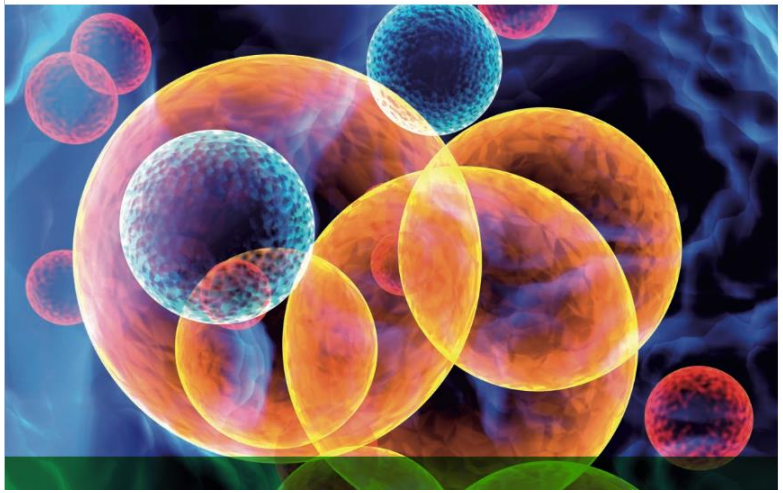
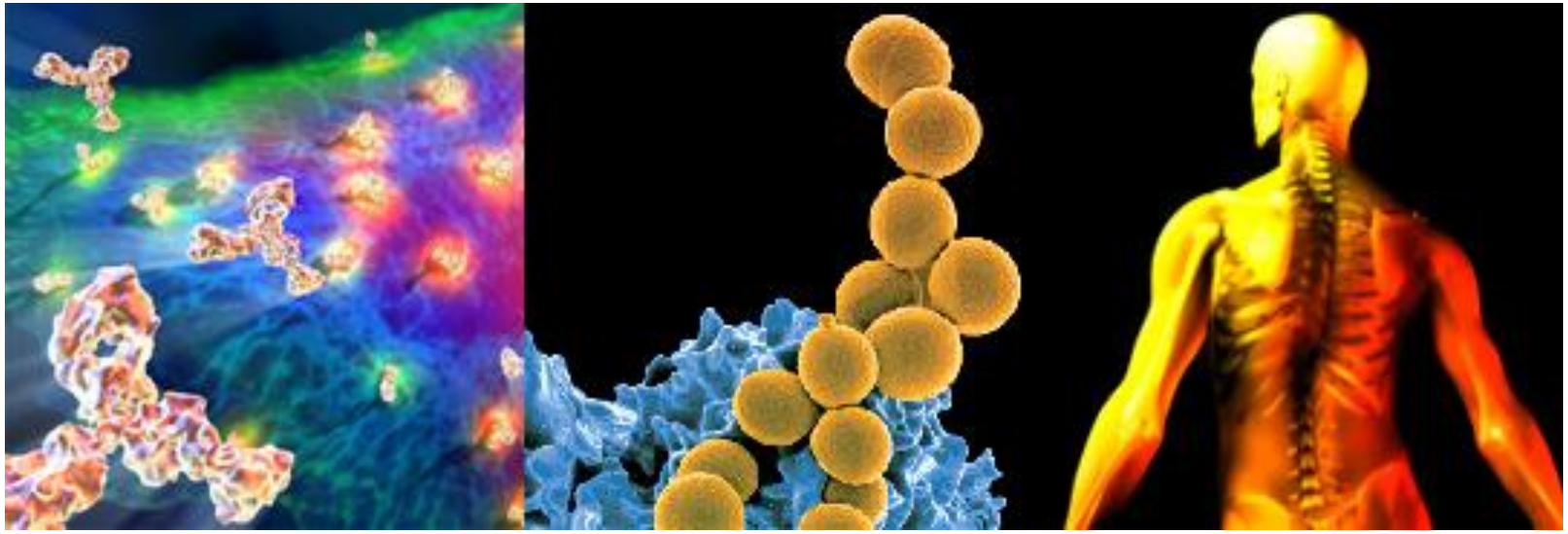
ICoMI
1st International Congress of Micro-Immunotherapy
18-20 May 2017, Mallorca, Spain



Key role of functional and nutritional medicine in the management of chronic inflammatory diseases

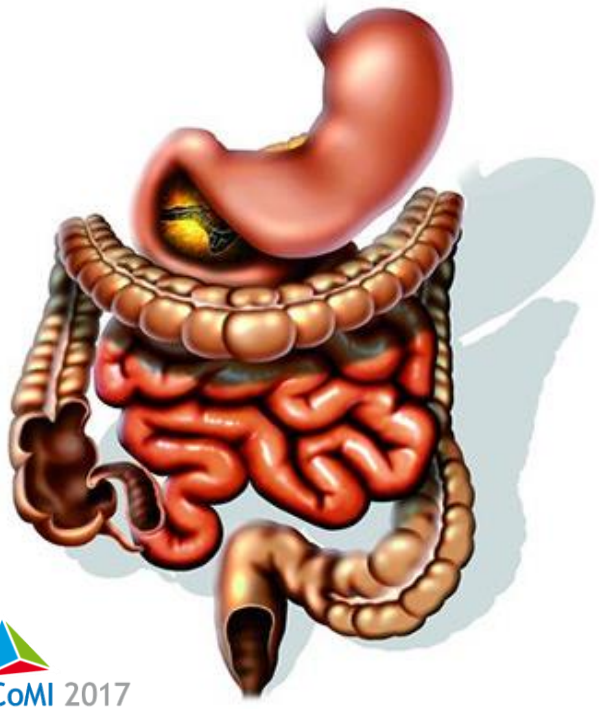
Vincent Castronovo, M.D. Ph.D.
University of Liège, Belgium

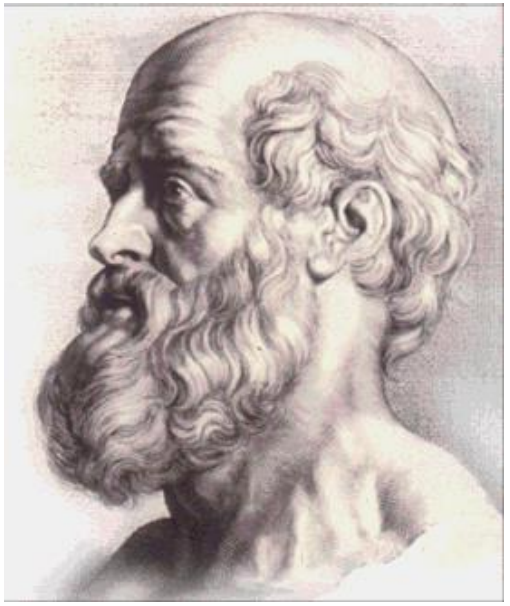


In 400 BC, Hippocrate wrote…

*" Let food be **medicine** and **medicine** be food "*

"All disease begins in the gut"

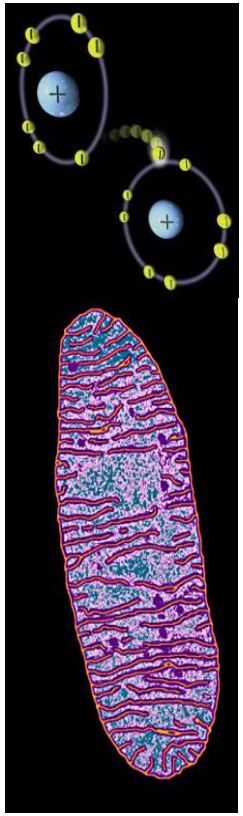




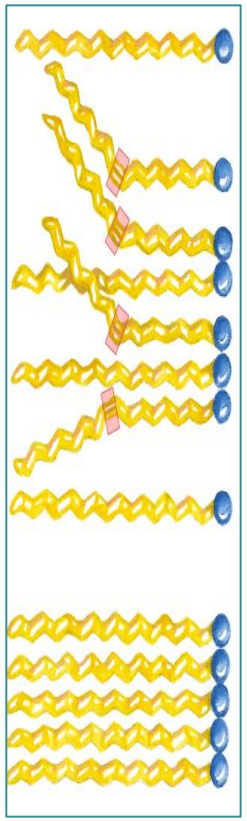
Hippocrates (460-370 BC)

The Seven 7 Pillars of Functionnal and Nutritional Medicine

Digestive system
Microbiota

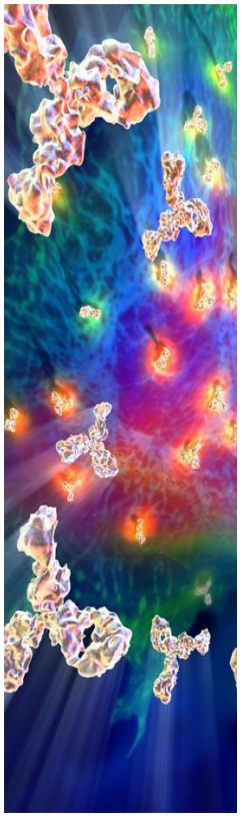


Energy
Mitochondria
Oxidative Stress



Fatty acids

Liver
Detoxication

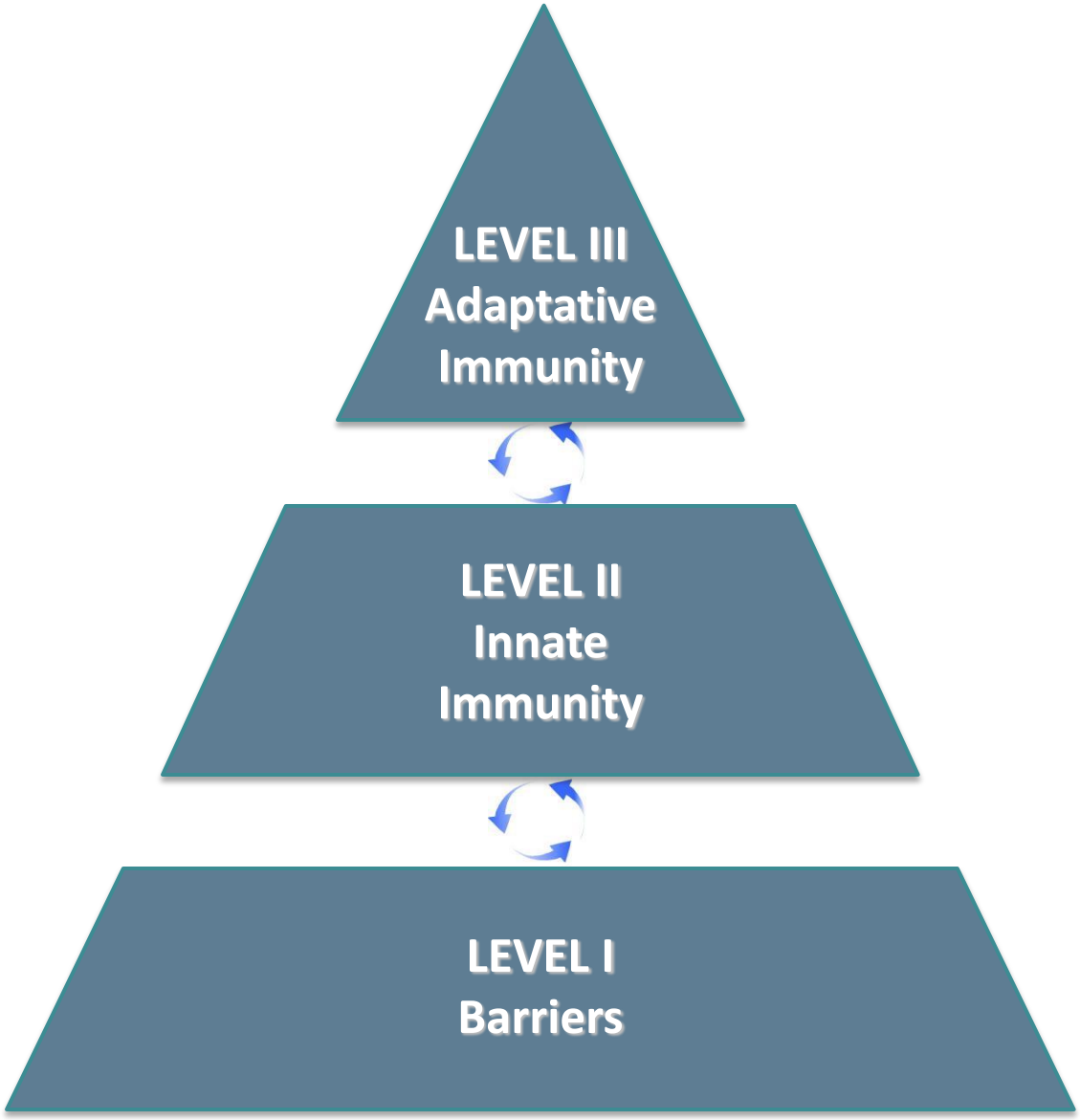


Immunity
Inflammation

Insuline
Glucose

Metals
Minerals
Vitamine

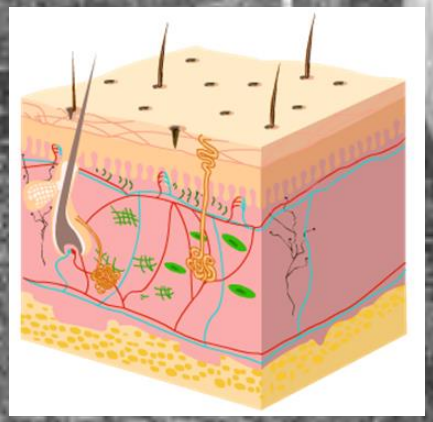
Defense


LEVEL III
Adaptative
Immunity
LEVEL II
Innate
Immunity
LEVEL I
Barriers

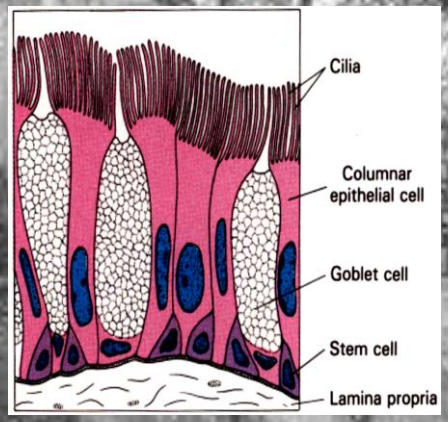
First Lines of Defenses

BARRIERS

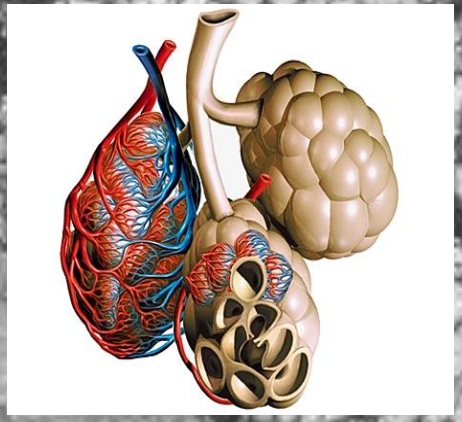
2 m^2



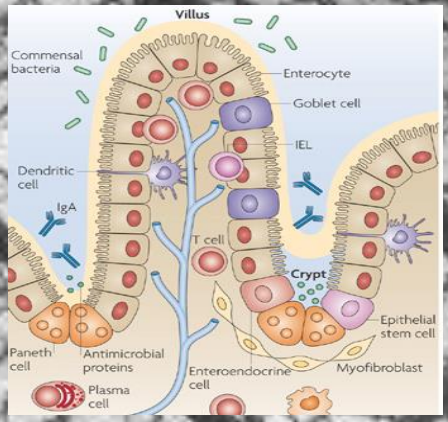
2 m^2



200 m^2



1000 m^2

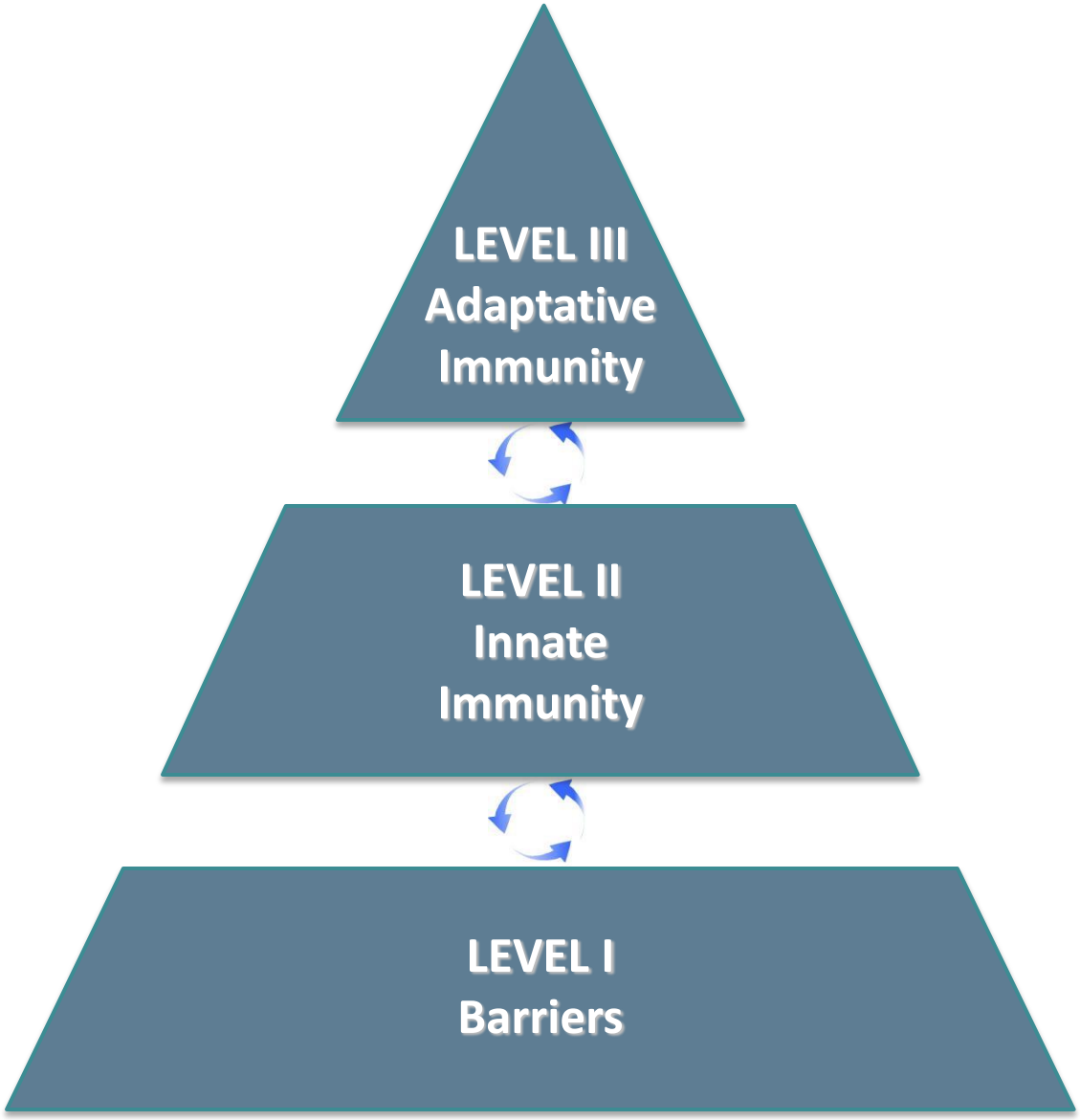


SECOND LINES OF DEFENSE

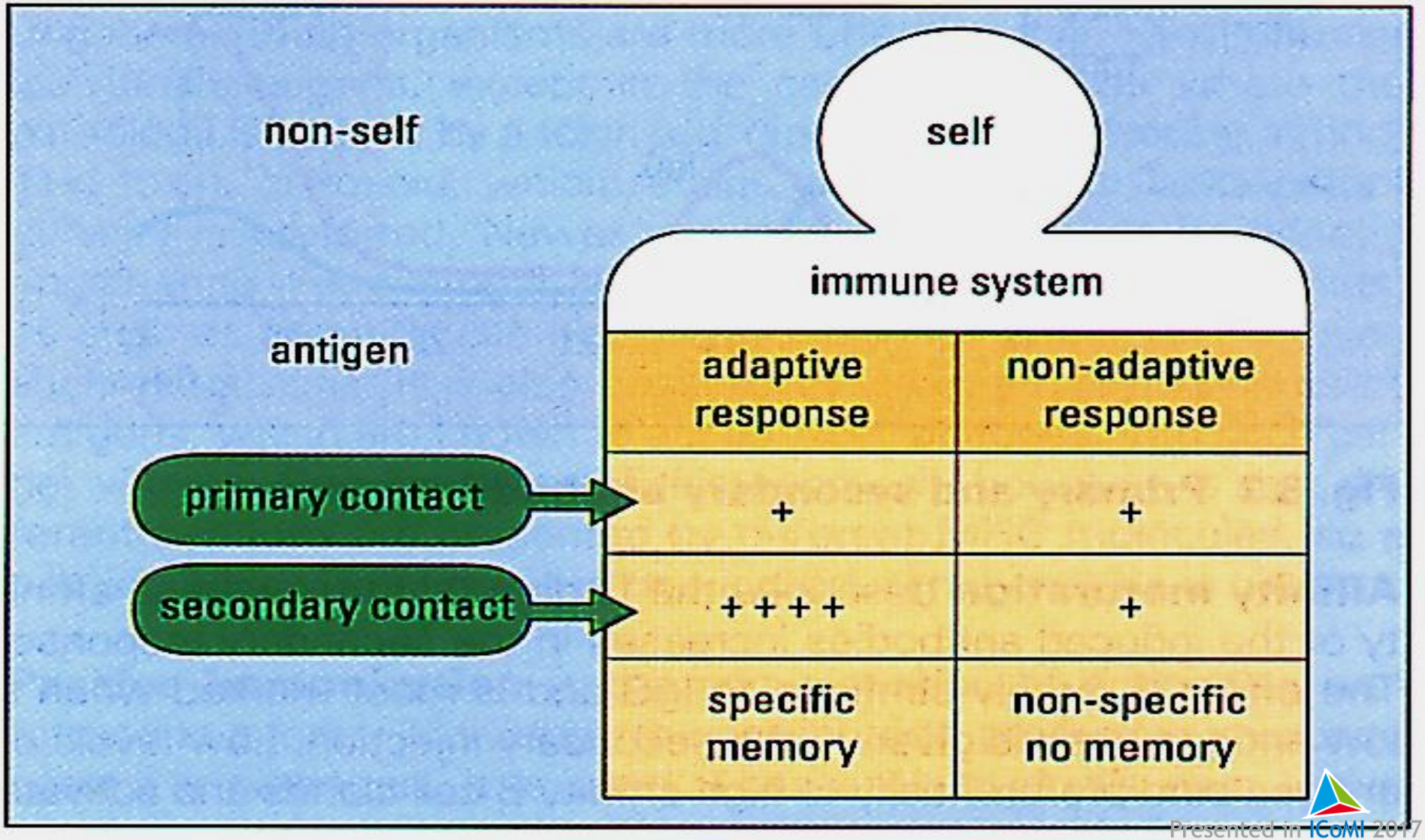
The ennemmy has enter our organism:

declaration of war

Defense

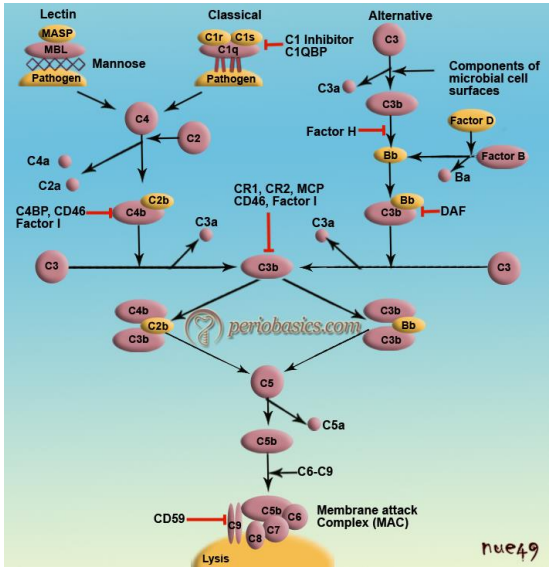

LEVEL III
Adaptative
Immunity
LEVEL II
Innate
Immunity
LEVEL I
Barriers

Immune system

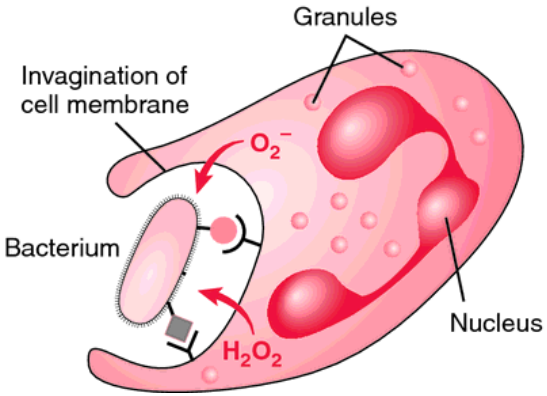


Both Innate and adaptative Immune systems use the same weapons

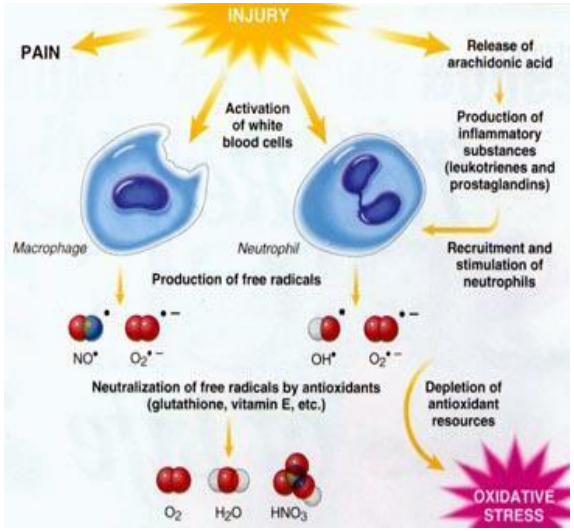
Complement



Phagocytosis



Oxidative Stress



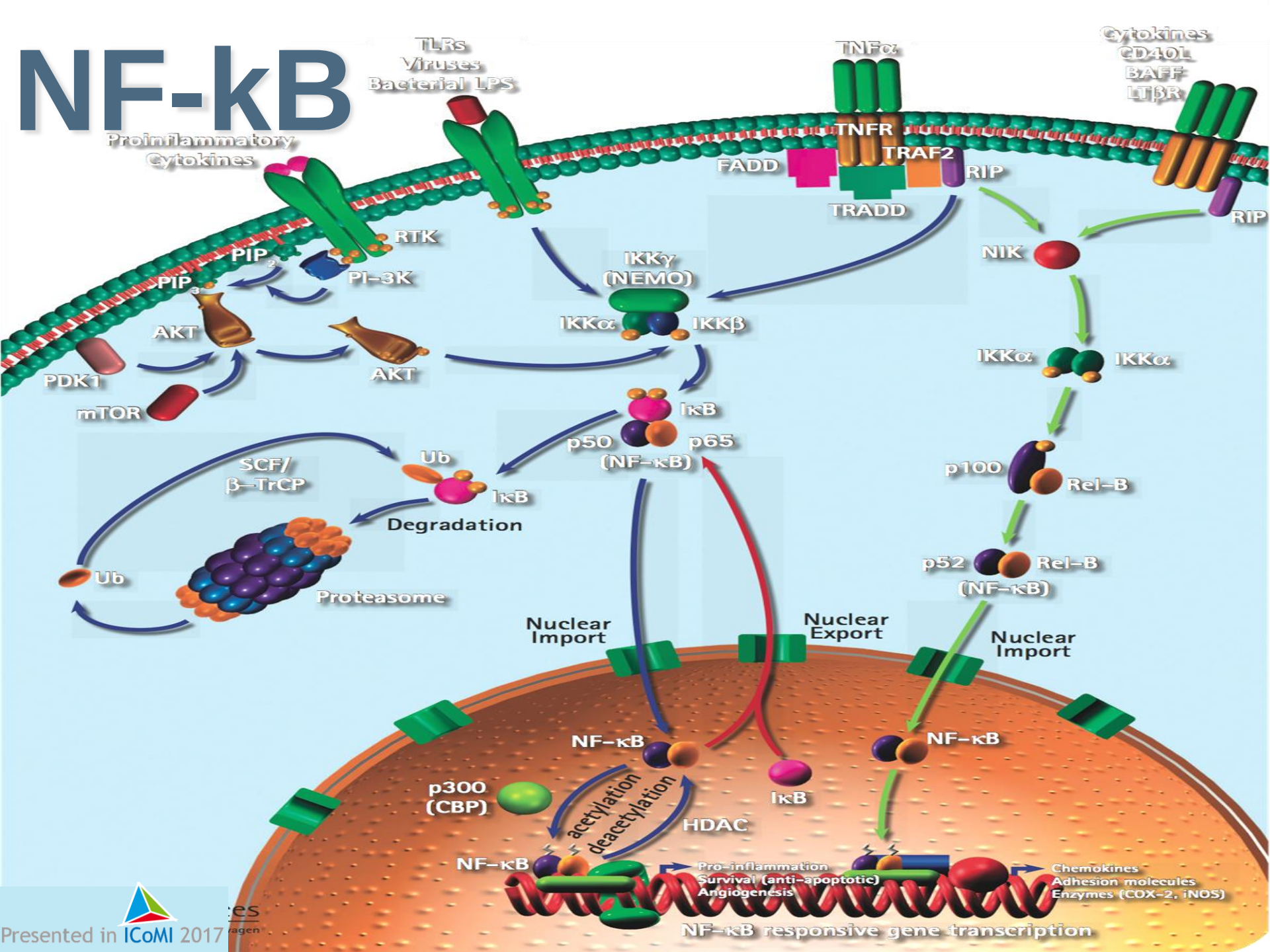
NF-kB

The master of war

NFKB

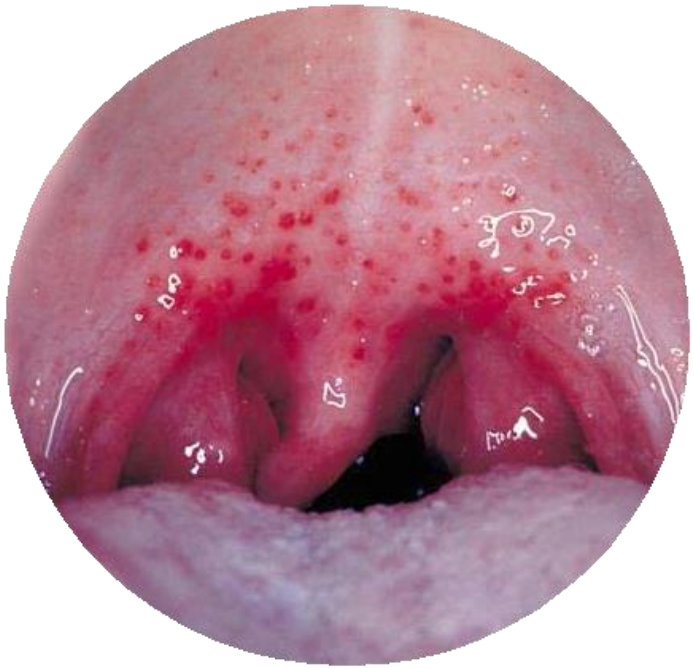
IKB

NF-kB



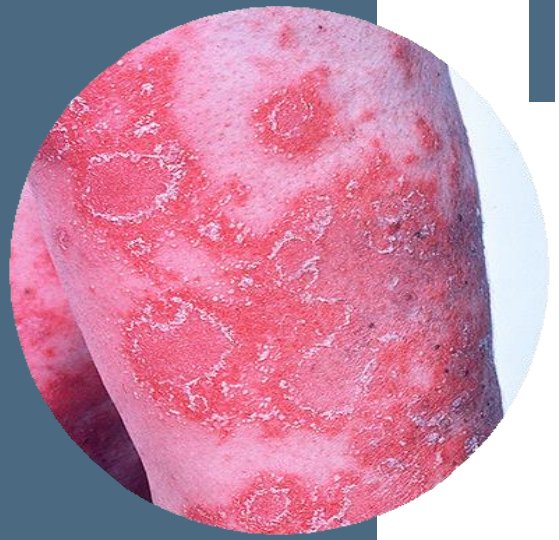
Inflammation *is the battle field where the molecular and cellular forces of our defense systems fight the enemies.*

INFLAMMATION

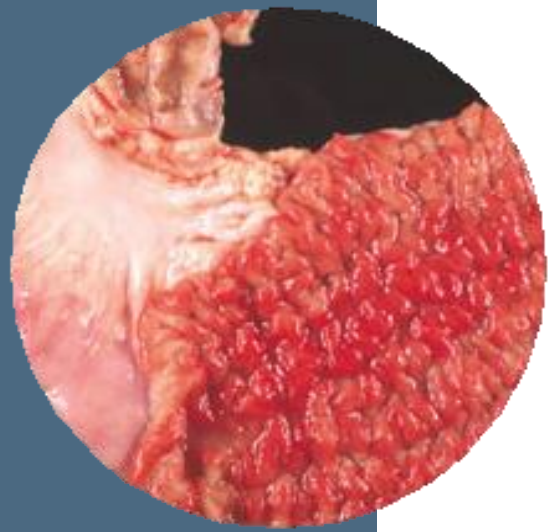


DEFENSE

INFLAMMATION



OFFENSE



Allergies
Auto-immunes Diseases

Functional and nutritional medicine management of chronic inflammatory diseases: A strategy in four points

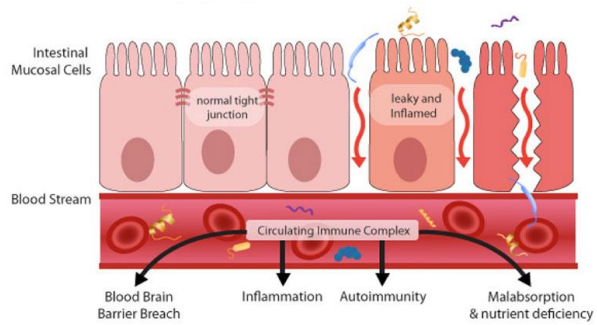
1. Restore Barriers and Microbiota

Clin Rev Allergy Immunol. 2012 Feb;42(1):71-8. doi: 10.1007/s12016-011-8291-x.

Leaky gut and autoimmune diseases.

Fasano A[1].

Author information



Abstract

Autoimmune diseases are characterized by tissue damage and loss of function due to an immune response that is directed against specific organs. This review is focused on the role of impaired intestinal barrier function on autoimmune pathogenesis. Together with the gut-associated lymphoid tissue and the neuroendocrine network, the intestinal epithelial barrier, with its intercellular tight junctions, controls the equilibrium between tolerance and immunity to non-self antigens. Zonulin is the only physiologic modulator of intercellular tight junctions described so far that is involved in trafficking of macromolecules and, therefore, in tolerance/immune response balance. When the zonulin pathway is deregulated in genetically susceptible individuals, autoimmune disorders can occur. This new paradigm subverts traditional theories underlying the development of these diseases and suggests that these processes can be arrested if the interplay between genes and environmental triggers is prevented by re-establishing the zonulin-dependent intestinal barrier function. Both animal models and recent clinical evidence support this new paradigm and provide the rationale for innovative approaches to prevent and treat autoimmune diseases.

Front Immunol. 2017 Mar 13;8:255. doi: 10.3389/fimmu.2017.00255. eCollection 2017.

Microbiota, Immune Subversion, and Chronic Inflammation.

Kramer CD[1], Genco CA[1].

Author information

Abstract

Several host-adapted pathogens and commensals have evolved mechanisms to evade the host innate immune system inducing a state of low-grade inflammation. Epidemiological studies have also documented the association of a subset of these microorganisms with chronic inflammatory disorders. In this review, we summarize recent studies demonstrating the role of the microbiota in chronic inflammatory diseases and discuss how specific microorganisms subvert or inhibit protective signaling normally induced by toll-like receptors (TLRs). We highlight our work on the oral pathogen *Porphyromonas gingivalis* and discuss the role of microbial modulation of lipid A structures in evasion of TLR4 signaling and resulting systemic immunopathology associated with atherosclerosis. *P. gingivalis* intrinsically expresses underacylated lipid A moieties and can modify the phosphorylation of lipid A, leading to altered TLR4 signaling. Using *P. gingivalis* mutant strains expressing distinct lipid A moieties, we demonstrated that expression of antagonist lipid A was associated with *P. gingivalis*-mediated systemic inflammation and immunopathology, whereas strains expressing agonist lipid A exhibited modest systemic inflammation. Likewise, mice deficient in TLR4 were more susceptible to vascular inflammation after oral infection with *P. gingivalis* wild-type strain compared to mice possessing functional TLR4. Collectively, our studies support a role for *P. gingivalis*-mediated dysregulation of innate and adaptive responses resulting in immunopathology and systemic inflammation. We propose that anti-TLR4 interventions must be designed with caution, given the balance between the protective and destructive roles of TLR signaling in response to microbiota and associated immunopathologies.

Anti-inflammatory effects of bifidobacteria by inhibition of LPS-induced NF-kappaB activation.

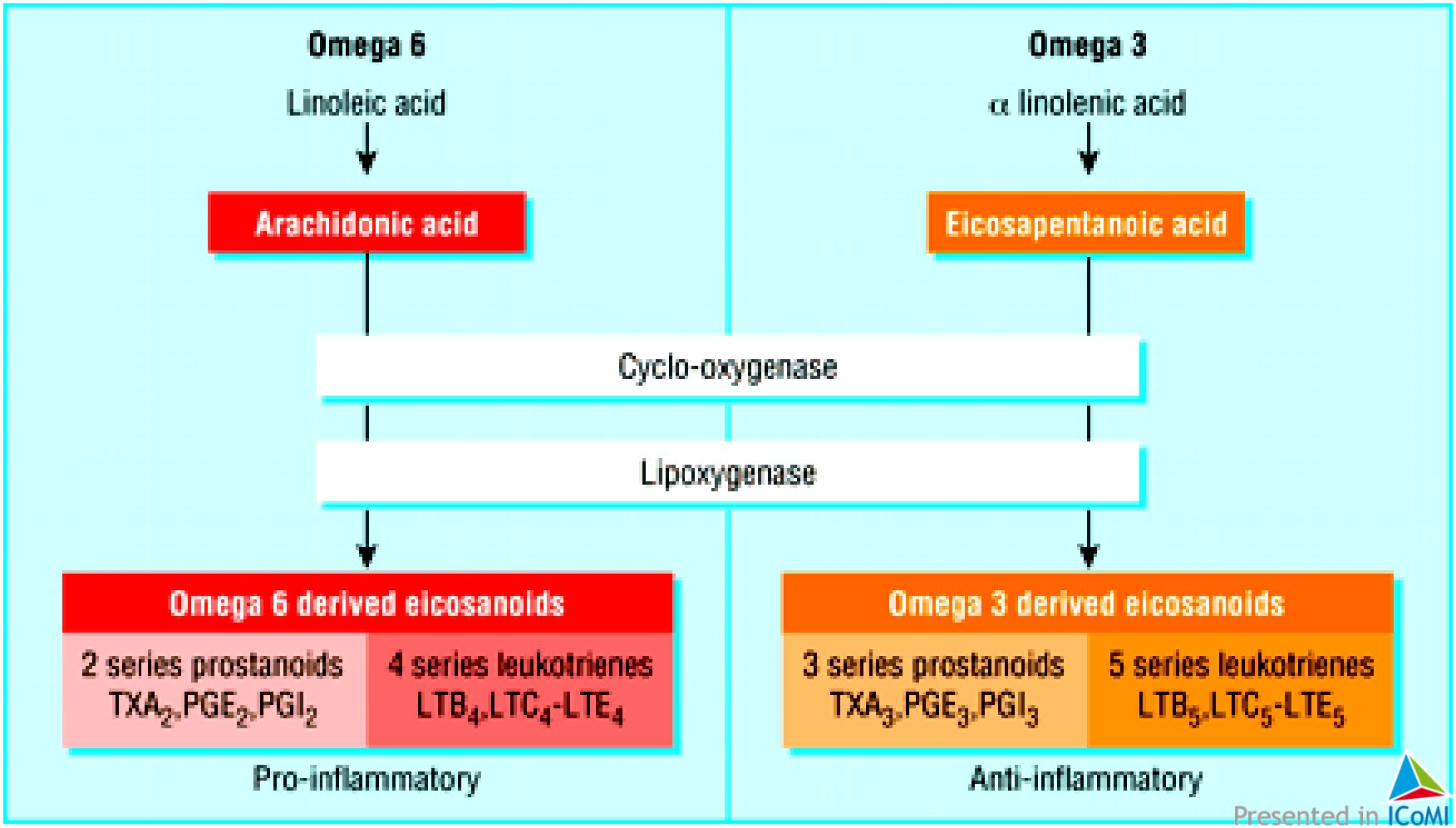
Riedel CU, Foata F, Philippe D, Adolfsson O, Eikmanns BJ, Blum S.
Microbiology Department and Alimentary Pharmabiotic Centre, University College Cork, Cork, Ireland. c.riedel@ucc.ie.
World J Gastroenterol. 2006

AIM: Different strains of bifidobacteria were analysed for their effects on HT-29 intestinal epithelial cells (IECs) in in vitro models both of the non-inflamed and inflamed intestinal epithelium. METHODS: A reporter gene system in HT-29 cells was used to measure levels of NF-kappaB activation after challenge with bifidobacteria or after bacterial pre-treatment following LPS challenge. IL-8 protein and pro-inflammatory gene expression was investigated using normal HT-29 cells. RESULTS: None of the bifidobacteria tested induced activation of nuclear factor kappaB (NF-kappaB) indicating that bifidobacteria themselves do not induce inflammatory events in IECs. However, six out of eight bifidobacteria tested inhibited lipopolysaccharide- (LPS-) induced NF-kappaB activation in a dose- and strain-dependent manner. In contrast, NF-kappaB activation in response to challenge with tumor necrosis factor-alpha (TNF-alpha) was affected by none of the tested bifidobacteria, indicating that the inhibitory effect of bifidobacteria is specific for LPS-induced inflammation in IECs. As shown with two of the six inhibition-positive bifidobacteria, LPS-induced inhibition of NF-kappaB activation was accompanied by a dose-dependent decrease of interleukin 8 (IL-8) secretion and by lower mRNA levels for IL-8, TNF-alpha, cyclooxygenase 2 (Cox-2), and intercellular adhesion molecule 1 (ICAM-1). CONCLUSION: Some strains of bifidobacteria are effective in inhibiting LPS-induced inflammation and thus might be appropriate candidates for probiotic intervention in chronic intestinal inflammation.

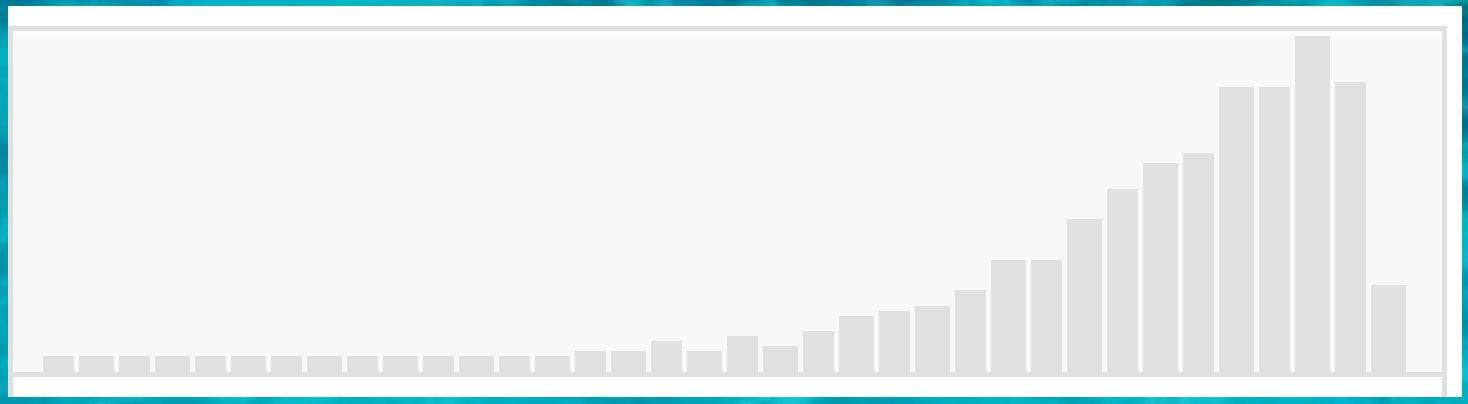
Functional and nutritional medicine management of chronic inflammatory diseases: A strategy in four points

2.Restore equilibria

The Intensity of Inflammation is controlled by ecosanoïds



OMEGA-3 fatty acids & inflammation



PubMed april 2017
2823 publications

Drugs. 2003;63(9):845-53.

The role of fish oils in the treatment of rheumatoid arthritis.

Cleland LG[1], James MJ, Proudman SM.

Author information

Abstract

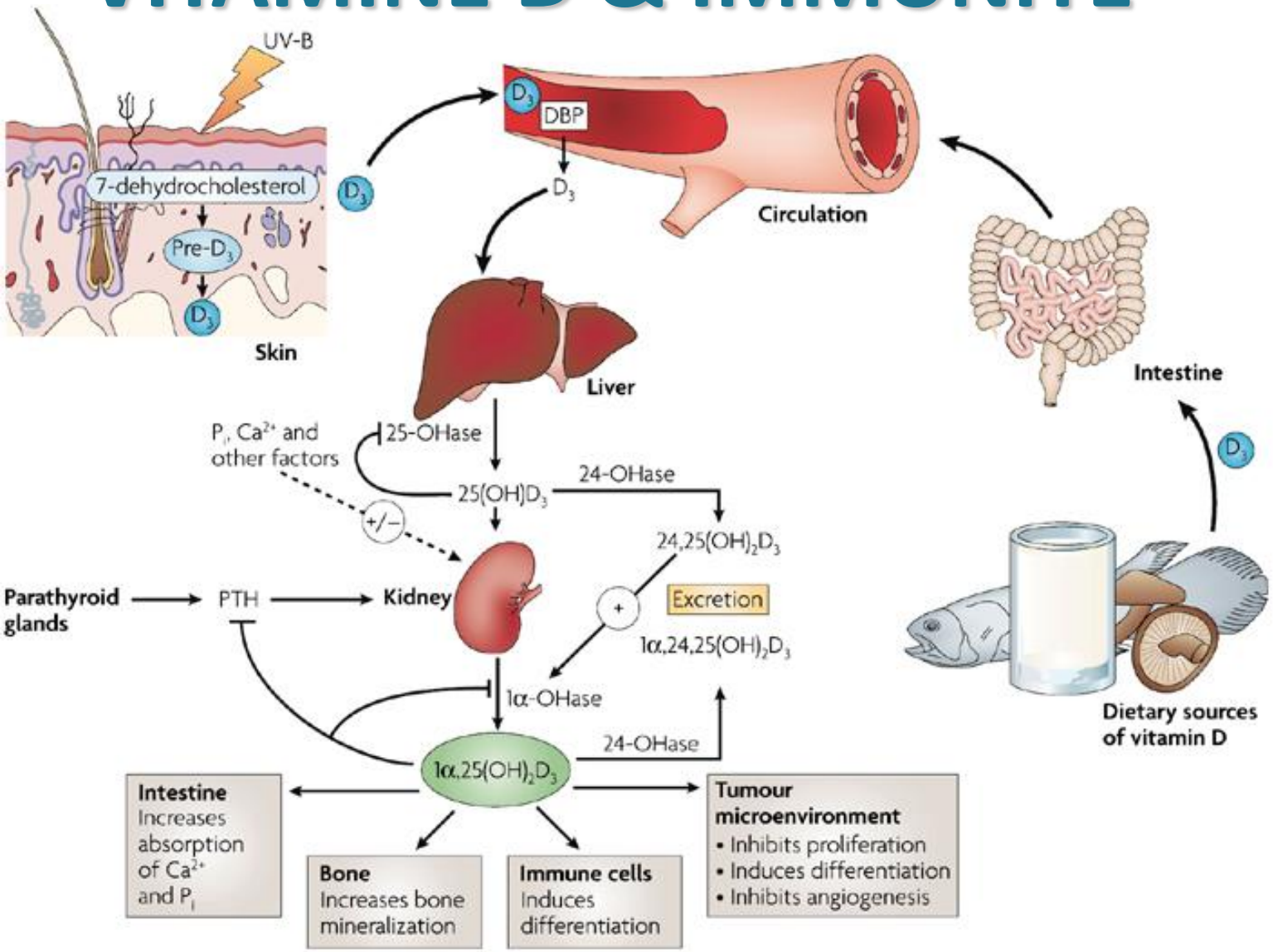
Fish oils are a rich source of omega-3 long chain polyunsaturated fatty acids (n-3 LC PUFA). The specific fatty acids, eicosapentaenoic acid and docosahexaenoic acid, are homologues of the n-6 fatty acid, arachidonic acid (AA). This chemistry provides for antagonism by n-3 LC PUFA of AA metabolism to pro-inflammatory and pro-thrombotic n-6 eicosanoids, as well as production of less active n-3 eicosanoids. In addition, n-3 LC PUFA can suppress production of pro-inflammatory cytokines and cartilage degradative enzymes. In accordance with the biochemical effects, beneficial anti-inflammatory effects of dietary fish oils have been demonstrated in randomised, double-blind, placebo-controlled trials in rheumatoid arthritis (RA). Also, fish oils have protective clinical effects in occlusive cardiovascular disease, for which patients with RA are at increased risk. Implementation of the clinical use of anti-inflammatory fish oil doses has been poor. Since fish oils do not provide industry with the opportunities for substantial profit associated with patented prescription items, they have not received the marketing inputs that underpin the adoption of usual pharmacotherapies. Accordingly, many prescribers remain ignorant of their biochemistry, therapeutic effects, formulations, principles of application and complementary dietary modifications. Evidence is presented that increased uptake of this approach can be achieved using bulk fish oils. This approach has been used with good compliance in RA patients. In addition, an index of n-3 nutrition can be used to provide helpful feedback messages to patients and to monitor the attainment of target levels.Collectively, these issues highlight the challenges in advancing the use of fish oil amid the complexities of modern management of RA, with its emphasis on combination chemotherapy applied early.

Functional and nutritional medicine management of chronic inflammatory diseases: A strategy in four points

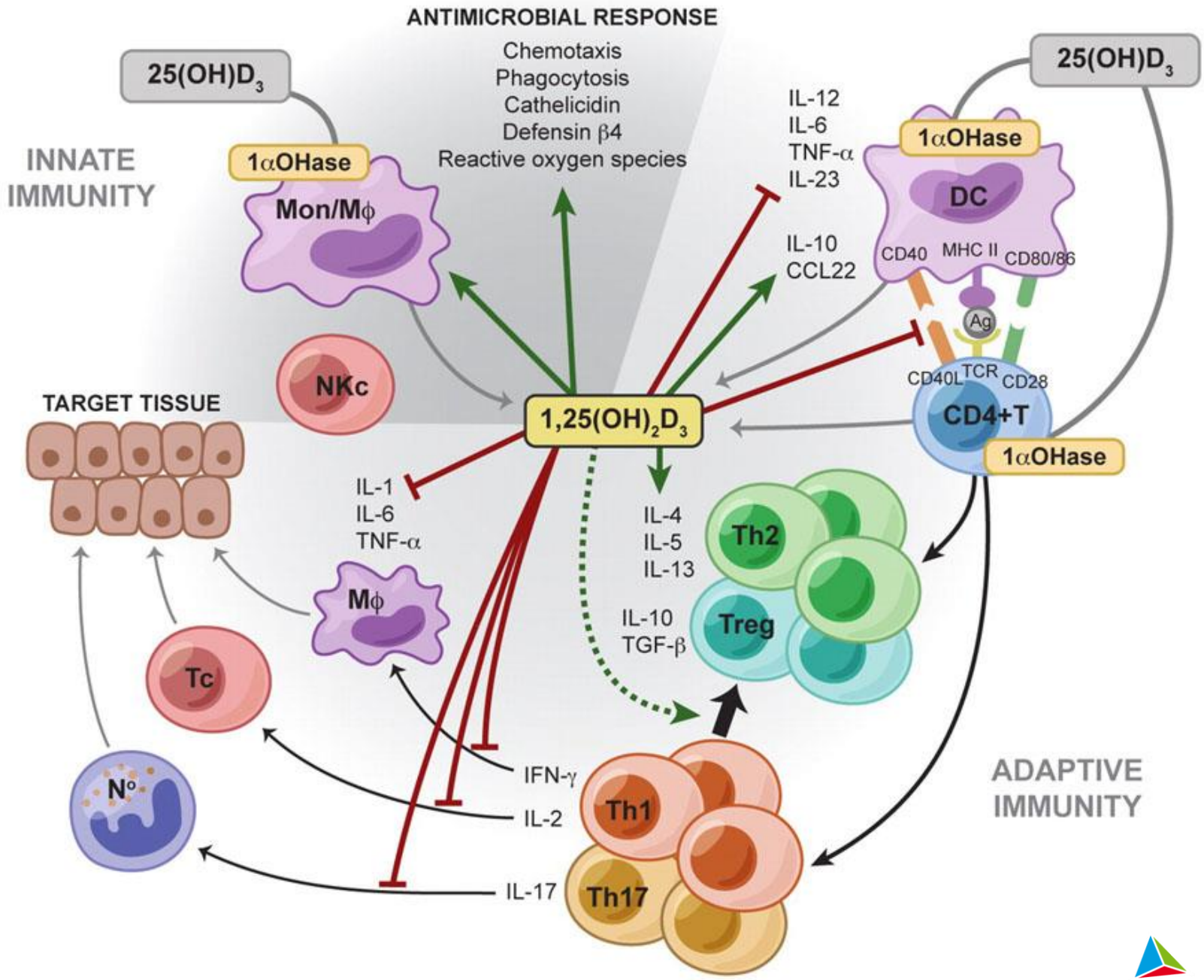
3. Restore the original molecular environment

- **Vitamin D**
- **Kinases regulators**

VITAMINE D & IMMUNITE



VITAMINE D & IMMUNITY



Presented in ICoMI 2017

Mol Cell Endocrinol. 2017 Apr 12. pii: S0303-7207(17)30223-X. doi: 10.1016/j.mce.2017.04.010. [Epub ahead of print]

Vitamin D signaling in intestinal innate immunity and homeostasis.

Dimitrov V[1], White JH[2].

Author information

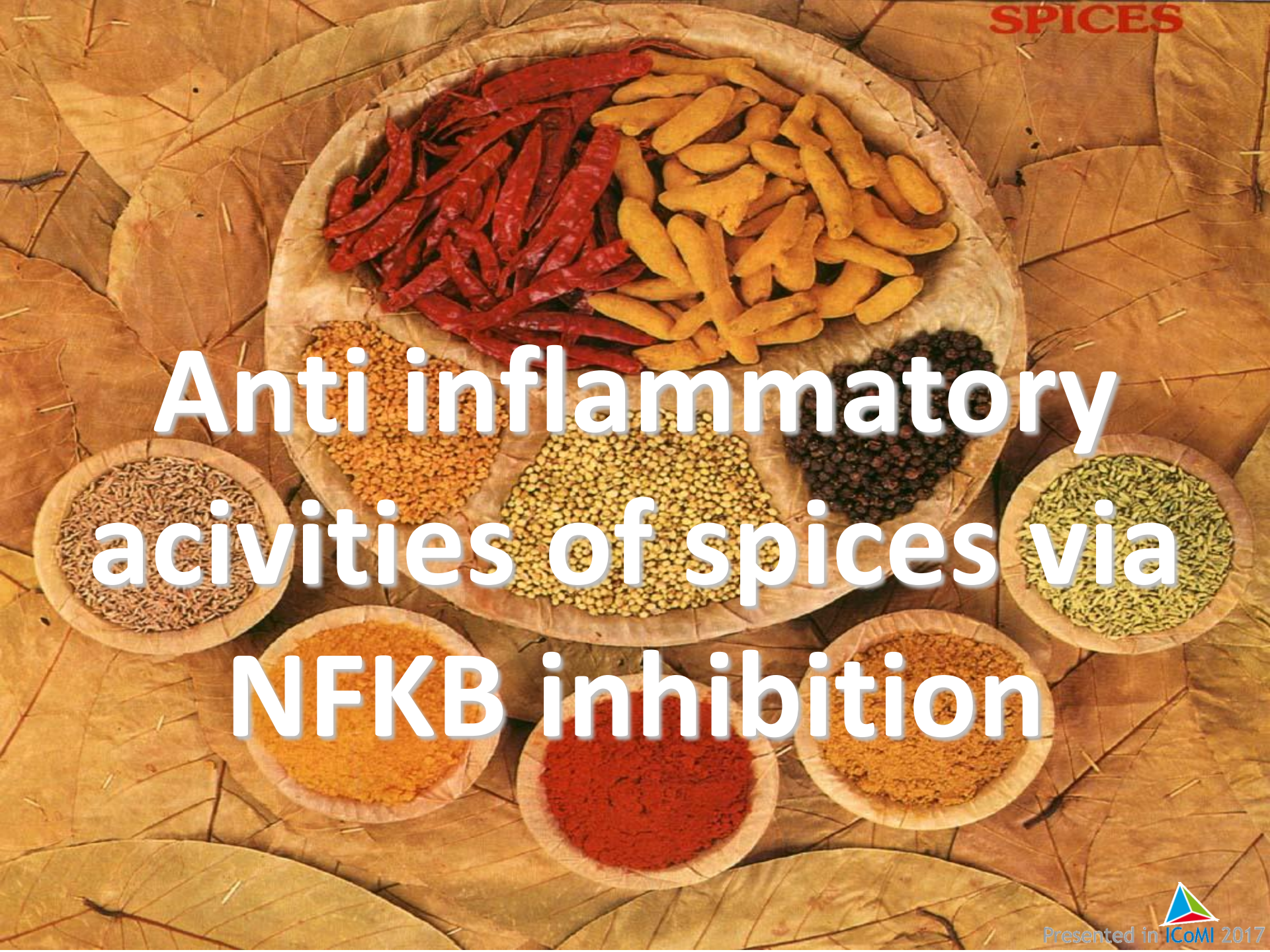
Abstract

The lumen of the gut hosts a plethora of microorganisms that participate in food assimilation, inactivation of harmful particles and in vitamin synthesis. On the other hand, enteric flora, a number of food antigens, and toxins are capable of triggering immune responses causing inflammation, which, when unresolved, may lead to chronic conditions such as inflammatory bowel disease (IBD). It is important, therefore, to contain the gut bacteria within the lumen, control microbial load and composition, as well as ensure adequate innate and adaptive immune responses to pathogenic threats. There is growing evidence that vitamin D (VD) signaling has impacts on all these aspects of intestinal physiology, contributing to healthy enteric homeostasis. VD was first discovered as the curative agent for nutritional rickets, and its classical actions are associated with calcium absorption and bone health. However, VD exhibits a number of extra-skeletal effects, particularly in innate immunity. Notably, it stimulates production of pattern recognition receptors, anti-microbial peptides, and cytokines, which are at the forefront of innate immune responses. They play a role in sensing the microbiota, in preventing excessive bacterial overgrowth, and complement the actions of VD signaling in enhancing intestinal barrier function. VD also favours tolerogenic rather than inflammogenic T cell differentiation and function. Compromised innate immune function and overactive adaptive immunity, as well as defective intestinal barrier function, have been associated with IBD. Importantly, observational and intervention studies support a beneficial role of VD supplementation in patients with Crohn's disease, a form of IBD. This review summarizes the effects of VD signaling on barrier integrity and innate and adaptive immunity in the gut, as well as on microbial load and composition. Collectively, studies to date reveal that VD signaling has widespread effects on gut homeostasis, and provide a mechanistic basis for potential therapeutic benefit of VD supplementation in IBD.

VITAMINE D & IMMUNITE

VITAMIN D LEVELS
25 HYDROXY D

Deficient	Optimal	Treat Cancer and Heart Disease	Excess
< 50 ng/ml	50-70 ng/ml	70-100 ng/ml	> 100 ng/ml



Anti inflammatory acivities of spices via NFKB inhibition

Table 2 | **Natural products that inhibit nuclear factor-κB**

Compounds	Derived from	Possible mechanism of NF-κB inhibition	References
Soya isoflavone genistein	Soyabean products	Partly mediated through the AKT pathway	91,123
Caffeic-acid phenethyl ester	Honeybee propolis	Delays IκBα synthesis; no significant effects on IκBα degradation	124,125
Benzyl isocyanate	Cruciferous vegetable	Decrease in nuclear translocation of NF-κB	126
Resveratrol	Skins of red grapes, various other fruits and root extract of the weed *Polygonum cuspidatum*	Inhibits IKK activity	127,128
Curcumin	Turmeric curry	Inhibits IKK activity	129,130,140
Lupeol	Various fruits and vegetables such as olive, mango, strawberry and fig plants	Inhibits IKK activity; inhibits the PI3K–AKT pathway	131
Epigallocatechin-3-gallate	Green tea	Intercellular accumulation of IκBα	132
Lycopene	Carotenoid in tomatoes	Directly suppresses the p65 nuclear translocation	133
Human breast milk	Human breast milk	Induces the production of IκBα	134
Andrographolide	*Andrographis paniculate*	Forms a covalent adduct with reduced cysteine 62 of p50, and blocking the binding of NF-κB oligonucleotide to nuclear proteins	135
Guggulsterone	*Commiphora mukul*	Suppresses NF-κB DNA-binding activity	136
Sesquiterpene lactones	*Asteracease* plants	Alkylation of cysteine 38 in the DNA-binding domain of the p65	137
Panepoxydone	Fungi	Inhibits TNFα-induced phosphorylation and degradation of IκBα	83
Cycloepoxydon	Fungi	Inhibits TNFα-induced phosphorylation and degradation of IκBα	138
Gliotoxin	Fungi	Prevents the degradation of IκBα	139

Functional and nutritional medicine management of chronic inflammatory diseases: A strategy in four points

4. Stop the fire

- **Antioxidants**

Lipids. 2016 Oct;51(10):1145-52. doi: 10.1007/s11745-016-4185-2. Epub 2016 Aug 16.

Alpha-Lipoic Acid Alleviates Acute Inflammation and Promotes Lipid Mobilization During the Inflammatory Response in White Adipose Tissue of Mice.

Guo J[1], Gao S[1], Liu Z[1], Zhao R[1], Yang X[2].

Author information

Abstract

Recently, white adipose tissue has been shown to exhibit immunological activity, and may play an important role in host defense and protection against bacterial infection. Alpha-lipoic acid (α-LA) has been demonstrated to function as an anti-inflammatory and anti-oxidant agent. However, its influence on the inflammatory response and metabolic changes in white adipose tissue remains unknown. We used male C57BL/6 mice as models to study the effect of α-LA on the inflammatory response and metabolic changes in white adipose tissue after stimulation with lipopolysaccharide (LPS). The non-esterified fatty acid content was measured by an automatic biochemical analyzer. The expression of inflammation-, lipid- and energy metabolism-related genes and proteins was determined by quantitative real-time polymerase chain reaction and western blotting. The results indicated that α-LA significantly decreased the epididymis fat weight index and the non-esterified fatty acid content in plasma compared with the control group. LPS significantly increased the expression of inflammation genes and α-LA reduced their expression. The LPS-induced expression of nuclear factor-κB protein was decreased by α-LA. Regarding lipid metabolism, α-LA significantly counteracted the inhibitory effects of LPS on the expression of hormone-sensitive lipase gene and protein. α-LA evidently increased the gene expression of fatty acid transport protein 1 and cluster of differentiation 36. Regarding energy metabolism, α-LA significantly increased the expression of most of mitochondrial DNA-encoded genes compared with the control and LPS group. Accordingly, α-LA can alleviate acute inflammatory response and this action may be related with the promotion of lipid mobilization in white adipose tissue.

THANK YOU FOR YOUR ATTENTION AND LONG HAPPY LIFE TO ICoMI

ICoMI

1st International Congress of Micro-Immunotherapy

18-20 May 2017, Mallorca, Spain