Key Aims

- Explain primary mechanisms
- Look for valid points of intervention
- Explore safe and cumulative strategies
- Tie the intervention to outcome

- Manage expectations
- Explore how changes in lifestyle will alter response to immune triggers, use of nutraceuticals etc.
Inflammation: The Dynamic Force of Health and Disease

V Vassileva¹ and M Piquette-Miller²

Replacing “happiness” with “inflammation” in Thomas Merton’s quotation holds true for the processes that govern our immune response and health. The balance between pro- and anti-inflammatory signals regulates inflammatory responses, leading to either restoration of health or the development and progression of disease, depending on whether it creates equilibrium or dysfunction. This issue of Clinical Pharmacology & Therapeutics highlights emerging research and concepts related to inflammation and its

“Happiness is not a matter of intensity but of balance order, rhythm and harmony.” Thomas Merton

Inflammation involves a continual ubiquitous cascade of complex signaling pathways and processes that are initiated and maintained by the immune system, affecting virtually all aspects of physiology, including energy metabolism. It can be defined as acute or chronic or unresolving.
**History of Depression**

- "Post partum depression" after each; no treatment

**Abdominal Pain**
- Missed school
- GI eval, no scopes
- Dx as lactose intolerance partial improvement.

**Signs, Symptoms or Diseases Reported**
- Gas & Bloating, Frequent non-bloody stools, “sensitive stomach”, Feeling of incomplete voiding, low energy, depressed mood.

**Triggers or Triggering Events**
- Solid foods at 6 months
- Bottle fed @ 4wks
- Colic @ 6 weeks
- Tonsillectomy @ 4yo
- 3-5 bouts of OM treated with ABX

**Mediators/Perpetuators**
- Weight has continued to “creep up” over the years

**Prenatal**
- Vag Birth prolonged ABX dt membrane rupture

**Parents**
- Parents divorced
- Mother Remarried

**Birth**
- Vag Delivery
- Vag Delivery
- Married

**Current Concerns**
- Weight gain in college

**Preconception**
- Fam Hx of IBS, Diverticulitis

Name: ______________________________  Date: __________________  CC: __________________
FUNCTIONAL MEDICINE MATRIX

Physiology and Function: Organizing the Patient’s Clinical Imbalances

- Assimilation
- Defense & Repair
- Structural Integrity
- Mental
- Emotional
- Spiritual
- Communication
- Biotransformation & Elimination
- Transport
- Energy

Antecedents

Triggering Events

Mediators/Perpetuators

Modifiable Personal Lifestyle Factors

- Sleep & Relaxation
- Exercise & Movement
- Nutrition
- Stress
- Relationships

Name: ______________________ Date: ____________ CC: ____________________________
Physiology and Function: Organizing the Patient’s Clinical Imbalances

**Antecedents**
- Mother SAD
- Fm Hx IBS, Diverticulitis
- Bottle @ 4 wk; Solid food @6mo
- Hx OM Rx ABX
- Tonsillectomy @ 4yo

**Triggering Events**
- Parents divorced @7
- Abdominal pain @10
- Lactose Intolerant
- Sensitive to tomato
- 2 kids @27&29 wt post part dep.
  Divorced at 34yo (two teen boys)

**Mediators/Perpetuators**
- SAD
- Weight gain in college

**Retelling the Patient’s Story**

**Assimilation**
- Gas and Bloating
- Freq stools

**Defense & Repair**
- SAD (inflammatory diet)

**Structural Integrity**

**Mental**

**Emotional**

**Spiritual**

**Energy**

**Communication**

**Biotransformation & Elimination**

**Stressful job**

**Family Dynamic?**
- Fatigue
- History of Depression

**Depression**

**Stress (adrenal reserve)**

**Sleep & Relaxation**
- Poor quality and quantity; has to be up to get the kids ready

**Exercise & Movement**
- NONE; “no time”

**Nutrition**
- SAD; quick meals due to being busy
- Eats out often

**Stress**
- Kids are a “handful”
- Job is stressful as bank exec asst.

**Relationships**
- Not dating and rarely has time to socialize
“Teach thy tongue to say ‘I do not know,’ and thou shalt progress.”

Moses Maimonides
ca 1200 A.D.
Key Concepts

• Inflammation is the body’s normal physiologic attempt to defend against foreign invasions and repair it from injury.
• Injury can result from trauma, infection, toxins, or foods (poor diet).
• Chronic inflammation occurs when the injury is ongoing or a predisposed immune system fails at counter-regulation.
• Most chronic diseases have been linked to excessive or persistent inflammation.
Key Concepts

• Pharmacology focuses on the downstream consequences of inflammation.
• Functional medicine works upstream by addressing the underlying conditions that initiate or perpetuate inflammation.
• Inflammation can be dampened by avoiding exposure to triggers and by modulating inflammatory mediators with lifestyle and diet.
Inflammation is an essential immune response that enables survival during infection or injury and maintains tissue homeostasis under a variety of noxious conditions. Inflammation comes at the cost of a transient decline in tissue function, which can in turn contribute to the pathogenesis of diseases of altered homeostasis.
Classical Signs and Symptoms of Inflammation
(Cornelius Celsus, 30–40 AD)

• *Tumor* (swelling)
• *Rubor* (erythema)
  • *Calor* (heat)
  • *Dolor* (pain)
Classical Signs and Symptoms of Inflammation
(Galen of Pergamum, 129–199 AD)

- *Tumor* (swelling)
- *Rubor* (erythema)
  - *Calor* (heat)
  - *Dolor* (pain)
- *Functio Laesa* (loss of function)
INFLAMMATION

HEAT  REDNESS  SWELLING  PAIN  LOSS OF FUNCTION
Calor, Rubor, Dolor, Tumor, Loss of function
Physiology of Inflammation: A Process with a Purpose

- Leukocyte stimulation / maturation
  - adhesion
  - migration
  - activation
- Altered vascular rheology
  - Changes in blood flow
  - Coagulation—fibrinolysis cascades
Physiology of Inflammation: A Process with a Purpose

- Mucous production (mucosa)
- Smooth muscle contraction
- Nociceptor activation
- Psycho-neuroendocrine reflex
INJURY

PAIN

Release of arachidonic acid

Production of inflammatory substances (leukotrienes and prostaglandins)

Recruitment and stimulation of neutrophils

Activation of white blood cells

Macrophone

Neutrophil

Production of free radicals

NO^*  O_2^-

OH^*  O_2^-

Neutralization of free radicals by antioxidants (glutathione, vitamin E, etc.)

Depletion of antioxidant resources

Oxidative stress

O_2  H_2O  HNO_3
Physiology of Inflammation: A Process with a Purpose

• Increased production of
  – Free radicals (oxidative burst)
  – Inflammatory cytokines & chemokines
  – Acute-phase reactants
The Local Acute Inflammatory Response

VCAM1 – vascular cell adhesion protein 1
Physiology of Inflammation: A Process with a Purpose

- Liberation (degranulation) of
  - Inflammatory autacoids
  - Proteases
- Activation of complement cascade
- Mobilisation of cell adhesion molecules
The Acute Inflammatory Response.

- Rolling
  - L-selectin
  - Neutrophil

- Shedding of L-selectin
  - Sialyl-Lewis^X

- Adhesion
  - Integrin
  - E-selectin

- Diapedesis
  - Blood-vessel wall

- Activating substances released by bacteria and damaged tissues

- Phagocytosis and destruction of C3b-coated bacteria

- Lipopolysaccharides, interleukin-1, and tumor necrosis factor α

- C3a, C5a, chemokines, histamine, prostaglandins, and leukotrienes
Inflammatory Autacoids: Locally Acting Inflammatory Mediators

• Histamine: mast cells, EC cells, neurons, and most others
• Serotonin: enterochromaffin cells (90%), platelets, CNS
• Bradykinin: systemic circulation (HMW kininogen)
• Tachykinins (e.g., substance P): gut, sensory neurons, CNS
Inflammatory Autacoids: Locally Acting Inflammatory Mediators

- Eicosanoids (prostanoids, leukotrienes): leukocytes and most other cells
- Platelet-activating factor: mast cells and basophils, neutrophils, platelets, endothelium
- Angiotensin II: systemic circulation
- Nitric oxide: endothelium, leukocytes, CNS
- Endothelins
Inflammation & Mood: The Body-Mind Connection

• Autacoids (serotonin, histamine, substance P, nitric oxide, vasoactive intestinal peptide VIP) can act as neuromodulators & neurotransmitters

• Cytokine sickness (behaviour): Inflammatory cytokines implicated in wide range of neuropsychiatric disorders
Histamine

• Prototypical autacoid: vasoactive biogenic amine
• Derived from histidine
• Stored in mast cells & basophils
• High concentrations in body surfaces (gut & lung mucosa, skin); CNS
Histamine

• Release triggered by trauma, immunogens (bacteria (dysbiosis), food, venom, pollens, chemicals)
• Present in foods, esp. fermented (sake, wine, cheese, sausage, sauerkraut, fish)
• Implicated in scombroid reactions
Histamine Effects

• Immune mediated reactions:
  – Itching, sneezing, pain, swelling, increased capillary permeability, mucous production
  – Smooth muscle contraction; bronchoconstriction
  – Chemotaxis, cytokine release
Histamine Effects

- Gastric acid production
- Neurotransmitter
  - Stimulatory: wakefulness, anxiety
  - Suppressive: raises seizure threshold (antihistamines increase risk of seizure)
Excessive accumulation of histamine in the body leads to miscellaneous symptoms mediated by its bond to corresponding receptors (H1---H4). Increased concentration of histamine in blood can occur in healthy individuals after ingestion of foods with high contents of histamine, leading to histamine intoxication.
In individuals with histamine intolerance (HIT) ingestion of food with normal contents of histamine causes histamine-mediated symptoms. HIT is a pathological process, in which the enzymatic activity of histamine-degrading enzymes is decreased or inhibited and they are insufficient to inactivate histamine from food and to prevent its passage to blood-stream.
Quercetin is more effective than cromolyn in blocking human mast cell cytokine release and inhibits contact dermatitis and photosensitivity in humans.

Abstract

Mast cells are important effector cells in allergic reactions [3-6] by secreting histamine, leukotrienes (LTs), prostaglandin D2 (PGD2), proteolytic enzymes, and several multifunctional cytokines, such as interleukin-6 (IL-6), IL-8, IL-15, tumor necrosis factor (TNF), and vascular endothelial growth factor (VEGF) [7-9]. These mediators contribute to the late-phase reactions and to inflammation through the recruitment and activation of immune cells [16,11]. In addition to IgE and antigen, anaphylatoxins, cytokines, hormones, and neuropetptides, such as substance P (SP), can trigger mast cell secretion [12] of several mediators often selectively [13]. More well as autoimmunity and inflammation [14], especially in the skin [17,18]. Mast cells were also shown to be involved in contact dermatitis in mice [19,20].

Mast cells play an essential role in contact hypersensitivity through a complex interaction with different kinds of immune cells, including antigen-presenting cells, T, B, NK lymphocytes, keratinocytes, endothelialium, and platelets [21]. In allergic contact dermatitis, mast cells regulate the inflammatory reactions by releasing mediators like histamine, TNF-α and IL-8, leading to local vascular activation and subsequent immune cell recruitment [22]. Contact dermatitis and photosensitivity are difficult to treat.

- Flavonol: yellowish antioxidant pigment found in tea, onions, berries, apple skins, berries, tomatoes
- Aglycone derived from rutin
- Potent mast cell stabiliser: inhibits release of histamine and other inflammatory mediators (more effective than cromolyn)
- Typical dose: 2000-3000 mg daily
Bradykinin

- Vasoactive autacoid peptide
- Circulates in inactive form (HMW Kininogen)
- Liberation triggered by tissue damage, exercise
- Increases histamine release
- Powerful algesic agent—stimulates nociceptors
- Causes redness, heat, swelling, bronchospasm, edema (vasodilation, capillary permeability)
- Primary mediator of hereditary angioedema
Bradykinin

- Tonic production maintains systemic BP
  - Activates nitric oxide, prostacyclin (vasodilation)
  - Levels increased by ACE inhibitors (snake venom)
  - This also causes dry cough (5-10% of patients)
- Increases insulin sensitivity
- May have renoprotective effects
- Overproduction inhibited by bromelain (pineapple enzyme), aloe, polyphenols
Sardines pack nutrition, flavor
Eicosanoids: Intercellular Messengers

- Signaling molecules produced by oxidation of 20-carbon long-chain PUFAs: omega-3 (from fish) and omega-6 (meat, plants)
- Short-lived (half-life = seconds to minutes): synthesised as needed, then inactivated
- EFAs stored in membrane-bound phospholipids: *relative concentrations heavily influenced by diet*
Eicosanoids: Intercellular Messengers

- Location and number of double bonds in precursor LCFA determines whether:
  - **Anti-inflammatory**
    - (eicosopentanoic acid) EPA = omega-3
    - (docosahexaenoic acid) DHA = omega-3
    - (dihomo-γ-linolenic acid) DGLA = omega-6
  - **Pro-inflammatory**
    - (oxidised or excess)
    - (arachidonic acid) AA = omega-6
Eicosanoids: Physiological Effects

- Modulate all aspects of inflammatory reactions: rubor, tumor, calor, and dolor
- Modulation of smooth muscle tone (vascular, uterine, bronchial, GI)
- Lipid metabolites are synthesised de novo by at least 50 unique enzymes
- Modulation of vascular rheology
- Triglyceride lowering via prostanoid binding to PPAR
- Influence nerve transmission and mood
- Influence hormone secretion
Eicosanoids - Classic Families

- Prostanoids: generated by Cyclooxygenase (COX)
  - Prostaglandins
  - Prostacyclins
  - Thromboxanes
- Leukotrienes: generated by Lipoxygenase (LOX)
- Specific production determined by predominant enzymes in cell type
  - Platelets: Thromboxane A2 (TXA2) (COX1)
  - Endothelium: prostacyclin (prostacyclin synthase)
Omega 3 Family
Cold water fish, flax oil

- Flax, walnut, canola, soy, chia, hemp

- Alpha-linolenic acid (ALA) 18:3n-3

- Stearidonic acid 18:4n-3

- Eicosatetraenoic acid (EPA) 20:4n-3

- Eicosapentaenoic acid (EPA) 20:5n-3

- Docosapentaenoic acid (DHA) 22:5n-3

- Docosahexaenoic acid (DHA) 22:6n-3

Omega 6 Family
vegetable oils, grains

- Linoleic acid (LA) 18:2n-6

- Gamma-linolenic acid (GLA) 18:3n-6

- Dihomo-gamma-linolenic acid 20:3n-6

- Arachidonic acid (AA) 20:4n-6

- Adrenic acid 22:4n-6

- Docosapentaenoic acid 22:5n-6

- Delta-5-desaturase (up-regulated by insulin)

- Delta-6-elongase

- Delta-6-desaturase (Inhibited by age, alcohol)

- Lipoxins (anti-inflammatory)

- More inflammatory eicosanoids

- Less inflammatory eicosanoids

- Inhibition

- Retro conversion

- Beta Oxidation

- Cold water fish, wild game, enriched eggs

- Retro conversion

- Cold water fish, wild game, enriched eggs, algae

- Less inflammatory eicosanoids

- Borage, black currant seed, evening primrose

- Sunflower, safflower, peanut, most vegetable oils

- Animal fat, dairy, shellfish
Eicosanoids - Non-Classic

- Antiinflammatory (resolution mediators)
  - Lipoxins: derived from AA
  - Resolvins: derived from EPA and DHA: (production enhanced by aspirin)
  - Protectins: derived from DHA
  - Epoxyeicosatrienoic acids = EETs: derived from EPA & AA via CYP450 epoxygenase

- Isoprostanes (nonenzymatic, peroxidation of EFAs): marker of oxidative stress

- Endocannabinoids (e.g. anandamide): derived from AA: neuropsychiatric effects
Cyclooxygenase 1

- Constitutive “house keeper”
- Present in most tissues: GI mucosa, kidneys, etc.
- The only COX in platelets: producing TXA2
- Can be induced by cytokines
Cyclooxygenase 2

• Levels very low under normal conditions
• Inducible inflammatory and anti-inflammatory
• Local expression induced by presence of
  – free radicals
  – elevated glucose levels (via increased superoxide)
  – cytokines
  – hormones and growth factors
  – hypoxia
  – essential for production of pro-resolution lipid mediators
AA/EPA Ratio
Rizzo et al. Lipids in Health and Disease 2010, 9:7

• Measured in plasma or whole blood
• Marker for eicosanoid balance - cellular inflammation
• Ideal: < 3
• Moderate inflammation: >5
• Severe inflammation: >10
Some Conditions Amenable to Treatment with EFAs

• Allergy / asthma / eczema
• Autoimmune disease
  – rheumatoid arthritis
  – systemic lupus erythematosus
  – psoriasis
• Cardiovascular disease
  – hypertriglyceridemia
  – hypertension
Some Conditions Amenable to Treatment with EFAs

- Chronic kidney disease
- Neurodegenerative disease
  - Alzheimer’s
- Mood disorders
  - depression
  - schizophrenia
- Dysmenorrhea
- Cancer cachexia
While the elderly well and well-nourished may be adequately protected and thus able to enjoy the benefits of Ω3 highly unsaturated fatty acids supplements, the pre-existence of inflammatory pathology and related oxidative stress, which is more prevalent in older subjects and in those who eat a poor diet, may be a contraindication to supplementation with purified Ω3 product.
Cytokines: Soluble Intercellular Messengers

• Interferons
  – INF-α and INF-γ: antimicrobial

• Tumor necrosis factors
  – TNF-α: endogenous pyrogen; stimulates (corticotropin-releasing factor) CRF → (adrenocorticotropic hormone) ACTH → (glucocorticoid) GC (activating negative feedback loop)
  – Increased in obesity, induces insulin resistance

• Transforming growth factor beta
  – Controls cellular proliferation, differentiation
  – T cell regulator
  – Both pro- and anti-inflammatory effects
Cytokines: Soluble Intercellular Messengers

• Interleukins
  – At least 17 identified
  – IL-1 is endogenous pyrogen; acts synergistically with TNF-α as the two main inducers of the acute-phase response
  – IL-6 augments effects of IL-1 and TNF-α; ↑ plasma levels are a strong marker of increased mortality in unstable CAD
**Figure 30-2.** The involvement of cytokines in response to injury response. (From Espat NJ, Moldawer LL, and Copeland EM: Cytokines, inflammation and nutrition. Support Line XVI(1):2, 1994. Reprinted by permission.)
What turns the cell on to make cytokines?

Answer = Signal transduction pathways
INFLAMMATORY SIGNAL TRANSDUCTION

MODIFIED FROM MAX PLANCK INSTITUTE

Signal \((\text{TNF}_\alpha, \text{AGE}, \text{PAMP}, \text{DAMP})\)

Receptor \((\text{TLR}, \text{TNFR}, \text{RAGE})\)

Cell

Kinasess

Transcription Factors \((\text{NF-kB}, \text{AP-1})\)

Nucleus

Gene Expression

DNA

Biological Answer
\((\text{Pro-inflammatory cytokines})\)
Nuclear Factor Kappa B: A Proinflammatory Transcription Factor

- Binds to DNA, activating numerous inflammatory genes (e.g. cytokines, COX2)
- Activated by:
  - infection (PAMPs, e.g. LPS)
  - tissue damage (DAMPs) - Sterile inflammation
  - oxidative stress (oxidised LDL)
  - advanced glycosylation end products (AGEs),
  - trans fats
  - synthetic toxins; heavy metals
  - inflammatory cytokines (IFN-α, TNF-α)
Chronic NF-κB Upregulation

- Chronic inflammation
- Persistent oxidative stress (cigarette smoking)
- Excess visceral fat (abdominal obesity)
- Diabetes
- Cardiovascular disease
Chronic NF-κB Upregulation

• Chronic infection
• Cancer
• Autoimmune disease
• Depression
• Aging
NF-kB Activation: Agents That Inhibit or Modulate

- Glucocorticoids
- Calorie restriction
- Fish oil (EPA, DHA)
- Alpha lipoic Acid
- N-Acetyl Cysteine (NAC) - GSH
- Antioxidants: vitamin C & E
- Tumeric (curcumin) and other plant compounds - polyphenols
Research for more than two decades has revealed the pleiotropic nature of the biological effects of this molecule. More than 7000 published articles have shed light on the various aspects of curcumin including its antioxidant, hypoglycaemic, anti-inflammatory and anti-cancer activities. Apart from these well-known activities, this natural polyphenolic compound also exerts its beneficial effects by modulating different signalling molecules including transcription factors, chemokines, cytokines, tumour suppressor genes, adhesion molecules, microRNAs, etc.
NF-kB Activation: Agents That Inhibit or Modulate

- Spice-derived phytochemicals, “reason for seasoning”
- Flavonoids & related compounds: quercetin, grape seed polyphenols, soy isoflavones, resveratrol, curcuminoids, green tea catechins
- Pomegranate juice (ellagitannins)
- Anatabine (alkaloid from Solanacea)
Throughput in the Innate and Acquired Immune Systems: A Brief Overview
Immune response

**Natural / Innate**
- Cells / Systems involved: neutrophils, monocytes / macrophages, natural killer cells, complement system
- Processes: phagocytosis, antigen presentation, oxidative burst, cytokine production

**Specific / Adaptive**
- Cell mediated immunity
- Humoral immunity

- B-cells
- T-cells (Th0)
  - Th1
  - Th2
  - Cytokine production, macrophage activation, lysis of infected cells

Antibody production
Innate Immunity

- Antigen-presenting cells (APCs) = Sentinels
  - Dendritic cells
  - Monocytes, macrophages
  - Melanocytes
- Activated by:
  - Trauma (mechanical, chemical, heat, UV, etc.)
  - Exposure to pathogenic structures (pathogen-associated molecular patterns)
  - Exposure to DAMPs
Innate Immunity

• Signal transduction leads to activation of transcription factors: NF-κB, AP-1, etc.
• Upregulated transcription factors increase inflammatory cytokine production.
• Consequence is release of inflammatory mediators, as well as maturation and recruitment of lymphocytes.
Pathogen-Associated Molecular Patterns

- Conserved motifs are abundant in microorganisms.
  - Fungi: zymosan, peptidoglycan, mannans, glucans
  - Bacteria: endotoxin (LPS), flagellin, teichoic acid
  - Viruses: CpG DNA, double-stranded RNA

- Since pathogen-associated molecular patterns (PAMPs) are *absent* from vertebrates, they signal presence of *foreign invaders*. 
Candida albicans
Pathogen-Associated Molecular Patterns

• Structures similar to PAMPs are also found in probiotics, plants and “medicinal” mushrooms (beta-glucans, arabinogalactans, aloe vera mucopolysaccharides, etc.).

• May help explain immunomodulating effects of these substances.
Toll-like (PAMP) Receptors

- Mammalian homologues of *Drosophila* toll receptors
- Frequently work in pairs
- Present on cell membranes of dendritic cells, mast cells, macrophages
- Play a central and critical role in *innate response against bacteria, viruses, and fungi*
- Activate maturation of dendritic cells
Innate immunity → Acquired immunity
The Inflammatory Process: A Physiologic Algorithm

Inducers (Molecular Triggers)

Sensors (Sentinel Cells)

Endogenous Mediators

Inflammatory Response ("...itis")

Antecedents
Molecular Inflammatory Triggers

– Trauma (mechanical, chemical, thermal, electromagnetic)
– Cellular debris (nucleic acids, uric acid, etc.)
– Pathogens (PAMPs), Sterile Inflammation DAMPs
– Advanced glycosylation end products
– Toxins (organic chemicals, heavy metals)
– Free radicals (oxidized lipids, glucose, proteins)
Clinical Pearl:

The mucosal surfaces are the largest source of exposure to potential inflammatory triggers. A healthy mucosal milieu conveys messages of “safety” to the entire immune system.
The Systemic Acute-phase Response

Hypothalamus

(prostaglandins → Fever)
(via pituitary)

ACTH

Adrenal cortex

(IL-1, TNF-α, IL-6)

Corticosteroids

(IL-1, TNF-α, IL-6, LIF, OSM)

Liver

Acute-phase proteins:
- C-reactive protein (CRP)
- Serum amyloid A (SAA)
- Fibrinogen
- Mannose-binding protein
- Complement components

Leukocytosis

(↑ white blood cells)

Bone marrow

(↑ CSF by stromal cells and macrophages)
“C-reactive protein is the classic ‘acute-phase reactant,’ the plasma levels of which can increase as much as 10,000-fold in response to tissue injury and infection.”

“The study [by Visser et al.] convincingly demonstrates that plasma CRP levels are substantially higher in obese and overweight people than in leaner people.”
Type 2 diabetes mellitus (T2DM) is a complex metabolic disease characterized by hyperglycemia (high blood sugar) resulting from insulin resistance and β-cell dysfunction. The involvement of inflammatory processes, such as immune cell infiltration, and chronic inflammation in the pathogenesis of diabetes is less well understood in T2DM than in T1DM.


Two immunological factors commonly contribute to the pathogenesis of diabetes: the activation of **inflammasomes** and the release of **proinflammatory cytokines** in response to damage-associated molecular patterns (DAMPs).
Elevated levels of CRP and IL-6 predict the development of type 2 DM. These data support a possible role for inflammation in diabetogenesis.
Inflammation: Acute vs. Chronic

• Acute:
  – Rejection or sequestration of stressor
  – Usually localised (anaphylaxis excepted)
  – Usually adaptive (allergy is exception)
Inflammation: Acute vs. Chronic

- Chronic: persistent acute-phase response
  - Maladaptive (more detrimental than beneficial)
  - Self-perpetuating/recursive
  - Disrupts homeostasis
  - Alters cellular physiology
  - Destruction of tissue
Chronic Inflammatory Disorders:

- Atopic syndrome/eczema
- Rheumatologic: autoimmune disorders
- Gastroenterologic: IBD, gluten intolerance
- Cardiovascular disease: atherosclerosis
- Neurodegenerative disease: PD, AD, MS
- Cancer
- Endocrinologic: diabetes
- Psychiatric disorders: schizophrenia, depressions
Chronic Inflammation: How and Why?

- Genetic susceptibility to triggers
- Overabundance of inflammatory precursors (high AA or glycating diet)
- Lack of antioxidant phytochemicals
- Insufficient dampening or excessive upregulation by endogenous mediators
- Malfunctioning “off switch”
  - Inadequate priming of T regulatory cells
  - imbalanced Th1/Th2 lymphocytes
  - Gene encoded errors in Inflammasomes (DAMPs too high)
Thoughts to Ponder

• Did natural selection favor those with a vigorous acute inflammatory response, which became problematic only when life spans started increasing or when excessive hygiene deprived us of immunological education?

• Could this help explain the current epidemic of chronic inflammatory diseases?
“Is it possible that the adaptive pattern of an earlier time has resulted in a maladaptive response in our modern environment dominated by increasingly sedentary habits, an abundance of high-carbohydrate foods, and a reduced risk of mortality due to common infections?”
The pharmacological approach to inflammation...
Synthetic Modulation of Arachidonic Acid Cascade

Cell Membrane

- Cortisone
- Phospholipase A2

Arachidonic Acid

- Indomethacin
- Aspirin
- Ibuprofen
- Acetaminophen (weak)
- Sulfasalazine (topically)
- 2 Series Prostaglandins
- Thromboxane A2
- Leukotrienes SRS-A
- Sulfasalazine (topically)
- Colchicine

Cyclooxygenase

Lipoxygenase
Pharmacologic Control of Inflammation

• Steroids: block NF-κB, PLA2
• NSAIDs: inhibit COX
• Leukotriene inhibitors: inhibit LOX
• Disease-modifying antirheumatic drugs (DMARDs): inhibit
  – Extracellular pathways (cell surface receptors)
  – Intracellular signaling pathways (kinases)
  – Genomic expression (cytotoxic agents)
A Functional Medicine Approach to Inflammation…
The Inflammatory Process (A Model)

Environment
- Allergens, Toxins, Stress, Infection, Trauma, Lowered oxygen, Drugs, Alcohol

Genes
- Polymorphisms which render individuals with different susceptibilities

Diet
- Macronutrients, micronutrients, accessory nutrients, phytonutrients

Function
- Shifts physiologic state into "alarm" reaction characterized by inflammatory process

Symptoms of Inflammation
- -osis becomes -itis with increasing severity
Inflammatory Disorders:

- Environmental modification (houseplants, air ionizers, water filters)
- Oligoantigenic diets/medical foods
- Detoxification protocols
- Correction of nutritional deficiencies and imbalances (minerals, EFAs)
- Botanical anti-inflammatory agents and antioxidants

Botanical Modulation of Arachidonic Acid Cascade

**Cell Membrane**
- **Glycyrrhiza glabra**
- **Quercetin**
- **Phospholipase A2**
- Potentiates cortisol: **Glycyrrhiza glabra**
- **Curcuma longa**

**Arachidonic Acid (AA)**
- **cyclooxygenase**
- **lipoxygenase**

**Zingiber officinale**
- **Curcuma longa**
- **Quercetin** (weak)
- **Ananas Comosus**?
- **Salix nigra**
- **Gaultheria procumbens**

**Prostaglandins Series 2**

**Thromboxane A2**

**Leukotrienes**
- **Quercetin**
- **Allium cepa**
- **Allium sativum**
- **Curcuma longa**
- **Boswellia serrata** (specific for 5-lipoxygenase)

**Other Anti-Inflammatory Botanicals**
- **Ananas Comosus** — fibrinolysis, inhibits bradykinin, increases Series I Prostaglandins
- **Tanacetum parthenium** — inhibits platelet aggregation
- **Scutellaria baicalensis** — stabilizes mast cell membranes
- **Quercetin** — stabilizes mast cell membranes
- **Matricaria chamomilla** — unknown
- **Capsicum Minimum** — depletes substance P
- **Ammi Visnaga** — stabilizes mast cell membranes
Natural Agents for Modulating Inflammation

- **EFAs**
  - EPA/DHA: 1000-4000 mg/d
  - GLA: 250-1200 mg/d (should be taken with at least 500 mg EPA to block AA production)

- **Niacinamide**: 2000-5000 mg/d

- **Alpha lipoic acid**: 300-1800 mg/d

- **N-acetylcysteine**: 500-3000 mg/d

- **Probiotics**: 10-100 billion CFUs qd – Strain specific Appears to confer additional benefits
Phytochemical Anti-inflammatories: Typical Doses

• Salicin (willow bark concentrate): 240-960 mg daily
• Quercitin: 1500-3000 mg/d
• Boswellia: 400-1200 mg/d
• Curcumin: 500-1500 mg/d
• Licorice root: 500-2000 mg/d
• Grape seed extract: 150-300 mg/d
Phytochemical Anti-inflammatory: Typical Doses

- Scute (Chinese skullcap): 1-2 g/d
- Ginger root: 2-4 g/d
- Milk thistle: 150-450 mg/d
- Devil’s claw root (*Harpagophytum procumbens*): 500-2000 mg/d
- Ginkgo biloba: 80-320 mg/d
Summary Points

- Inflammation is the body’s normal physiologic attempt to defend against foreign invasions and repair it from injury.
- Injury can result from trauma, infection, toxins, or foods (poor diet).
- Most chronic diseases have been linked to excessive or persistent inflammation.
- Chronic inflammation occurs when the injury is ongoing or a predisposed immune system fails at counter-regulation.
- The role of the microbiota, in numerous sites represents an alternate mechanism for intervention.
Changes in microbial composition are implicated in the increasing propensity for a broad range of inflammatory diseases, such as allergic disease, asthma, inflammatory bowel disease (IBD), obesity, and associated noncommunicable diseases (NCDs). There are also suggestive implications for neurodevelopment and mental health.
These diverse multisystem influences have sparked interest in strategies that might favorably modulate the gut microbiota to reduce the risk of many NCDs. For example, specific prebiotics promote favorable intestinal colonization, and their fermented products have anti-inflammatory properties. Specific probiotics also have immunomodulatory and metabolic effects.
Summary Points

• Pharmacology focuses on the downstream consequences of inflammation.
• Functional medicine works upstream by addressing the underlying conditions that initiate or perpetuate inflammation.
• Inflammation can be dampened by avoiding exposure to triggers and by modulating inflammatory mediators with lifestyle, diet, and nutraceuticals targeted at specific pathways as well as managing overall increased nutrient intake needs.
End
Thank you