BALANCING YOUR IMMUNE SYSTEM

"Gutting" Your Body of Inflammation

Have you ever contemplated what it means that 75% of your Immune System resides in the mucosa of your GI tract? You may have long been aware that the lining of your alimentary canal is fully equipped as your first line of defense against microbial pathogens. But the critical essence of the immune cell presence in the gut is its effects extending far beyond the gut, exercising control over all aspects of systemic immune responses. Do you marvel that immune cells use the gut lining as their home base, from which they are commanded by microbiota to mobilize in combat against immune system stress assaults on any tissue? Truly, it is the power of the intestinal microbiota that commands both activation and inhibition of dendritic cells, macrophages, mast cells, and eosinophils in the gut lining. (1-5)

Your Microbiota Is the "Major General" of Your Immune System Forces.

The effects of a healthy microbiota include …

- initiating either the release or inhibition of pro-inflammatory cytokines (2, 4)
- initiating either the release or inhibition of anti-inflammatory cytokines (2, 4)
- activating or inhibiting billions of mast cells, the most fundamental component of the innate immune response (4, 5)
- connecting the immune system to the nervous system, as mast cells cluster around sympathetic and parasympathetic nerve endings in the gut wall (4, 5)
- activating anti-inflammatory functions of the Vagus Nerve (6)
- responding with an alarm reaction to the toxins produced by abnormal bacteria, fungi, yeast, or viruses in the GI tract --- triggering the release of pro-inflammatory cytokines in defense (7)

The microbiota controls the enteroendocrine cells communicating with a broad array of immuno-neuro-endocrine functions. The communication network includes the gut-liver axis, the gut-brain axis, the gut-hypothalamus axis, the gut-adipose axis, and the gut-pancreas axis. However, the overarching influence of the microbiota is via ...

The Gut-Immune Axis.

Researchers have identified a select group of probiotics that are essential, not only for gut health, but for a highly responsive yet thoroughly controlled and balanced systemic immune system. One specific component of immune balance is the antagonism/balance between Lymphocytic T-Helper Cell-1 (Th1) and T-Helper Cell-2 (Th2) function. The Th1 inflammatory cytokine family includes Interferon-γ (IFN-γ), Tumor Necrosis Factor-α (TNF-α), and

Interleukins (IL) 1, 2, 8, and 12. Th2 inflammatory cytokines include the pro-inflammatory IL-5, 6, and 13, along with the anti-inflammatory IL-4 and 10. Deficiency in either family of Th1 or Th2 cytokines is characteristic of both acute and chronic inflammatory processes. But more significant than deficiencies of these inflammatory cytokines are uncontrolled excesses. (2,4,5,8-11)

Uncontrolled immune reactivity of Th1 inflammatory cytokines is typical of chronic auto-immune diseases such as Rheumatoid Arthritis, Crohn's Disease, Type 1 Diabetes, and Multiple Sclerosis. Dysregulated Th2 reactivity, often accompanied by a deficiency of Th1 immune defense, is characteristic of Immunoglobulin-E-mediated allergies, with elevated eosinophil and mast cell reactivity, along with other histamine-mediated reactions, and asthma. (2,4,5,8-11)

Probiotic supplementation is required for optimum immune balance, assuring a decreased capacity to cause deviation of inflammatory response toward systemic, Th1- and, Th2-activated pathology. (1,3,9,10,12)

Here is where you must appreciate the concept of …

Specificity in Probiotic Supplementation

In patients with a proclivity toward either Th1- or Th2-dominant health problems, you must be selective in probiotic supplementation. To do otherwise, is to potentially exacerbate inflammatory symptoms and intensify the processes of INFLAM-AGING.

The probiotic species are most immune-reactive in humans can be divided into two "teams". One team strongly inhibits excessive Th1 inflammatory cytokines, and to a certain extent helps activate the anti-inflammatory Th2 cytokines. That team includes *L. reuteri, B. breve,* and *B.longus*. The probiotics controlling Th2 inflammation while strengthening a weak Th1 defense include *L. rhamnoses, L. casei,* and *L. gasseri*. (2,5,7,13)

To supplement in accord with every patient's specific needs, you must be particular in recommending probiotics suitable for the individual's tendency to be either Th1 or Th2 dominant in immune reactivity.

In Consideration of Patients With High Th1 and Low Th2 Reactivity:

- *L. reuteri* reduces the production of pro-inflammatory cytokines in dendritic cells. Research shows it is perhaps the most powerful anti-inflammatory of all probiotics. (4,8-10,14)

- *L. gasseri* induces high levels of Th1 inflammatory IFN-γ, and a low level of Th2 anti-inflammatory IL-10. In contrast, *L. reuteri* activates anti-inflammatory IL-10. Which should you choose for your ulcerative colitis patient? Your better choice is to carefully avoid the Th1-activating probiotics in this auto-immune condition. (8-11)

- *L. reuteri* induces the expression of a stress-inducible enzyme with antioxidant and anti-inflammatory properties. (9)

- *L. reuteri* primes monocyte-derived dendritic cells to drive the development of T cells. These T cells produce increased levels of anti-inflammatoryIL-10. *L. reuteri* binds C-type lectin of dendritic cells. This targeting of dendritic cells by *L. reuteri* explains its beneficial effect in the treatment of Th1-mediated inflammatory diseases, including atopic dermatitis and Crohn's disease, as well as its benefit in increasing bone density. (8,9,13,14,17)

- Research suggests *L. reuteri* is effective for down-regulating production of IL-12 and TNF-α, while inducing the anti-inflammatory IL-10, thus representing an effective anti-inflammatory therapy in all Th1-mediated auto-immune diseases. (8-11)

- *B. breve* produces peripheral blood mononuclear cell release of the Th2 anti-inflammatory IL-10. It is one of the 3 probiotics shown to skew immune reactivity away from Th1-mediated inflammation toward anti-inflammatory Th2 cytokines. (1,2)

- In human monocyte-derived dendritic cells, *L. rhamnosus* increases Th1 inflammatory TNF-α. It is not a good choice for your rheumatoid arthritis patients.

- *L. rhamnosus* should <u>not</u> be given to patients with Crohn's disease or other Th1-driven inflammatory conditions. In contrast, beneficial effects of the inhibition of IFN-γ and TNF-α production by *B. breve*, may result in an ideal tolerant state, with decreased Th1 immune responses, while other immune pathways remain intact. Such balance sustains immune competence of the host. Supplementation thus offers an alternative to immune-suppressing drugs that impair immune defense. *B. breve* is therefore an extremely effective probiotic for patients with inflammatory conditions.

- Probiotics that attenuate IBD are those that down-regulate Th1 cytokines while maintaining TGF-β.

- In humans suffering from auto-immune ulcerative colitis, the Bifidobacteria population is about 30-fold lower compared to that in healthy individuals. Supplementation of ulcerative colitis patients with oligofructose-enriched inulin as a prebiotic, together with *B. longum* for 1 month, results in a 42-fold increase in bifidobacteria. (4,5,8,9,13,14,17)

- Th2 anti-inflammatory IL-10 production is induced by *B. breve* and *B. longum*. These Bifidobacterial species, along with *L. reuteri*, are among the few probiotics that induce a Th2-driven immune response. (8-10,17)

In Consideration of Patients With High Th2 and Low Th1 Reactivity:

- *L. rhamnosus* induces a significant Th1 response in peripheral monocytes by significantly increasing IFN-γ, TNF-α, and IL-1- β. It also, however, induces significant activation of IL-10, a TH2 anti-inflammatory cytokine. (18-21)

- In human macrophages, *L. rhamnosus* activates NF-KappaB, a powerful protector against stress, inflammatory cytokines, free radicals, heavy metals, UV radiation, oxidized LDL cholesterol, and of course, viral and bacterial infection. (4,16)

- *L. casei* induces the release from peripheral blood mononuclear cells of moderate amounts of IFN-γ, TNF-α, IL-1-β, and IL-6, which is critical to anti-microbial immune defense. (18-21)

- *L. rhamnosus* stimulates rotavirus-specific IgA antibody responses, which are significant in the prevention of reinfections. (20-22)

- *L. rhamnosis* and *L. casei* are shown to inhibit the secretion of Th2 cytokines IL-4 and IL-5. The mechanism is dependent on antigen-presenting cells (i.e. monocytes/macrophages/dendritic cells), and involves the release of Th1 cytokines IL-12 and IFN-γ. These benefits are effective in the control of asthma and histamine-mediated allergies. (18-21,23)

- *L. casei* increases the activity of enzymes from macrophages six-fold. There is also a beneficial effect of *L. casei* on the phagocytic function of the reticuloendothelial system. (18-21)

- *L. casei* exhibits marked anti-tumor activity. Research suggests that anti-tumor activity may be macrophage-dependent. (24)

- It is also reported that Natural Killer Cell activity is augmented by *L. casei*. (25)

Considering this concept of microbiota specificity, you clearly see that supplementation with the random assortment offered by most probiotic supplements can be of limited efficacy, and even be counterproductive. It is imperative that you offer synbiotic supplementation in accordance with all patients' specific needs, helping them battle inflammation with a powerfully mobilized microbiota.

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