Advanced Therapies in GI Disorders

presented by :

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Performance Health

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Disclosure of Financial Relationships:

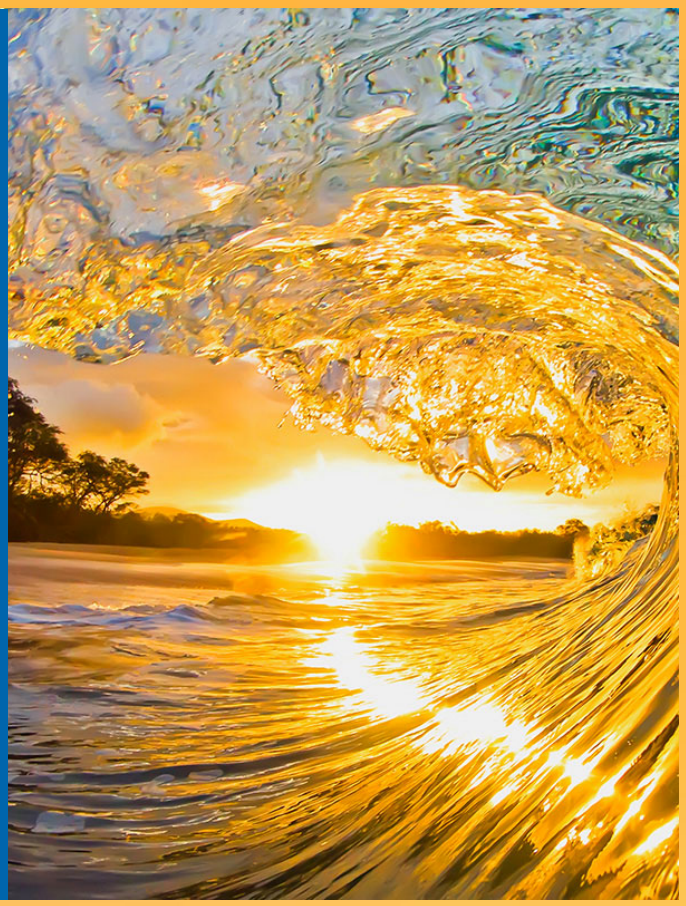
- Disclosures
  - Chairman Metabolic Code Enterprises
  - Educational Co-Chair A4M/MMI
  - Director of Integrative Medicine: The NFL Hall of Fame Health and Performance Program

Learning Objectives

- To review the basics of metaflammation and metabolic disruption which can result in GI disorders.
- To discuss vectors associated with metaflammation, including GUT – IMMUNE – BRAIN and other organ systems
- To be able to choose appropriate dietary supplements, peptides and lifestyle changes to support metainflamamtory constructs.

METABOLISM

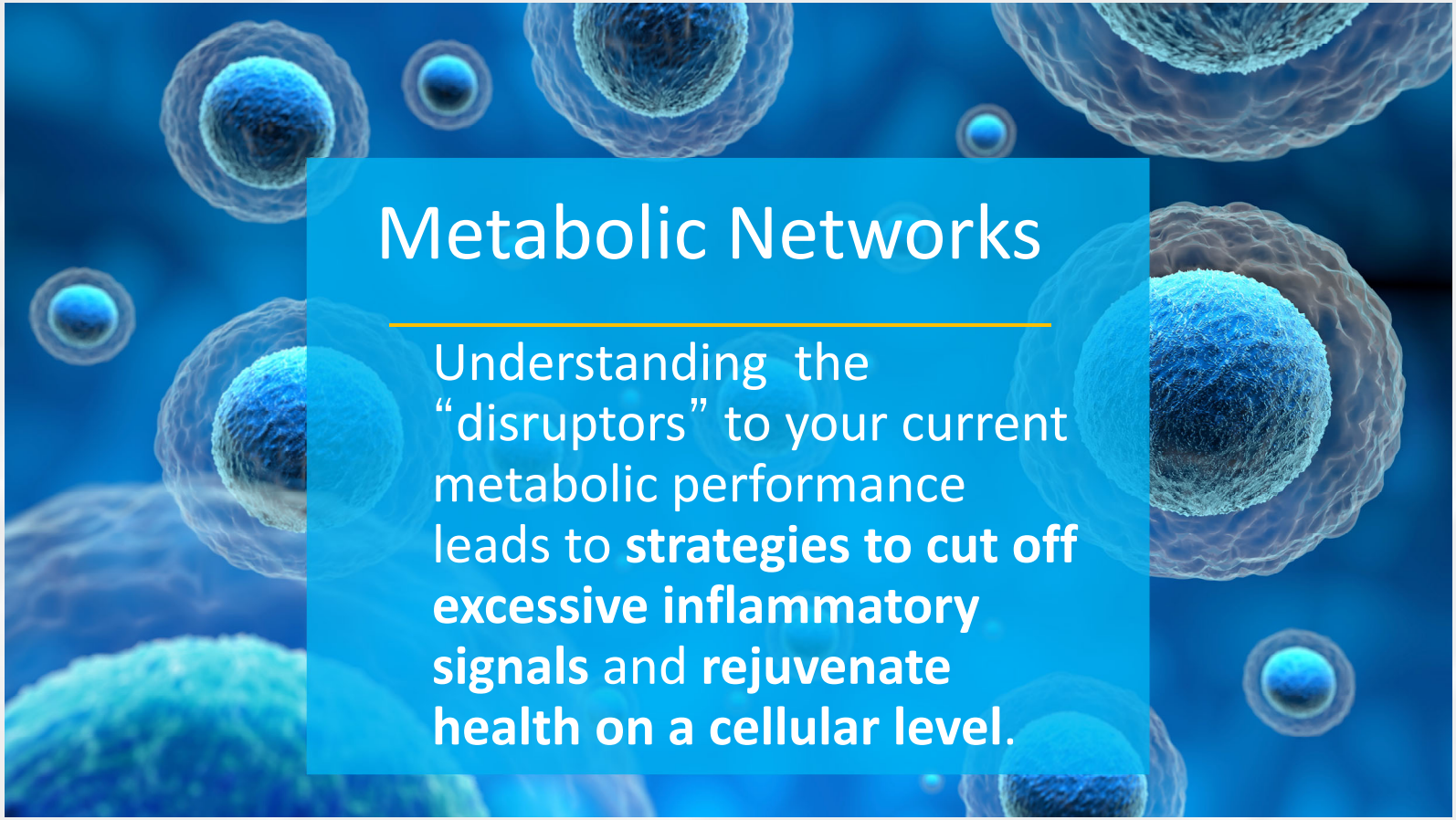
The sum total of all the chemical reactions **driving how you feel today** and creating the chemistry **moving you toward future health**.



METABOLISM

Directly under the influence of Global Metabolic Inflammatory Signaling =

Metaflammation drives Metabolic Dysregulation


Metabolic Networks
Understanding the "disruptors" to your current metabolic performance leads to **strategies to cut off excessive inflammatory signals** and **rejuvenate health on a cellular level**.

Key Tenants of

Aging, Performance and Vitality

- Oxidative Stress / Inflammation
- Hormonal Balance
- Stress Hormones
- Glucose / Insulin Regulation
- GUT integrity and microbiome diversity
- Immune Balance
- Environmental Burden
- Individuality

Metaflammation

- Also know as “Inflammaging” and metabolism induced inflammation
- Chronic low-grade inflammatory sequela
- Increases aging processes and metabolic signaling issues
- Increased **peripheral and central** inflammation

Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

Metaflammation

Results in co-morbid conditions:

- Altered methylation patterns
- Cardiovascular issues – lipid, vascular
- Hormonal imbalances
- Liver and kidney diseases
- Immune dysfunction
- Thyroid, fatigue
- Sleep problems
- Cognitive and mood problems
- Sarcopenia
- Osteoporosis
- Cancer

Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

Metaflammation Contributors

- STRESS
- Caused by AND leads to “diabesity”:
  - Insulin resistance; type 2 diabetes
  - Obesity
  - Stress
  - Diet
  - LPS induced
  - Liver / kidney issues
- GUT microbiome issues - Leaky GUT

Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

Metaflammation Contributors

- Chronic bacterial or viral infections
- Periodontitis/ gingivitis
- Cellular debris
- Misplaced self molecules
- Misfolded/oxidized proteins
- DIET
- Lifestyle – overexercise?
- SLEEP quality and quantity
- Environmental factors – metals, artificial food additives, sweeteners, POPs, others

Prattichizzo F, et al. Inflammageing and metaflammation: the yin and yang of type 2 diabetes. Ageing Res Rev. 2018;41:1-17.

Gut as a Source of Metaflammation

- Over-activation of immunity in GUT leads to increased production of inflammatory cytokines
- Leaky guy allows bacterial and toxins to enter bloodstream
- Leads to peripheral and central inflammation

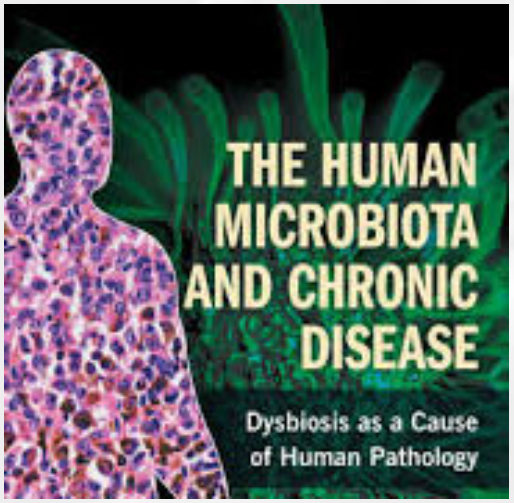
Viera M, et al. Translocation of a gut pahobiont drives autoimmunity in mice and humans. Science. 2018;359(6380):1156-61.

Gut as a Source of Inflammation

- Recent study reports 75% with new onset RA (rheumatoid arthritis) have microbiome problems

- Presence of *Prevotella copri in GUT* correlates with RA in US
  - Other countries reported different microbiome disturbances in RA
  - Japan and US = *Prevotella*

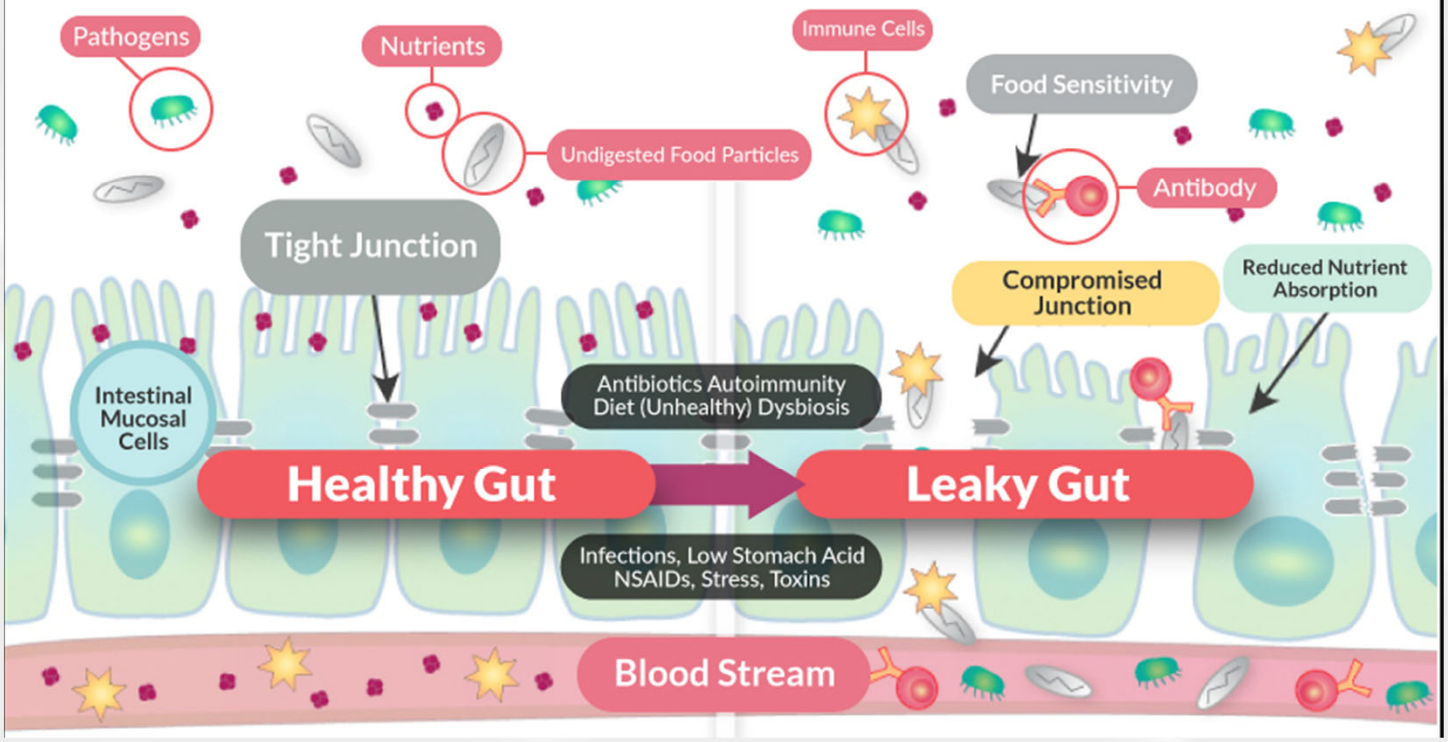
Maeda Y, et al. Role of gut microbiotic in rheumatoid arthritis. J clin Med. 2017;6(6):60.



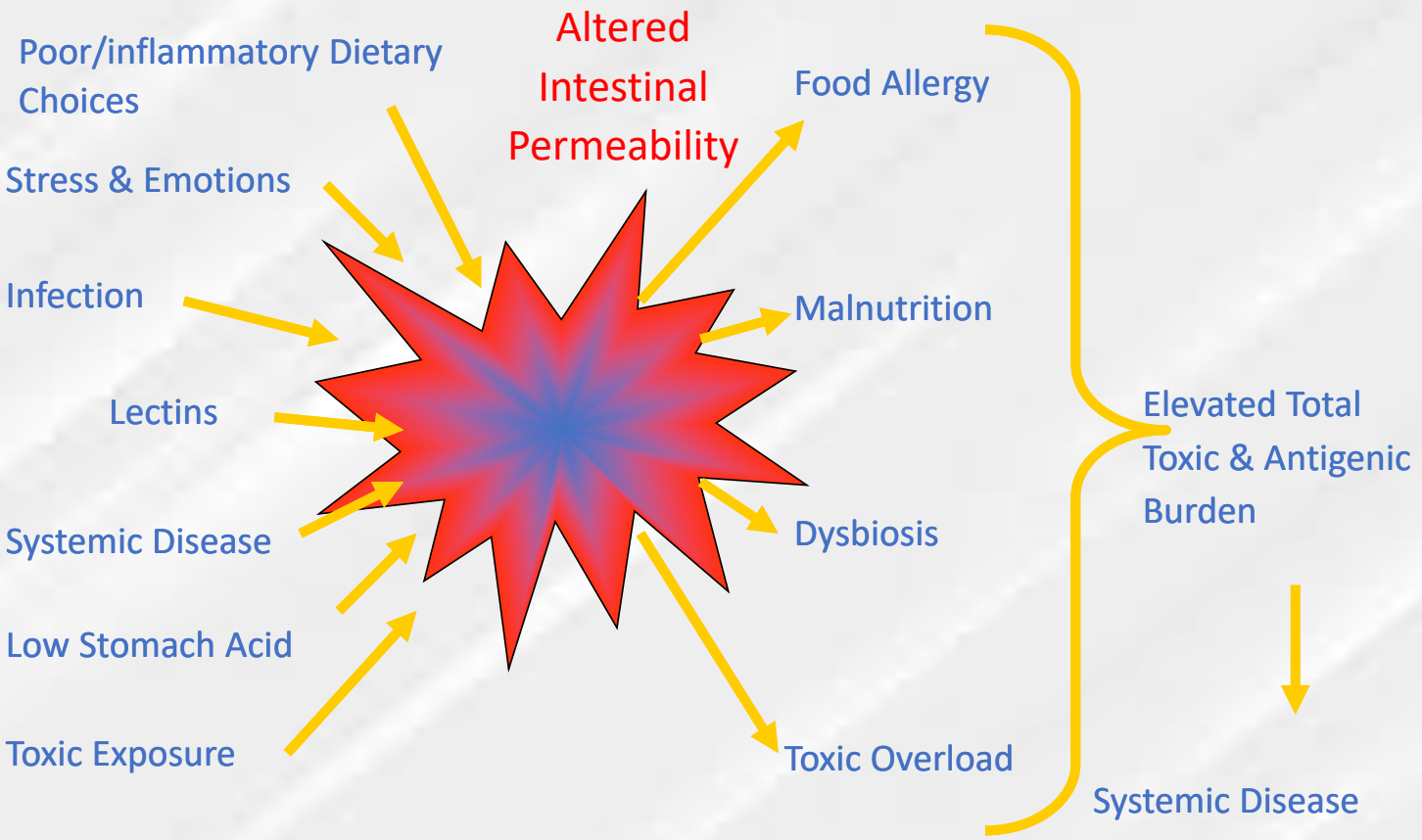
Most All Chronic Diseases Are Reporting Dysbiosis - Altered Microbiomes

Healthy Gut Versus Leaky Gut

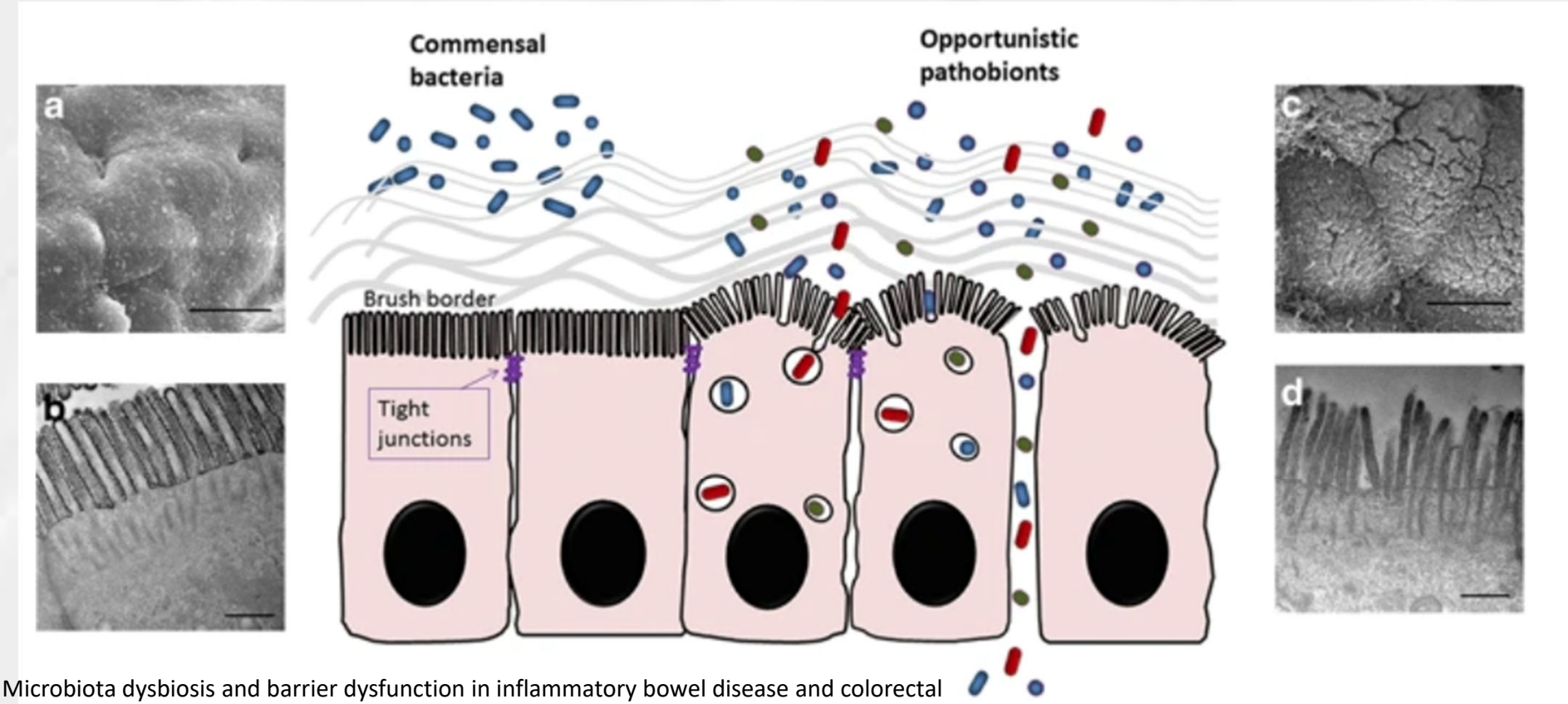
A healthy gut works like a cheese cloth, allowing only nutrients through, but keeping larger food particles and pathogenic bacteria, yeast and parasites out. In a leaky gut, the tight junctions are loosened so undigested food particles and pathogens can get through and activate the immune system, causing inflammation and food sensitivities.



Leaky Gut - Pathophysiology



Electron Microscopy of GUT Epithelial Barrier Healthy vs. Non-Healthy



Yu, LC. Microbiota dysbiosis and barrier dysfunction in inflammatory bowel disease and colorectal cancers: exploring a common ground hypothesis. J Biomed Sci. 2018;25:79.

Results of Dysbiotic GUT

- METAFLAMMATION
- Increased food allergies/intolerances
- Digestive problems like IBDs, IBS, Crohn's, colitis
- Increased sleep and mood disturbances
- Fatigue
- Increased time to recovery
- Increased joint and connective tissue issues
- Decreased performance and exercise ability
- Memory and cognitive decline
- Sex hormone issues – testosterone, estrogen
- Thyroid imbalance
- Nutrient deficiencies – vitamin D, B vits
- Food cravings
- Immune problems
- Cardiovascular problems
- Chronic Inflammation
- Weight gain
- Infections
- ↑ Environmental toxicities

Inflammasomes

- Family of proteins in charge of the initiation of inflammatory process during innate immune response
- Pattern recognition receptors – stress, danger
- Major actors in metaflammation construct
- Signaling platforms associated with stress and damage
- No drug on the market targeting these proteins
- Most characterized = $NLRP_3$ nucleotide-binding domain leucine-rich repeat

Zahid A, et al Pharmacological inhibitors of the NLRP3 inflammasome. Front Immunol. 2019;2019:02538

GUT-LIVER AXIS

- GUT connects the liver w/ intestines via bile acid metabolism
- Bile acid (BA) dysregulation leads to intestinal dysbiosis
- Allows Gram (-) enterogenous pathogenic bacteria and LPS to enter liver via portal vein
- Triggers hepatic inflammation via inflammasomes

Wang J, et al. Roles of the inflammasome in the gut-liver axis. Mol Mol Rep. 2019;19(1):3-14.

GUT-LIVER AXIS

- **Decreased** Bile acids (BAs) in the gut lead to intestinal dysbiosis
- Impairs intestinal barrier function – lead to leaky gut
- Induces bacterial translocation to allow pathogens i.e. *Bacteroidetes* (Gram-negative bacteria) and LPS into the liver
- Aggravates hepatic inflammation
- Loss of intestinal epithelial stemness also contributes to bile duct ligation-induced cholestatic liver injury

Wang J, et al. Roles of the inflammasome in the gut-liver axis. Mol Mol Rep. 2019;19(1):3-14.
Sabino J, Vieira-Silva S, Machiels K, Joossens M, Falony G, Ballet V, Ferrante M, Van Assche G, Van der Merwe S, Vermeire S, Raes J. Primary sclerosing cholangitis is characterised by intestinal dysbiosis independent from IBD. Gut. 2016;65:1681–1689.

GUT-LIVER Inflammasomes

- Inflammasomes mediate innate immunity in liver / GUT
- (NLRP)6 protein dominant in intestinal microbial balance
  - Via NACHT, LRR and PYD domains
- Promotes IL-18-dependent antimicrobial peptide (AMP) synthesis
- Promotes mucus secretion from goblet cells

Wang J, et al. Roles of the inflammasome in the gut-liver axis. Mol Mol Rep. 2019;19(1):3-14.

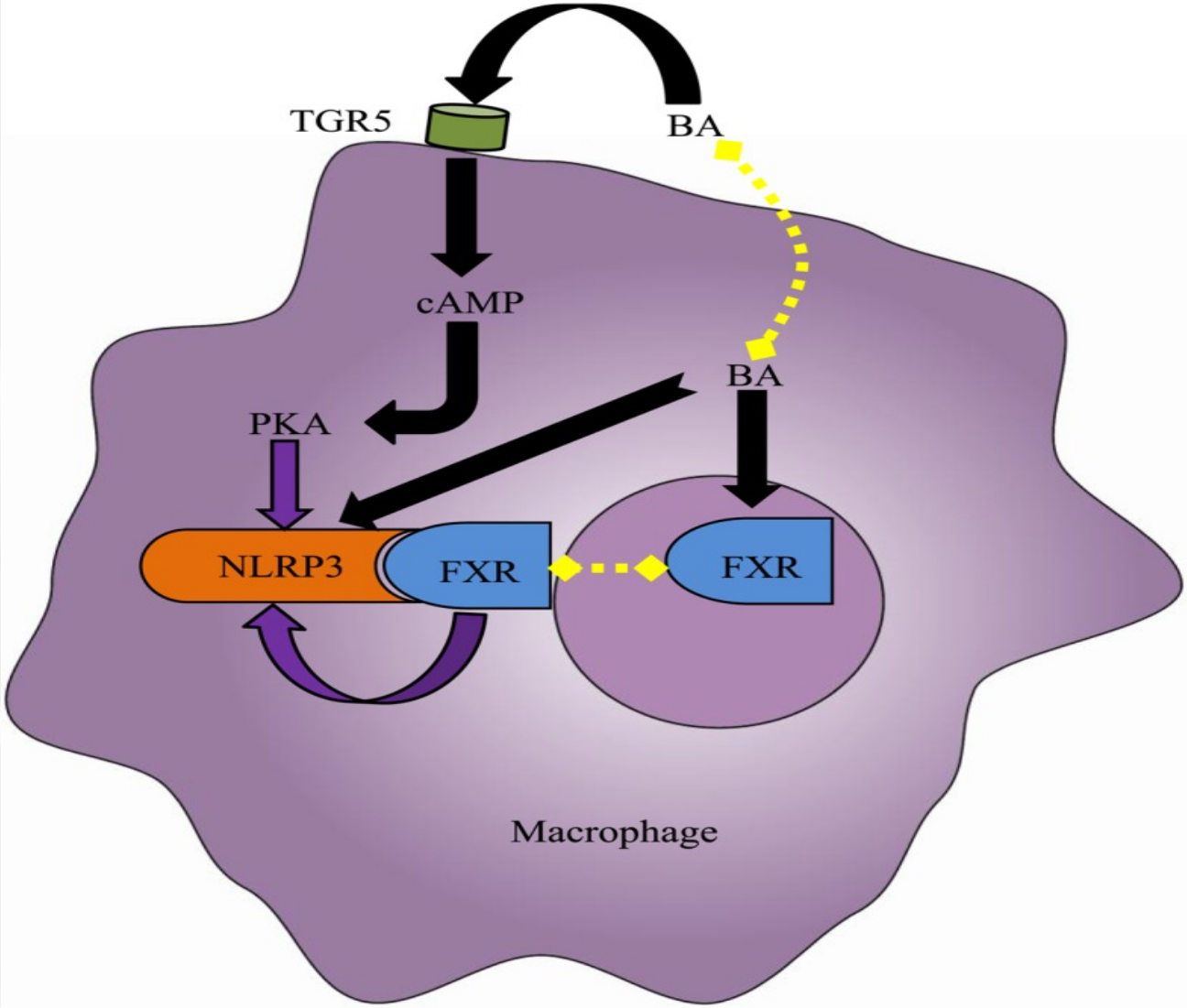
GUT-LIVER Inflammasome Interaction

- In contrast, NLRP3 inflammasome primarily induces IL-1beta

- BAs activate NLRP3 inflammasome in macrophages
  - Aggravates inflammatory liver injury
  - Affects the epithelial integrity of cholangiocytes by inducing the production of pro-inflammatory cytokines
  - Excessive Bas induce hepatocyte death

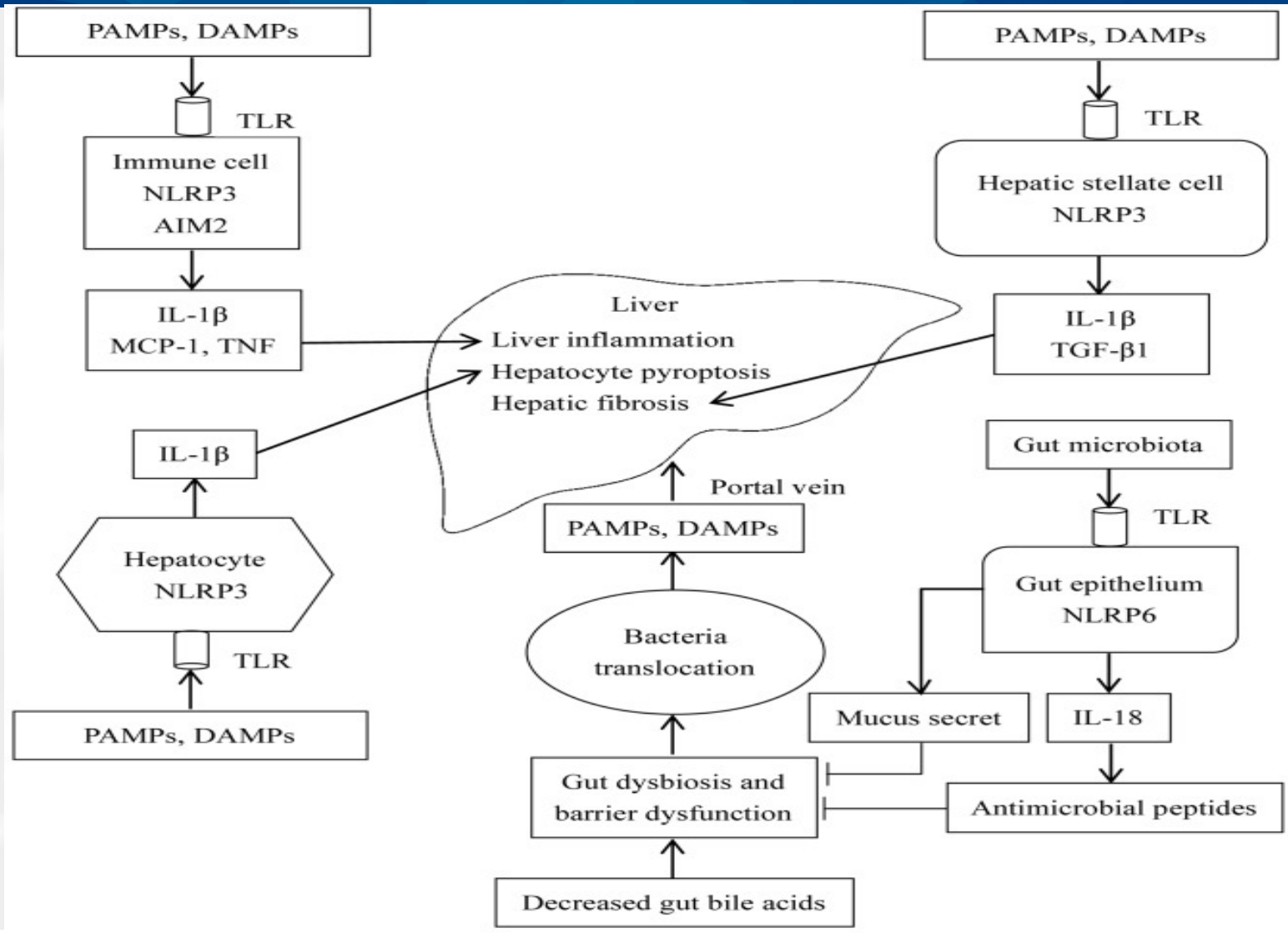
Wang J, et al. Roles of the inflammasome in the gut-liver axis. Mol Mol Rep. 2019;19(1):3-14.

Bile Acid Effects on NLRP3 Inflammasome in Macrophage



Wang J, et al. Roles of the inflammasome in the gut-liver axis. Mol Mol Rep. 2019;19(1):3-14.

Role of Inflammasome in GUT-LIVER Axis



Wang J, et al. Roles of the inflammasome in the gut-liver axis. Mol Mol Rep. 2019;19(1):3-14.

EH3

Slide 26

EH3 Ernie Hawkins, 9/17/2020

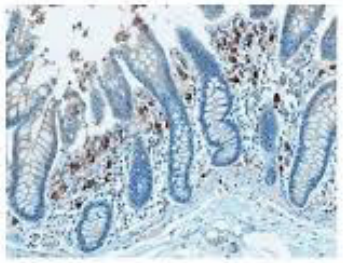
GUT-LIVER Axis Study

- 2011 2-part cohort study
  - 2754 IBD patients
  - 82 primary sclerosing cholangitis (PSC)
- RESULTS:
- An inflammed colon, but not small bowel, is important in PSC development
- Bacterial translocation and subsequent portal bacteremia is important in PSC development in IBD

O'Toole A, Alakkari A, Keegan D, Doherty G, Mulcahy H, O'Donoghue D. Primary sclerosing cholangitis and disease distribution in inflammatory bowel disease. Clin Gastroenterol Hepatol. 2012;10:439–441.

LPS Effects

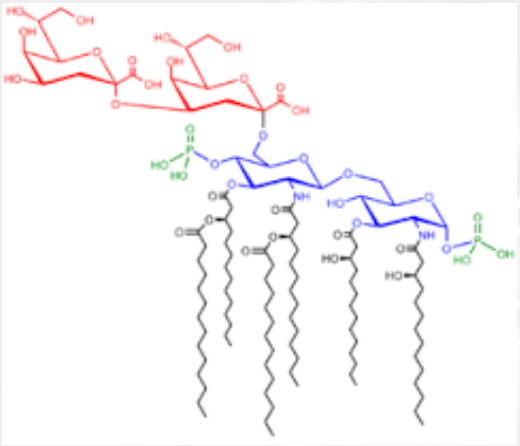
- ↑ inflammatory response (TNFα and Il-6)
- ↑ WBC's
- ↑ MCP-1
- ↑ Transient HR
- ↑ Cortisol
- ↑ Autoimmune
- ↑ Resistin
- ↑ Adipocyte inflammation



- ↓ Insulin sensitivity
- ↓ Glucose transport in skeletal muscle
- ↓ Thyroid function
- ↓ Alters tryptophan metabolism and increase quinolinic acid and kynurenine
- ↓ Melatonin
- ↓ Glutathione pool via increased ROS

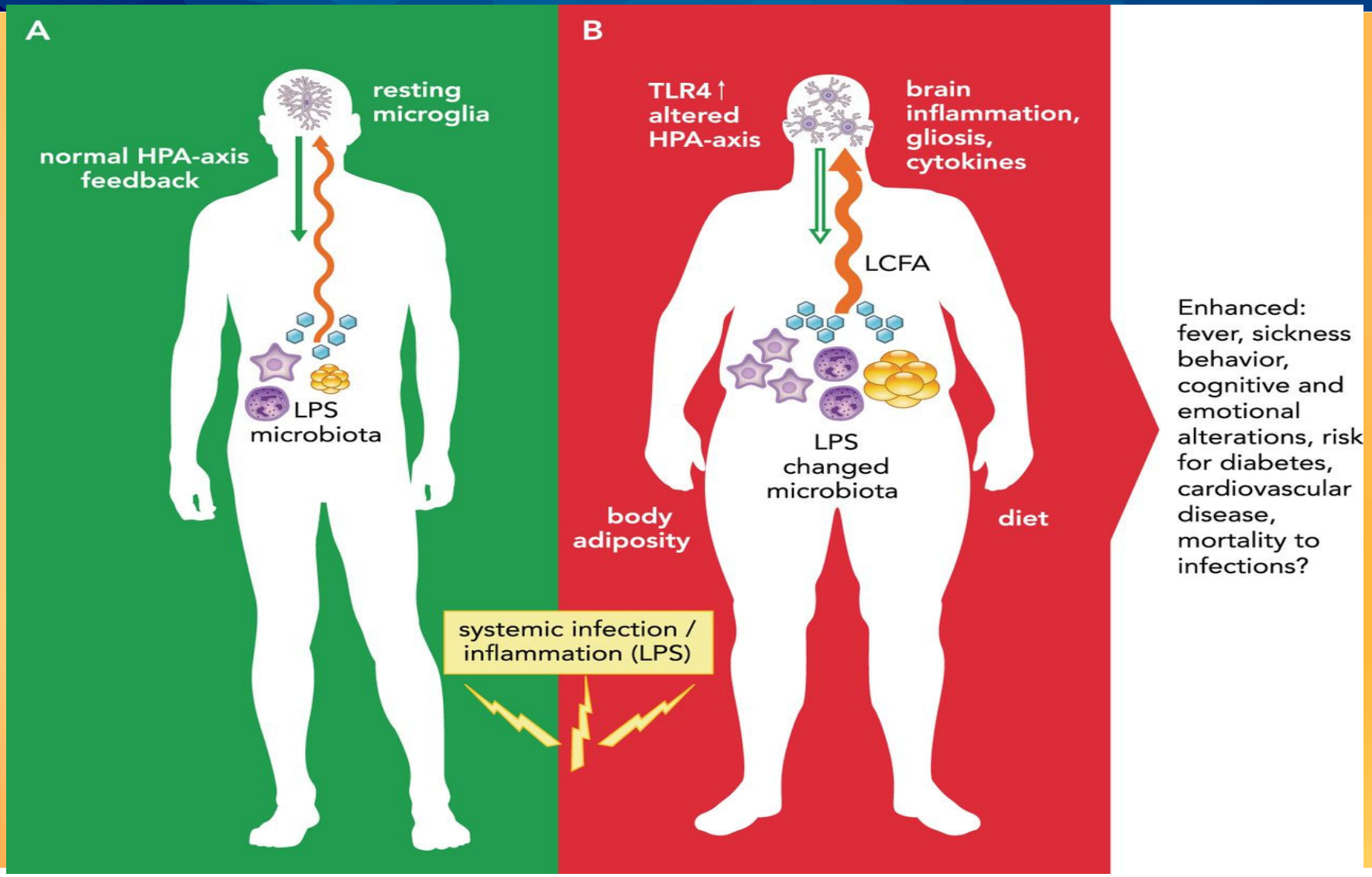
Lipopolysaccharides in Food Food Supplements and Probiotics: Should we be worried? Eur J Microbiol Immunon(Bp). 2018;8(3):63-69.

Endotoxin Production

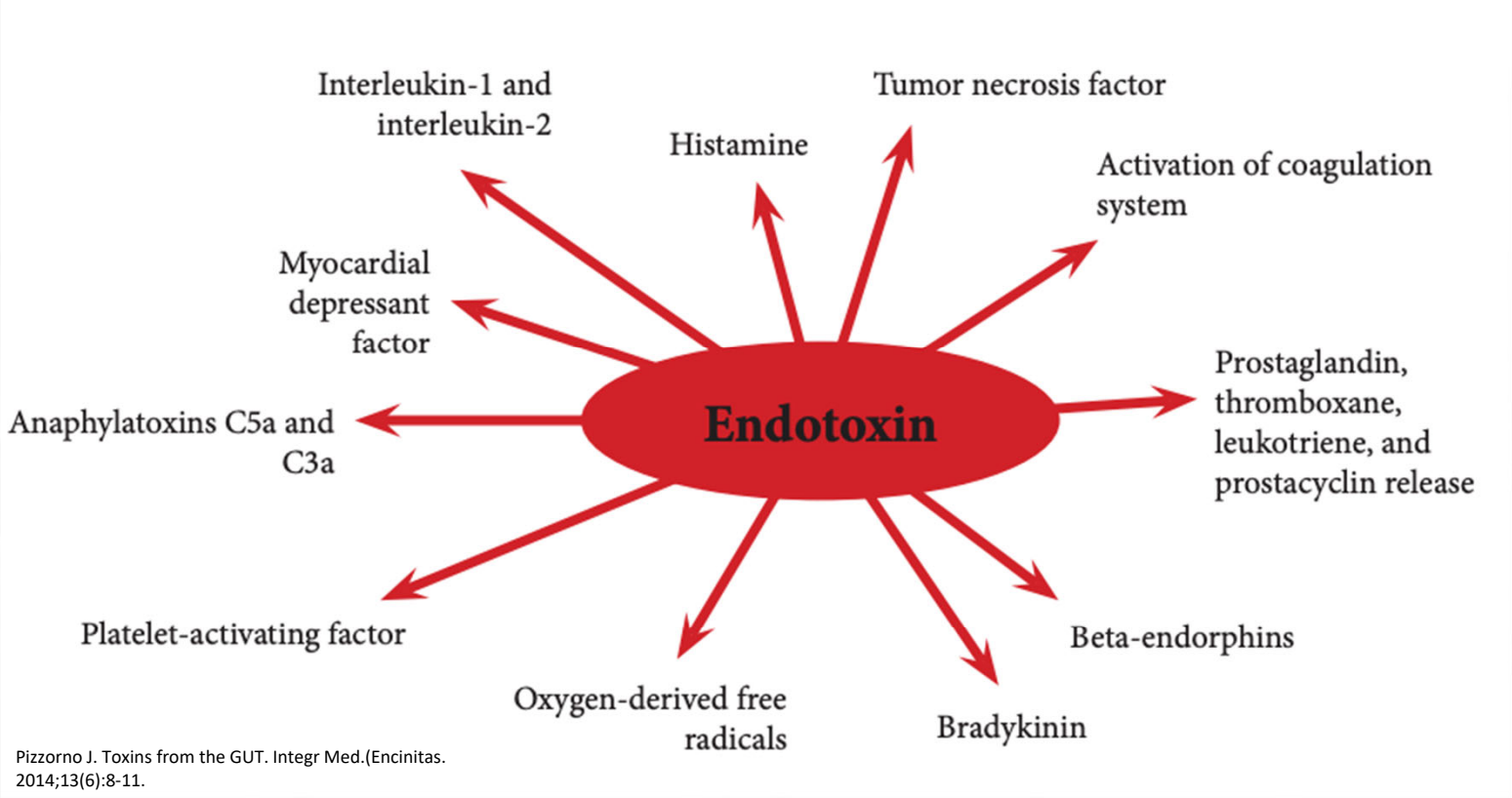


- LPS represent 80% of the cell-wall mass of Gram-negative gut bacteria.
- Disturbances in microbiome can release endotoxin
- Long Duration Exercise induces Endotoxemia due to plasma ↑ Lipopolysaccharide (LPS) levels
  - LPS leads to:↑cytokine release ↑oxidative stress and alterations in gut function
  - Vitamin C reduced nitrate and LPS serum levels
- Ketogenic Diets induce endotoxin production

Guy JH, et al. Nutrition and Supplementation Considerations to Limit Endotoxemia When Exercising in the Heat. Sports (Basel). 2018;6(1):12.


A
resting microglia
normal HPA-axis feedback
LPS microbiota
B
TLR4 ↑ altered HPA-axis
brain inflammation, gliosis, cytokines
LCFA
LPS changed microbiota
body adiposity
diet
systemic infection / inflammation (LPS)
Enhanced: fever, sickness behavior, cognitive and emotional alterations, risk for diabetes, cardiovascular disease, mortality to infections?

Metabolic Effects of Endotoxin



Pizzorno J. Toxins from the GUT. Integr Med.(Encinitas. 2014;13(6):8-11.

TBI and GUT-BRAIN Disruption

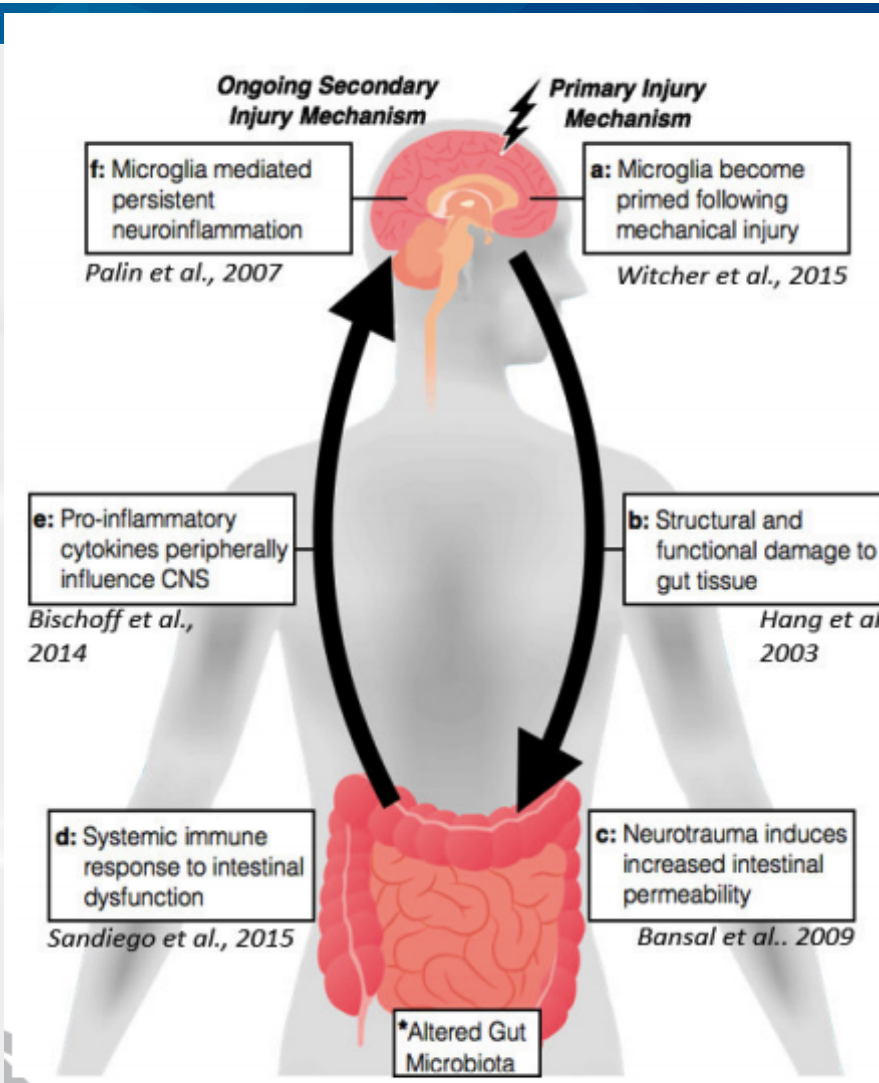
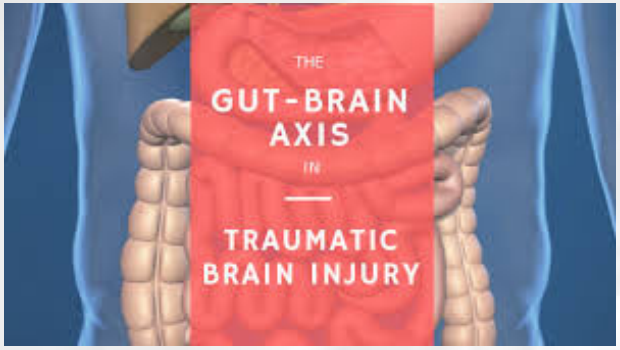


Figure 1: Proposed Conceptual Model for the Bidirectional Involvement of GBMAx following TBI: a) Neurotraumatic event

Zhu CS, et al. A review of traumatic brain injury and the gut microbiome: insight into novel mechanisms of secondary brain injury and promising targets for neuroprotection. Brain Sci. 2018 Jun; 8(6):113.

TBI and GUT-BRAIN Disruption

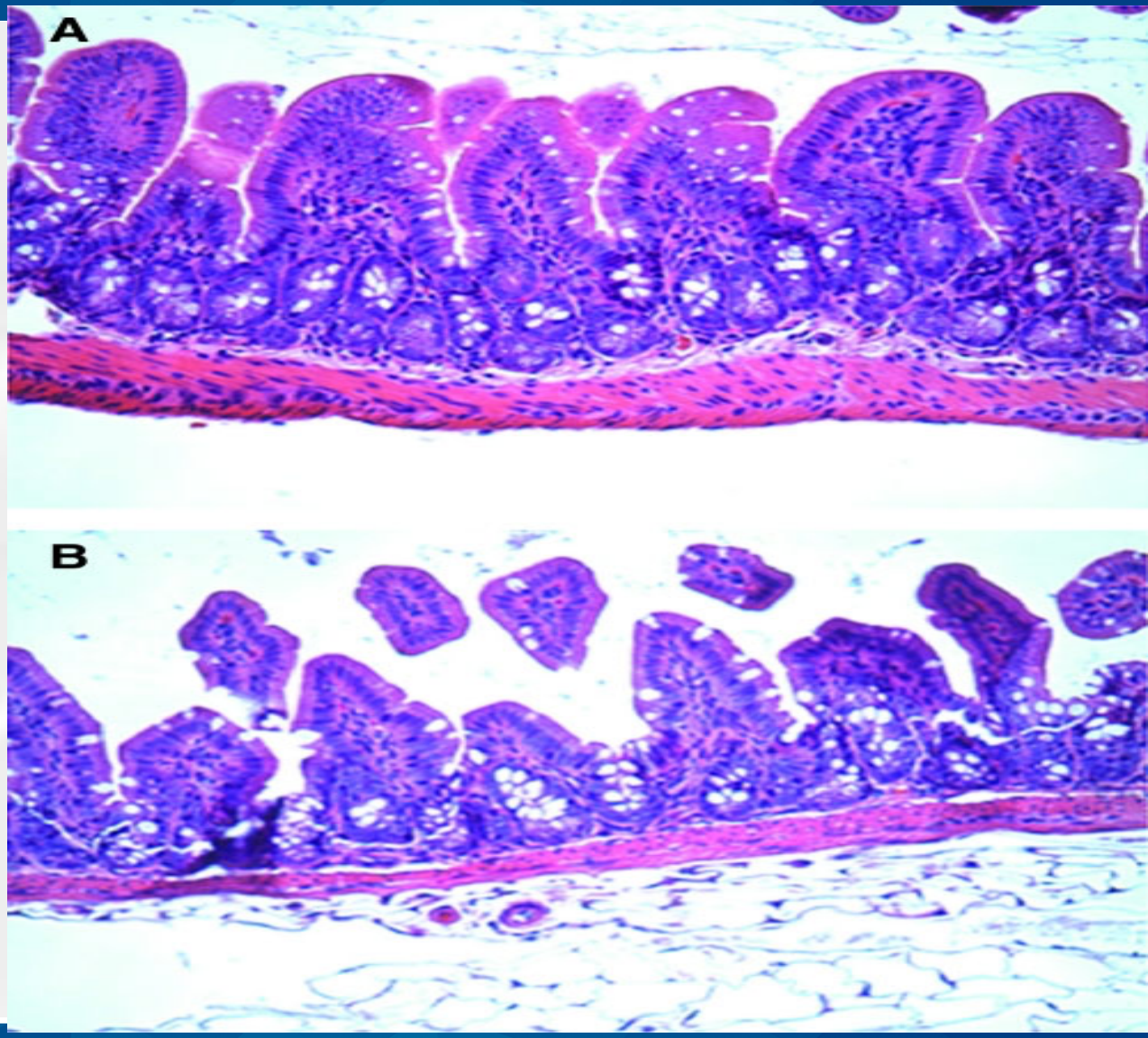


- ↓ intestinal absorption and contractility
- Microbiome disruption
- ↑ defective tight junctions and intestinal permeability
- ↑ GUT issues – Crohn's, Celiac disease
- ↑ Insulin dysregulation
- ↑ Immune dysregulation
- ↑ Brain issues – sleep, cognition, mood disturbances, anxiety and psychiatric disorders

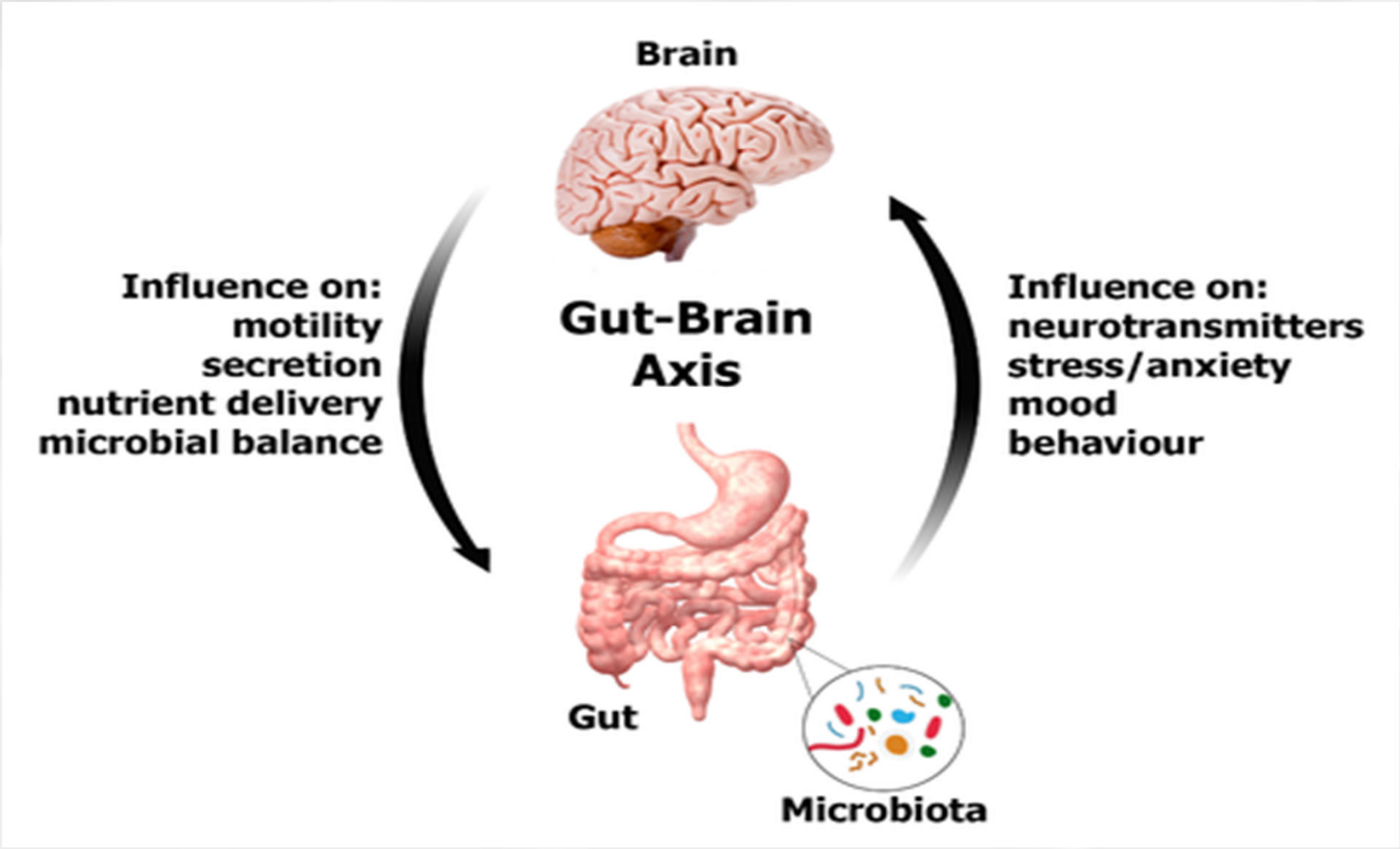
Terminal ileum 6 hr post-TBI

A –normal villi consistent villous height

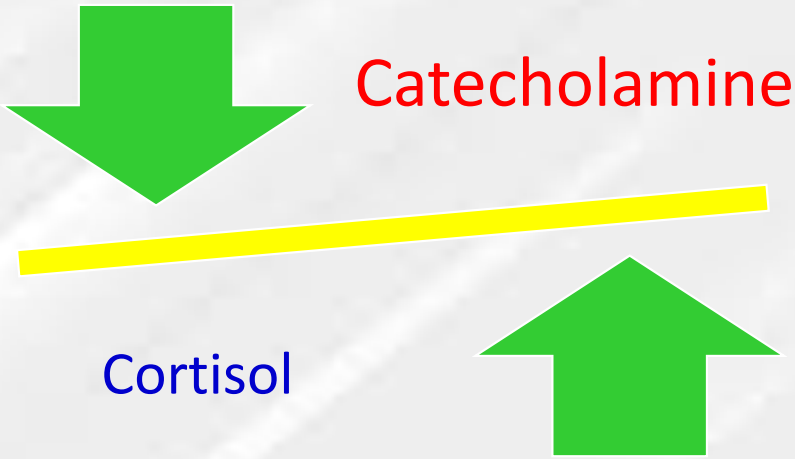
B – post-TBI villi



Bansai V, et al. Traumatic brain injury and intestinal dysfunction: uncovering the neuro-enteric axis. J Neurotrauma. 2009;26(8):1353-59.


Brain
Influence on:
motility
secretion
nutrient delivery
microbial balance
Gut-Brain Axis
Influence on:
neurotransmitters
stress/anxiety
mood
behaviour
Gut
Microbiota

SNS Hyperactivity and Stress



- Loss of negative feedback from cortisol results in a rise in catecholamine production and sympathetic overdrive
- RHR (resting heart rate) increases
- Palpitations

Central Nervous System

- Prolonged hypercortisolism leads to degeneration of the:
  - Hippocampus – memory
  - Hypothalamus – CFS, FM, Depression, PTSD
  - Pre-Frontal Cortex – executive decision making
  - Amygdala – emotional stability
- fMRI Pathologic changes seen, some irreversible despite treatment
- Effects remain after hypocortisolism has developed

Aging, Inflammation and Gut Permeability

IL-6 is unregulated with aging leading to disruption of the permeability of the gut.

Age Associated modifications of intestinal permeability and innate immunity inhuman small intestine, Man, A., Bertelli, E.,etal; Clinical Science Jul 03, 2015 129 (7) 515-527; DOI 10.1042/CS20150046

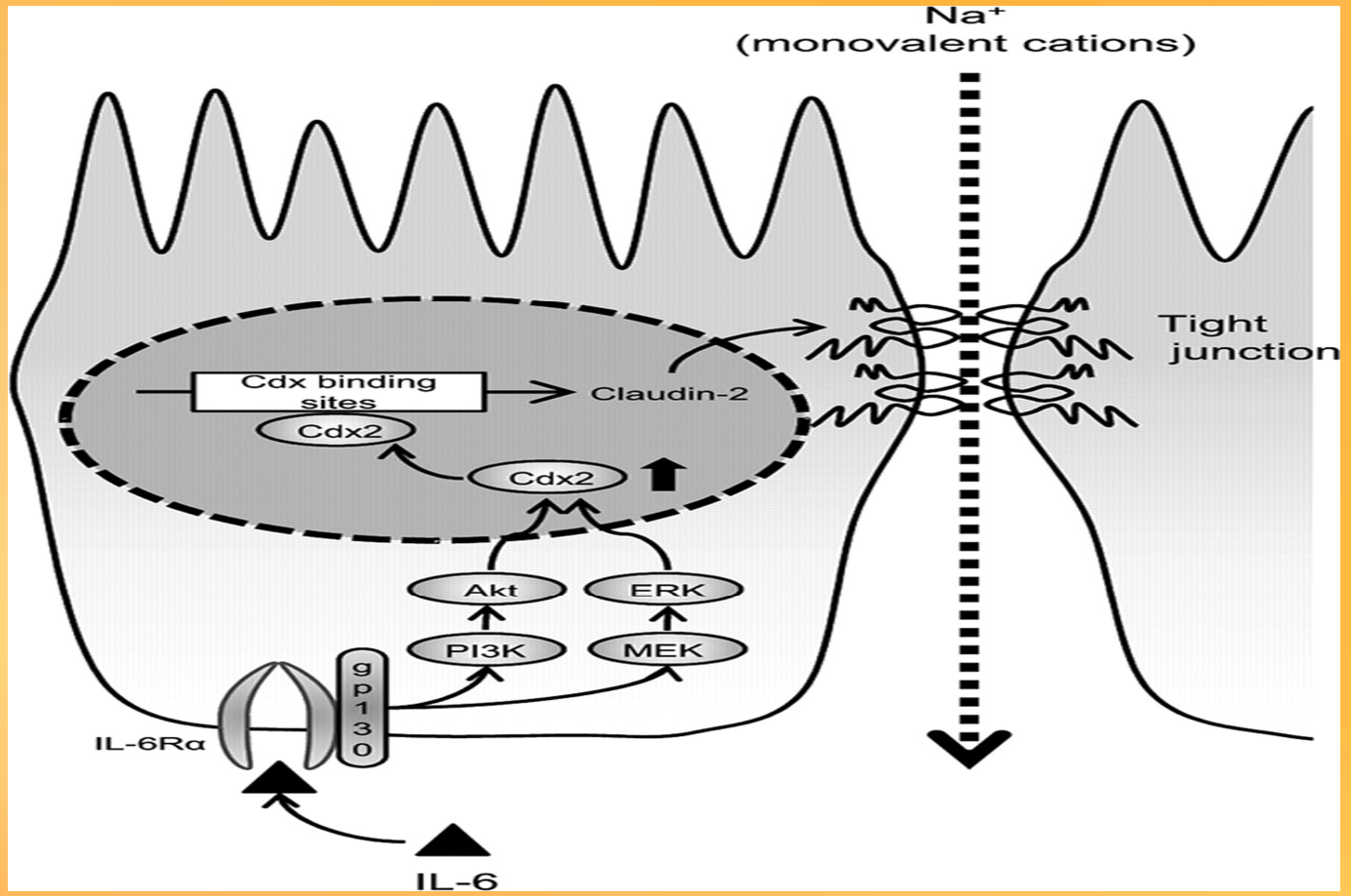
IL-6 regulates Claudin 2 Expression of Tight Junction Permeability in Intestinal Epithelium

-

- Key immune cytokine in chronic inflammation
- Induced by chronic hypercortisolism and flattening of cortisol curve
- Induced in overtraining in athletes
- Markedly induces expression of Claudin-2
- Disrupts tight junction structure (TJ) multi-protein structure (disrupts protein scaffold cytoskeleton)

Susuki, Takuya, Yoshinaga N,, Tanabe, Soichi; IL-6 regulates expression of Tight Junction Permeability in the Epithelium; September 9, 2011 The Journal of Biological Chemistry, 286, 31263--31271

Schematic representation showing the mechanism for the IL-6-mediated increase in the TJ permeability in intestinal epithelium cells.



Takuya Suzuki et al. J. Biol. Chem. 2011;286:31263-31271

Drug Induced Microbioime Disruption (DIMD)

- Prescription and non-prescription drugs can alter the microbiome
- Potentially disrupting metabolic Pathways
- DIMD can lead to metaflammation if not corrected
- Affects all facets of metabolism
  - Nutrient absorption
  - GUT-IMMUNE-BRAIN axis
  - Blood glucose balance/insulin resistance
  - Hormonal balance – sex / thyroid / appetite
  - Sleep
  - Detoxification

Bastard QL, et al. Systematic review: human gut dysbiosis induced by non-antibiotic prescription medications. Aliment Pharmacol Ther. 2018;47(3):332-45.

What Drugs Commonly Affect the Microbiome

- Antibiotics
- NSAIDs
- Corticosteroids
- OCs/HRT
- PPIs / H2 blockers
- Metformin
- Statins
- Antisychotics
- Opioids
- OTHERS not studied??

Bastard QL, et al. Systematic review: human gut dysbiosis induced by non-antibiotic prescription medications. Aliment Pharmacol Ther. 2018;47(3):332-45.

Dietary Issues and Metaflammation

- Excess caloric intake can disrupt microbiota circadian fluctuations
  - Increases appetite dysregulation
  - Increases inflammatory tone
  - Increased chronic inflammation

- Postprandial lipoproteins are involved in the inflammatory process that precedes the development of cardiometabolic diseases

- VLDL and chylomicrons bind to endothelial cells and circulating lympohocytes
  - Atherosclerotic cardiovascular disease
  - Non-alcoholic fatty liver disease
  - Non-alcoholic steatohepatitis
  - T2DM

Franceshi C, et la. Inflammaging: a new immune-metabolic viewpoint for age-related diseases. Nature. 2018;14:576-590.

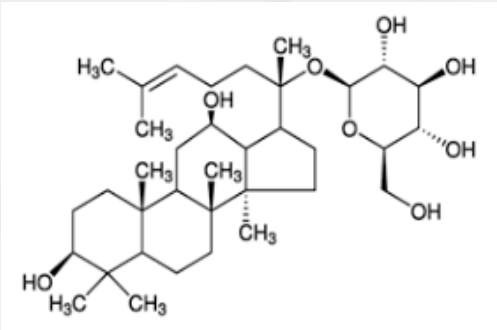
Western Diet and Metaflammation

- Chronic consumption of Western Diet + sedentary behavior = Metaflammation
- High fat, high fructose-based and excessive calories induces metaflammation
- Memorized' by innate immune cells through long-lasting metabolic and epigenetic cellular reprogramming
- Increased link between Western Diet and CKD (chronic kidney disease) and CHF (congestive/chronic heart failure)

Christ A, et al. The Western lifestyle has lasting effects on metaflammation. 2019;19:267-68.
Kanbay M, et al. **A journey from microenvironment to macroenvironment: the role of metaflammation and epigenetic changes in cardiorenal disease.** Clin Kidney J. 2019;12(6):861-70.

Controlling Metaflammation

Compound K Metaflammation



- New to US market in 2020
- Used in China for over a decade
- Compound K is a product of ginseng fermentation – either in manufacturing using bacterial fermentation or by human GUT microflora
- Compound K is the ginsenoside component that exerts biological activity in vivo
- The “STEM cell” of ginsenosides
- All other ginsenosides metabolized to Compound K in vivo

Yang XD, et al. A review of biotransformation and pharmacology of ginsenoside compound K. Fitoterapia. 2014;209-17.

Compound K ginsenoside - Lab and Human Studies

- Gut/microbiome supportive
- Antiinflammatory/antioxidant
  - regulation of iNOS, PGs, cytokines, COX-2
- Anti-aging
  - photoprotective, increases Type 1 procollagen, increase hyaluronan production
- Neuroprotection/neurogenesis
  - inhibits microglial inflammation
  - Regulates $GABA_A$ transmission and suppresses NMDA excitotoxicity via Nrf2-mediated induction of antioxidant enzymes

Wang HY, Qi LW, Wang CZ, Li P. Bioactivity enhancement of herbal supplements by intestinal microbiota focusing on ginsenosides. Am J Chin Med 2011;39:1103e15.

Compound K ginsenoside

- Cognitive support – improves learning
- Immune supportive – Th1/Th2; antiviral
- Anticancer – increases apoptosis, decreases angiogenesis, decreases proliferation and motility of cancer cell lines
- Cardiovascular – increased nitric oxide, improves lipids
- Hepatoprotective

Wang HY, Qi LW, Wang CZ, Li P. Bioactivity enhancement of herbal supplements by intestinal microbiota focusing on ginsenosides. Am J Chin Med 2011;39:1103e15.

Compound K ginsenoside

- Blood glucose/insulin regulation
  - In vivo and in vitro comparable to Metformin antidiabetic activity
  - Enhances insulin secretion
  - Improved glucose tolerance – increases glucose uptake
  - Up regulates glucose transporter
  - Inhibits lipogenesis
  - PPAR gamma stimulation
  - Improved glucose uptake in adipocytes
  - Stimulates GLP-1 release in hepatic cells via bile acid receptor activation

- Yoon SH, et al. Antidiabetic effects of compound K versus metformin versus compound K-metformin combination therapy in diabetic db/db mice. Biol Pharm Bull. 2007;30(110:2196-200.
- Yuan HD, et al. Ginseng and diabetes: the evidences from invitro animal and human studies. J Ginseng Res. 2012;36(1):27-39.

Compound K - Antiviral Activity

- Modulates Th1/Th2 antibody responses
- Direct antiviral activity against influenza subtypes (H1N1
- Ginseng inhibits biofilm formation
- Induces the dispersion and dissolution of mature biofilms
- Improves viral clearance

Alipour M. Ginseng aqueous extract attenuates the production of virulence factor, stimulates twitching and adhesion and eradicates biofilms of Psuedomonas aeroginosa. Can J Physiol Pharmacol. 2011;89(6):419-27.
Kim DH. Gut microbiota-medicated pharmacokinetics of ginseng saponins. J Ginseg Res. 2018;42:255-63.

Compound K

- Chinese developing pharmaceuticals using CK for :
  - Epilepsy
  - Rheumatoid arthritis

- Dosage = 150mg BID
  - Standardized to 5% CK
  - Take on empty stomach if possible
- Reported safe in recommend doses
- Ginsenosides reported to decrease platelet aggregation Monitor patients appropriately

Zhou CL, et al. Single and multiple dose trials to determine the pharmacokinetics, safety, tolerability and sex effect of oral ginsenoside Compound K in healthy Chinese volunteers. Front Pharmacol. 2016;8:965.

Curcumin

- From turmeric (*Curcuma longa)* root/rhizome
- Traditionally for dyspeptic conditions
- Curcuminoids reported:
  - Antiinflammatory
  - Decreases inflammasome signaling
  - Supports musculoskeletal system
  - Joints/connective tissue support
  - Helps improve flexibility and mobility

Curcumin - Metaflammation

- Decreases oxidative stress via Nrf2-keap1 pathway
- Inhibits nuclear factor-kappaB
- Inhibits Toll-like receptor 4-dependent signaling pathways
- Inhibits activation of a peroxisome proliferator-activated receptor-gamma pathway.

Castro CN, et al. Curcumin ameliorates autoimmune diabetes,. Evidence in accelerated murine models of type 1 diabetes. Clin Exp Immunol. 2014;177(1):149-60.

Curcumin Metaflammation

- Modulates multiple cell signaling molecules
  - TNF-alpha
  - IL 1, IL-6
  - COX-2 and 5-lipoxygenase
  - NF-kappaB
  - CRP
  - PgE2
  - TGF-beta
  - AST/ALT
  - Malondialdehyde MDA
- Lab study reports curcumin ameliorates pancreatic beta cell destruction in autoimmune diabetes

Castro CN, et al. Curcumin ameliorates autoimmune diabetes,. Evidence in accelerated murine models of type 1 diabetes. Clin Exp Immunol. 2014;177(1):149-60.

Oral, GI Absorbed Curcumin – Dosage

- Oral encapsulated
  - 300-750mg BID of curcuminoids 95-98%
  - + added Bioperine (extract of black pepper, piperine) for improved bioavailability – NOT OPTIMAL
- Bioavailability of active curcuminoid compounds still suffers -1st pass effect
- Take with food

Prasad S, et al. Cancer Res Treat. 2014;46(1):2-18.

Recent Curcumin Headlines….

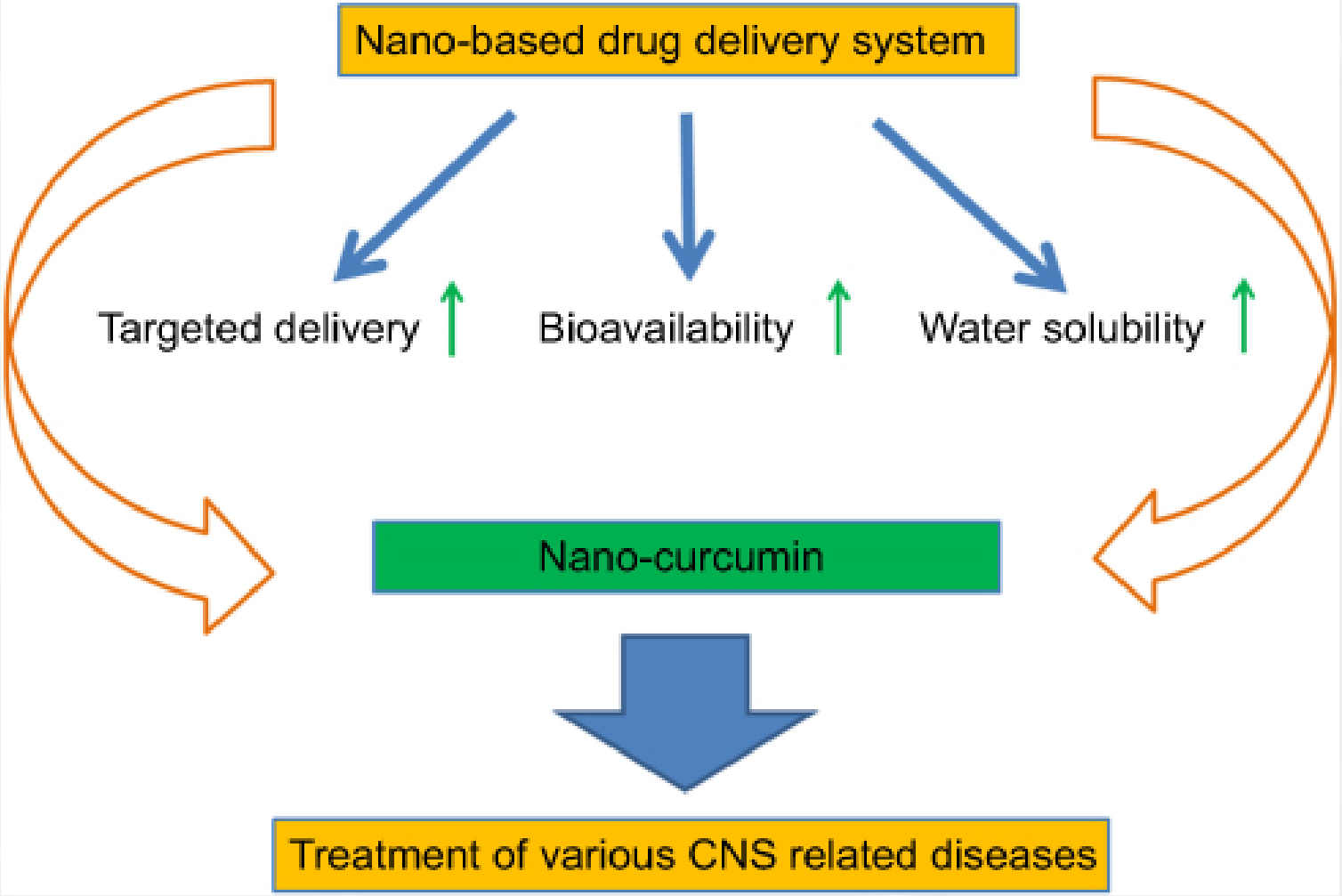

CHEMICAL BIOLOGY

Curcumin Will Waste Your Time

By Derek Lowe | 12 January, 2017

- Curcuminoids (I, II, and III) are poorly bioavailable orally
  - IV curcumin – Asia, Europe, Central and S. America
  - Topical curcumin
  - Intranasal curcumin
  - Improved oral extractions – 95% curcuminoids + bioperine
  - Water-soluble curcumin
  - Sublingual liposomal curcumin
  - Sublingual nanoparticle curcumin
- Led to development of superior bioavailable and clinically useful curcumin product - an oral nanospray
- SMART technology using safe ingredients for the microbiome

Enter into the Market - NanoCurcumin



Nanotized Oral Curcumin Spray

- 99% curcuminoid oral spray; Curcuminoids I, II and III
- 94% higher absorption than a curcumin capsule with optimized uptake at 1/10 of the dose =
  - 313-fold higher absorption than a curcumin capsule at 3% of the dose
- 410% higher absorption compared to curcumin infusion at a comparable dose =
  - 50% better absorption than 1/3 of the dose of curcumin infusion
- Consistently high level of curcuminoids for daily use at a fraction

Of oral doses

Castro CN, et al. Curcumin ameliorates autoimmune diabetes,. Evidence in accelerated murine models of type 1 diabetes. Clin Exp Immunol. 2014;177(1):149-60.

Nanotized Curcumin Oral Spray – Dosage

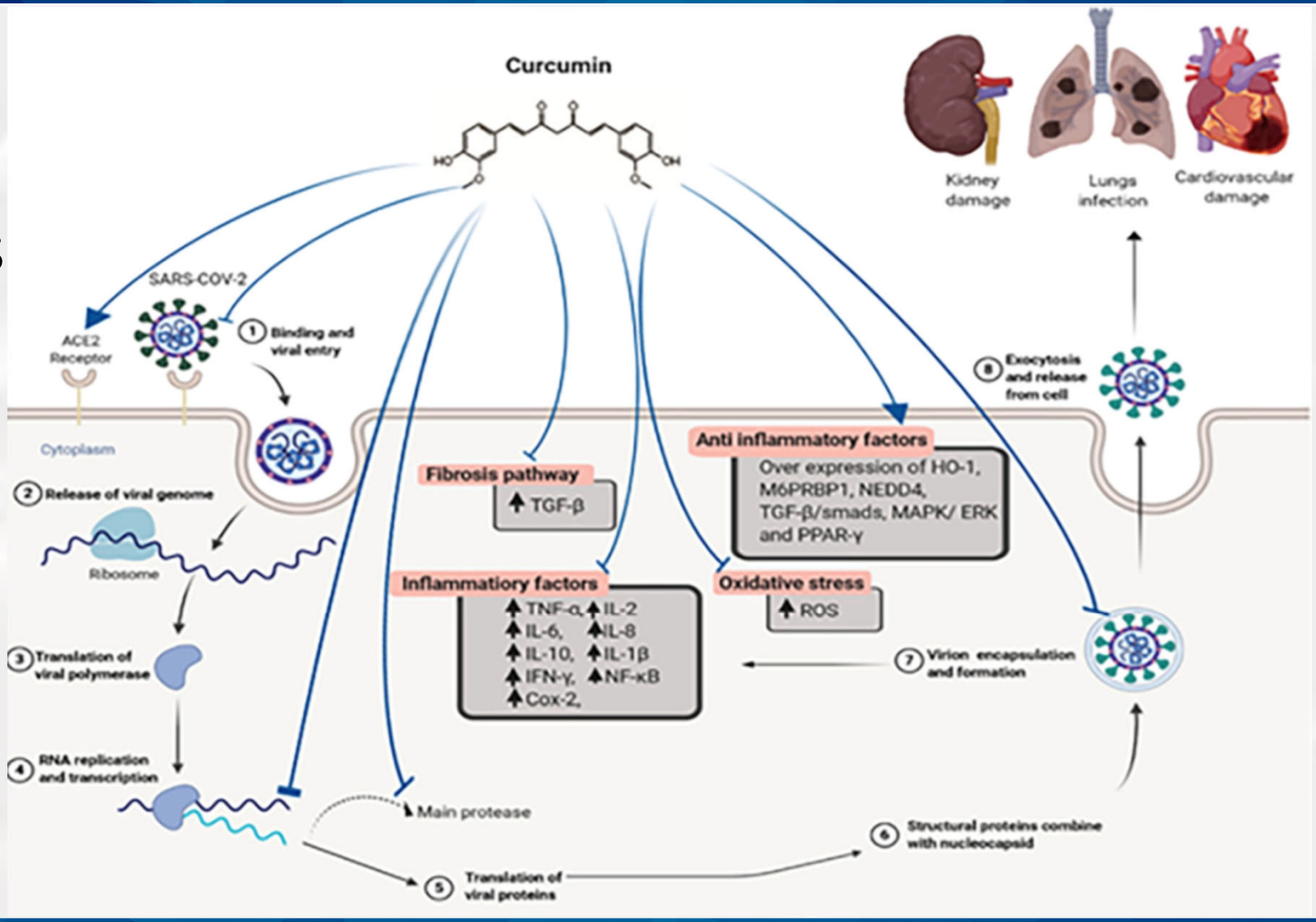
- Oral Water soluble nanospray
  - 9 sprays daily (3 sprays TID) = 42mg
  - 20ml glass bottle – 15 days therapy
  - 42 mg is bioequivalent to approx. 465mg “regular” 95% curcumin extracts
  - **Nanocurcumin effective at 9% of general oral dose**
  - **20ml bottle contains 840mg curcumin**
  - EU proprietary formulation
  - Improved bioavailability over C3 and other curcumin products
  - Physical stability studies x 24mo – microbial x 16 mo
  - Sublingual delivery
  - Pharmaceutically manufactured - sterile

Prasad S, et al. Cancer Res Treat. 2014;46(1):2-18.

NOTE

The AUC of Nanotized Curcumin is about 50 % better than a Curcumin **infusion** at only 1/3 of the dose and price. Less risks also.

NanoCurcum and the Pathogenesis of COVID-19



CurcumaXan NanoSpray Indications

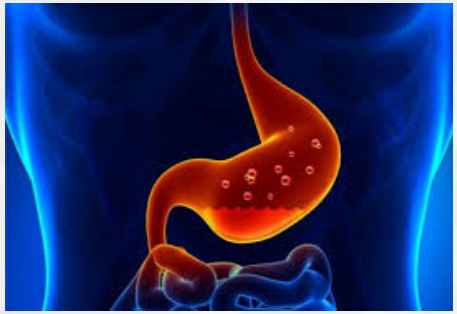
- Control metainflammatory responses
- Osteoarthritis
- MetS – insulin/blood glucose,
- Cardiovascular support – atherosclerosis;
- Exercise recovery
- VIRAL infections
- Oncological indications - cancer
- IBDs - inflammatory bowel diseases
- Postoperative inflammation/pain
- Skin issues – psoriasis, eczema, dermatitis

Curcumin Contraindications/Side Effects

- Studies have assessed safety of doses from 500mg - 12,000 mg
  - Transient side effects most common – diarrhea, headache, rash, yellow stool, abdominal pain
- Potential to increase ALP (alkaline phosphatase) & LD (lactate dehydrogenase)
- As per German Commission E monographs:
- Turmeric should not be used in biliary obstruction
- Curcuminoids are reported to have biliary stimulatory activity

Gupta SC, et al. AAPS Journal. 2013;15(1):195-206.

Peptides - BPC-157



- BPC-157 – Body Protection Compound
- Gastric Pentadecapeptide – 15 Amino Acids
- Gly-Glu-Pro-Pro-Pro-Gly-Lys-Pro-Ala-Asp-Asp-Ala-Gly-Leu-Val
- Derived from human gastric juice
- GUT IMMUNE BRAIN axis
- Cytoprotective
- Anti-inflammatory
- Supports GUT mucosal lining
- Protects and heals inflamed GUT mucosa

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.
Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

BPC-157

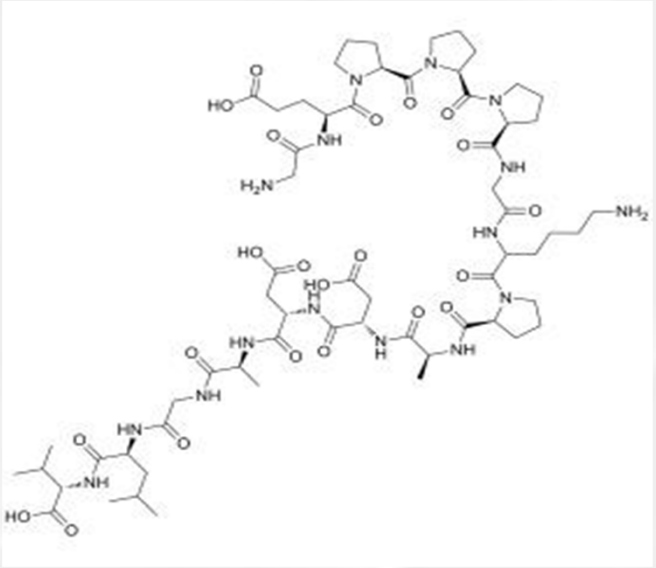
- Effective in decreasing metainflammatory signaling
- Downregulates TNF-alpha
- Improves cell survival under oxidative stress conditions
- Decreases neuroinflammation

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.

Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

BPC-157 Patient Benefits

- Accelerated wound healing
- Decreases inflammation
- Increased fibroblast
- Nitric oxide improvement
- Improves digestive function
- Enhanced vascular expression of VEGFR2



Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.

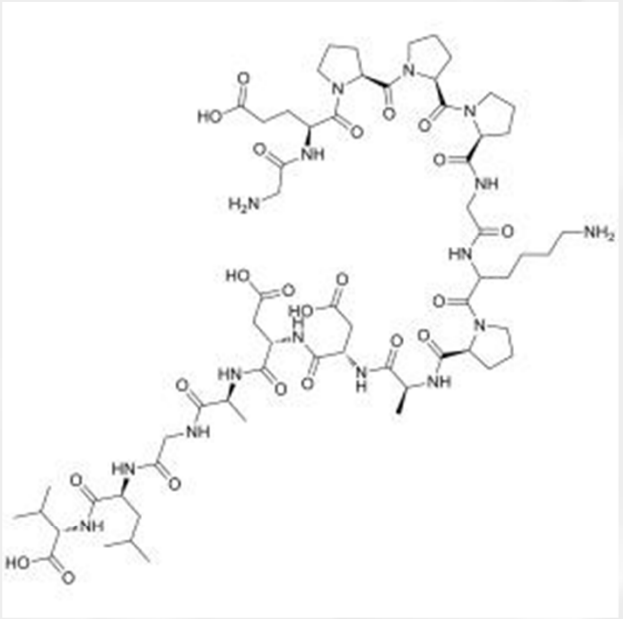
Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

BPC-157

- Potent angiomodulatory factor
- Improves tissue regeneration
  - Granulation
  - Fibroblast recruitment
  - Collagen formation
- Upregulates growth hormone

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.
Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

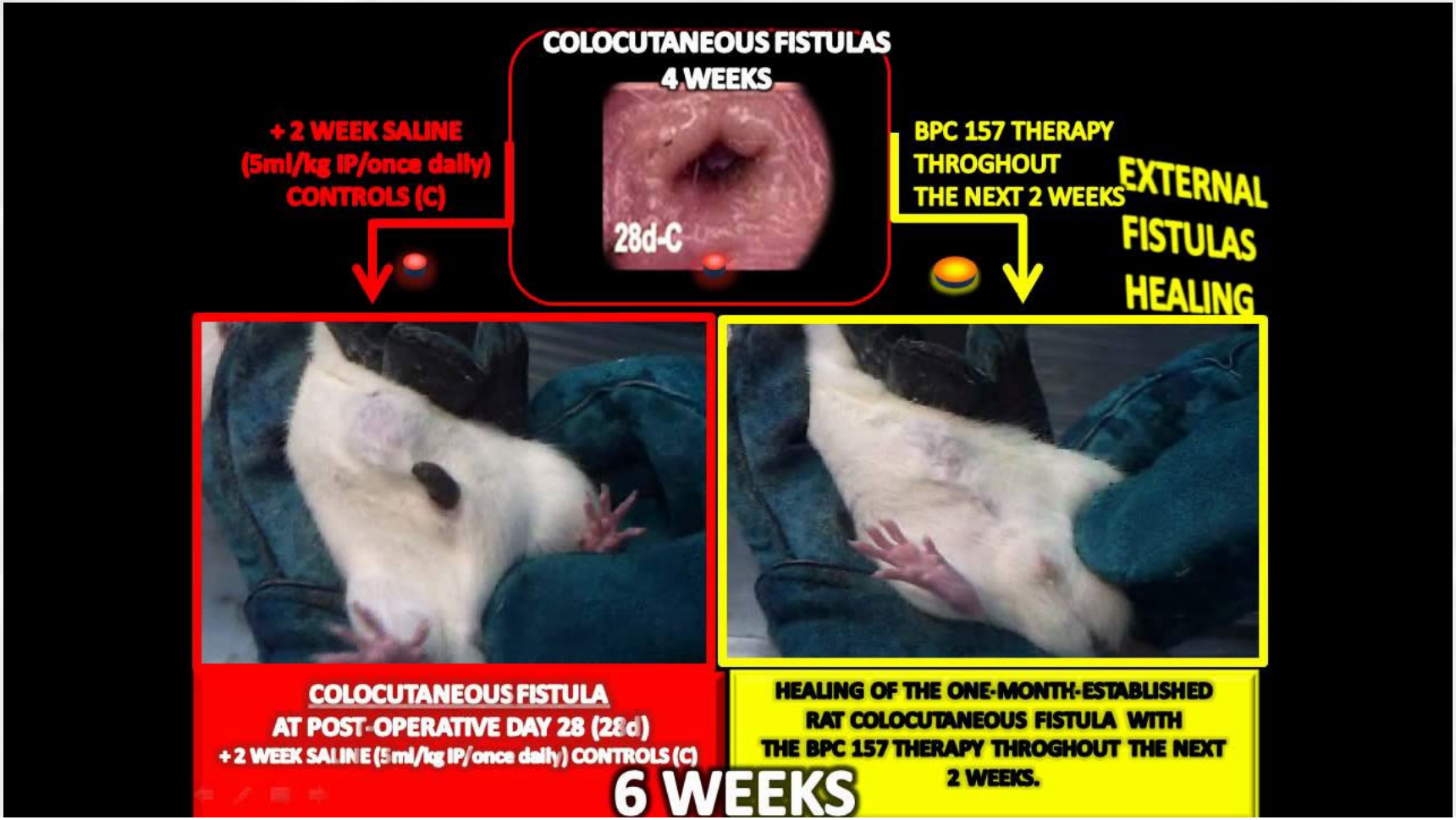
BPC 157 - GUT



- Gastric protection
  - Antiulcer peptidergic agent
  - Cytoprotective
  - Nitric Oxide (NO) improvement
    - BPC 157 interacts with nitric oxide (NO) system, both NOS-substrate (L-arginine) and NOS-blocker (L-NAME), including the regulation of a blood pressure
  - Helps improve GI mucosal integrity
  - Ulcerative colitis in lab studies
  - Decreases NSAID and alcohol gastric side effects

Sikiric P, et al. Focus on ulcerative colitis: stable gastric pentadecapeptide BPC 157. Curr Med Chem. 2012;19(1):126-32.

BPC 157 and Colovesical Fistulas – 2016 RAT study



Grgic T, et al. Stable gastric pentadecapeptide BPC 157 heals rat colovesical fistula. Eur J Pharmacol. 2016;780:1-7.

BPC-157

- INJECTION - Prescribing is often based on body weight using 2mcg/kg to as much as 10mcg/kg twice daily
- Commonly used doses range from 200mcg - 400mcg twice daily (400mcg to 800mcg daily)
- If used twice daily, intramuscular injection as close to the injury as possible or via subcutaneously for systemic purposes
- Use for 2-4 weeks before discontinuing; cease therapy for 2weeks, then restart therapy if needed

- BPC-157 is angio**modulatory** – however, use with caution in conditions where angiogenesis may be a problem (tumors)

Sikiric P, et al. Brain-gut axis and pentadecapeptide BPC 157: Theoretical and practical implications. Curr Neuropharmacol. 2016;14:857-65.

Seiwerth S, et al. BPC157 and blood vessels. Curr Pharm Des. 2014;20(7):1121-5.

Step by Step

Test for Food or elimination diet

Assess if the Gut is the primary driver or if it is secondary due to stress, biotoxins, drug history diet previous drug history.

- Cat's Claw, Berberine, Grapefruit Seed Extract, Olive leaf ex. Etc
- Pre/Probiotic
- Assess need for enzyme
- Rebuild Aloe, Zinc Carnosine, DGL, Arabinogalactan, Sialic Acid
- Serum Bovine Immune globulin
- Prebiotic Fiber
- Phospholipids
- Relora, holy basil, theanine