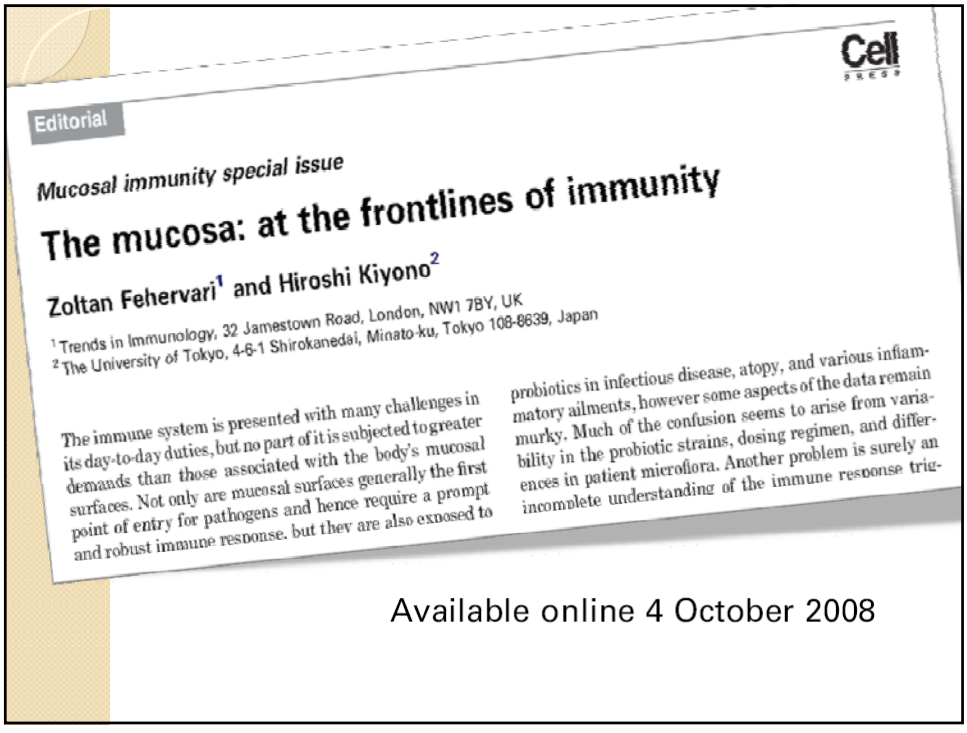
Immunonutrition – Its Role In Managing Inflammation

Michael Ash

BSc(Hons) DO ND Dip ION

BANT National Conference

29th Nov 2008



Cell Press

Editorial

Mucosal immunity special issue

The mucosa: at the frontlines of immunity

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The immune system is presented with many challenges in its day-to-day duties, but no part of it is subjected to greater demands than those associated with the body's mucosal surfaces. Not only are mucosal surfaces generally the first point of entry for pathogens and hence require a prompt and robust immune response, but they are also exposed to

probiotics in infectious disease, atopy, and various inflammatory ailments, however some aspects of the data remain murky. Much of the confusion seems to arise from variability in the probiotic strains, dosing regimen, and differences in patient microflora. Another problem is surely an incomplete understanding of the immune response trig-

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5-10 minutes !

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.

- Calder PC. Immunonutrition. BMJ. 2003 Jul 19;327(7407):117-8.

Inflammation

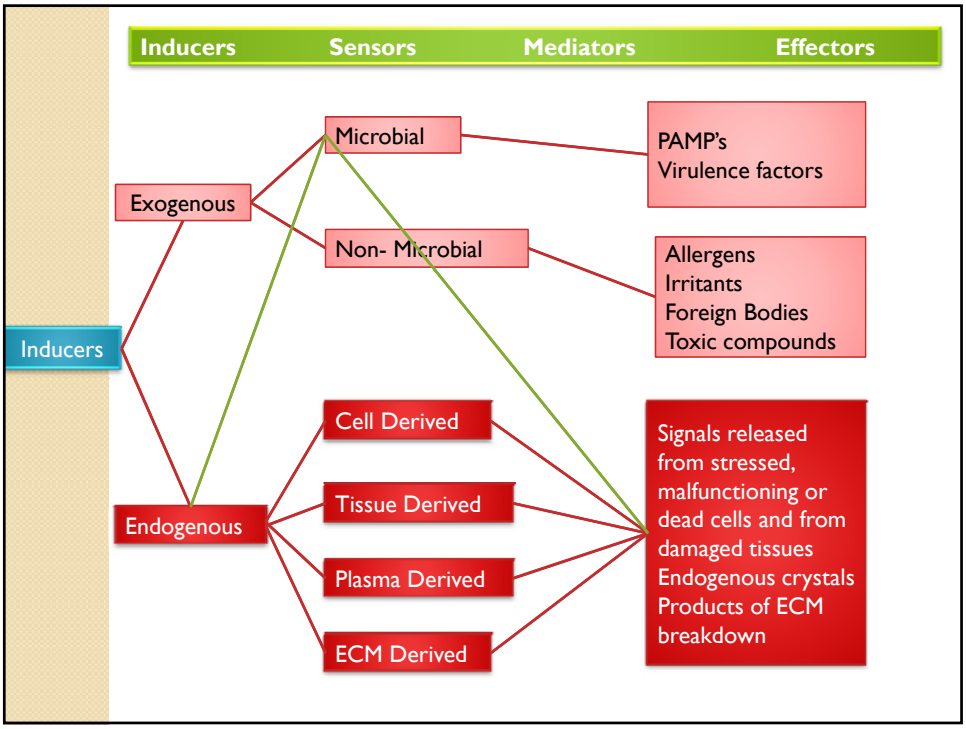
- Inflammation is an adaptive response that is triggered by noxious stimuli and conditions, such as infection and tissue injury
- Majno, G. & Joris, I. Cells, Tissues and Disease (Oxford Univ. Press, 2004)

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

Inducer	Sensor	Mediator	Effector
LPS	TLR4	TNFα,IL-6 & PGE_2	Endothelial cells, Hepatocytes, CNS. Etc.
Allergens	IgE	Vasoactive Amines	Endothelial cells, smooth muscle cells. Etc
Bacterial Imbalance	TLR4, TLR2	IL10, TGFβ, TNFα IL-2, IL-6	Epithelial Cells, T Cells, lymphoid tissue

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)

- Janeway, C.A. Jr., Immunol. Today 13, 11–16 (1992).

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.

- Matzinger, P. Annu. Rev. Immunol. 12, 991–1045 (1994).
- Matzinger, P. Science 296, 301–305 (2002).

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_H1-T_H2 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).

Innate Immunity

- For the most part, PRRs recognise conserved molecular patterns that distinguish foreign organisms—viruses, bacteria, fungi and parasites—from cells of their hosts[1]

1. Janeway, C.A. Jr & Medzhitov, R. Innate immune recognition. Annu. Rev. Immunol. 20, 197–216 (2002)

- 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.

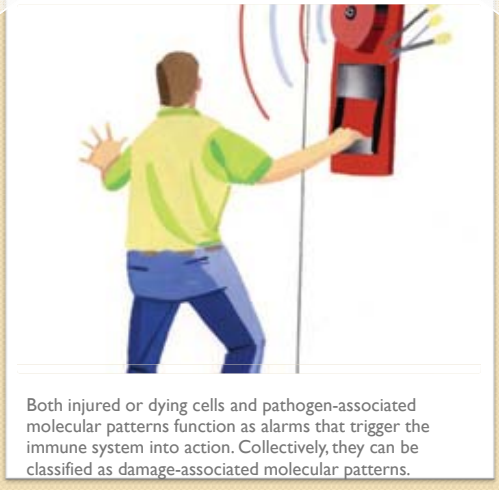
1. Karin, M., Lawrence, T. & Nizet, V. Innate immunity gone awry: linking microbial infections to chronic inflammation and cancer. Cell 124, 823–835 (2006)

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.
- Seong, S. & Matzinger, P. Nat. Rev. Immunol. 4, 469–478 (2004)



Both injured or dying cells and pathogen-associated molecular patterns function as alarms that trigger the immune system into action. Collectively, they can be classified as damage-associated molecular patterns.

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.
- Johansson, C. & Kelsall, B.L. Semin. Immunol. 17, 284–294 (2005).

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 immuoglobulin 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 responces 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.
- Takabayshi, K. *et al*. Immunity 24, 475–487 (2006).

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

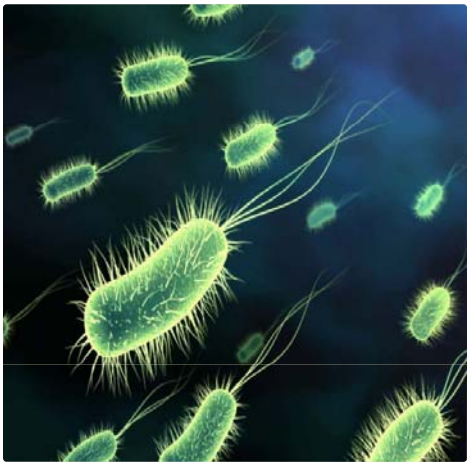
& forget to look at the bigger picture……

Innate And Adaptive Immunity In The Gut

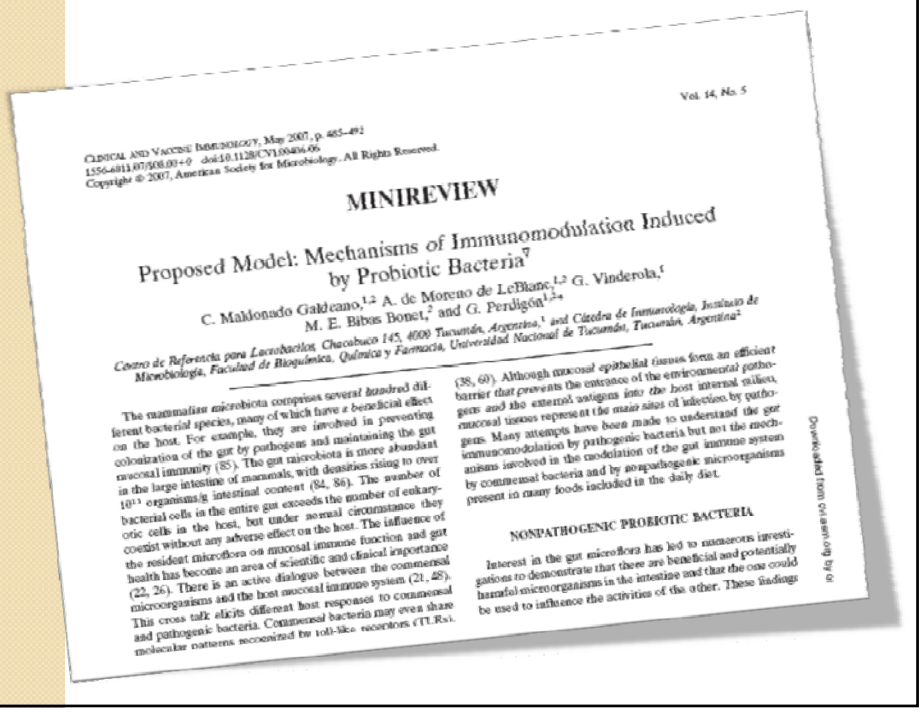
Innate and Adaptive Immunity in the Gut

Innate immunity		adaptive immunity
physicochemical	cellular	
Mucus	NK cells (? some IELs)	IEL
Tight junctions	Macrophages	LPL
Epithelial membranes	Polymorphonuclear leukocytes	Regulatory cytokines
Luminal/brush border enzymes	PRRs (Toll-like receptors)	sIgA
Bile salts	Epithelial cells	Peyer's patches
pH ranges		Epithelial cells/antigen presentation
somatostatin		
trefoil factors		

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



Pro Biotics and prebiotics as immunomodulating organisms can provide local and systemic anti inflammatory effects.



CLINICAL AND VACCINE IMMUNOLOGY, May 2007, p. 485–492 Vol. 14, No. 5
1556-6811/07/$08.00+0 doi:10.1128/CVI.00406-06

MINIREVIEW

Proposed Model: Mechanisms of Immunomodulation Induced by Probiotic Bacteria[▽]

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The mammalian microbiota comprises several hundred different bacterial species, many of which have a beneficial effect on the host. For example, they are involved in preventing colonization of the gut by pathogens and maintaining the gut mucosal immunity (85). The gut microbiota is more abundant in the large intestine of mammals, with densities rising to over 10^{11} organisms/g intestinal content (84, 86). The number of bacterial cells in the entire gut exceeds the number of eukaryotic cells in the host, but under normal circumstance they coexist without any adverse effect on the host. The influence of the resident microflora on mucosal immune function and gut health has become an area of scientific and clinical importance (22, 26). There is an active dialogue between the commensal microorganisms and the host mucosal immune system (21, 48). This cross talk elicits different host responses to commensal and pathogenic bacteria. Commensal bacteria may even share molecular patterns recognized by toll-like receptors (TLRs). (38, 60). Although mucosal epithelial tissues form an efficient barrier that prevents the entrance of the environmental pathogens and the external antigens into the host internal milieu, mucosal tissues represent the main sites of infection by pathogens. Many attempts have been made to understand the gut immunomodulation by pathogenic bacteria but not the mechanisms involved in the modulation of the gut immune system by commensal bacteria and by nonpathogenic microorganisms present in many foods included in the daily diet.

NONPATHOGENIC PROBIOTIC BACTERIA

Interest in the gut microflora has led to numerous investigations to demonstrate that there are beneficial and potentially harmful microorganisms in the intestine and that the one could be used to influence the activities of the other. These findings

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.

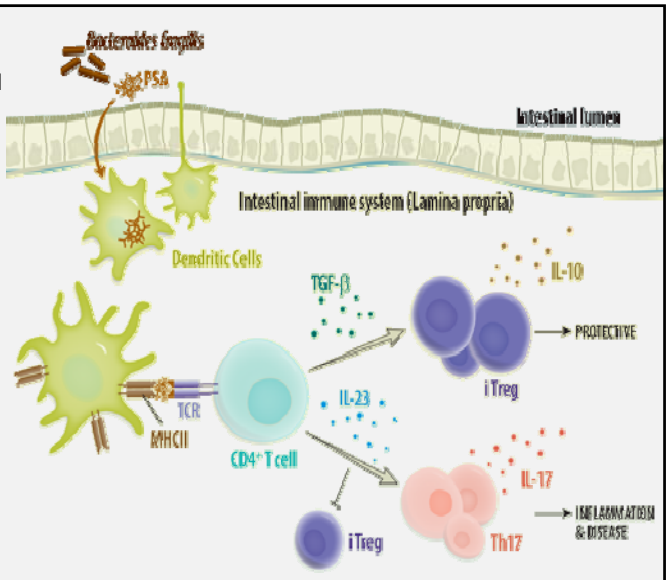
- Quigley EM, Quera R. Small intestinal bacterial overgrowth: roles of antibiotics, prebiotics and probiotics. Gastroenterology 2006;130(2Suppl 1):S78 S90.

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.

Mazmanian, S.K. & D.L. Kasper (2006) Nat. Rev. Immunol. **6**:849.



What It Is They Appear To Do?

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

- sIgA ⇧
- Cytokine modulation
- Epithelial Cell manipulation
- Dendritic Cell maturation
- Treg ⇧
- **Immunocommunication improvement**

Why It Is Good To Eat Human Strain Bacteria?

- 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
2. Differential cytokine response from dendritic cells to commensal and pathogenic bacteria in different lymphoid compartments in humans Am J Physiol Gastrointest Liver Physiol 290: G839-G845, 2006.
3. van der Kleij D, Latz E, Brouwers JF, *et al.* A novel host-parasite lipid cross-talk. Schistosomal lyso-phosphatidylserine activates Toll-like receptor 2 and affects immune polarization. *J Biol Chem* 2002;277:48122–9
4. Adams VC, Hunt J, Martinelli R, *et al.* Mycobacterium vaccae induces a population of pulmonary antigen presenting cells that have regulatory potential in allergic mice. *Eur J Immunol* 2004;34:631–8

Review

Probiotics and immunology: separating the wheat from the chaff

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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 relieve the symptoms of various diseases caused by dysregulated immune responses. Probiotics 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. Caveats remain and, distinct ecological niche that can resist the colonization of exogenous pathogenic microorganisms. Moreover, normal immune system development can occur in response to stimuli from gut microflora. Therefore, individuals whose normal gut microflora are destabilized might in turn exhibit disrupted immune function and and/or 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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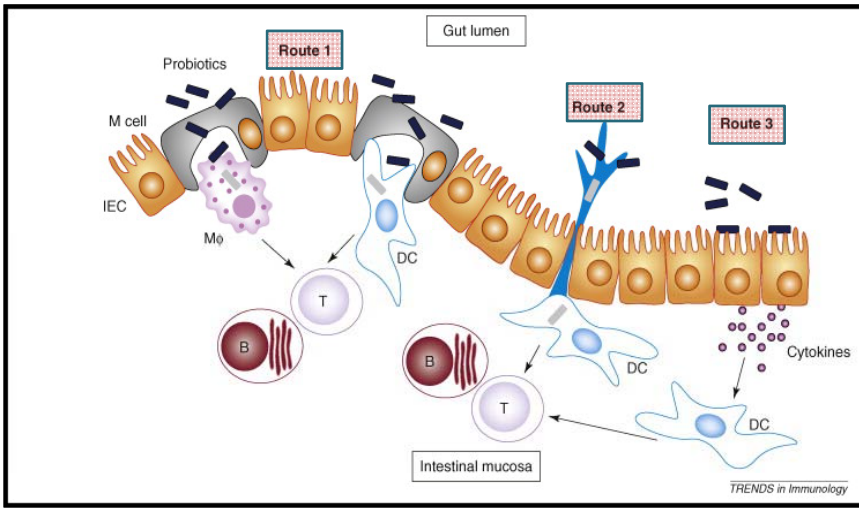
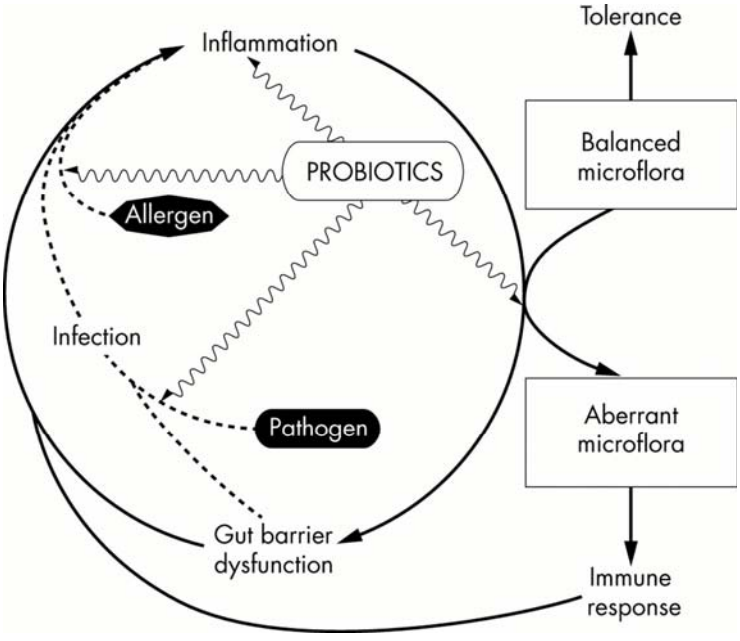
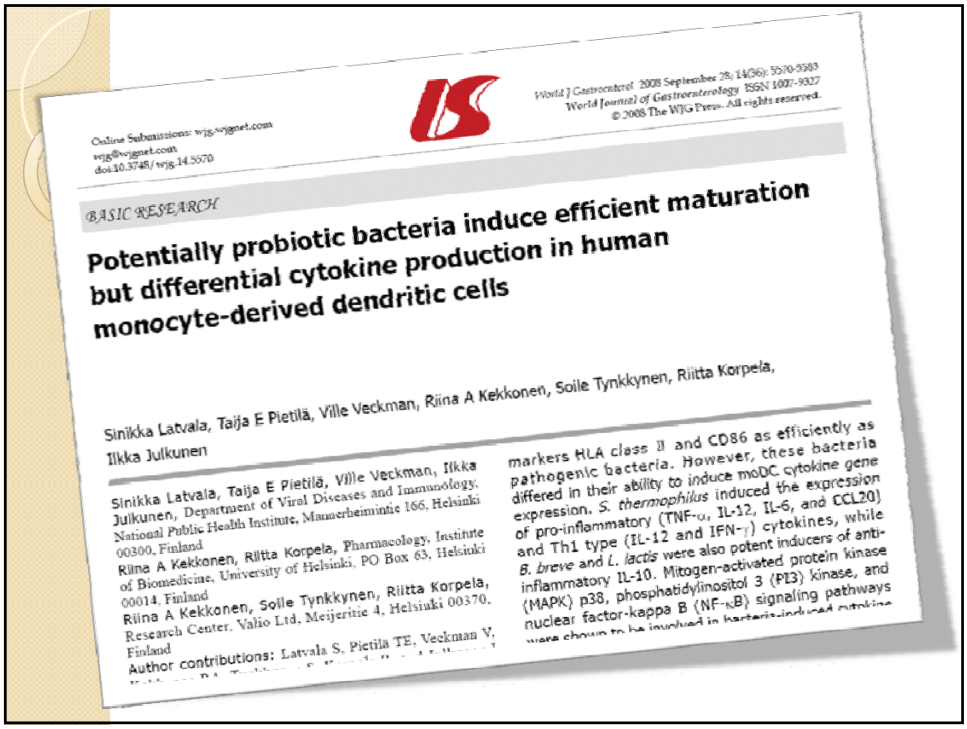


3 likely pathways for PB's to influence immunity

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 (M s) 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).





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BASIC RESEARCH

Potentially probiotic bacteria induce efficient maturation but differential cytokine production in human monocyte-derived dendritic cells

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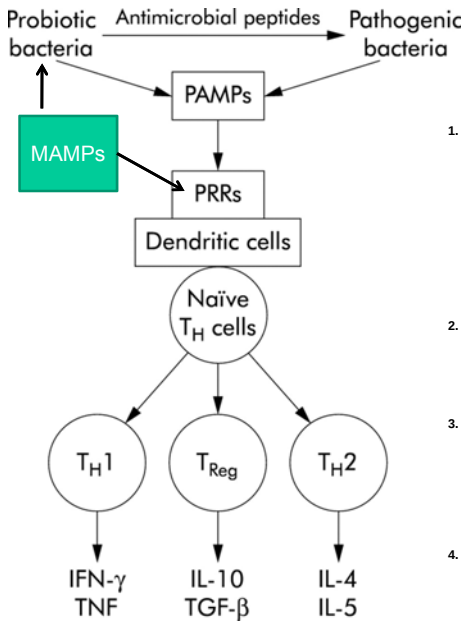
Author contributions: Latvala S, Pietilä TE, Veckman V,

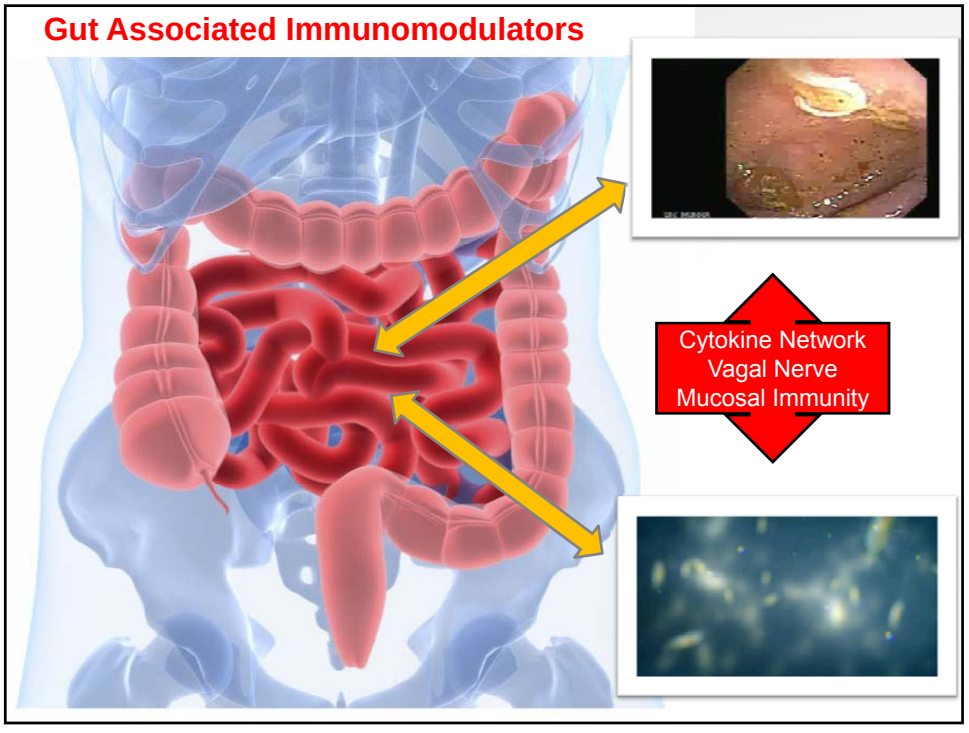
markers HLA class II and CD86 as efficiently as pathogenic bacteria. However, these bacteria differed in their ability to induce moDC cytokine gene expression. *S. thermophilus* induced the expression of pro-inflammatory (TNF-α, IL-12, IL-6, and CCL20) and Th1 type (IL-12 and IFN-γ) cytokines, while *B. breve* and *L. lactis* were also potent inducers of anti-inflammatory IL-10. Mitogen-activated protein kinase (MAPK) p38, phosphatidylinositol 3 (PI3) kinase, and nuclear factor-kappa B (NF-κB) signaling pathways



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.



- 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.

6. Ewaschuk, J.B. & L.A. Dieleman (2006) World J. Gastroenterol. **12**:5941.
7. O'Mahony, L. *et al.* (2006) Am. J. Physiol. Gastrointest. Liver Physiol. **290**:G839.
8. Imaoka, A. *et al.* (2008) World J. Gastroenterol. **14**:2511.
9. Ott, S.J. *et al.* (2004) Gut **53**:685.

The Gut - Source Of All Disease?

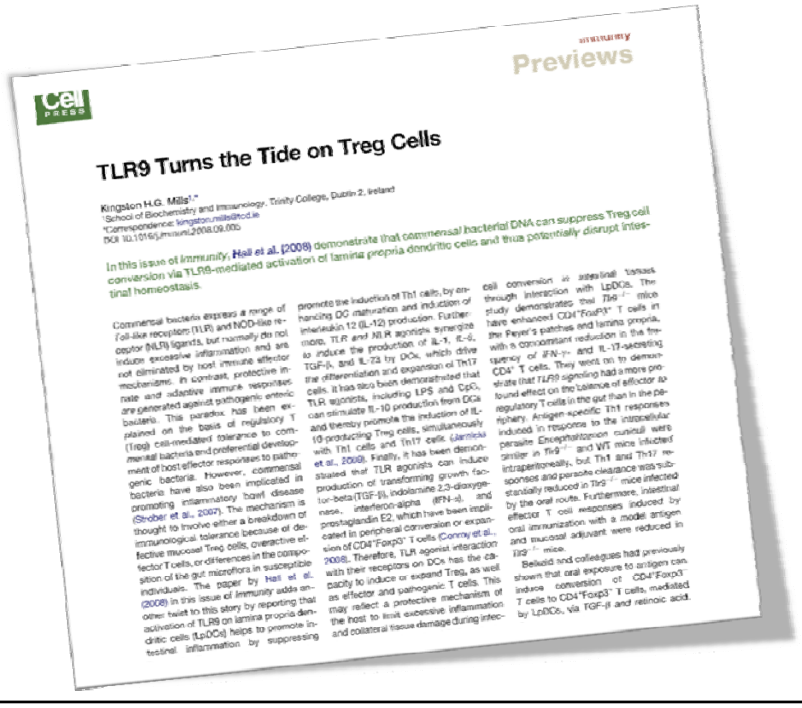
- Numerous chronic diseases may occur as a result of disturbances of mucosal barrier function or of changes in mechanisms regulating mucosal immunity.[1,2,3]

1. Tlaskalová-Hogenová, H., L. Tucková, R. Lodinová-Zádníková, *et al.* 2002. Mucosal immunity: its role in defense and allergy. Int. Arch. Allergy Immunol. 128: 77-89
2. Tlaskalová-Hogenová, H. 1997. Gnotobiology as a tool—an introduction. *In* Immunology Methods Manual. I. Lefkovits, Ed.: 1524-1559. Academic Press. London
3. Tlaskalová-Hogenová, H., R. Stepánková, T. Hudcovic, *et al.* 2004. Commensal bacteria (normal microflora), mucosal immunity and chronic inflammatory and autoimmune diseases. Immun. Lett. 93: 97-108

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

1. Bonizzi, G. & Karin, M. The two NF-B activation pathways and their role in innate and adaptive immunity. *Trends Immunol.* **25**, 280–288 (2004)
2. Karin, M. & Ben-Neriah, Y. Phosphorylation meets ubiquitination: the control of NF-B activity. *Annu. Rev. Immunol.* **18**, 621–663 (2000)
3. Hoffmann, A., Levchenko, A., Scott, M. L. & Baltimore, D. The IB-NF-B signaling module: temporal control and selective gene activation. *Science* **298**, 1241–1245 (2002)



Immunity

Previews

Cell PRESS

TLR9 Turns the Tide on Treg Cells

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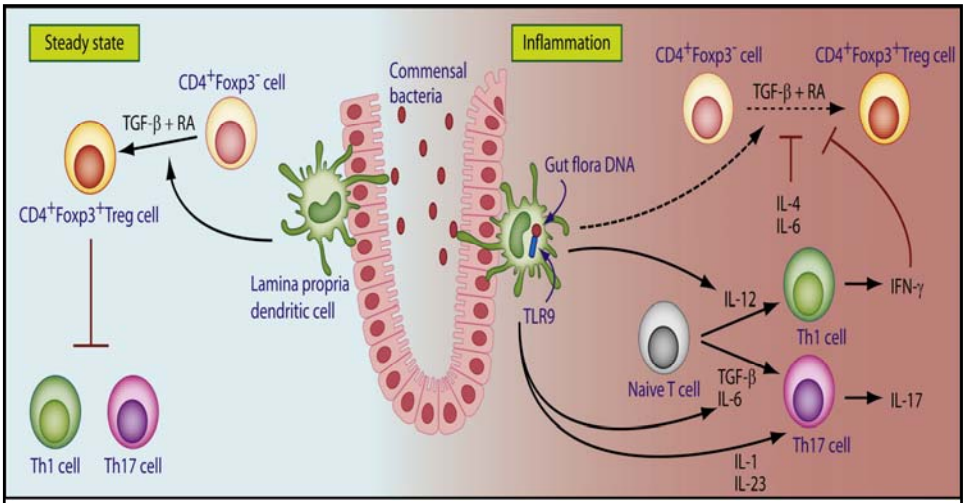
In this issue of *Immunity*, Hall et al. (2008) demonstrate that commensal bacterial DNA can suppress Treg cell conversion via TLR9-mediated activation of lamina propria dendritic cells and thus potentially disrupt intestinal homeostasis.

Commensal bacteria express a range of Toll-like receptor (TLR) and NOD-like receptor (NLR) ligands, but normally do not induce excessive inflammation and are not eliminated by host immune effector mechanisms. In contrast, protective innate and adaptive immune responses are generated against pathogenic enteric bacteria. This paradox has been explained on the basis of regulatory T (Treg) cell-mediated tolerance to commensal bacteria and preferential development of host effector responses to pathogenic bacteria. However, commensal bacteria have also been implicated in promoting inflammatory bowel disease (Strober et al., 2007). The mechanism is thought to involve either a breakdown of immunological tolerance because of defective mucosal Treg cells, overactive effector T cells, or differences in the composition of the gut microflora in susceptible individuals. The paper by Hall et al. (2008) in this issue of *Immunity* adds another twist to this story by reporting that activation of TLR9 on lamina propria dendritic cells (LpDCs) helps to promote intestinal inflammation by suppressing

promote the induction of Th1 cells, by enhancing DC maturation and induction of interleukin 12 (IL-12) production. Furthermore, TLR and NLR agonists synergize to induce the production of IL-1, IL-6, TGF-β, and IL-23 by DCs, which drive Th17 differentiation and expansion of Th17 cells. It has also been demonstrated that TLR agonists, including LPS and CpG, can stimulate IL-10 production from DCs and thereby promote the induction of IL-10-producing Treg cells, simultaneously with Th1 cells and Th17 cells (Jankovic et al., 2008). Finally, it has been demonstrated that TLR agonists can induce production of transforming growth factor-beta (TGF-β), indoleamine 2,3-dioxygenase, interferon-alpha (IFN-α), and prostaglandin E2, which have been implicated in peripheral conversion or expansion of CD4$^+$Foxp3$^+$ T cells (Conroy et al., 2008). Therefore, TLR agonist interaction with their receptors on DCs has the capacity to induce or expand Treg, as well as effector and pathogenic T cells. This may reflect a protective mechanism of the host to limit excessive inflammation and collateral tissue damage during infec-

cell conversion in intestinal tissues through interaction with LpDCs. The study demonstrates that *Tlr9*$^{-/-}$ mice have enhanced CD4$^+$FoxP3$^+$ T cells in the Peyer's patches and lamina propria, with a concomitant reduction in the frequency of *IFN-γ*- and IL-17-secreting CD4$^+$ T cells. They went on to demonstrate that *TLR9* signaling had a more profound effect on the balance of effector to regulatory T cells in the gut than in the periphery. Antigen-specific Th1 responses induced in response to the intracellular parasite *Encephalitozoon cuniculi* were similar in *Tlr9*$^{-/-}$ and WT mice infected intraperitoneally, but Th1 and Th17 responses and parasite clearance was substantially reduced in *Tlr9*$^{-/-}$ mice infected by the oral route. Furthermore, intestinal effector T cell responses induced by oral immunization with a model antigen and mucosal adjuvant were reduced in *Tlr9*$^{-/-}$ mice.

Belkaid and colleagues had previously shown that oral exposure to antigen can induce conversion of CD4$^+$Foxp3$^-$ T cells to CD4$^+$Foxp3$^+$ T cells, mediated by LpDCs, via TGF-β and retinoic acid.



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.

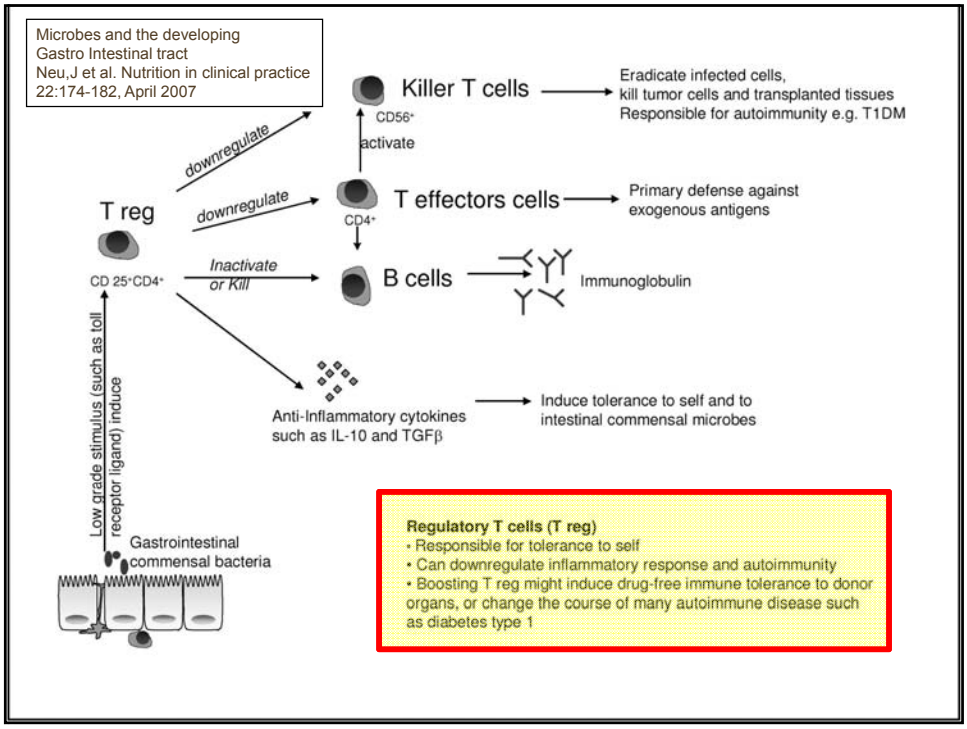
Regulatory T (Treg) Cells

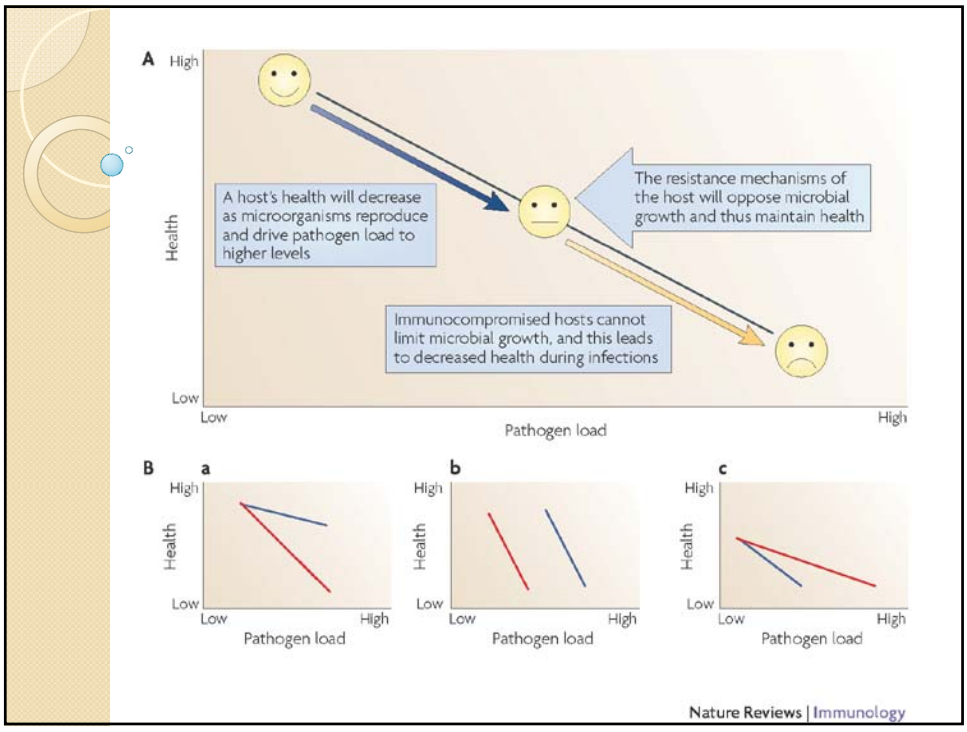
It is not yet known which particular organism(s) are the most potent in inducing Treg responses to suppress NFkB

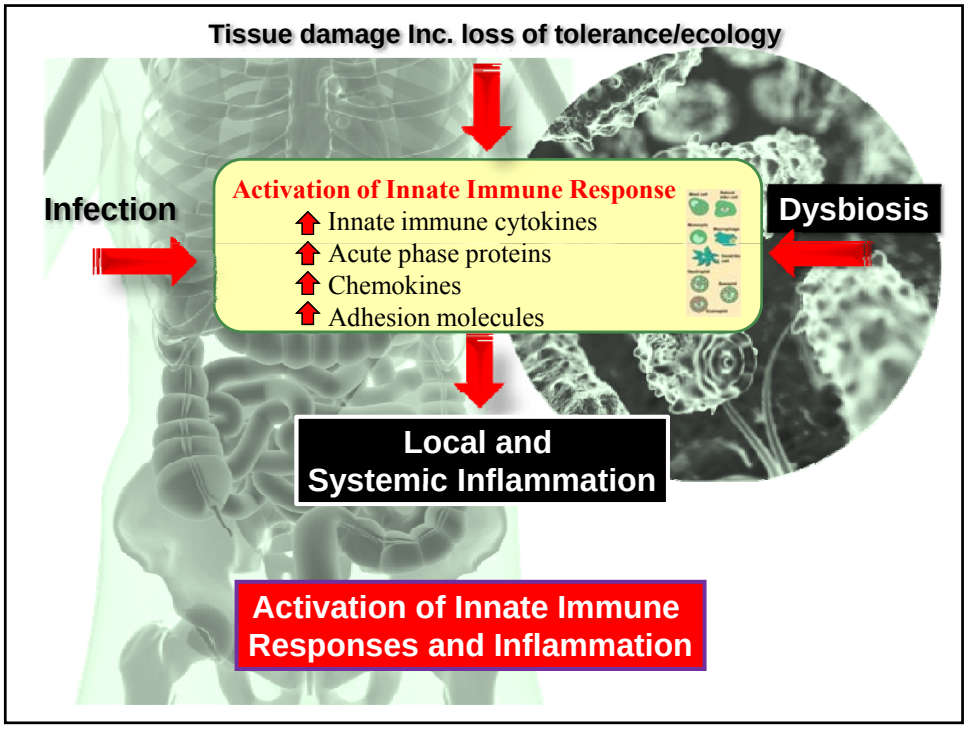
- commensals and other gut based organisms likely have the greatest efficacy[1,2]

1 Murch ,S. Probiotics as mainstream allergy therapy? *Archives of Disease in Childhood* 2005;90:881-882

2 O'Mahony C, et al. PLoS Pathog. 2008 Aug 1;4(8):e1000112. Commensal-induced regulatory T cells mediate protection against pathogen-stimulated NF-kappaB activation.


Microbes and the developing
Gastro Intestinal tract
Neu,J et al. Nutrition in clinical practice
22:174-182, April 2007
Killer T cells
CD56+
Eradicate infected cells,
kill tumor cells and transplanted tissues
Responsible for autoimmunity e.g. T1DM
activate
downregulate
downregulate
T reg
T effectors cells
CD4+
Primary defense against
exogenous antigens
CD 25+CD4+
Inactivate
or Kill
B cells
Immunoglobulin
Low grade stimulus (such as toll
receptor ligand) induce
Anti-Inflammatory cytokines
such as IL-10 and TGFβ
Induce tolerance to self and to
intestinal commensal microbes
Gastrointestinal
commensal bacteria
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


A
High
Health
Low
A host's health will decrease as microorganisms reproduce and drive pathogen load to higher levels
The resistance mechanisms of the host will oppose microbial growth and thus maintain health
Immunocompromised hosts cannot limit microbial growth, and this leads to decreased health during infections
Low
High
Pathogen load
B
a
b
c
Nature Reviews | Immunology



Treg Cells Are Inflammation Controllers

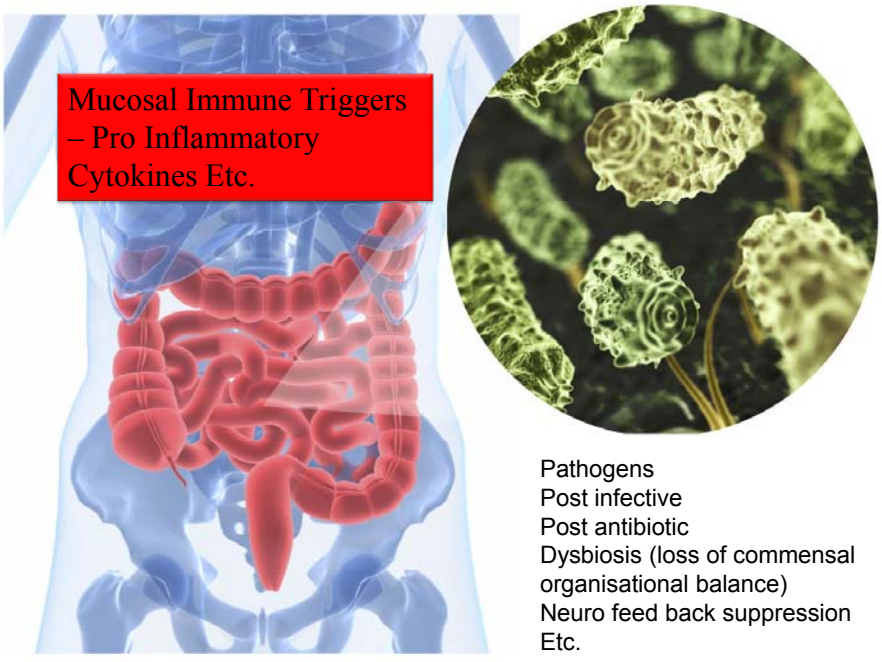
- Such mechanisms include the development of regulatory T cells that secrete interleukin 10 (IL-10), which has many immunosuppressive and anti-inflammatory effects.

1. Yazdanbakhsh, M., Kremsner, P. G. & van Ree, R. Allergy, parasites, and the hygiene hypothesis. Science 296, 490–494 (2002).
2. Galli, S. J. & Askenase, P.W. in The Reticuloendothelial System: A Comprehensive Treatise Vol. IX: Hypersensitivity (eds Abramoff, P., Phillips, S. M. & Escobar, M. R.) 321–369 (Plenum, 1986).
3. Fallon, P. G. & Mangan, N. E. Suppression of T_H2-type allergic reactions by helminth infection. Nature Rev. Immunol. 7, 220–230 (2007).

Dendritic Cells are APCs

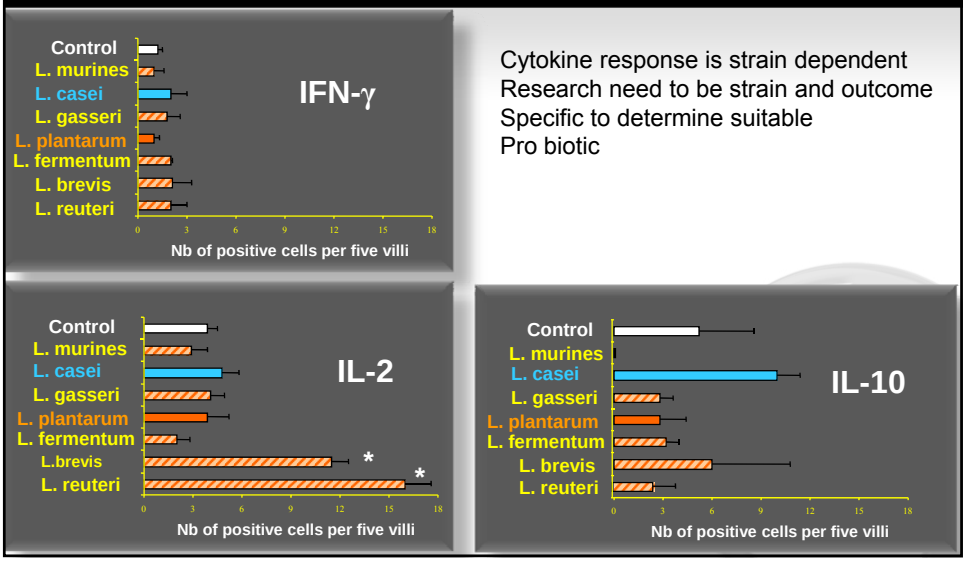
- Dendritic cells have important roles in the activation and resolution of innate immune responses

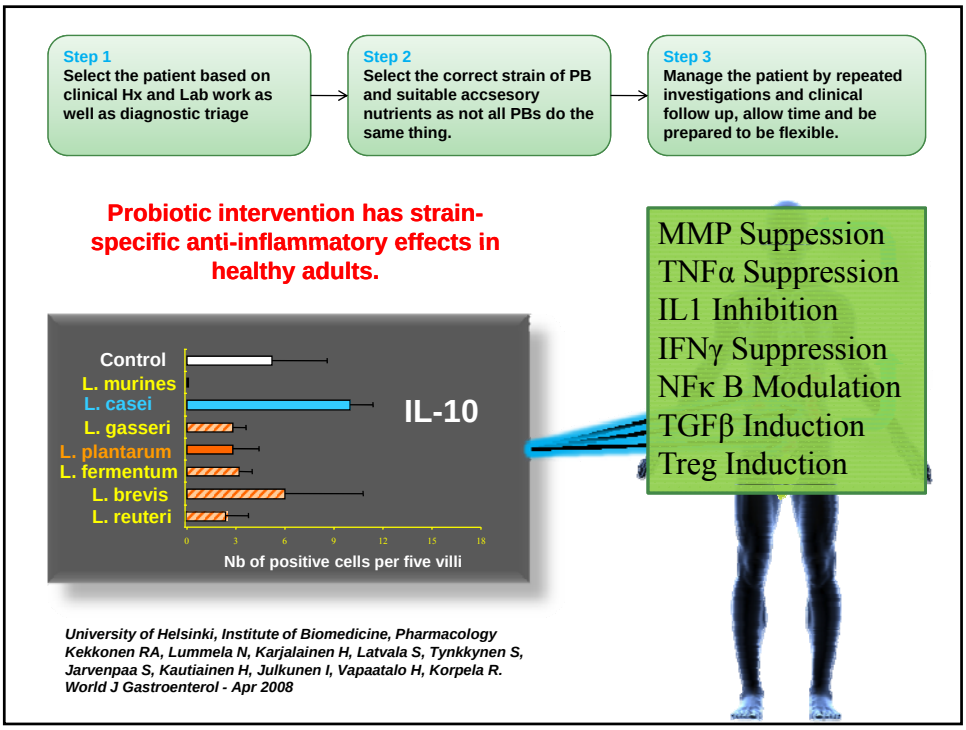
- Shortman, K. & Naik, S. H. Steady-state and inflammatory dendritic-cell development. Nature Rev. Immunol. 7, 19–30 (2007)
- Steinman, R. M. & Banchereau, J. Taking dendritic cells into medicine. Nature 449, 419–426 (2007)



Pathogens
Post infective
Post antibiotic
Dysbiosis (loss of commensal organisational balance)
Neuro feed back suppression
Etc.

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





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.

- Sheil B, et al. Probiotic effects on inflammatory bowel disease. J Nutr 2007;137:819S-24S.

GIT- Immuno Regulation Of Inflammation-Increase

- IL-10, IL-4 IL-13, TGFβ
- Treg
- SIgA
- 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

Dietary Sources Of PPARγ Modulators

Alpha Linolenic Acid	Leafy Greens/Flax
Capsaicin	Cayenne Pepper
Conjugated Lino Acid	Beef, Bovine Milk
Curcumin	Tumeric
DHA	Fish
EPA	Fish
Resveratrol	Grapes, Wine Peanuts
Ginsenosides	Ginseng
Hesperidin	Citrus Fruits
Butyrate	SCFA's

GIT- Immuno Regulation of Inflammation - Decrease

- TNFα, 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 30-60^{9} CFU (Lactobacillus casei, subspecies rhamnosus GG, ATCC strain 53103))
- Lactobacillus, plantarum, rhamnosus, salivarius 20-60^{9} CFU
- B. Bifidus Bacteria 20-60^{9} 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.

Sartor RB. Therapeutic manipulation of the enteric microflora in inflammatory bowel diseases: antibiotics, probiotics, and prebiotics. Gastroenterology 2004;126:1620-1633

MacDonald TT, Monteleone G. Immunity, inflammation, and allergy in the gut. Science 2005;307:1920-1925.

- 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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