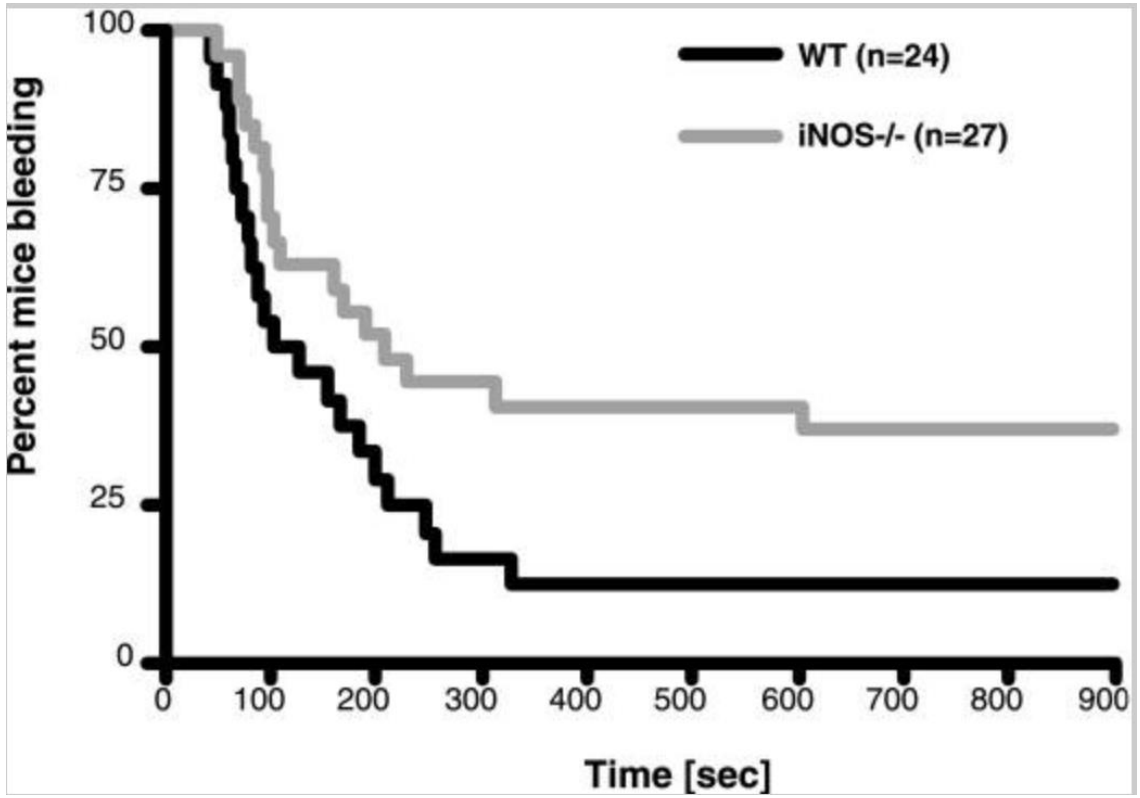
iNOS Stimulation & NOS Uncoupling



Map can be downloaded at: https://www.nutrigeneticresearch.org/research

iNOS Activation and Platelet Secretion

- iNOS activation influences platelet secretion via NO-cGMP-dependent platelet secretion pathway
- iNOS knock-out mice have prolonged bleeding time
  - Shows a physiologically relevant role in hemostasis of this new mode of iNOS activity regulation



Marjanovic JA, 2008

Expression and Activity of Platelet Endothelial Nitric Oxide Synthase Are Decreased in Patients with Coronary Thrombosis and Stenosis

Zahra Emami,[1,2] Alireza Mesbah Namin,[1] Javad Kojuri,[3] Farideh Mashayekhi Jalali,[4] and Mozhgan Rasti[2,*]

Results:

There was a significant decrease in the amount of NO concentration in the plasma of subjects with CT (0.53±0.09 μM, p<0.01) and CS (1.31±0.11 μM, p<0.01) compared to the control group (2.6±0.10 μM). The activity levels of eNOS enzyme were significantly lower in patients' platelets with CT (0.68±0.013 *UF/mn*, p<0.01) and CS (0.85±0.017 *UF/mn*, *p*<0.01) than the control cases (1.29±0.019 *UF/mn*). These data were consistent with the reduction of the expression levels of eNOS in patients with CT (75 folds) and CS (4 folds) lower than the control cases.

Conclusion:

Patients with CT and CS possessed reduced eNOS activity and gene expression in their platelets. Decreased plasma concentration of NO in these patients confirmed the potential significance of the diagnostic and prognostic value of NO in the subjects' plasma with vascular disease risk.

- There was a significant decrease in the amount of Nitric Oxide concentration in the plasma of subjects with Coronary Thrombosis (blood clots) compared to the control group
- The activity levels of eNOS enzyme were significantly lower in patients' platelets with Coronary Thrombosis
- These data were consistent with the reduction of the expression levels of eNOS in patients with Coronary Thrombosis (75 folds) than the control cases.

Emami Z, 2019

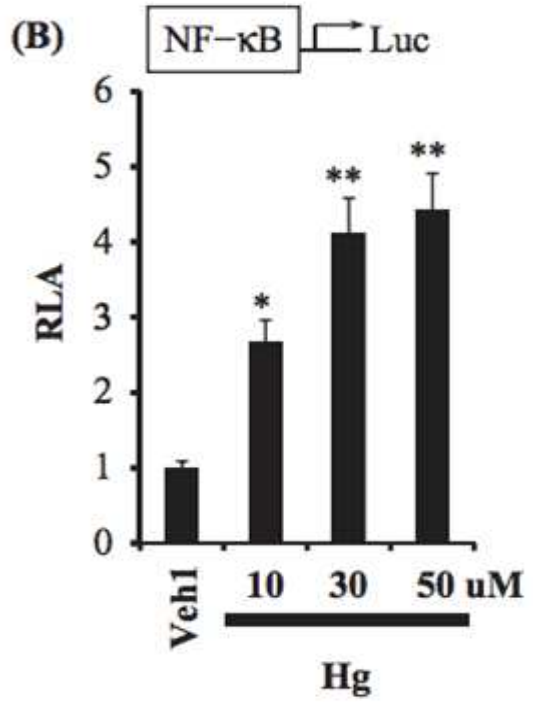
Potential iNOS Stimulators

NutriGenetic RESEARCH INSTITUTE

- Aluminum, Mercury, Uranium
- BPA (Plastics)
- Ethanol
- EMF
- Lyme Disease (LPS)
- Mold/Mycotoxins
- Histamine
- Fluoride
- Clostridia (LPS)
- High Fructose Corn Syrup
- Gluten
- Glyphosate (Round-Up)
- Homocysteine
- Iron

Potential iNOS Stimulators: Mercury

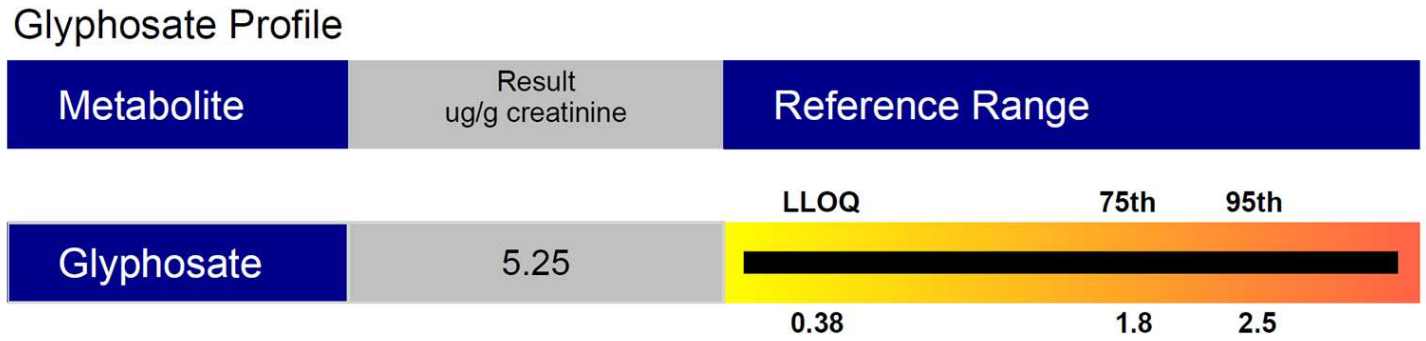
- *Mercury has been shown to solely induce NF-κB activation*
  - *This results in the induced expression of COX-2 and iNOS*
- Suggests that mercury can induce inflammatory diseases by lowering host defense



Park HJ, 2011

Potential iNOS Stimulators: glyphosate-based herbicide

- Glyphosate (GLY) exposure inhibited SOD, CAT, and GPx activities as well as reduced GSH contents
- Also ***promoted expression of NF-κB, iNOS,*** IL-1β, IL-6, IL-8, and TNF-α; altered the levels of IL-10 and TGF-β
  - Indicates that GLY exposure induced an inflammatory response



Ma J, 2019; Vermeire B, 2019

Published online 2019 Jun 7. doi: 10.1016/j.toxrep.2019.06.004 PMID: 31293901

Genetic polymorphisms as determinants of pesticide toxicity: Recent advances

Michele Teodoro,[a] Giusi Briguglio,[a] Concettina Fenga,[a,*] and Chiara Costa[b]

- The susceptibility to exposure can be evaluated by studying the most common polymorphisms of cytochrome P450, of glutathione transferases (including GSTM1, GSTP1, GSTT1); of acetyltransferases (NAT2) and paraoxonases (mostly PON1), which are mainly involved in the metabolism of organophosphorus compounds

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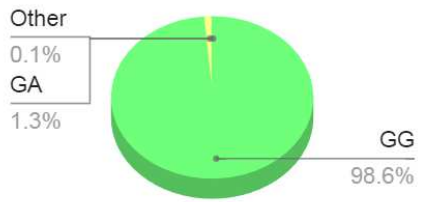
Supporting Health through Science & Nutrition

PON1 (rs705379)	1	GA 1.3%
PON1 (rs854570) ?	1	AC 45.9%
PON1 (rs854560)	2	TT 12.5%
PON1 (rs854569) ?		GG 58.5%
PON1 (rs854566) ?		GG 66.6%
PON1 Q192R (rs662) ?		TT 48.4%
PON1 (rs854571)	1	CT 41.5%

PON1 (rs705379) Close



Teodoro M, 2019

Arterioscler Thromb Vasc Biol. 2007 Jul;27(7):1556-61. doi: 10.1161/ATVBAHA.106.139089.
Epub 2007 May 3.

Histamine upregulates the expression of inducible nitric oxide synthase in human intimal smooth muscle cells via histamine H1 receptor and NF-kappaB signaling pathway

Abstract

Objective: Histamine increases endothelial nitric oxide (NO) production as an endothelium-dependent vasodilator, which acts as a vasoconstrictor in atherosclerotic coronary arteries. To investigate the relation between histamine and NO production in intimal smooth muscle cells (SMCs), we studied the effect of histamine on inducible NO synthase (iNOS) expression in the SMCs.

Methods and results: In cultured human intimal SMCs, histamine increased NO production, iNOS expression, and NF-kappaB nuclear translocation, which were inhibited by histamine H1 blocker and NF-kappaB inhibitor. Luciferase assay using -8.3 kb upstream of human iNOS promoter region and electrophoretic mobility shift assay suggested that a NF-kappaB motif located at -3922 to -3914 would be necessary for histamine-inducible promoter activity. In addition, H1 blocker, NF-kappaB inhibitor, and dominant negative IkappaB alpha or IkappaB kinase beta downregulated the histamine-induced iNOS promoter activity. In the human aorta, histamine content was estimated to be 310+/-66 pmol/mg protein in the atherosclerotic intima, while that was to be 43+/-22 pmol/mg protein in the media ($P<0.001$).

Conclusions: Histamine stimulates intimal SMCs to increase iNOS expression via H1 receptors and NF-kappaB signaling pathway. Histamine could be one of NO-regulating factors, by inducing iNOS expression in intimal SMCs, and may be related to atherogenesis.

- Histamine stimulates intimal smooth muscle cells to increase iNOS expression via H1 receptors and NF-kB signaling pathway.

Tanimoto A, 2007

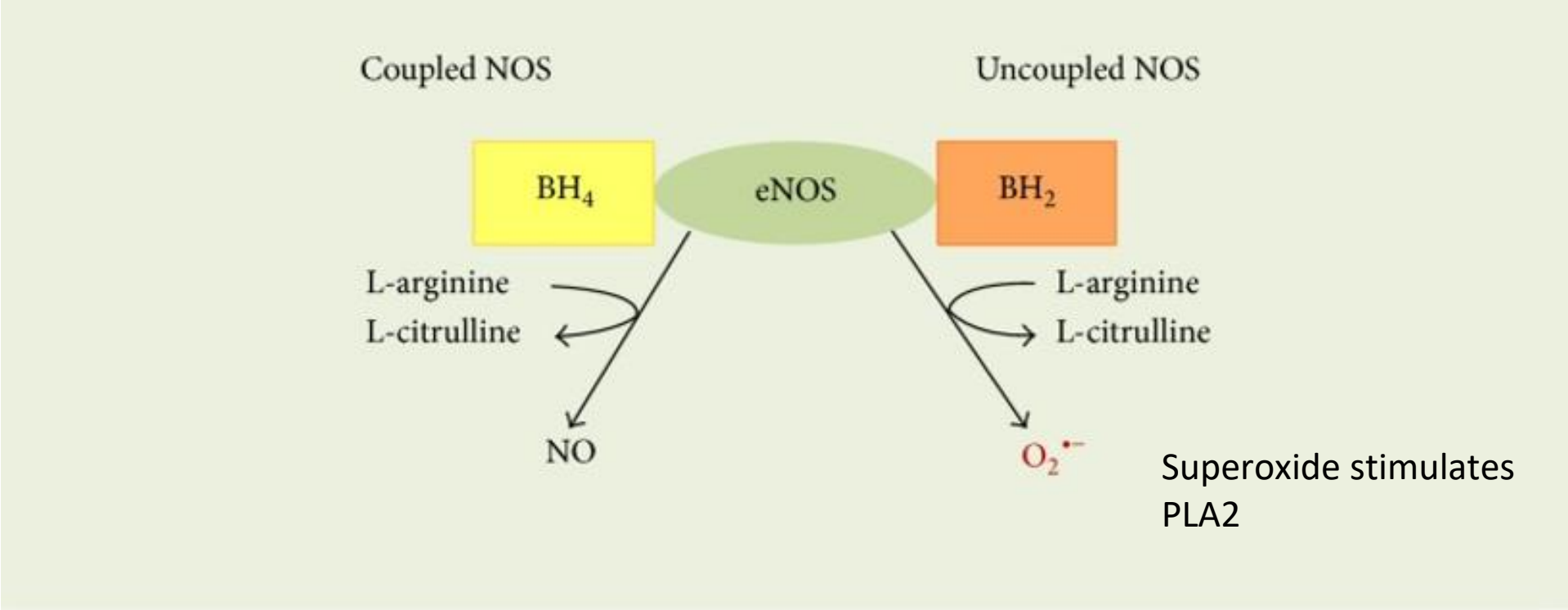
NADPH Oxidase Stimulates IL-6, Creates Histamine& Superoxide

NOS Uncoupling

NOS Enzyme Making Superoxide vs Nitric Oxide

NOS Uncoupling

NOS Enzyme Making Superoxide vs Nitric Oxide



Superoxide stimulates PLA2

Increased iNOS function

Increased iNOS function

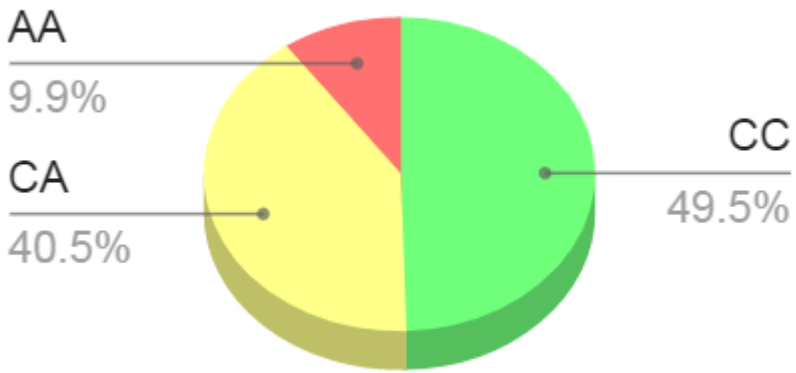
- Gain of function mutations in NOS2 (iNOS) enzymes, mutations in other enzymes over stimulating iNOS along with environmental and endogenous stimulation of NOS2 (iNOS) creates;
  - Inflammation from excess Nitric Oxide (Or Superoxide)
  - Excess Superoxide through NOS uncoupling
  - Depletion of BH4 creating more superoxide and potential disruption of Neurotransmitters

Common Functional iNOS polymorphisms

• rs2779249 (C–1026A) – Located in the promoter region, the A-allele has been associated with:

- 4.73x increased iNOS expression during an in vitro functional analysis
- Increased iNOS expression in a control group, and increased iNOS expression and plasma nitrite/nitrate levels among participants with cervical abnormalities or cancer
- In a control group during a clinical analysis, the heterozygous genotype was associated with increased levels of salivary nitrates and nitrites

rs2779249
Wild C Risk A

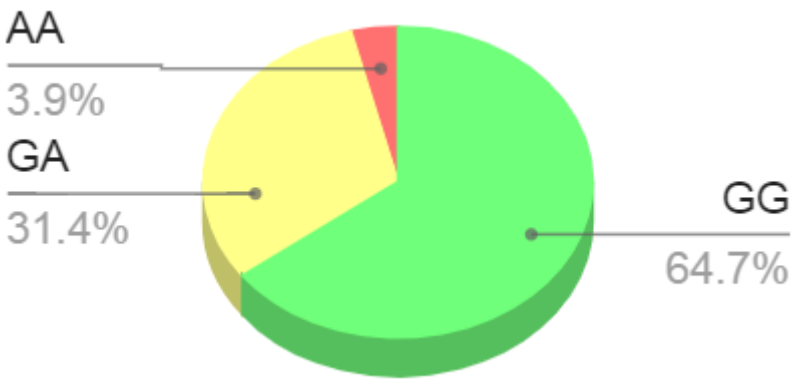


Fu L, 2009; Sowjanya AP, 2016; Scarel-Caminaga R, 2017

Common Functional iNOS polymorphisms

- rs2297518 (G2087A/S608L) – A-allele has been associated with:
  - Increased iNOS activity, and increased NO production in during *in vitro* functional analyses in 2 different cell lines
  - Very early onset Crohn's disease, ulcerative colitis, and IBD: the association with IBD was replicated in an independent cohort
    - Increased nitrosative stress, indicative of peroxynitrite and oxidative stress, in colonic biopsies in the GI disorder group
    - In older children and adults, the A-allele was associated with ulcerative colitis diagnosis between 11 -17 years of age, but not adult onset IBD

RS2297518
Wild G Risk A



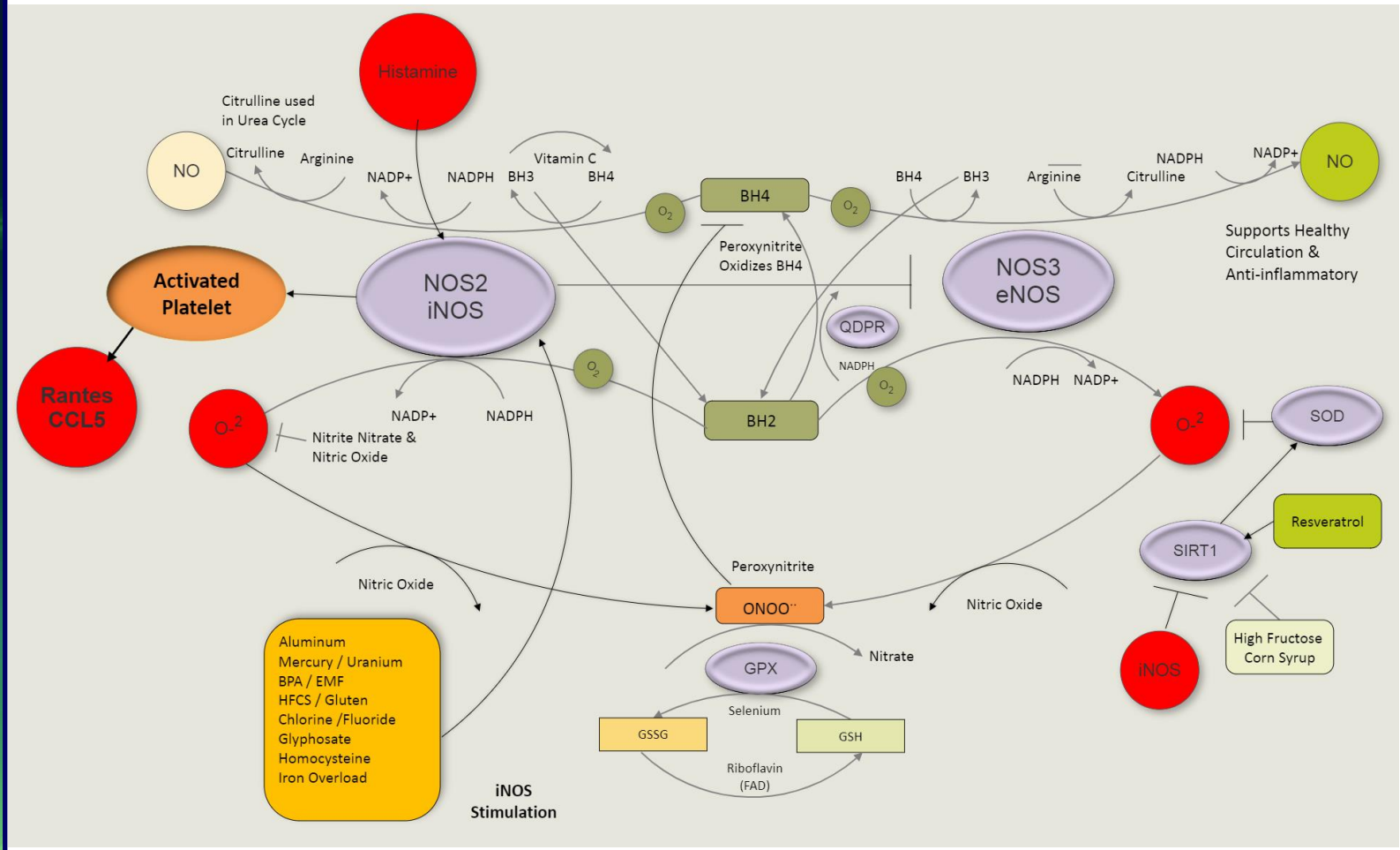
Dhillon SS, 2014

iNOS

- Mutations in NOS2, (iNOS) may increase iNOS production.

NOS2		
Gene Name	Variants	Metrics
NOS2 (rs3729508)		CC 37%
NOS2 (rs4795067)	2	GG 12.1%
NOS2 (S608L) (rs2297518) ?	2	AA 3.9%
NOS2 (rs8072199)	2	TT 17.7%
NOS2 (rs2274894) ?		GG 39.1%
NOS2 (rs1137933) ?	2	AA 5.1%
NOS2 (rs8078340)		GG 74.1%
NOS2 (rs2248814)		GG 40.1%
NOS2 (C-1026A) (rs2779249) ?	2	AA 9.9%

Carnahan Reaction



Environmental Factors

- Aluminum/Mercury/Uranium
- BPA
- EMF
- HFCS / Gluten
- Chlorine / Flouride
- Glyphosate
- Excess Iron and Homocysteine

SNPS Impacting

- NOS2 (gain of function)
- NOS3 (lack of function)
- SOD1,2,3
- SIRT1
- DHHR
- QDPR
- MTHFTR A1298C
- Others involved in BH4 produciton

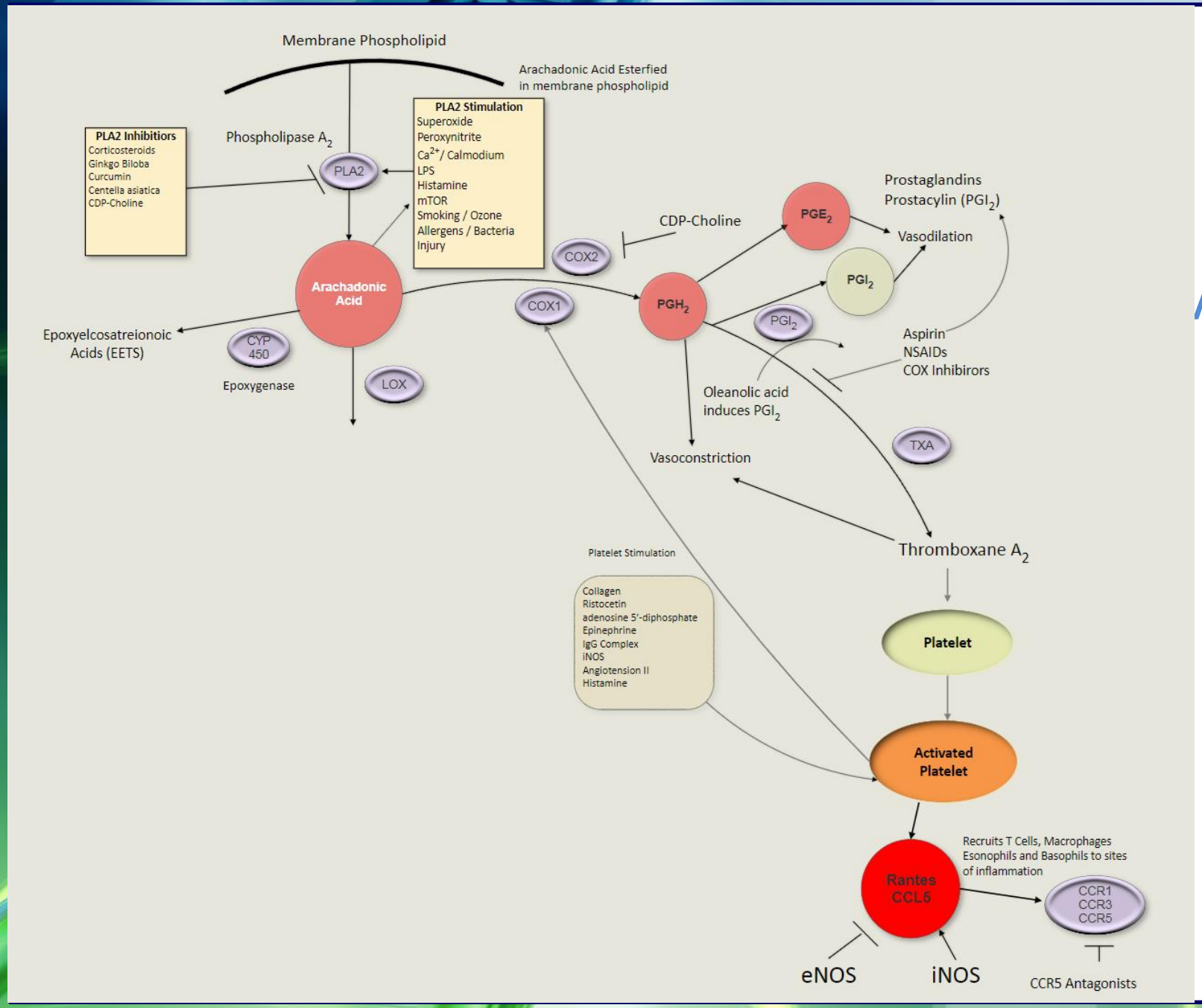
#82: Dr. Jill interviews Bob Miller on The Carnahan Reaction and iNOS

1.1K views • 3 months ago

Jill Carnahan, MD

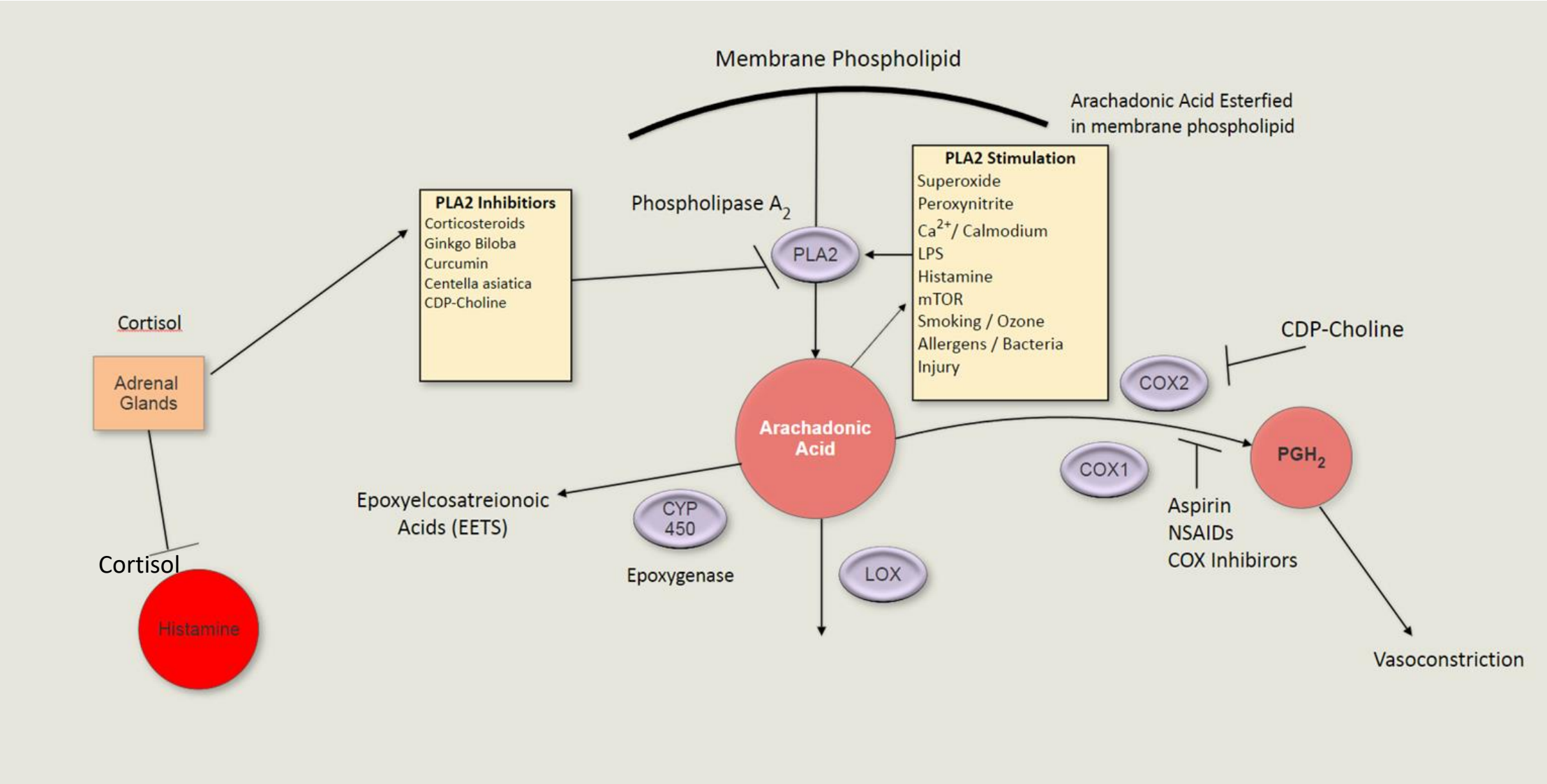
In Episode #82, Dr. Jill interviews Bob Miller on The **Carnahan** Reaction: everything you need to know about **iNOS** and NOS ...

Search **Carnahan iNOS** on YouTube



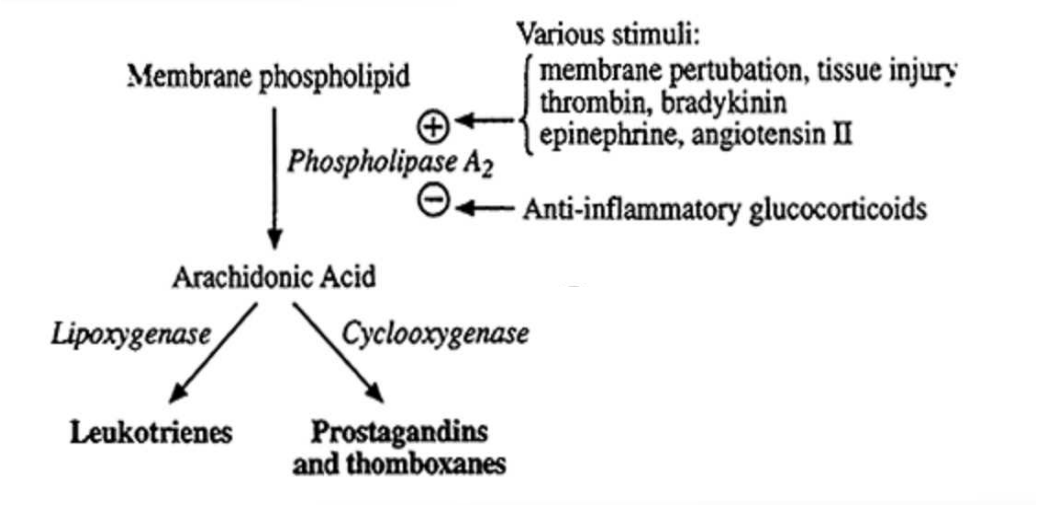
Pathway #2 Arachidonic Acid from PLA2

PLA2 - Phospholipase A2



PLA2 - Phospholipase A2

- Phospholipase A2 (PLA2) *liberates arachidonic acid (AA)* by catalyzing the hydrolysis of the sn-2 position of membrane glycerophospholipids
  - AA is a precursor of eicosanoids including prostaglandins (PGs) and leukotrienes (LTs)
- When rat platelets are incubated with phospholipase A2, thromboxane A2-like activity and prostaglandins are formed



Murakami M, 2002; Sturm N, 2019; Vincent JE, 1977

PLA2 Overview

• When experiencing infections, PLA2 can break down the phospholipids in the membranes of bacteria, fungi, and parasites leading to their death.

• However, inflammation, like many other biological processes often becomes excessive and may have negative effects. The same phospholipase that attacks infectious agents may also *attack the cell membranes of the human host, damaging or killing those cells.*

• The most common free fatty acid produced by PLA2 is arachidonic acid which can increase the production of powerful mediators of inflammation called prostaglandins, leukotrienes, and thromboxanes, collectively known as eicosanoid

Shaw W, 2015

PLA2 and Superoxide

- Superoxide anions could stimulate phospholipase A2
  - This could be prevented by superoxide scavenging agents and PLA2 inhibitors
- The products of phospholipase A2 are membrane-damaging agents
  - May be responsible for mitochondrial damage during oxidative stress

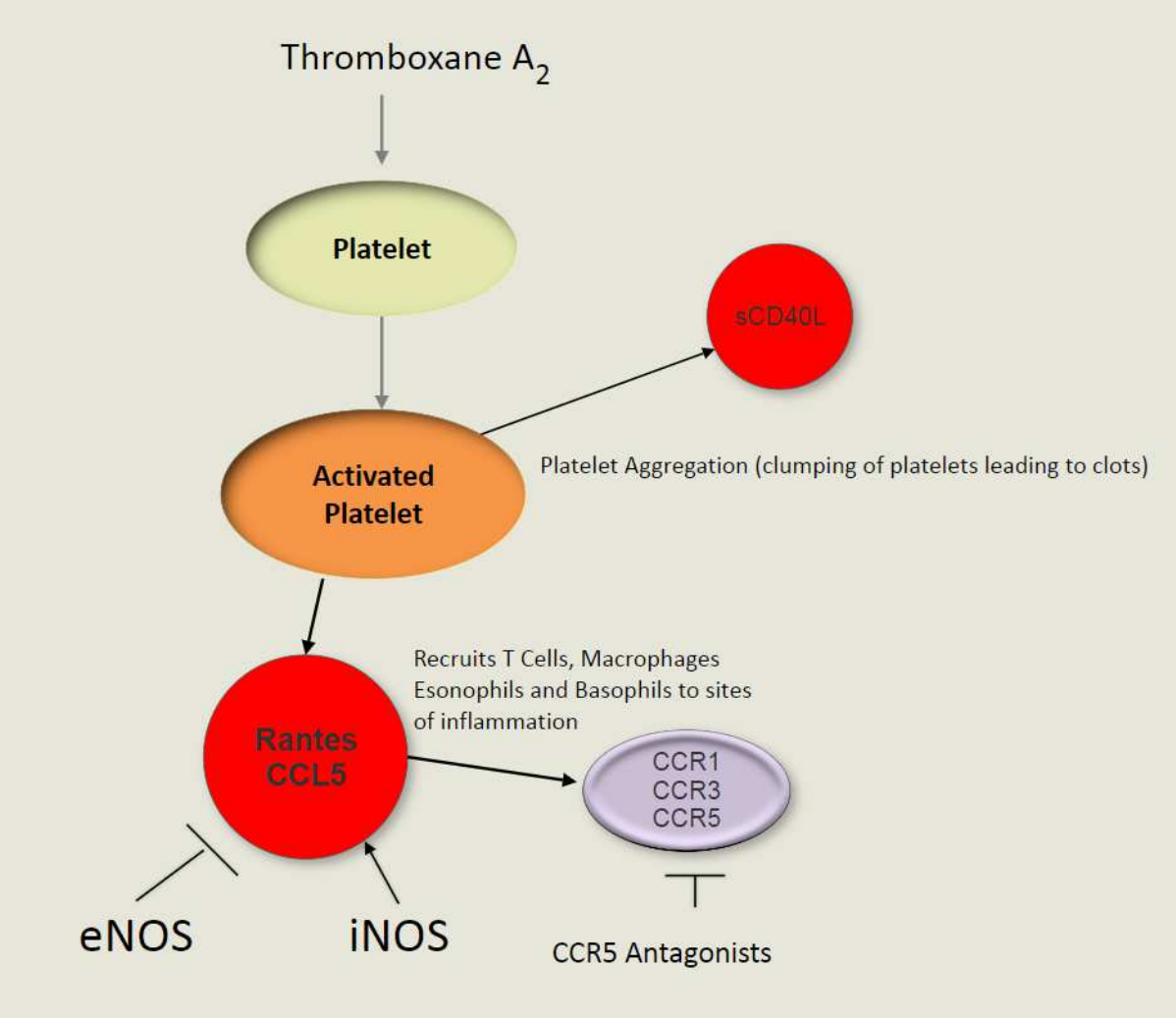
Madesh M, 1997

PLA2 and Tumor Necrosis Factor-Alpha (TNF-Alpha)

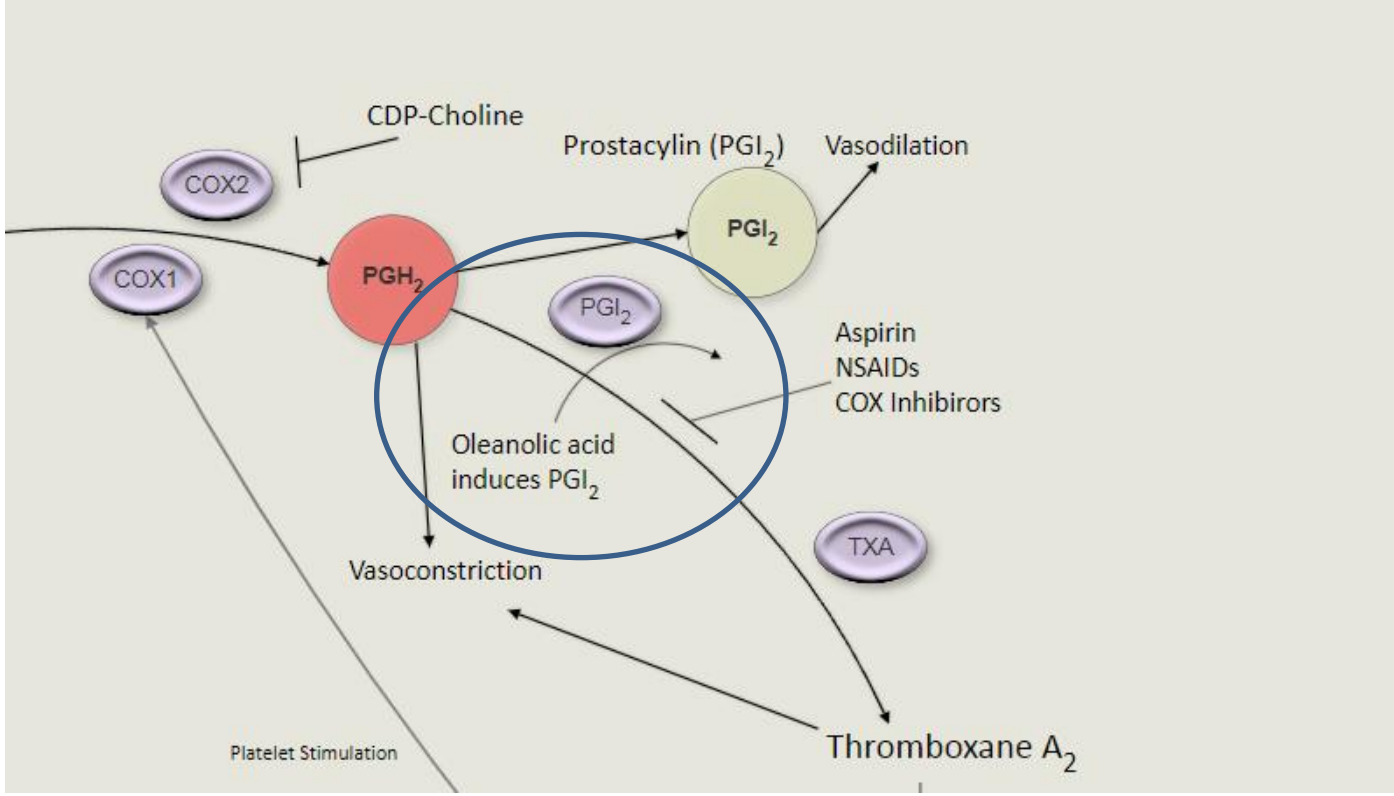
- A study of cultured intestinal epithelial cells has shown that TNF-alpha potentiates the release and metabolism of arachidonic acid
  - This indicates that TNF-alpha potentiates phospholipase A2-stimulated AA release
- A follow-up study determined that TNF-alpha may modulate the intestinal mucosal content of biologically active AA metabolites by priming PLA2- and COX-2-mediated processes in the epithelial cells

Gustafson-svärd C, 1993; Gustafson-Svärd C, 1995

Platelet Aggregation from Thromboxane A2



Oleanolic Acid



- Oleanolic acid from olive oil contributes to vascular homeostasis
  - Induces PGI_2 release in a Cox-2-dependent manner
- May contribute to the beneficial effects of the Mediterranean diet working as a bioactive molecule

Martínez-González J, 2008

Thromboxane A2 (TxA2)

- Prostaglandin counterbalances the thrombotic and vasoconstrictor properties of TxA2
- This balance can become dysregulated in various pathological and physiological situations
  - Increased activity of TxA2 could be associated with myocardial infarction, stroke, atherosclerosis, and bronchial asthma
  - Increased action of TxA2 could be associated with pulmonary hypertension, kidney injury, hepatic injury, allergies, angiogenesis, and metastasis of cancer cells
    - When activation of TxA2 is uncontrolled, there could be *pathological consequences*

Platelet Activation: The Mechanisms and Potential Biomarkers

Seong-Hoon Yun, [1] Eun-Hye Sim, [1] Ri-Young Goh, [2] Joo-In Park, [1] and Jin-Yeong Han [2,*]

- Beyond hemostasis and thrombosis, an increasing number of studies indicate that platelets play an integral role in intercellular communication, mediating inflammatory and immunomodulatory activities.
- The basic function of platelets is rapidly binding to damaged blood vessels, aggregates to form thrombi, and prevents excessive bleeding. However, activated platelets also aggregate at the site of atherosclerotic plaque rupture or endothelial cell erosion, stimulating thrombus formation and promoting atherothrombotic disease
- Activated platelets also express sCD40L
- In addition to playing a central role in normal hemostasis and thrombosis, platelets can make important contributions to host inflammatory and immune responses to infection or injury. Under uncontrolled pathological conditions, they have profound roles in pathogenic processes underlying atherosclerosis and cardiovascular diseases, uncontrolled inflammation, tumor metastasis, and neurodegenerative diseases including Alzheimer's disease

Yun S-H, 2016

Hamostaseologie. 2009 Nov;29(4):356-9.

[The role of serotonin in haemostasis]

[Article in German]
D Duerschmied [1], C Bode

Abstract

Serotonin is transported by platelets and released upon activation. This induces constriction of injured blood vessels and enhances platelet aggregation to minimize blood loss. Consequently, serotonin receptor antagonists have been tested for their anti-ischemic potency in atherothrombotic disease. Unfortunately, the results have been contradictory. Recent murine studies found that activation of the platelet serotonin receptor induces shedding of important adhesion molecules. As a consequence, platelets lose their ability to contribute to thrombus formation and may be cleared from the circulation. Serotonin effects on platelets are not only mediated by receptor binding but also by covalently binding effector proteins (serotonylation) in the platelet cytoplasm and on the platelet surface. In conclusion, the effects of serotonin on haemostasis are complex and new antithrombotic strategies have to account for this complexity.

- Serotonin is transported by platelets and released upon activation.
- This induces constriction of injured blood vessels and enhances platelet aggregation to minimize blood loss.

World J Psychiatry. 2012 Dec 22; 2(6): 91–94.
Published online 2012 Dec 22. doi: 10.5498/wjp.v2.i6.91
PMCID: PMC3782188
PMID: 24175174

Platelets in psychiatric disorders

Daniela Ehrlich and Christian Humpel

Abstract

Go to:

Several parallels exist between platelets and the brain, which make them interesting for studying the neurobiology of psychiatric disorders, such as Alzheimer's disease, depression, schizophrenia and anxiety disorders. Platelets store, secrete and process the amyloid precursor protein which is cleaved into the β-amyloid (Aβ) peptides. The accumulation of Aβ in brain (plaques) and vessels (Aβ-angiopathy) is a major hallmark in AD. Platelets contain high amounts of serotonin and a dysfunction of the serotoninergic system is involved in the development of several behavior disorders, such as depression, anxiety disorders and self aggressive disturbances. Furthermore, platelets are able to take up dopamine and express various dopamine receptors, which make them to an interesting tool to study the underlying mechanisms of schizophrenia. In summary, platelets are an interesting and easily accessible cell type to study changes related to different psychiatric disorders and platelets proteins may be useful as diagnostic biomarkers for some psychiatric disorders.

- Platelets contain high amounts of serotonin and a *dysfunction of the serotoninergic system* is involved in the development of several behavior disorders, such as *depression, anxiety disorders and self aggressive disturbances.*
- Furthermore, platelets are able to take up dopamine and express various dopamine receptors, which make them to an interesting tool to study the underlying mechanisms of schizophrenia.

Platelet Serotonin Aggravates Myocardial Ischemia/Reperfusion Injury via Neutrophil Degranulation

Maximilian Mauler, Nadine Herr, Claudia Schoenichen, Thilo Witsch, Timoteo Marchini, Carmen Härdtner, Christoph Koentges, Korbinian Kienle, Véronique Ollivier, Maximilian Schell, Ludwig Dorner, Christopher Wippel, Daniela Stallmann, Claus Normann, Heiko Bugger, Paul Walther, Dennis Wolf, Ingo Ahrens, Tim Lämmermann, Benoît Ho-Tin-Noé, Klaus Ley, … See all authors

Originally published 25 Oct 2018 | https://doi.org/10.1161/CIRCULATIONAHA.118.033942 | Circulation. 2019;139:918–931

Background:

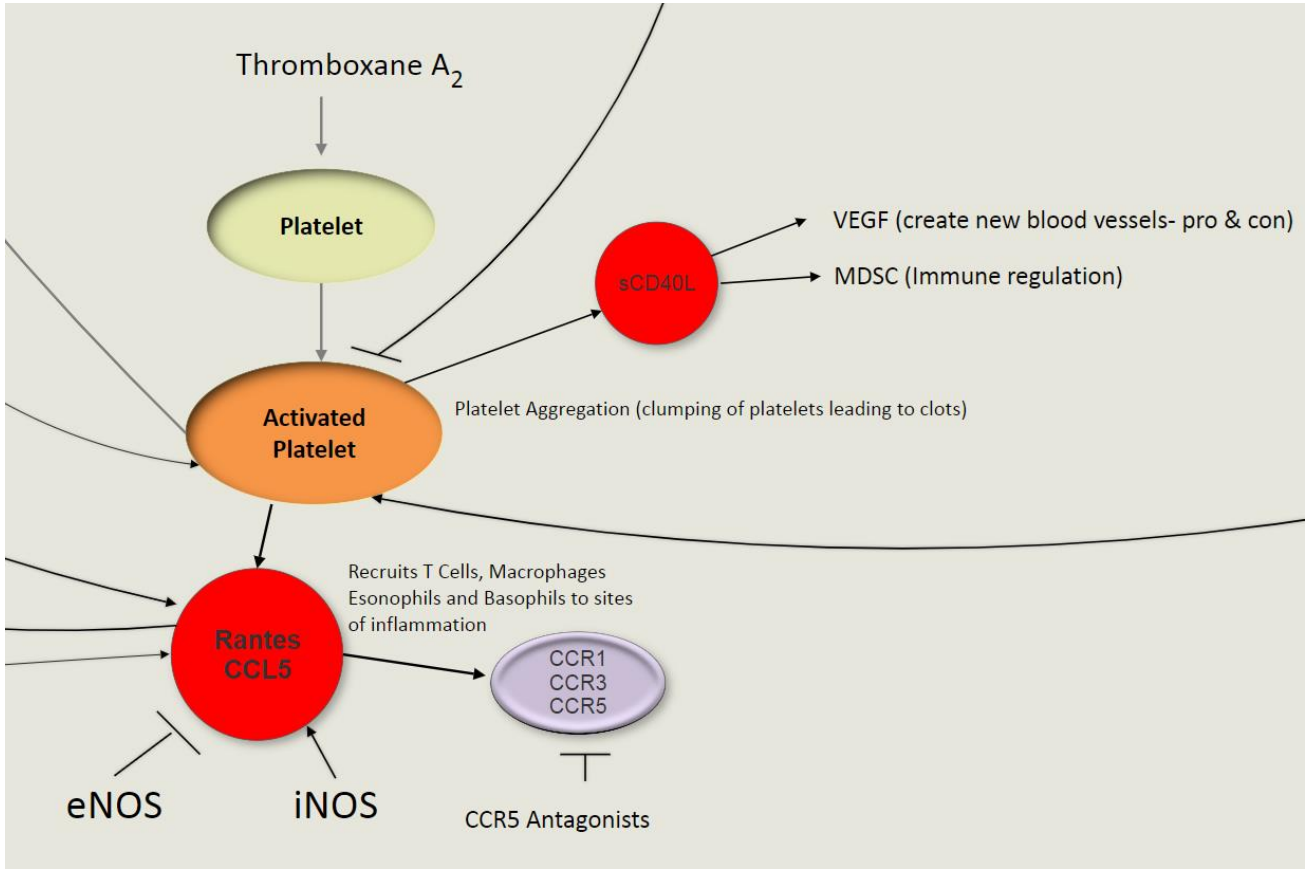
Platelets store large amounts of serotonin that they release during thrombus formation or acute inflammation. This facilitates hemostasis and modulates the inflammatory response.

Results:

Platelet-derived serotonin induced neutrophil degranulation with release of myeloperoxidase and hydrogen peroxide (H_2O_2) and increased expression of membrane-bound leukocyte adhesion molecule CD11b, leading to enhanced inflammation in the infarct area and reduced myocardial salvage. In patients hospitalized with acute coronary syndrome, plasmatic serotonin levels correlated with CD11b expression on neutrophils and myeloperoxidase plasma levels. Long-term serotonin reuptake inhibition—reported to protect patients with depression from cardiovascular events—resulted in the depletion of platelet serotonin stores in mice. These mice displayed a reduction in neutrophil degranulation and preserved cardiac function. In line, patients with depression using serotonin reuptake inhibition, presented with suppressed levels of CD11b surface expression on neutrophils and lower myeloperoxidase levels in blood.

- Platelets store large amounts of serotonin that they release during thrombus formation or acute inflammation.
- This facilitates hemostasis and modulates the inflammatory response.
- Platelet-derived serotonin induced neutrophil degranulation with release of myeloperoxidase and hydrogen peroxide (H_2O_2) and increased expression of membrane-bound leukocyte adhesion molecule CD11b, leading to enhanced inflammation in the infarct area and reduced myocardial salvage

sCD40L



- Activated platelets are the major source of sCD40L, which has been implicated in platelet and leukocyte activation.
- Recent work has revealed an essential involvement of soluble CD40L (sCD40L) in inflammation and vascular disease.

Jin R, 2013

J Thromb Haemost. 2012 Feb;10(2):207-16. doi: 10.1111/j.1538-7836.2011.04589.x.

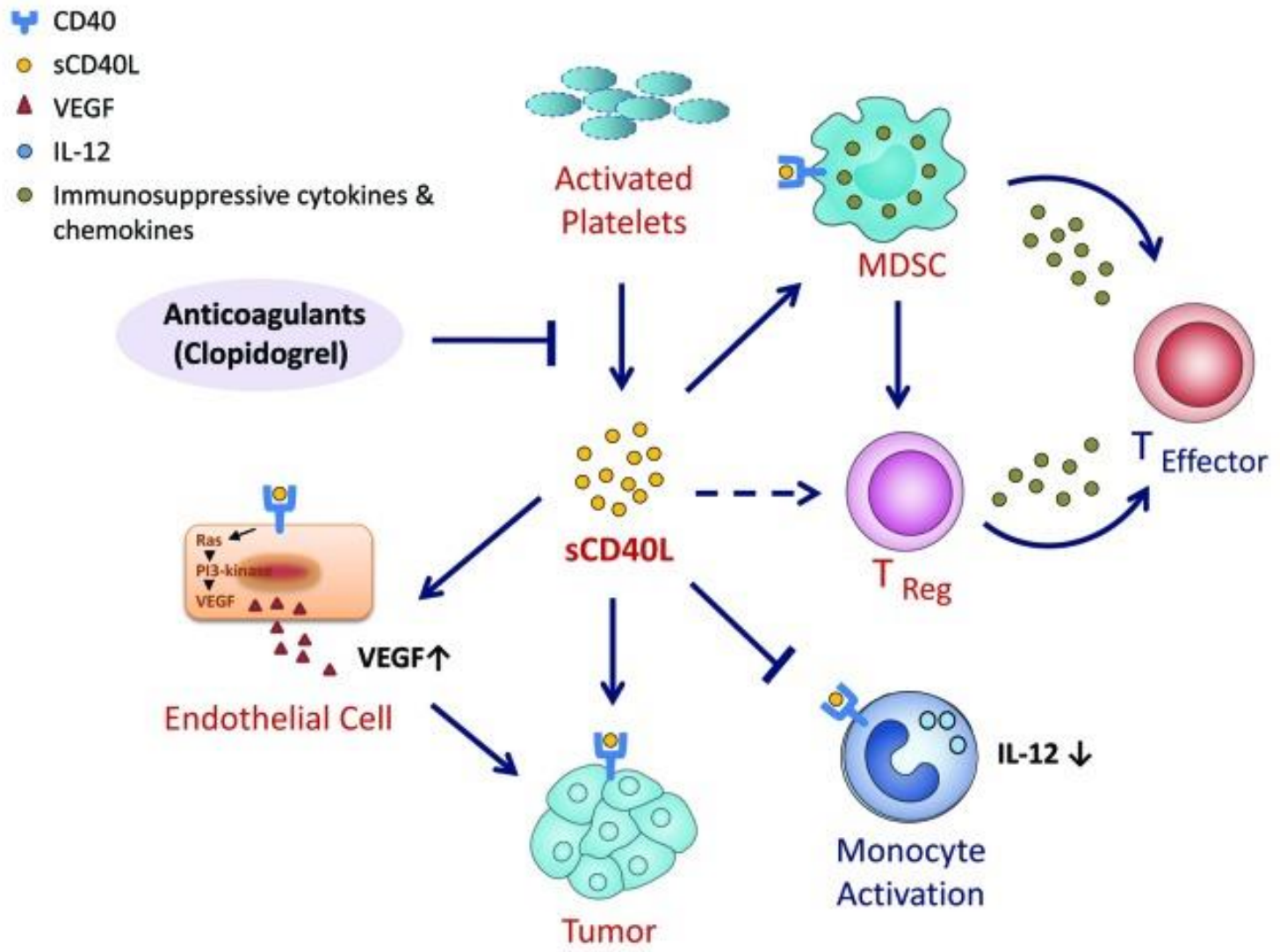
High sCD40L levels early after trauma are associated with enhanced shock, sympathoadrenal activation, tissue and endothelial damage, coagulopathy and mortality

P I Johansson [1], A M Sørensen, A Perner, K-L Welling, M Wanscher, C F Larsen, S R Ostrowski

Results: High circulating sCD40L was associated with enhanced tissue and endothelial damage (ISS, hcDNA, Annexin V, syndecan-1 and sTM), shock (pH, standard base excess), sympathoadrenal activation (adrenaline) and coagulopathy evidenced by reduced thrombin generation (PF1.2), hyperfibrinolysis (D-dimer), increased activated partial thromboplastin time (APTT) and inflammation (IL-6) (all $P < 0.05$). A higher ISS ($P = 0.017$), adrenaline ($P = 0.049$) and platelet count ($P = 0.012$) and lower pH ($P = 0.002$) were associated with higher sCD40L by multivariate linear regression analysis. High circulating sCD40L (odds ratio [OR] 1.84 [95% CI 1.05-3.23], $P = 0.034$), high age ($P = 0.002$) and low Glasgow Coma Score (GCS) pre-hospital ($P = 0.002$) were independent predictors of increased mortality.

- High early sCD40L levels in trauma patients reflect tissue injury, shock, coagulopathy and sympathoadrenal activation and predict mortality.
- As sCD40L has pro-inflammatory activity and activates the endothelium, sCD40L may be involved in trauma-induced endothelial damage and coagulopathy.

sCD40L Impact on Immunity



Review | Open Access | Published: 22 October 2019

Myeloid-derived suppressor cells in hematological malignancies: friends or foes

Meng Lv, Ke Wang & Xiao-jun Huang

Journal of Hematology & Oncology **12**, Article number: 105 (2019) | Cite this article

7115 Accesses | **30** Citations | **1** Altmetric | Metrics

Abstract

Myeloid-derived suppressor cells (MDSCs) are newly identified immature myeloid cells that are characterized by the ability to suppress immune responses and expand during cancer, infection, and inflammatory diseases. Although MDSCs have attracted a lot of attention in the field of tumor immunology in recent years, little is known about their multiple roles in hematological malignancies as opposed to their roles in solid tumors. This review will help researchers better understand the various characteristics and functions of MDSCs, as well as the potential therapeutic applications of MDSCs in hematological malignancies, including lymphoma, multiple myeloma, leukemia, and hematopoietic stem cell transplantation.

- Myeloid-derived suppressor cells (MDSCs) are newly identified immature myeloid cells that are characterized by the ability to suppress immune responses and expand during cancer, infection, and inflammatory diseases.
- The role of MDSCs in solid tumors has been extensively characterized as pro-tumorigenic In intensive clinical studies, circulating and/or infiltrating MDSCs at the tumor site were associated with poor prognosis in patients with solid tumors.

Myeloid-Derived Suppressor Cells (MDSC)

- In a study of breast cancer patients, the overall survival of preoperative patients with MDSC levels >1.0% of total PBMCs with stage IV disease was significantly shorter compared with other disease stages and when compared with patients with MDSC levels <1.0% of total PBMCs
  - MDSC levels could work as a good prognostic indicator, especially in those with advanced breast cancer

Gonda K, 2017

Vascular Endothelial Growth Factor (VEGF)

- Angiogenesis = the formation of new blood vessels from preexisting vasculature
  - Important for tumor growth and metastasis formation
    - Inhibiting tumor angiogenesis may be a promising therapeutic strategy
- Vascular endothelial growth factor (VEGF) = potent and specific angiogenic factor
  - The inhibition of VEGF-induced angiogenesis significantly inhibits tumor growth in vivo

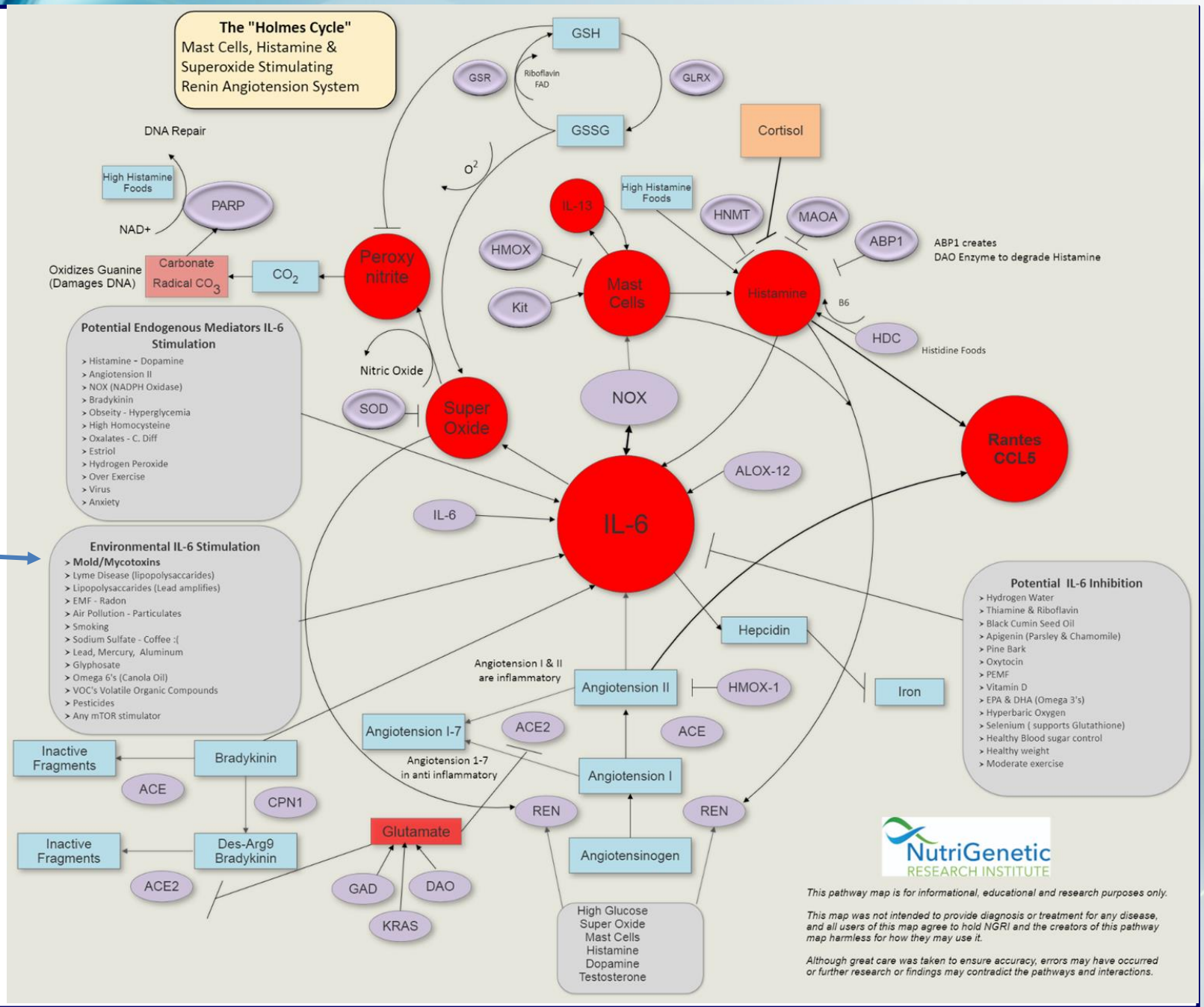
Verheul HMW, 2000

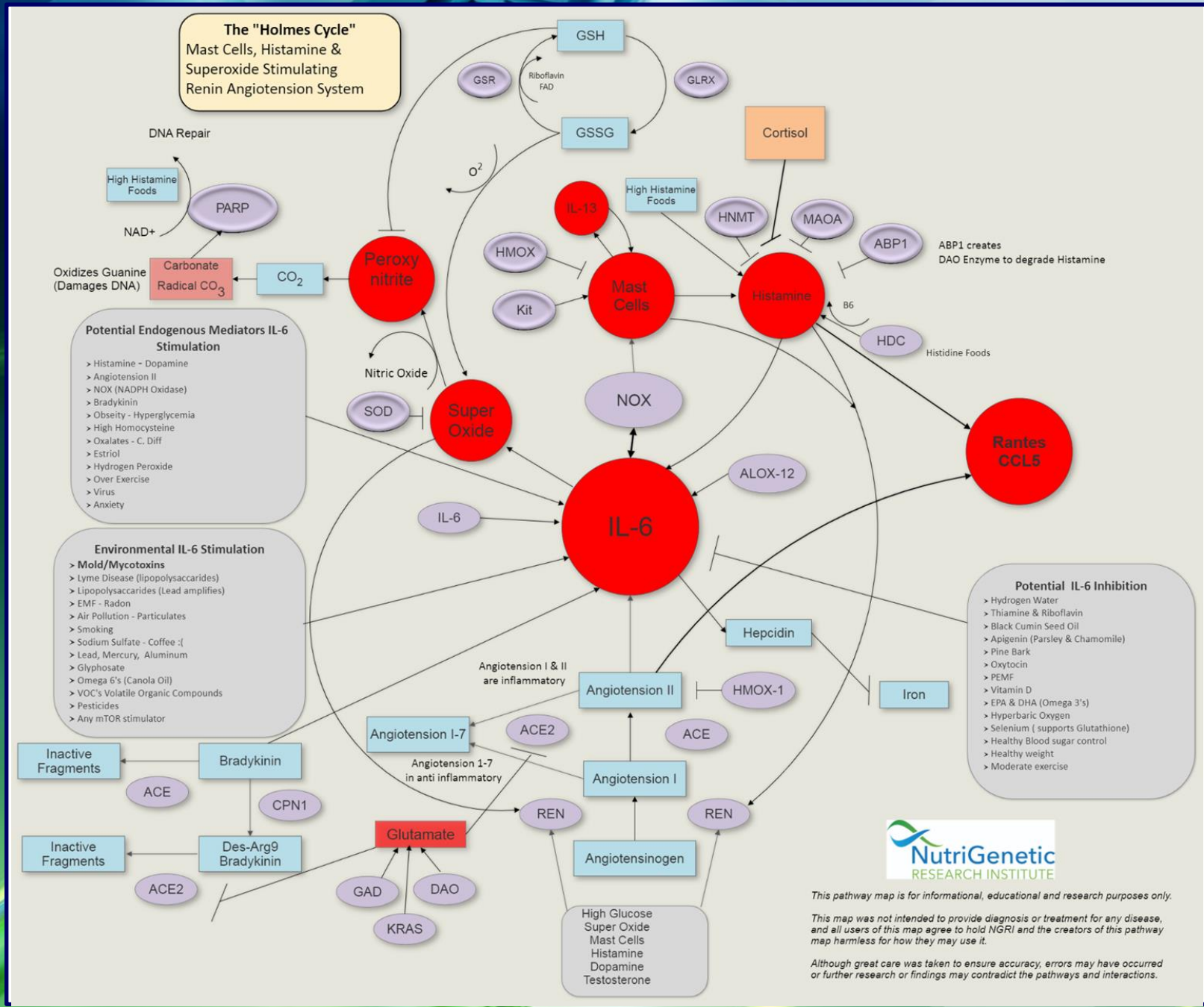
Pathway # 3
Angiotensin II, Histamine from "Holmes Cycle" Stimulating RANTES

See Appendix B for slides detailing this pathway

- In a study of glomerular endothelial cells, vasoactive peptide ***ANG II*** demonstrated a potential role in the local ***induction of the chemokine RANTES***

Wolf G, 1997





NutriGenetic RESEARCH INSTITUTE

SNPS Impacting

- IL-6
- SOD1,2,3 / SIRT1
- KIT (Mast cells)
- ABP1, HNMT,MAOA, MAOB, HDC (histamine)
- GSR (glutathione recycling)
- DAO & GAD (excess glutamate)
- REN (excess renin)
- CACNA1C (EMF)
- HMOX
- ACE2
- NOX (NADPH Oxidase)

The Role of Histamine and Histamine Receptors in Mast Cell-Mediated Allergy and Inflammation: The Hunt for New Therapeutic Targets

Elden Berla Thangam[1], Ebenezer Angel Jemima[1], Himadri Singh[2], Mirza Saqib Baig[3], Mahejibin Khan[4], Clinton B. Mathias[5], Martin K. Church[6] and Rohit Saluja[2,7]*

Histamine H1 receptor is also expressed in dermal dendritic cells and keratinocytes in the skin tissue, and histamine increases the NGF production *via* H1R in human keratinocytes (66). The secretion of NGF is caused by the phosphorylation of protein kinase C, extracellular signal-regulated kinases (ERK), and the activation of AP-1 resulting from H1R stimulation. Similarly, histamine, acting *via* H1R, has also been shown to enhance the production of chemokines, such as granulocyte macrophage colony stimulating factor, regulated on activation T cell expressed and secreted (RANTES), and monocyte chemotactic protein-1 (MCP-1) in IFN-γ-stimulated keratinocytes. It also upregulates the antigen-presenting capability of dendritic cells, and leads to Th1 polarization through H1R (67).

- Mast cells are multifunctional bone marrow-derived tissue-dwelling cells that are the major producer of histamine in the body.
- The Histamine, from the mast cells, acting *via* H1R, has also been shown to ***enhance the production*** of chemokines, such as ***RANTES***.

Thangam EB, 2018

Mast Cells

- A study of cardiac mast cells showcased these ***mast cells as an additional renin source***
  - Could be involved in a unique extrarenal renin-angiotensin system
  - The renin from these mast cells could be crucial to the local formation of angiotensin II
  - This could be applied to other tissues, not just cardiac
- Mast cells could be targeted, along with renin-angiotensin system inhibitors, to manage angiotensin II-related dysfunctions

Silver RB, 2004

Histamine and Renin

- Histamine has been shown to stimulate the release of renin
  - Activation of the H2-receptors may be particularly important for histamine-induced renin release

Superoxide and Renin

- An in vivo study has shown that superoxide potentially activates renal Sp3 via lysine acetylation
  - Thus increasing renin activity, AT1R function, and blood pressure

Gerber JG, 1983; Saleem M, 2018

Open access peer-reviewed chapter

Regulation of the Renin-Angiotensin-Aldosterone System by Reactive Oxygen Species

By Manuela Morato, Marta Reina-Couto, Dora Pinho, António Albino- Teixeira and Teresa Sousa

Submitted: May 24th 2016 Reviewed: November 22nd 2016 Published: July 12th 2017
DOI: 10.5772/67016

In the last two decades, reactive oxygen species (ROS) have emerged as downstream mediators of angiotensin II (Ang II) effects. The Ang II-induced activation of nicotinamide adenine dinucleotide phosphate (NADPH) oxidases within the cardiovascular system, the kidney and the brain result in increased generation of ROS, such as superoxide radical ($O_2^{\bullet -}$) and hydrogen peroxide (H_2O_2), which are involved in diverse signaling functions. Interestingly, increasing evidence suggests that ROS also act as upstream regulators of the renin-angiotensin-aldosterone system (RAAS) in various cells and tissues. In several pathological conditions, ROS have been shown to increase RAAS activation, thus creating a vicious cycle that amplifies the deleterious signaling pathways orchestrated by this endocrine system. This chapter aims at giving an overview of the interactions between ROS and RAAS, focusing on the effects of ROS on the expression, secretion and/or activity of RAAS components that may contribute to the development and progression of cardiometabolic and renal diseases.

Morato M, 2017

#42: Dr. Jill Interviews Bob Miller about Interleukin 6 (IL-6)

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Jill Carnahan, MD

In Episode #42, Dr. Jill interviews Bob Miller on **IL-6**: Everything you need to know about this cytokine: The Good, The Bad, and ...

Explains Genetic and Environmental Stimulation & Inhibition of IL-6

Search **Carnahan IL-6** on YouTube

#26: Dr Jill Interviews Bob Miller on Overstimulation of NOX and Functional Genomics

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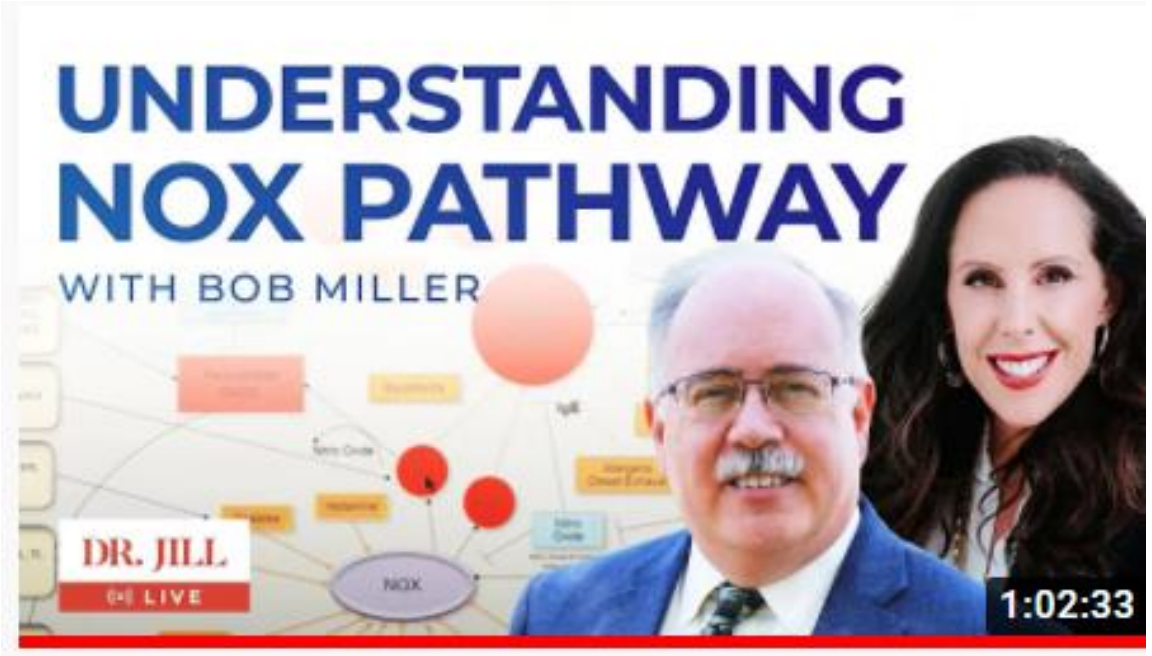
Jill Carnahan, MD

In Episode #26, Part 3: **Dr. Jill** Interviews **Bob Miller** of Tree of Life Health on How Overstimulation of NOX (NADPH Oxidase) from ...



Explains the "Holmes Cycle" and the creation of Angiotensin II and Histamine

Search **Carnahan NOX Pathway** on YouTube

Omega 3’s - Resolvins and Protectins

Omega 3's and Platelet Aggregation

- A meta-analysis of randomized controlled trials revealed an association between n-3 PUFA-supplementation and a reduction in platelet aggregation when the participants were at poor health status, but not at a good health status
  - High-risk patients with cardiovascular disease or diabetics could benefit from n-3 PUFAs therapy

Gao L, 2013

Importance of maintaining a low omega-6/omega-3 ratio for reducing platelet aggregation, coagulation and thrombosis

James J DiNicolantonio [1] and James OKeefe [2]

- Both EPA and DHA get incorporated into platelet phospholipids at the expense of arachidonic acid (AA), which may help reduce platelet aggregation via a reduction in AA-derived platelet-aggregating/procoagulant metabolites.

- Additionally, *EPA competes with AA for cyclo-oxygenase reducing its action on AA.*

- Thus, EPA both directly and indirectly reduces the formation of the AA proaggregatory metabolite TXA2.20

- EPA/DHA also gets incorporated into neutrophils and red blood cells at the expense of both LA and AA.

- The incorporation of omega-3s in red blood cells seems to decrease whole blood viscosity and increase red blood cell flexibility thus likely reducing the risk of thrombosis

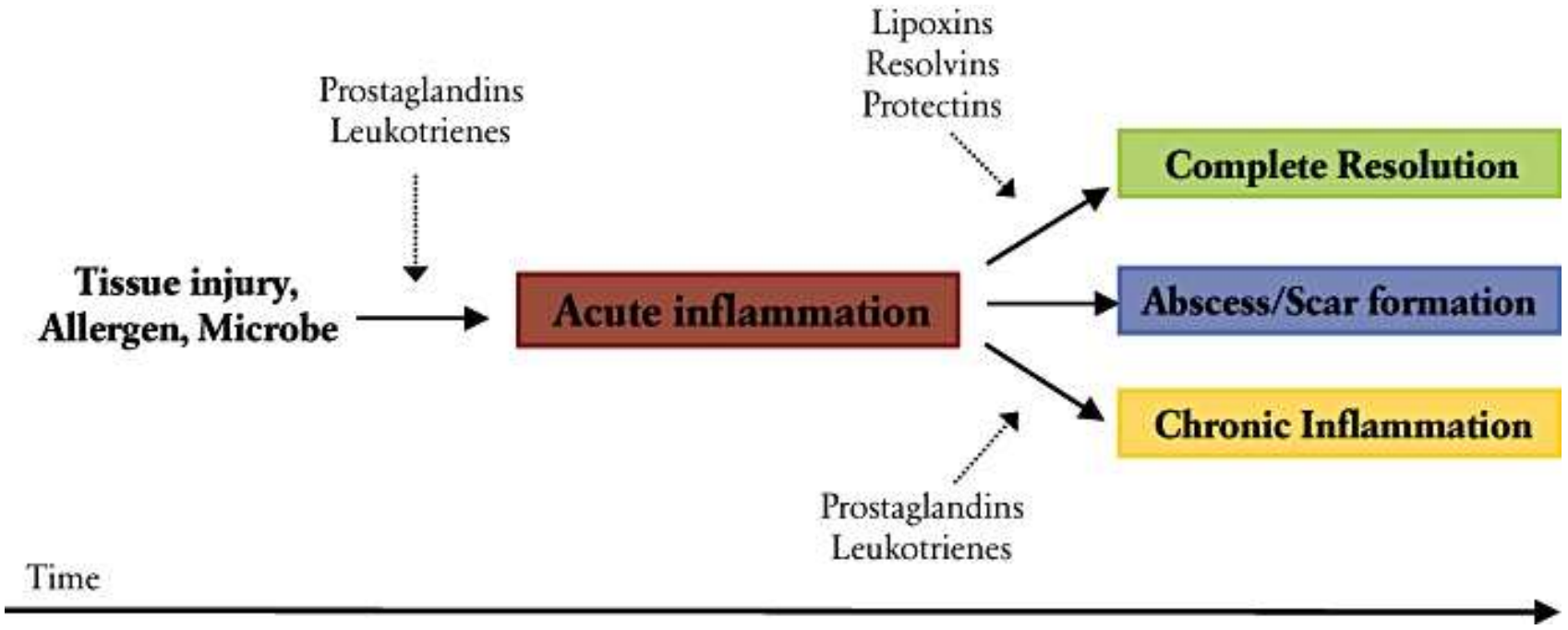
DiNicolantonio JJ, 2019

Omega 3's - Resolvins and Protectins

- Resolvins and protectins = potent lipid mediators
  - First molecular basis for the many health benefits attributed to the omega-3 fatty acids: EPA and DHA
    - Associated with various beneficial effects and the prevention of various diseases, such as: immunomodulation, autoimmune diseases, rheumatoid arthritis, cardiovascular diseases, Alzheimer's disease, type-2 diabetes, cancer, etc.

Serhan CN, 2011

Managing Inflammation with Resolvins and Protectins



Kohli P, 2009

Omega 3's - Resolvins and Protectins

- Resolvins and protectins = potent lipid mediators
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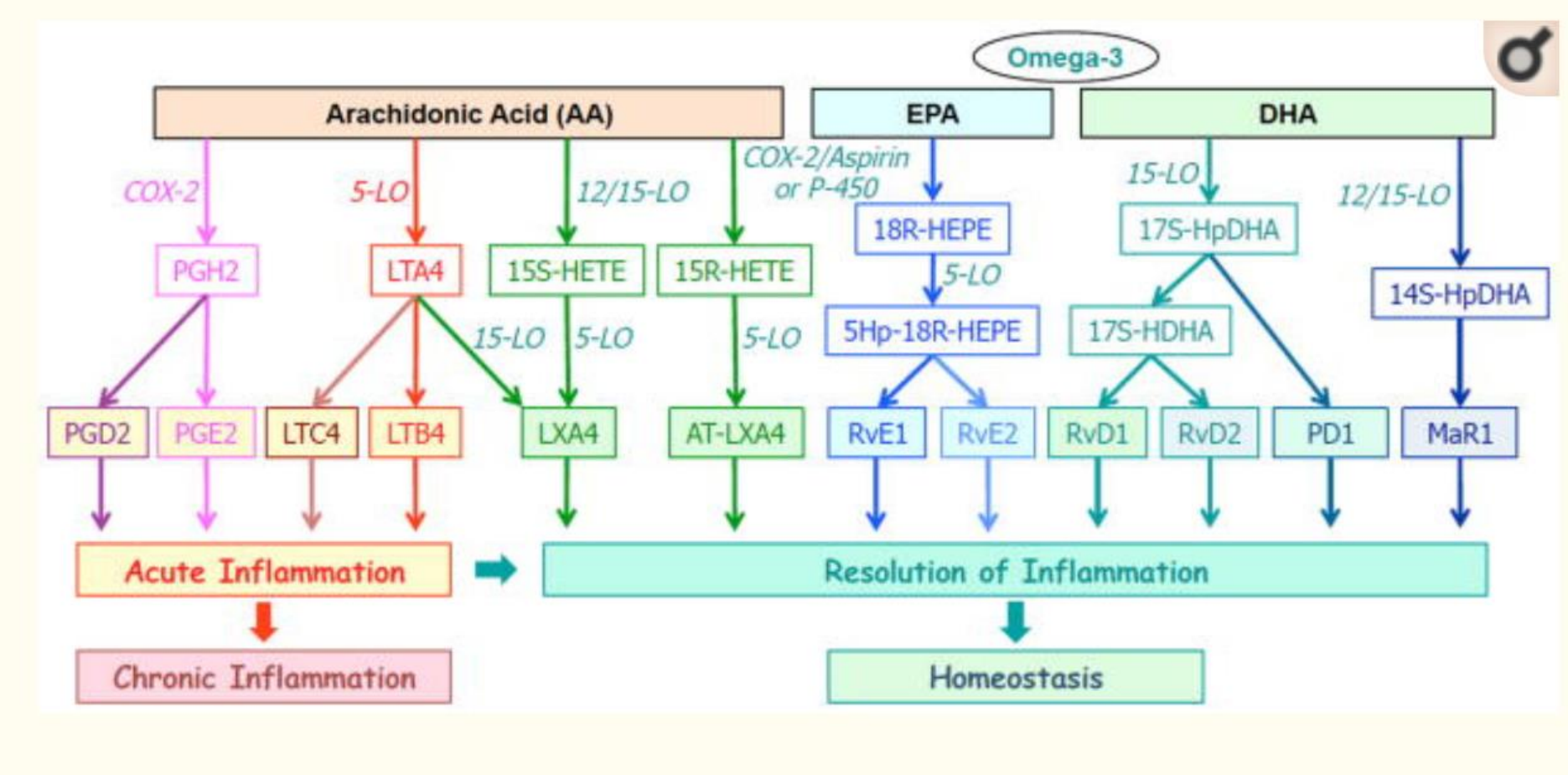
Serhan CN, 2011

Omega 3's - Resolvins and Protectins

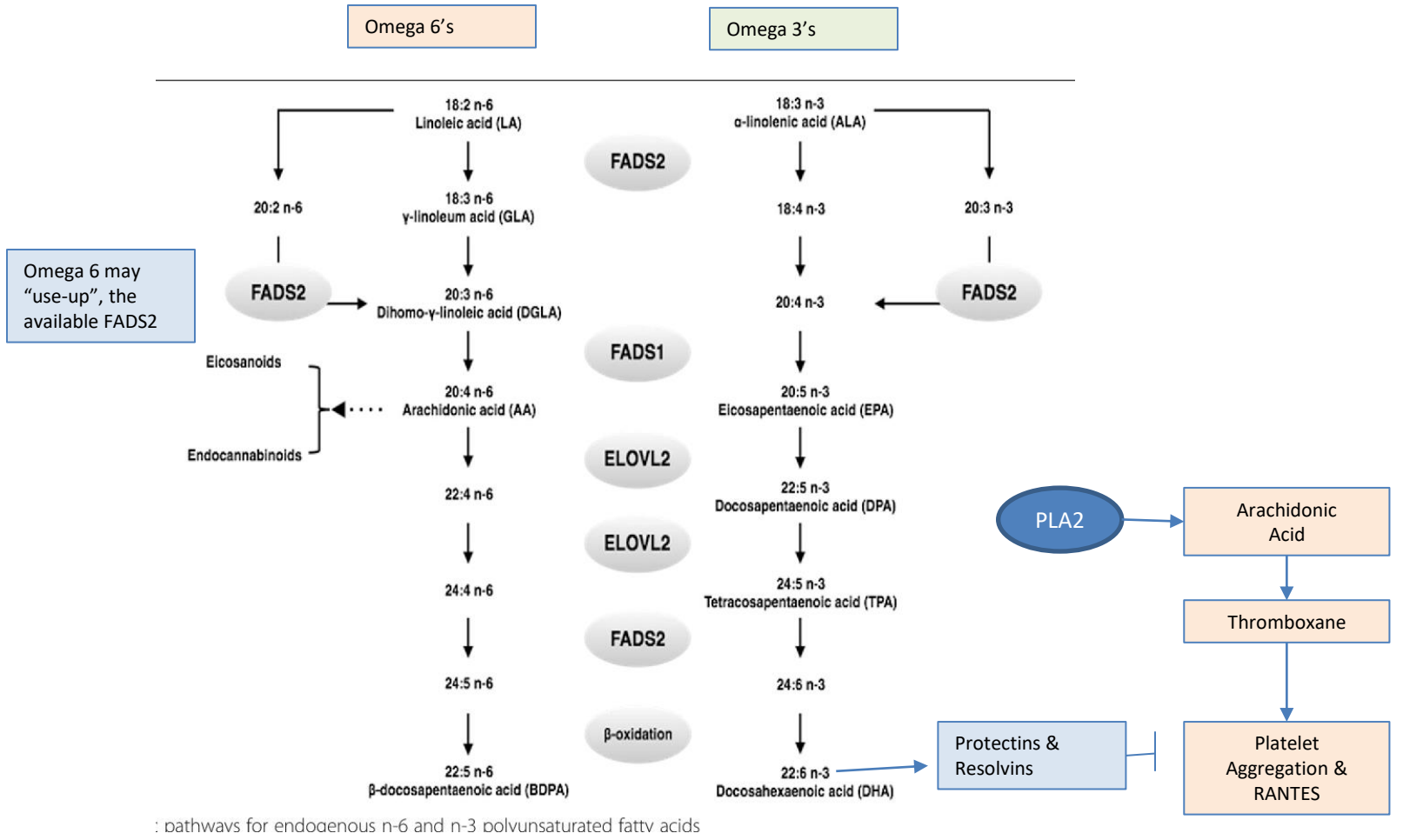


Serhan CN, 2011

Resolvins E1 (RvE1)

- RvE1 = omega-3 eicosapentaenoic acid (EPA)-derived lipid mediator
  - Generated during resolution of inflammation
  - Made in human vasculature via leukocyte-endothelial cell interactions
- A study has shown new potent agonist-specific antiplatelet actions of RvE1
  - These actions could underlie some of the beneficial actions of EPA in humans

Dona M, 2008



: pathways for endogenous n-6 and n-3 polyunsaturated fatty acids

Nutrients. 2017 Nov; 9(11): 1165.
Published online 2017 Oct 25. doi: 10.3390/nu9111165
PMCID: PMC5707637
PMID: 29068398

Precision Nutrition and Omega-3 Polyunsaturated Fatty Acids: A Case for Personalized Supplementation Approaches for the Prevention and Management of Human Diseases

Floyd H. Chilton,[1,*] Rahul Dutta,[2] Lindsay M. Reynolds,[3] Susan Sergeant,[4] Rasika A. Mathias,[5] and Michael C. Seeds[6]

Abstract

Go to:

Background: Dietary essential omega-6 (*n*-6) and omega-3 (*n*-3) 18 carbon (18C-) polyunsaturated fatty acids (PUFA), linoleic acid (LA) and α-linolenic acid (ALA), can be converted (utilizing desaturase and elongase enzymes encoded by *FADS* and *ELOVL* genes) to biologically-active long chain (LC; ≥20)-PUFAs by numerous cells and tissues. These *n*-6 and *n*-3 LC-PUFAs and their metabolites (ex, eicosanoids and endocannabinoids) play critical signaling and structural roles in almost all physiologic and pathophysiologic processes. Methods: This review summarizes: (1) the biosynthesis, metabolism and roles of LC-PUFAs; (2) the potential impact of rapidly altering the intake of dietary LA and ALA; (3) the genetics and evolution of LC-PUFA biosynthesis; (4) Gene–diet interactions that may lead to excess levels of *n*-6 LC-PUFAs and deficiencies of *n*-3 LC-PUFAs; and (5) opportunities for precision nutrition approaches to personalize *n*-3 LC-PUFA supplementation for individuals and populations. Conclusions: The rapid nature of transitions in 18C-PUFA exposure together with the genetic variation in the LC-PUFA biosynthetic pathway found in different populations make mal-adaptations a likely outcome of our current nutritional environment. Understanding this genetic variation in the context of 18C-PUFA dietary exposure should enable the development of individualized *n*-3 LC-PUFA supplementation regimens to prevent and manage human disease.

- *FADS* and *ELOVL* genes may have a role in differences in omega 3 requirements

Chilton F, 2017

FADS1 and FADS2 Mutations Impact EPA, DHA, Resolvins and Protectins

FADS1		
Gene Name	Variants	Metrics
FADS1 (rs174550)	1	TC 43.5%
FADS1 (rs174549)	1	GA 40.7%
FADS1 (rs174556)	1	CT 40.5%
FADS1 (rs174548) ?	1	CG 41.6%
FADS1 (rs174547) ? ▾	1	TC 43.5%
FADS1 (rs174546) ? ▾	1	CT 43.5%
FADS1 (rs174534) ?	1	AG 43.6%
FADS1 (rs174541)	1	TC 29.7%
FADS1 (rs174568)	1	CT 43.6%
FADS1 (rs174545)	1	CG 43.4%
FADS1 (rs174555)	1	TC 40.5%

FADS2		
Gene Name	Variants	Metrics
FADS2 (rs2072114)	1	AG 21.8%
FADS2 (rs1535)	1	AG 43.8%
FADS2 (rs174570)	1	CT 24.1%
FADS2 (rs174576)	1	CA 44.4%
FADS2 (rs174575)		CC 56.1%
FADS2 (rs422249)		CC 46.8%
FADS2 (rs174601)	1	CT 45.8%
FADS2 (rs2526678)	1	GA 17.4%
FADS2 (rs3834458)	1	ID 43.4%
FADS2 (rs174583)	1	CT 44.5%
FADS2 (rs2727270)	1	CT 21.6%
FADS2 (rs2727271)	1	AT 21.6%
FADS2 (rs2524299)	1	AT 22.7%
FADS2 (rs174577)	1	CA 44.4%
FADS2 (rs174578)	1	TA 44.4%
FADS2 (rs2851682)	1	AG 17.1%
FADS2 (rs498793)		TT 30.3%
FADS2 (rs482548)		CC 84%
FADS2 (rs968567) ? ▴		CC 73.4%
FADS2 (rs174574)	1	CA 44.6%
FADS2 (rs2845573)	1	AG 16%
FADS2 (rs174449)		AA 40%

rs953413 Regulates Polyunsaturated Fatty Acid Metabolism by Modulating ELOVL2 Expression

Gang Pan [1], Marco Cavalli [1], Björn Carlsson [2], Stanko Skrtic [3], Chanchal Kumar [4], Claes Wadelius [5]

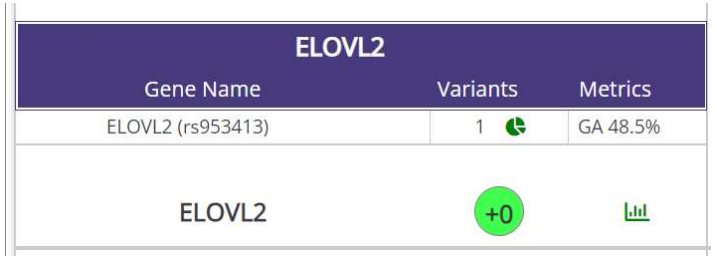
Affiliations + expand

PMID: 31928966 PMCID: PMC7033636 DOI: 10.1016/j.isci.2019.100808

Abstract

Long-chain polyunsaturated fatty acids (LC-PUFAs) influence human health in several areas, including cardiovascular disease, diabetes, fatty liver disease, and cancer. ELOVL2 encodes one of the key enzymes in the in vivo synthesis of LC-PUFAs from their precursors. Variants near ELOVL2 have repeatedly been associated with levels of LC-PUFA-derived metabolites in genome-wide association studies (GWAS), but the mechanisms behind these observations remain poorly defined. In this study, we found that rs953413, located in the first intron of ELOVL2, lies within a functional FOXA and HNF4α cooperative binding site. The G allele of rs953413 increases binding of FOXA1/FOXA2 and HNF4α to an evolutionarily conserved enhancer element, conferring allele-specific upregulation of the rs953413-associated gene ELOVL2. The expression of ELOVL2 was significantly downregulated by both FOXA1 and HNF4α knockdown and CRISPR/Cas9-mediated direct mutation to the enhancer element. Our results suggest that rs953413 regulates LC-PUFAs metabolism by altering ELOVL2 expression through FOXA1/FOXA2 and HNF4α cooperation.

- Our results suggest that rs953413 regulates LC-PUFAs metabolism by altering ELOVL2 expression through FOXA1/FOXA2 and HNF4α cooperation.



Pan G, 2020

Importance of maintaining a low omega-6/omega-3 ratio for reducing platelet aggregation, coagulation and thrombosis

James J DiNicolantonio [1] and James OKeefe [2]
Correspondence to Dr James J DiNicolantonio; jjdinicol@gmail.com

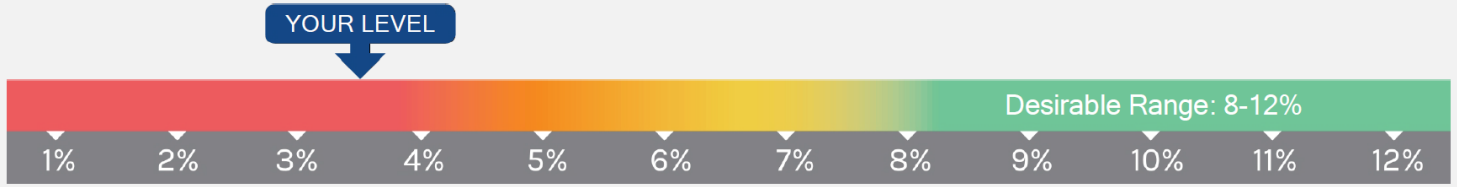
• Clinical studies in humans clearly show that marine omega-3s provide antiplatelet effects. Indeed, a meta-analysis of 15 randomized controlled trials (RCT) in humans has confirmed that omega-3 polyunsaturated fatty acids (PUFA) inhibit platelet aggregation.
• In healthy borderline overweight men, 3 g of omega-3 PUFAs for 4 weeks lowered fibrinogen, thrombin and factor V levels; these benefits occurred mainly in those with high fibrinogen carrying alpha-chain fibrinogen polymorphism.
• *Both EPA and DHA get incorporated into platelet phospholipids at the expense of arachidonic acid which may help reduce platelet aggregation via a reduction in AA-derived platelet-aggregating/procoagulant metabolites.* Additionally, EPA competes with AA for cyclo-oxygenase reducing its action on AA. Thus, EPA both directly and indirectly reduces the formation of the AA proaggregatory metabolite TXA2 (Thromboxane)

DiNicolantonio JJ, 2019; Gao L, 2013; Vanschoonbeek K, 2004; VON SCHACK CY, 1987

Your Omega-3 Index

Reference Range*: 3.00% - 14.10%

3.51%



Omega-6:Omega-3

Reference Range*: 2.1:1 - 13.6:1

11.9:1

AA:EPA

Reference Range*: 1.3:1 - 59.9:1

35.1:1

Test Name	Test Score*
Chronic Inflammation Test 11-Dehydro Thromboxane B_2	643

Individuals *not taking* aspirin

Potential Action Plan

- Make sure in mold free environment and clear mold if an issue. Consider urine mold testing to see if mold detox is needed.
- May consider testing heavy metals, & glyphosate levels
- Check for Lyme disease, Clostridia, LPS
- High Fructose Corn Syrup free, and especially if SIRT1 mutations.
- Low Histamine diet if recommended
- Check Omega 3,6 AA and work with health professional to balance
- Check Thromboxane A2
- Consider checking for RANTES, sCD40L, VEGF, TNF-a, IL-6, etc.
- Consider Your Genomic Resource test to find mutations that may worsen the situation

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