Immunonutrition – Its Role In Managing Inflammation

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Definition

- The potential to modulate the activity of the immune system by interventions with specific nutrients is termed **immunonutrition**.
- This concept may be applied to any situation in which an altered supply of nutrients or other ingested agents are used to modify inflammatory or immune responses.

Inflammation

- Inflammation is an adaptive response that is triggered by noxious stimuli and conditions, such as infection and tissue injury

Systemic Chronic Inflammation

- Much less is known, however, about the causes and mechanisms of systemic chronic inflammation, which occurs in a wide variety of diseases
- Including type 2 diabetes and cardiovascular diseases amongst others.
- These chronic inflammatory states seem to be associated with the malfunction of tissue: that is, with the homeostatic imbalance of one of several physiological systems that are not directly functionally related to host defence or tissue repair
The Inflammatory 'pathway'

- The inflammatory response is coordinated by a large range of mediators that form complex regulatory networks. To dissect these complex networks, it is helpful to place these signals into functional categories and to distinguish between inducers and mediators of inflammation.
Examples of Inflammatory Pathways

<table>
<thead>
<tr>
<th>Inducer</th>
<th>Sensor</th>
<th>Mediator</th>
<th>Effector</th>
</tr>
</thead>
<tbody>
<tr>
<td>LPS</td>
<td>TLR4</td>
<td>TNFα, IL-6 &amp; PGE₂</td>
<td>Endothelial cells, Hepatocytes, CNS. Etc.</td>
</tr>
<tr>
<td>Allergens</td>
<td>IgE</td>
<td>Vasoactive Amines</td>
<td>Endothelial cells, smooth muscle cells. Etc</td>
</tr>
<tr>
<td>Bacterial Imbalance</td>
<td>TLR4,TLR2</td>
<td>IL10, TGFβ, TNFα</td>
<td>Epithelial Cells, T Cells, lymphoid tissue</td>
</tr>
</tbody>
</table>

Evolving Models of Immunity

- When faced with a potential threat, the immune system has two main questions to answer.
The First, 'shall I respond?'

- Is what most models of immunology deal with.
- The old 'self–non-self' model assumed that the answer was 'yes' if the potential threat were foreign (as seen by the antigen-specific receptors of T and B cells).

Pattern Recognition Receptor Model (PRR)

- The newer (PRR) model assumes that the answer is 'yes' if the potential threat is very foreign — for example, bacterial or viral pathogen-associated molecular patterns (PAMPs) as seen by the Toll-like receptors (TLRs) of antigen-presenting cells (APCs)

Danger Model

...and the 'danger' model assumes that the answer is 'yes' if the potential threat does damage that elicits antigen presenting cell (APC)-activating alarm signals from the damaged tissues.


Tissues Have Some Control

In their own defence, tissues send a panoply of signals that initiate immunity and guide the choice of effector class.

- $T_H^1$-$T_H^2$ and $T_{reg}$ is far too simple a representation of the breathtaking variety of the resulting responses.
Innate Immunity

- Unlike adaptive immunity, which is based on millions of lymphoid cell-surface receptors (generated by complex gene rearrangements) that recognise an infinite variety of antigens,
- The innate immune system is based on a much smaller number of receptors, called pattern recognition receptors (PRRs).

For the most part, PRRs recognise conserved molecular patterns that distinguish foreign organisms—viruses, bacteria, fungi and parasites—from cells of their hosts

Such pathogen-associated molecular patterns (PAMPs) include viral nucleic acids, components of bacterial and fungal cell walls, flagellar proteins, and more.

However, this detection system is not foolproof and it can also be activated by a variety of normal host proteins and danger signals that are released by dying cells.


DAMP’s

A category of damage-associated molecular patterns (DAMPs) that encompasses both PAMPs and alarm signals.

DAMPS would be useful as quorum-sensing signals to bacteria, for the initiation of repair and of immunity.
DAMPs

- If we look at PAMPs (& MAMPs or microbe associated molecular patterns) and alarm signals as different forms of DAMPs, it is no longer necessary to argue whether these are pathogen specific or endogenous.
- They are both. Many of them serve to initiate both repair and immunity.

DAMP’s are a class of triggering agent that activates immune activity, including: Repair and defence activities.

They can be from pathogens as well as commensals.
2nd Question

- What type of response should be made?

Potential Mechanism 1

- Organ tissue can control the local effector class by directly educating its resident antigen presenting cells (APCs) such that those APCs, in turn, stimulate certain types of responses from T cells.
- There is direct evidence for such education in the gut (from analysis of APCs called Dendritic Cells in Peyer's patches and mesenteric lymph nodes, plus other tissues).

2nd Potential Mechanism

- By the invitation, the immigration and residency of particular populations of 'innate' lymphocytes. Many of these cells seem to be tuned to recognise stress-induced 'self' molecules rather than foreign pathogens.

What Is Their Function?

- Perhaps it is to help heal the tissue (such as with epidermal growth factor made by the dendritic epidermal T cell) or to ensure that a local immune response is shifted to the appropriate effector class to clear a pathogen without doing excess damage to the tissue itself.
Who Decides on Effector Response?

• When an immune response is initiated, what or who decides whether to produce immunoglobulin G1 (IgG1) or IgG2a, IgG2b or IgG2c, or IgG3, or IgE or IgA?
• Who determines whether to activate natural killer (NK) cells or eosinophils, or superoxide-producing macrophages or cytotoxic T lymphocytes (CTLs)?
• Neither the old self–non-self model nor the newer PRR model explain this.

What decides to switch off?

• The counter regulatory responses can be driven by natural feedback mechanisms, or may be driven by the associated tissues of the affected organ.
• The health of the tissues including nutrient status will determine the quality and resolution of the effector cells.
Consider the possibility that the ultimate control lies with the tissues in which the response occurs, rather than with the pathogen against which it is directed.


Complexity

- Does not stop with the cells of the immune system and the tissues they interact with.
- We are just beginning to scratch the surface of the communication between our commensals and us.
- We are an environment to an uncountable number of symbiotic, commensal and pathogenic organisms, each of which has had evolutionary time to learn how to use and misuse our immune system.
Microbiota

- As we expand our picture of the immune system from an army of lymphocytes patrolling the body for foreigners to an integrated group of communicating tissues, all working to maintain tissue integrity and health, we will necessarily need to include the signals from the non-self organisms that take advantage of that health or that help maintain it.

Why Is This Relevant To Nutritionists?

- The GI tract is the principle organ of immune activation we use in clinical life.
- Too often we approach this tube of life in a cavalier manner
- **Immune Tolerance** must be our primary aim
- Understanding mechanisms allows for therapeutic specificity
It can be all too easy to get focussed on the small aspects & forget to look at the bigger picture......

### Innate And Adaptive Immunity In The Gut

**Innate and Adaptive Immunity in the Gut**

<table>
<thead>
<tr>
<th>Innate immunity</th>
<th>Adaptive immunity</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>physicochemical</strong></td>
<td><strong>cellular</strong></td>
</tr>
<tr>
<td>Mucus</td>
<td>NK cells (? some IELs)</td>
</tr>
<tr>
<td>Tight junctions</td>
<td>Macrophages</td>
</tr>
<tr>
<td>Epithelial membranes</td>
<td>Polymorphonuclear leukocytes</td>
</tr>
<tr>
<td>Luminal/brush border enzymes</td>
<td>PRRs (Toll-like receptors)</td>
</tr>
<tr>
<td>Bile salts</td>
<td>Epithelial cells</td>
</tr>
<tr>
<td>pH ranges</td>
<td>Regulatory cytokines</td>
</tr>
<tr>
<td>somatostatin</td>
<td>sIgA</td>
</tr>
<tr>
<td>trefoil factors</td>
<td>Peyer’s patches</td>
</tr>
</tbody>
</table>

Epithelial cells/antigen presentation

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Mayer, L. Paediatrics 2003;111:1595-1600

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Pro Biotics and prebiotics as immunomodulating organisms can provide local and systemic anti-inflammatory effects.
What PB’s Do Not Do

- It seems unlikely, given the enormous size and diversity of the colonic flora, that the administration of a probiotic in what will, inevitably, be relatively tiny numbers can exert its effects by simple replacement or displacement of “bad” bacteria.


Polysaccharide A (PSA) is taken up by lamina propria dendritic cells, processed, and presented to naïve CD4+ T cells. In the presence of activated TGF-beta, these cells can become induced regulatory T cells (iTreg).

Production of IL-10 by these and other T-lineage cells promotes control of immune activation. IL-23 inhibits control by Treg, and promotes expansion of inflammatory Th17 cells.

For simplicity, many other pro- and anti-inflammatory mechanisms present in the intestines are not shown.

Much interest has been generated by the demonstration of a host of immune-modulating effects for certain probiotics:

- slgA
- Cytokine modulation
- Epithelial Cell manipulation
- Dendritic Cell maturation
- Treg
- Immunocommunication improvement

Rather than priming aggressive immune responses, these organisms mainly prime immunoregulation. They do it by inducing an unusual pattern of maturation of specialised immune priming cells called dendritic cells in such a way that these retain the ability to drive immune anergic inducing regulatory T cells (Treg).

1. Liam O’Mahony, Louise O’Callaghan, Jane McCarthy, David Shilling, Paul Scully, Shomik Sibartie, Eamon Kavanagh, William O. Kirwan, Henry Paul Redmond, John Kevin Collins, and Fergus Shanahan
Probiotics and immunology: separating the wheat from the chaff

Kan Shida and Masanobu Nanno
Yokohama Central Institute for Microbiological Research, Kanagawa, Japan

Probiotics are live bacteria exhibiting health-promoting activities. Recent research has demonstrated that probiotics can prevent pathogen colonization of the gut and reduce the incidence or severity of various diseases caused by dysregulated immune responses. Probiosis seem to function by influencing both intestinal epithelial cells and immune cells of the gut, but the details of these effects are still being unraveled. Therefore, probiotics, through their effects on the host immune system, might ameliorate diseases triggered by disordered immune responses. Covets remain and distinct ecological niches that can resist the colonization of exogenous pathogenic microorganisms. Moreover, normal immune system development can occur in response to stimuli from gut microbiota. Therefore, individuals whose normal gut microflora are destabilized might in turn exhibit disrupted immune function and thus become vulnerable to infectious diseases. Probiotics can assist in the recovery of gut microflora disturbed by a variety of causes and are expected to prevent or ameliorate certain diseases, at least in part, by modulation of the host immune system (see Table 1).

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3 likely pathways for PB’s to influence immunity
1. M Cells
2. DC penetration
3. IEC activation
Figure 1. Three hypothetical pathways by which probiotics can trigger and modulate immune function in the intestine. (a) Specialized epithelial cells called M (microfold) cells in the follicle-associated epithelium covering Peyer's patches or in the villi can take up probiotics directly by transcytosis. Macrophages (Mφ) or dendritic cells (DCs) are present immediately below M cells and then engulf probiotics and trigger immune responses. (b) DCs in the intestinal lamina propria have been found to extend their dendrites between intestinal epithelial cells (IECs) and might directly sample and process probiotics in the gut lumen. (c) Probiotics directly affect IECs to secrete an array of cytokines, which in turn modulate the immune functions of DCs, T cells, and B cells in the gut-associated lymphoid tissue (GALT).
1. Pathogen associated molecular patterns (PAMPs) derived from bacteria (including probiotics) are recognised by pattern recognition receptors (PRRs, such as Toll-like receptors).
2. Initiation of dendritic cell (DC) maturation starts after ligation of PRRs.
3. Type of PAMPs determines the selective priming of DCs for production of TH1, TH2, and Treg lymphocyte polarising factors.
4. Different PAMPs ligate to specific corresponding PRRs.
Three Potential Targets

- For immunonutrition via GI activity
- Mucosal barrier function and tolerance
- Cellular defence
- & local or systemic inflammation. management
- Also consider arginine, glutamine, branched chain amino acids, n-3 fatty acids, yeasts, prebiotics and nucleotides as well as many other micronutrients.

Gut Associated Immunomodulators

Cytokine Network
Vagal Nerve
Mucosal Immunity
• Cells from human mesenteric lymph nodes that drain inflamed intestines secrete more anti-inflammatory cytokines (IL-10, TGF-beta) when stimulated with pro-biotic variants of Bifido-bacterium or Lactobacillus, but more pro-inflammatory cytokines (TNF-alpha, IL-12) when stimulated with patho-genic Salmonella.7

• Specific IL-10 secretion is also seen upon stimulation of peripheral blood mononuclear cells from ulcerative colitis patients with heat-killed variants of Bifidobacterium sp.8

• Early clinical trials of these and other potential probiotics have been encouraging.6 Since Bacteroides and Lactobacillus are genera that show decreased representation in the intestines of many IBD patients,9
it is intriguing to speculate that symbiont colonisation may be deficient in these patients.

It will also be interesting to see whether, like PSA, poly-saccharides expressed by other probiotics play an active role in controlling intestinal immune responses.


The Gut - Source Of All Disease?

Numerous chronic diseases may occur as a result of disturbances of mucosal barrier function or of changes in mechanisms regulating mucosal immunity.1,2,3

NFk-B

Transcription factors are pivotal regulators of inflammation and immunity that control expression of important immunoregulatory genes. NFk-B activation and activity are tightly controlled by a number of endogenous mechanisms that limit the excessive and prolonged production of pro-inflammatory mediators, which can cause tissue damage during the inflammatory response.

In steady-state conditions, intestinal homeostasis is maintained through Treg cell suppression of effector T cells, and lamina propria dendritic cells (LpDCs) play a role by enhancing conversion of CD4+Foxp3− to CD4+Foxp3+ Treg cells, through retinoic acid (RA) and TGF-β. However, in susceptible individuals (e.g., with polymorphisms in key innate receptors or with altered gut microflora composition), LpDCs, which can sample bacteria across the intestinal epithelium, are likely activated by the commensal bacterial DNA through TLR9. After TLR9 activation, the LpDCs secrete IL-6 and probably other cytokines that promote differentiation and expansion of Th17 and Th1 cells. In addition, the TLR9-activated LpDCs suppress Treg conversion, through negative feedback by Th1-derived IFN-γ, in combination with IL-4 and IL-6. Thus, TLR9-activated LpDCs can alter the balance of effector over regulatory T cells and thereby promote intestinal inflammation.

Regulatory T (Treg) Cells

It is not yet known which particular organism(s) are the most potent in inducing Treg responses to suppress NFκB - commensals and other gut based organisms likely have the greatest efficacy\(^1,2\)

\(^1\) Murch S. Probiotics as mainstream allergy therapy? Archives of Disease in Childhood 2005;90:881-882
Microbes and the developing Gastro Intestinal tract


Killer T cells
- Eradicate infected cells, kill tumor cells and transplanted tissues
- Responsible for autoimmunity e.g. T1DM

T effector cells
- Primary defense against exogenous antigens

B cells
- Immunoglobulin

Anti-inflammatory cytokines such as IL-10 and TGFβ
- Induce tolerance to self and to intestinal commensal microbes

T reg
- Downregulate of IL-10 and TGFβ
- CD25+CD4+

Regulatory T cells (T reg):
- Responsible for tolerance to self
- Can downregulate inflammatory response and autoimmunity
- Boosting T reg might induce drug-free immune tolerance to donor organs, or change the course of many autoimmune disease such as diabetes type 1

Nature Reviews | Immunology
Activation of Innate Immune Response
Innate immune cytokines
Acute phase proteins
Chemokines
Adhesion molecules

Tissue damage Inc. loss of tolerance/ecoology
Infection
Dysbiosis

Local and Systemic Inflammation

Activation of Innate Immune Responses and Inflammation

Treg Cells Are Inflammation Controllers

- Such mechanisms include the development of regulatory T cells that secrete interleukin 10 (IL-10), which has many immunosuppressive and anti-inflammatory effects.


Dendritic Cells are APCs

- Dendritic cells have important roles in the activation and resolution of innate immune responses

Strain-dependent effect of *Lactobacillus* given orally to conventional mice on cytokine profile secretion in gut villi (Maassen et al, Vaccine, 2000, 18)

Cytokine response is strain dependent
Research need to be strain and outcome
Specific to determine suitable
Probiotic

Probiotic intervention has strain-specific anti-inflammatory effects in healthy adults.

Step 1
Select the patient based on clinical Hx and Lab work as well as diagnostic triage

Step 2
Select the correct strain of PB and suitable accessory nutrients as not all PBs do the same thing.

Step 3
Manage the patient by repeated investigations and clinical follow up, allow time and be prepared to be flexible.

MMP Suppression
TNFα Suppression
IL1 Inhibition
IFNγ Suppression
NFκ B Modulation
TGFβ Induction
Treg Induction

University of Helsinki, Institute of Biomedicine, Pharmacology
World J Gastroenterol - Apr 2008
**Migrationary Immunological Effects**

These latter effects have been associated with an amelioration of mucosal inflammation in a variety of animal models of inflammatory bowel disease and have even been shown to modify inflammatory process’s distant from the gut, in the liver and in the synovium and potentially the brain.


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**GIT- Immuno Regulation Of Inflammation-Increase**

- IL-10, IL-4 IL-13, TGFβ
- Treg
- SlgA
- Spermine
- Brush border enzymes
- Digestive enzymes
- PPARγ
- TLR control
- DC maturation
- Anti oxidants
- Cholinergic pathways
- Zymogen
**Peroxisome Proliferator-Activated Receptor Gamma**

- The Dietary Modulation Of PPARγ
- Published in GUT
- Nov 18th 2008

- Mainstream medical journals are exploring nutrition as a therapeutic tool in inflammation control

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**Dietary Sources Of PPARγ Modulators**

- Alpha Linolenic Acid
- Capsaicin
- Conjugated Lino Acid
- Curcumin
- DHA
- EPA
- Resveratrol
- Ginsenosides
- Hesperidin
- Butyrate

- Leafy Greens/Flax
- Cayenne Pepper
- Beef, Bovine Milk
- Tumeric
- Fish
- Fish
- Grapes, Wine Peanuts
- Ginseng
- Citrus Fruits
- SCFA’s
GIT- Immuno Regulation of Inflammation - Decrease

- TNF$\alpha$, IL-1, IL-8, IL-18, high IL-6 IL-17
- NFkB
- COX1,2,3,
- PGE2, ESR
- Ammonia
- CRP
- AA
- Leukotrienes,
- Lipoxygenase
- ROS
- NO
- MMP
- Bradykinins
- Substance P
- Thromboxanes

Clinical Strategies

- Assess patient as potential long term inflammation – loss of tolerance candidate
- Improve daily nutrition – Dietetic anti-inflammatory
- Include probiotics (Human Strain)
- Build beneficial Bio Film
- Include PUFA’s for improving Bacterial/Immunological cross talk
- Pro-biotics can be pro inflammatory
## Protocol

- Saccharomyces Boulardii 150-600mg
- Lactobacillus GG 30-60⁹ CFU (Lactobacillus casei, subspecies rhamnosus GG, ATCC strain 53103))
- Lactobacillus, plantarum, rhamnosus, salivarius 20-60⁹ CFU
- B. Bifidus Bacteria 20-60⁹ CFU
- EPA/DHA concentrate 2-4gms
- VitA 5000 iu & Vit D 6-12000
- Digestive enzymes Hcl and Proteolytic enzymes
- Anti inflammatory diet

## What Are The Clinical Implications

- The answer seems simple: we need only a few commensal bugs in the gut to be immunologically fit.
- If this is true, why do we carry billions of microbial species in our intestines?
- The reason may also be simple: in addition to balancing our immunologic act, bacteria perform countless other physiologic tasks.


The corollary to both conclusions is obvious: we must keep enteric bacteria happy. At the moment it appears that we are not doing a very good job, given that allergic and autoimmune diseases, including those that affect the gastrointestinal tract, are on the rise.

Using the principles of the "hygiene hypothesis," we can try to manipulate flora with antibiotics, probiotics, and prebiotics.

The End

THANK YOU

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