THE STANDARD

ROAD MAP SERIES

Supporting Immune Function

A Lifestyle and Nutrient Approach

Principles and Protocols for Heathcare Professionals

By Thomas G. Guilliams Ph.D.

POINT INSTITUTE
STEVENS POINT, WI

The Point Institute was founded by Thomas Guilliams, Ph.D. as an independent research organization focused on examining and disseminating information about the use of natural therapeutic options for treating and preventing chronic disease. Along with therapies generally defined as lifestyle interventions, the Point Institute specializes in the evidence and application of nutraceuticals (dietary supplements, herbs, vitamins, minerals, etc.) as therapeutic and preventative agents in clinical practice.

Table of Contents

Lifestyle-Based Therapies-Our Core Philosophy 9
- Physiological Resilience and Metabolic Reserve 9
- Prevention-to-Intervention Hierarchy 12
- The Seven Spheres of Lifestyle Signals 13

Basic Principles for Building Immune Health **14**

The Immune System: A Functional Overview **18**
- The Innate and Adaptive Immune Systems 18
- Antigen Presentation and MHC Classes 20
- T-Helper Cells and the Control of the Adaptive Immune Response 21
- Mitochondrial Function and Supporting the Immune System 23
- Pattern Recognition Receptors and the Innate Immune System 24
- Immunosenescence 27

The Role of the GI Tract in Immune Function **29**
- Intestinal Permeability: A Breach in the Barrier 31
- Commensal-Friendly Environment 31
- Heal the Gut First 31
- Reducing Inflammation 32
- GI-Specific Nutrients 33

Autoimmune and Autoinflammatory Conditions **35**
- How Autoimmunity Works 35
- Auto-antibodies: Up or Down-Regulation? 36
- Immunoglobulin Gene Recombination: A Creative Solution to an Immunity Dilemma 37
- Autoinflammatory Diseases 40
- Commonalitites of Autoimmune Diseases 41
- The Immune Complex 42
- DHEA Supplementation for Autoimmune Conditions 43

Immune Support through Lifestyle Interventions **45**
- Diet and Nutrition 46
  - General Dietary Patterns 46
  - Macronutrients 47
  - Micronutrients 48
  - Multivitamin/Minerals for Immune Enhancement 51
- Physical Activity and Immune Function 52
- The Stress Response and Immune Function 54
  - The Stress Response System 54
  - Cortisol and DHEA: Opposing Immune Regulators 54
- Chronicity (Circadian Control and Sleep) 56
  - Molecular Control of Circadian Clock(s) 57
  - The Role of Melatonin in Immune Function 58
  - The Menstrual Cycle and Immune Function 60
- Environmental Signals (Good & Bad) 61
- Hygiene and Habits 64
- Community and Purpose 67

Table of Contents

Testing Immune Function 71
- Allergy Testing 71
- Celiac Disease and Gluten Sensitivity 71
- Antibody Testing: General and Specific 72
- Autoimmune Testing 73
- Inflammatory Markers 74
- Cytokines 75
- Immune Cell Types and Activities 75
- Adjunct Tests for Immune Function 75

Reducing Chronic Inflammatory Triggers and Mediators 76
- Mediators of Inflammation 76
- Lifestyle Factors Contributing to Chronic Inflammation 77
- Clinical Markers of Chronic Inflammation 79
- Lifestyle Interventions to Prevent and Reduce Inflammation 80
- Nutraceutical Intervention for Acute and Chronic Inflammation 81
- NF-kB Pathway and Inflammatory Activation 84

The Allergic Response (Allergic Rhinitis) 89
- Common Allergens 90
- Allergic Susceptibility 90
- Prevention and Treatment 91
- Avoidance 91
- Drug Therapies 91
- Immunotherapy 92
- Diet and Allergy Risk 92
- Dietary Supplements (Probiotics, Quercetin, Petasites, Stinging Nettles, Other Agents) 93
- Natural Bronchodilators and Mucolytics 96

Natural Immune-Modulating Agents 100
- Herbs and Botanical Extracts 100
- Antimicrobial, Antiviral or Antifungal Agents 102
- Non-herbal Immune-modulating Ingredients 102
- Probiotics 103
- Omega-3 Fatty Acids 106

Mushroom-Derived Dietary Supplements as Immunomodulators 111
- Mushroom Bioactive Constituents 111
- Mushroom as Immunomodulators 112
- Effect of Mushrooms on the Innate Immune System 112
- Effect of Mushrooms on the Adaptive Immune System 113
- Direct Antimicrobial Actions of Mushrooms 114
- Direct Anti-tumor Actions of Mushrooms 114

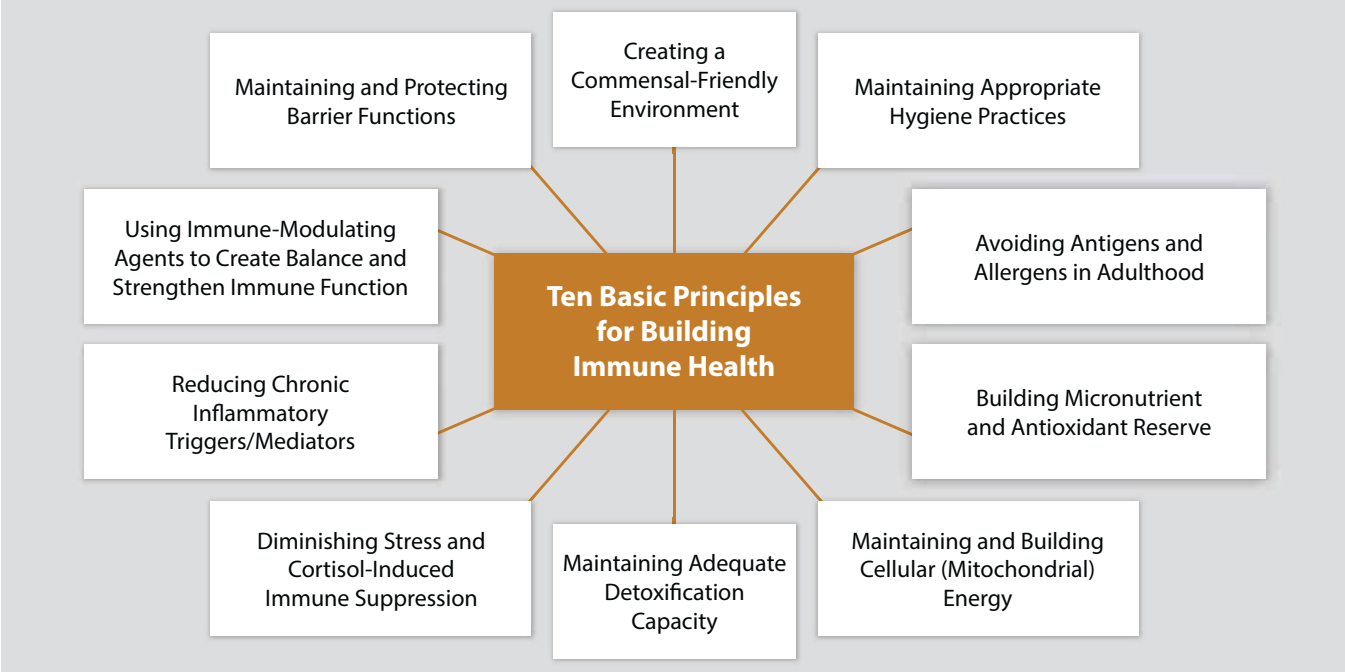
Supporting Immune Challenges 117
- Supporting Immune Challenges: Candidiasis 117
- Supporting Immune Challenges: The Urinary Tract 120
- Supporting Immune Challenges: Sinusitis 122

Anti-Inflammatory/Inflammatory Foods Handout 124

Basic Principles for Building Immune Health

Throughout this guide there is an abundance of detailed information about the specific mechanisms that allow the immune system to function properly. While these details are important for the clinician dealing with complex immune-related health concerns, it is equally important to keep in mind the fundamental principles at work within those details—those that build and maintain the foundation of a strong immune system.

As more research is published, our detailed understanding of the mechanisms will change, but these fundamental principles will not. Likewise, strategies for supporting immune function vary widely among various healing disciplines and will often need to be tailored to each patient's situation. For this reason, we believe it is important clinicians keep in mind the core principles that form the basis of any immune-supporting strategy. Here we outline 10 of those principles, built upon throughout the rest of this guide.



Maintaining and Protecting Barrier Functions

Even though immune system function is often measured by immune cell numbers or cytokine concentrations in the peripheral blood, most of the activity of the immune system occurs within the various tissues and specialized organs/glands that control the interface between our bodies and the outside world. In fact, most immune system cells are found within specialized mucosal membranes that make up the gastrointestinal tract, respiratory tract, genitourinary tract and lungs. Generically, this is known as the mucosa-associated lymphoid tissue (MALT). The largest portion of this is the gut-associated lymphoid tissue (GALT), where it is said greater than 75% of all mature immune cells reside and function. (See page 29 for a detailed description).

Breaches in barrier function are one of the most potent immune challenges a person can face. This is why protecting barrier function, especially the integrity of the barrier within the intestinal mucosa, is vital for basic immune function and appropriate immune responses. Understanding the integrity of the gut mucosa, then, is one of the hallmarks of functional (and naturopathic) medicine, where "heal the gut first" has become a common theme. There is a section (pages 31–33) dedicated to appropriate ways to maintain and protect the barrier function of the gastrointestinal tract.

Creating a Commensal-Friendly Environment

This support mechanism is closely related with barrier function as friendly commensal organisms reside almost exclusively in the skin or mucosal membranes (mouth, GI, vagina, etc.). An environment that allows for the proper number and type of commensal organisms, and is unfriendly to most harmful organisms, is important for overall health and vital for proper immune function. Because so much of the immune system resides in the GI tract, the "training" and maturation of immune system cells is dependent on the interaction with commensal organisms within the gut microflora. There is a discussion on the detailed relationship between commensal organisms and immune system health and function (mostly as it relates to the GI-tract) starting on page 31. The role of probiotic therapies for immune modulation and disease outcomes are reviewed on page 103.

Maintaining Appropriate Hygiene Practices

In the historic battle between human health and infectious diseases stands the appropriate role of personal and community hygiene practices. Changes in personal hygiene practices, water and sewage facilities, quarantine of infectious individuals and similar practices have saved countless lives. Where these practices are less common throughout developing nations, infectious diseases are still common and devastating.

Ironically, the modern trend toward a highly sanitized environment in developed countries like the United States has led to a host of other immune-related and infectious disease-related dilemmas. The overuse/abuse of antibiotics over the past half-century has led to a variety of antibiotic-resistant organisms difficult or nearly impossible to treat, even in healthy subjects. Likewise, the so-called "hygiene hypothesis" predicts children with little or no access to "germs" during the early stages of immune development will have adverse or inappropriate immune responses (higher levels of autoimmune and atopic conditions).

While we will not review the history of hygiene practices, we will cover some basic personal hygiene issues that (still) need to be emphasized to patients (page 64).

Avoiding Antigens and Allergens in Adulthood

This advice appears basic but it is fundamentally associated with the phenomenon of immune system aging known as immunosenescence (see page 27). As we age, our immune system appears less able to adapt new strategies when encountering new antigens, and it appears to be more vulnerable to immune-related disorders. The elderly seem to be especially vulnerable to seasonal infectious agents, chronic inflammatory diseases and, of course, malignantly transformed cells not removed by the immune system before multiplying.

As the rest of this road map will elaborate, there are many ways to build a stronger immune response and increase the metabolic reserve our immune system relies on every day. However, it is clear that avoiding unnecessary exposure or purposefully avoiding antigens and allergens may be a prudent way to stay healthy and avoid episodes of critical illness. While the hygiene hypothesis may explain the need for appropriate antigen/allergen exposure in children, this is not a strategy for improving immune health in the elderly.

Building Micronutrient and Antioxidant Reserve

One of the hallmarks of modern nutrition is the connection between specific nutrient deficiencies and disease susceptibility. No one questions that when we are truly deficient in one or more vitamin or mineral, we have reduced capacity to fight off various diseases. However, the notion that there is a continuum between micronutrient deficiency on one end and optimal immune-enhancing levels of micronutrient intake on the other is often underappreciated. Put another way, in many individuals, especially those with immune challenges or illnesses, the USRDA levels of particular vitamins or minerals may not be sufficient to create the optimal immune-supporting level of those micronutrients. While the body has the ability to store some minerals and fat-soluble vitamins, an immune challenge can quickly deplete the reserve of critical micronutrients, leaving the individual vulnerable.

Throughout this guidebook, we will outline specific micronutrients known to be depleted during immune challenges or shown to affect immune- or illness-related outcomes when used as therapeutic agents.

An active and challenged immune system produces a wide-range of oxygen radicals as a natural consequence of mounting a strong defense. It is critical these oxygen radicals are swiftly neutralized by a strong network of antioxidants. While many micronutrients are vital to the antioxidant reserve (vitamin C, E, selenium, etc.), building antioxidant reserve requires manufacturing adequate glutathione levels, as well as triggering appropriate upregulation of antioxidant response element (ARE) modulated genes.

We will discuss the role of antioxidants in maintaining immune health throughout this guidebook, especially as it relates to the next two key elements: mitochondrial energy and detoxification capacity. Since most therapeutic antioxidants are consumed in the diet, or as dietary supplements, specific antioxidant therapies will mostly be covered in the diet and nutrition section starting on page 46.

Maintaining and Building Cellular (Mitochondrial) Energy

When the immune system is under attack, every bit of the metabolic reserve available for energy can be quickly depleted, leaving the patient exhausted and even lethargic, which is part of the classic illness syndrome. When our cellular energy reserves are depleted due to poor diet, stress, strenuous exercise, short sleep duration, or to perform other critical metabolic functions such as detoxification, our immune system can be easily overwhelmed. In addition, recent studies have shown mitochondria are critical to the function of both the innate and adaptive immune systems, participating in antiviral signaling and antibacterial activities. For an overview of the mechanisms relating mitochondrial functions and the immune system see page 23.

Maintaining Adequate Detoxification Capacity

Another important area of metabolic reserve that directly impacts immune function is liver function, and more specifically, detoxification capacity. When liver function and detoxification capacity are functioning appropriately, removing exogenous and endogenous toxins, a significant burden is removed from internal immune and GI functions. However, slow or incomplete detoxification allows for cell damage and GI irritation that can exacerbate immune-system inflammatory responses, deplete nutrient resources, and create opportunities for additional immune-related vulnerabilities.

While most patients can benefit from an appropriate detoxification protocol, patients with immune system challenges may greatly benefit from annual or semi-annual detoxification protocols that allow them to systematically remove allergens and toxins from their diet and use targeted nutrients known to upregulate both phase I and phase II liver detoxification enzymes. These will usually boost glutathione and antioxidant levels as well. We will cover some of the principles of toxic burden and the role of detoxification in the section covering environmental signals (page 61). For a more complete approach to detoxification, see our principles and protocols for comprehensive liver detoxification in our guidebook, "*Gastrointestinal Health: A Lifestyle and Nutrient Approach,*" (available in 2015).

Diminishing Stress and Cortisol-Induced Immune Suppression

Stress in general, and cortisol specifically, is a powerful inhibitor of the innate immune response. Cortisol is known as one of the most potent endogenous anti-inflammatory molecules, whereas inflammatory mediators such as IL-6 and TNF-α are strong triggers of the HPA axis. While these compensatory actions are critical for healthy immune and stress responses, chronic stress can lead to long-term immune suppression and autoimmune susceptibility. We will cover the relationship of stress and stress-reduction on immune outcomes as part of the lifestyle interventions in immune support (page 54).

Reducing Chronic Inflammatory Triggers/Mediators

Inflammation is one of the core functions of the innate immune system and is vital to a healthy immune response. However, inappropriate or chronic inflammatory signaling is a hallmark of almost every chronic disease, and the appropriate modulation of inflammation is critical for a healthy immune system. There is a complete section dedicated to the mechanisms and consequences of chronic inflammation, including the many ways clinicians can help a patient modulate their inflammatory responses without pharmaceutical intervention (pages 76–88).

Using Immune-Modulating Agents to Create Balance and Strengthen Immune Function

While the foundation of immune support is in building metabolic reserve, there are a number of ways to specifically enhance immune function using agents generally referred to as immune modulators. These agents vary in their mechanisms, but are mostly derived from plants or fungi. Some of these agents are antimicrobial, antiviral, antifungal or antiparasitic; while other agents act to stimulate or modulate immune cell function. While we will discuss the mechanisms of numerous such agents throughout this guidebook, there is a section exclusively covering this topic (pages 100–116).

The Immune System: A Functional Overview

Assessing and supporting the functions of the immune system, or providing remedies to increase someone's ability to prevent or shorten an illness, are hallmarks of the art of medicine from ancient times to the present day. While often successful, these remedies were given with little knowledge of either the immune system or the disease processes driving the visible symptoms. Our current knowledge of the immune system has grown tremendously over just the past few decades, giving us many new potential avenues for creating effective immune system support protocols; and while many infectious diseases of the past have ceased to be major threats in Western societies, new stressors have been placed upon the human immune system that requires a robust and comprehensive strategy to maintain optimal health.

The immune system acts to protect us from a myriad of potentially harmful organisms, often with an efficiency that goes unnoticed. However, if invading organisms get the upper hand, or our immune system begins to manifest dysfunction, a host of illnesses can ensue. It is these challenges to the immune system that result in the vast majority of hospital and physician visits, often resulting in a prescription designed to kill the invading organism or mitigate the damage. Our understanding of the immune system has advanced far beyond the simplicity of the "Germ Theory" of disease, where all ills were blamed on intruding organisms. Today we are more familiar describing the complex, and often dichotomous, role of immune cells in both the risk and resolution of chronic diseases (e.g., the inflammatory process). For better or worse, the legacy of the germ theory still leads many to assume that infectious organisms, rather than the immune system of the host, is the main target of therapy. The best strategies, however, are therapies directed at strengthening host immune function while using safe and targeted anti-infectious strategies when necessary.

The immune system is a complex network of specialized cells and tissues that interact through a multitude of coordinated cell-to-cell-signaling molecules, membrane receptors and intracellular signaling mechanisms. Immune cells are found in nearly every tissue of the body, where they act as sentries detecting foreign antigens or damaged cells, and throughout the circulatory system, where they can quickly mobilize to the site of an ongoing immune challenge. The immune system is one of the body's most important surveillance systems, protecting it from "outside" invaders and "inside" damage that have the potential to produce harm. This surveillance system is coordinated and modulated by two other surveillance systems designed to help us respond to the environment around us: the hypothalamus-pituitary-adrenal (HPA) axis and the gastrointestinal tract.[1] As we will show throughout this guidebook, both the HPA axis and the GI interface play a tremendous role in facilitating the maturation and response of the immune system.[2]

The Innate and Adaptive Immune Systems

Traditionally, the immune system is described as being divided into two sub-systems: the innate immune system and the adaptive immune system (see Figure 4). Both are vital for protecting our bodies from invading organisms and are interrelated to, and highly dependent upon, one another. In fact, the more we learn about the functions of each, the less "divided" they appear.

Generally, the innate immune system is considered the "first line of defense" and is usually considered to be nonspecific. This system involves mechanical barriers to pathogens (skin, mucous membranes, etc.), chemical barriers (stomach acid), secretory barriers (enzymes, immunoglobulin (sIgA)) and the inflammatory processes. Immune cells typically associated with the innate immune system include

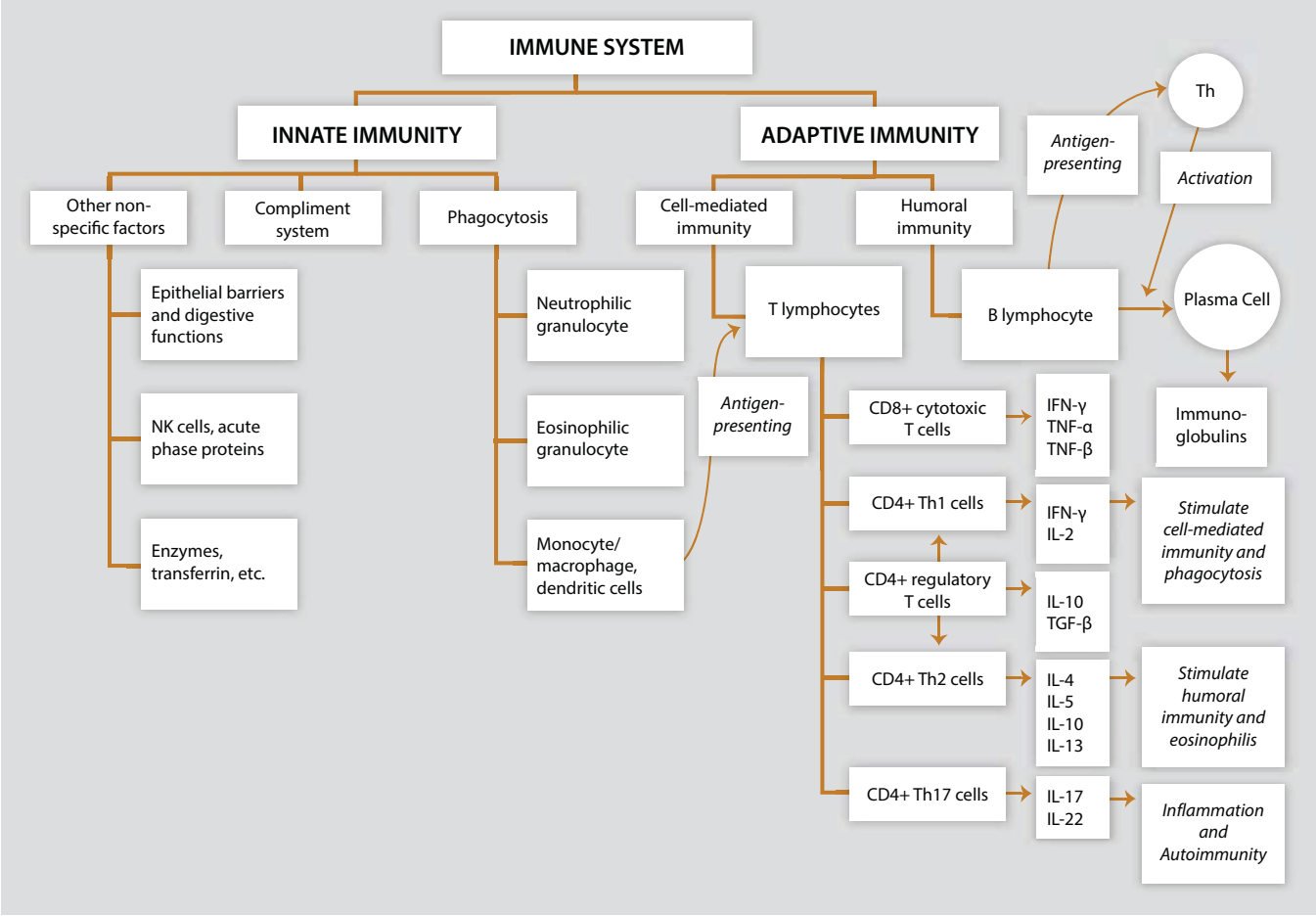


Figure 4: Schematic representation of the human immune system. CD = Cluster of differentiation; INF-γ = interferon-γ, IL = interleukin; NK cell = natural killer cell; TH = T helper lymphocyte; TGF = transforming growth factor; TNF = tumor necrosis factor. Adapted from Wintergerst ES, Maggini S, Hornig DH. Contribution of selected vitamins and trace elements to immune function. *Ann Nutr Metab*. 2007;51(4):301-23.

neutrophils, basophils, eosinophils, macrophages, dendritic cells, mast cells and natural killer (NK) cells (see Figure 5). These cells are generally non-antigen-specific and appear to have no "memory" of previous antigen encounters. These barriers and cells often prevent pathogens from getting a foothold in sensitive tissues, limiting the necessity of an adaptive immune system response.

In contrast to the innate immune system, the adaptive immune system adapts to invading organisms over time. The primary cells involved in this system are the T and B lymphocytes (see Figure 5). They are able to recognize invading organisms with a high degree of specificity using T-cell receptors (TCR)

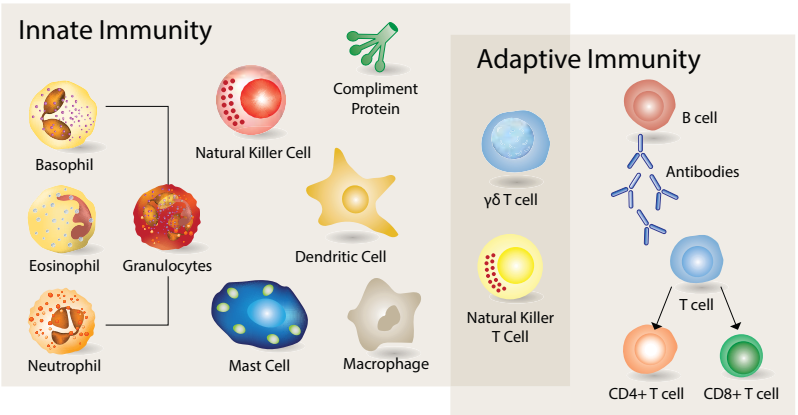


Figure 5: The Cells of the Innate and Adaptive Immune System. This diagram shows the basic types of cells of the innate and adaptive immune system. As the figure shows, natural killer T cells and gamma-delta T cells (a special lymphocyte that expresses a unique T-cell receptor) function in ways that are intermediate between the innate and adaptive immune systems. [Adapted from *Nature Reviews Cancer* 4, 11-22 (January 2004)]

and immunoglobulin (Ig) proteins (aka antibodies). The adaptive immune cells also have "memory," allowing a second invasion of the same (or cross-reactive) antigen to stimulate a quicker, more potent response. This memory is achieved by clonal expansion of a T or B cell after it encounters an antigen for which it has specificity. By expanding the number of memory cells, the response to the next encounter with the same antigen can be swift and potent. Also, memory cells undergo antigen-stimulated metabolic priming that allows them to quickly engage the necessary metabolic machinery to mount a more immediate secondary immune response.

Much of the interaction between the innate and the adaptive immune response comes through the process of antigen presentation. Various antigen-containing particles (virus, bacteria, fungi, food peptides, etc.) are taken up by certain antigen presenting cells (generally macrophages or dendritic cells, but sometimes B cells) through phagocytosis or receptor-mediated endocytosis before being processed for presentation to T cells (see Figure 6). This presentation is done by displaying the processed antigenic portions (sometimes called epitopes) within a pocket of a membrane-associated molecules known as major histocompatibility complexes (MHC), also known in humans as human leukocyte antigens (HLA). When an antigen-presenting cell docks with a T cell that recognizes the particular antigen being presented and the appropriate secondary receptors and cytokines

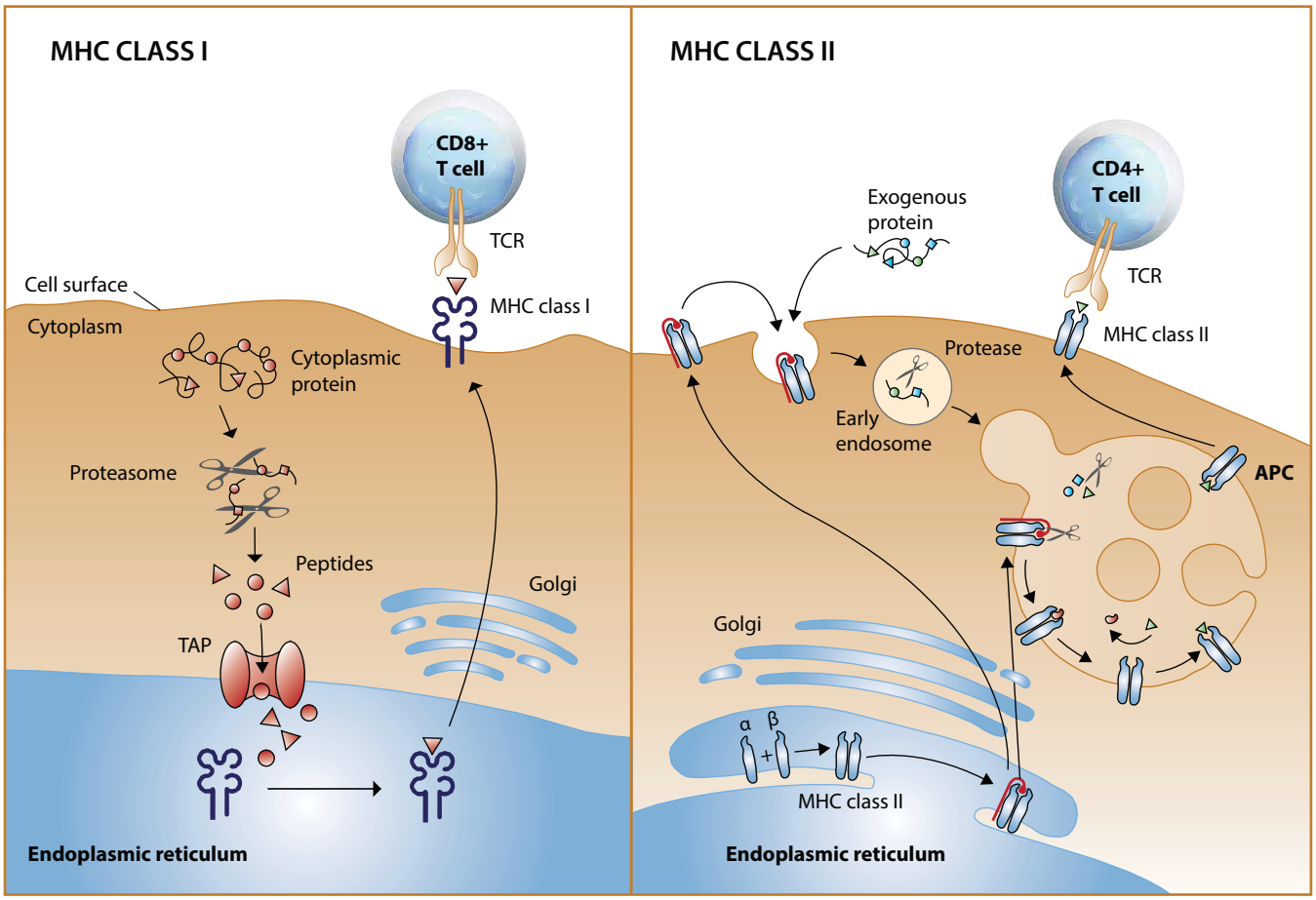


Figure 6: Antigen presentation by MHC Class I and II. Left Panel: Cytosolic and nuclear proteins (self or viral proteins) are degraded by the proteasome into peptides. The transporter for antigen processing (TAP) translocates peptides into the lumen of the endoplasmic reticulum. MHC class I heterodimers wait in the ER for the third subunit, a peptide. Peptide binding is required for correct folding of MHC class I molecules and release from the ER and transport to the plasma membrane, where the peptide is presented to CD8+ T cells. Right Panel: MHC class II α- and β-chains assemble in the endoplasmic reticulum and form a complex with the invariant chain (red peptide). The MHC class II heterotrimer is transported through the Golgi to the MHC class II compartment, either directly and/or via the plasma membrane. Endocytosed proteins and the invariant chain are degraded by resident proteases. The small remaining portion of the invariant chain in the peptide-binding groove of the MHC class II dimer is exchanged for an antigenic peptide. MHC class II molecules are then transported to the plasma membrane to present antigenic peptides to CD4+ T cells. APC, antigen-presenting cell; TCR, T cell receptor. Adapted from *Nature Reviews Immunology* 3, 952-961 and *Nature Reviews Immunology* 11, 823-836

are triggered, the T-cell differentiates into one of several mature T cells (see Figure 7 below). Molecular patterns on the antigen interact with the antigen-presenting cell (via pattern recognition receptors, see page 26), influencing signals between the cells and the T cell-maturation process.

Antigen-presenting cells trigger T cell effects by presenting processed *foreign* antigens via MHC class II molecules; however, all nucleated cells display various internal "self-antigens" and/or viral antigens from infected cells. These internal antigens are presented via MHC class I molecules. Presentation of viral-antigens using MHC class I molecules is an important way to trigger killer T cell activation toward a virus-infected cell, and presenting self-antigen is also a way to prevent immune activation against one's own healthy cells. Not only are there two major classes of MHC/HLA molecules, there are numerous alleles and polymorphisms of these protein molecules, allowing different antigenic peptides to be presented in a slightly different manner to the adaptive immune cells. Genetic testing of various alleles and polymorphisms is often helpful in diagnosing or ruling out various immune or autoimmune diseases. Some of the most well-known among such alleles are HLA-DQ2 and HLA-DQ8, related to celiac disease. While gluten/gliadin sensitivity is still possible without the expression of these MHC molecules, a diagnosis of celiac disease requires the expression of one of these two alleles; although expressing them is not sufficient for a diagnosis of celiac disease (see table of HLA regions associated with risk of autoimmune diseases on page 40).

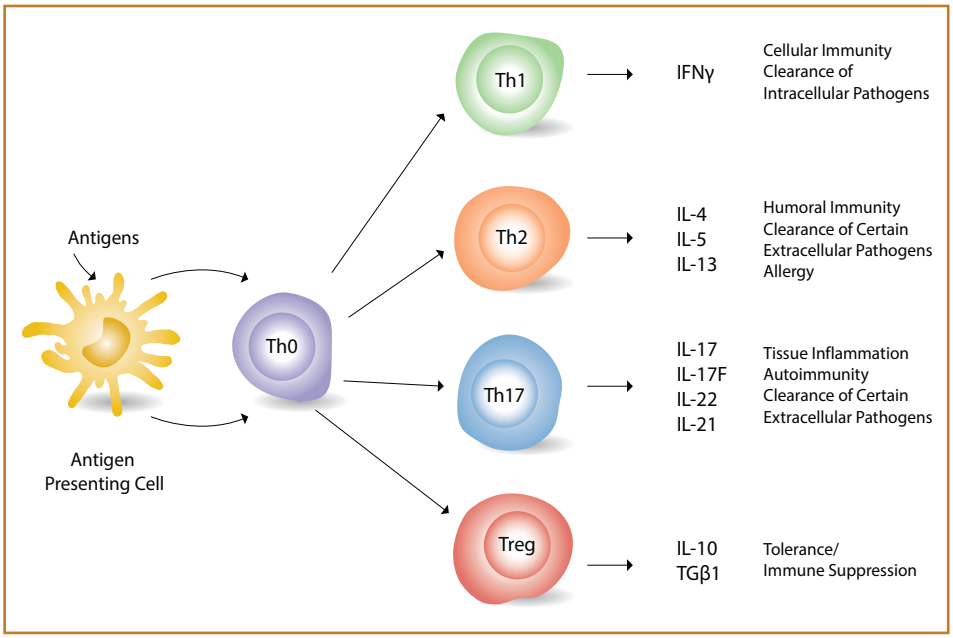


Figure 7: Antigen-dependent T-helper maturation: When a naïve helper T cell encounters antigen (via antigen presenting cell) it differentiates into one of many subsets of T-helper/T-regulatory cells. See text for more details.

T-Helper (Th) Cell Types Control Adaptive Immune Responses

The maturation and specificity of the adaptive immune response are partially centered on the differentiation of a specific set of CD4+ T lymphocytes, called T-helper cells (Th). The two most well understood are the Th1 and Th2 subsets, but new research has defined a Th17 subset (named for its expression of IL-17) as well.[1,2] When a naïve T-helper cell (Th0) interacts with an antigen (presented in the context of an MHC molecule on an antigen-presenting cell) it differentiates into one of these T-helper cell subsets. Since T-helper cells coordinate how the rest of the adaptive immune system will respond to the antigen (primarily through cytokine production, see Table 2), their differentiation determines which portions of the immune system will mount a response to the antigen.

In general, Th1 cells secrete interferon-gamma and TNF-α, stimulating both cell-mediated immunity (via macrophages) and the inflammatory pathways. These cellular responses are typically beneficial when defending against viral and bacterially infected cells and cancer. Conversely, Th2 cells secrete cytokines that upregulate antibody production (B-cells/humoral immunity), including the IgE allergic response. Though much less is known about them, Th17 cells are involved in stimulating a portion of the inflammatory response while activating neutrophils.

While both Th1 and Th2 are necessary for a comprehensive adaptive immune response, if either is overrepresented there is the

possibility of immune system dysregulation. When Th1 is overly active, increased inflammation and autoimmune reactions may occur, whereas allergic oversensitivity may result from over-activation of the Th2-mediated response. Many factors can influence a shift in the balance of an individual's Th1/Th2 ratio, including maternal diet and immune challenges during fetal development, early childhood exposure to antigens or allergens, diet, gut microflora and immunizations. The so-called "hygiene hypothesis" suggests children with more exposure to pathogens earlier in life will preferentially develop a Th1 profile, which results in less allergic susceptibility. The inverse relationship between atopic diseases and exposure to childhood pathogens seems to confirm the hygiene hypothesis, although the relationship is far from reaching scientific agreement.[3]

Another population of CD4+ T cells also plays an important role in modulating the immune response. The regulatory T cells (Treg cells, aka suppressor T cells) are key regulators of immune tolerance, helping the immune system to recognize certain potential antigens without eliciting an immune response. Treg cells play an important role in preventing inappropriate immune responses by actively suppressing responses to self-antigens (limiting autoimmunity), harmless food antigens, or antigens from friendly commensal organisms. (For a discussion of self-tolerance, see the section on autoimmune conditions, page 35).

Table 2: Functional Groups of Selected Cytokines*

Cytokine†	Secreted by‡	Targets and effects
SOME CYTOKINES OF INNATE IMMUNITY		
Interleukin 1 (IL-1)	Monocytes, macrophages, endothelial cells, epithelial cells	Vasculature (inflammation); hypothalamus (fever); liver (induction of acute-phase proteins)
Tumor necrosis factor-α (TNF-α)	Macrophages	Vasculature (inflammation); liver (induction of acute-phase proteins); loss of muscle, body fat (cachexia); induction of death in many cell types; neutrophil activation
Interleukin 12 (IL-12)	Macrophages, dendritic cells	NK-cells; influences adaptive immunity (promotes Th1 subset)
Interleukin 6 (IL-6)	Macrophages, endothelial cells	Liver (induces acute-phase proteins); influences adaptive immunity (proliferation and antibody secretion of B cell lineage)
Interferon α (IFN-α) (this is a family of molecules)	Macrophages	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK-cells
Interferon β (IFN-β)	Fibroblasts	Induces an antiviral state in most nucleated cells; increases MHC class I expression; activates NK-cells
SOME CYTOKINES OF ADAPTIVE IMMUNITY		
Interleukin 2 (IL-2)	T cells	T-cell proliferation; can promote activication-induced cell death. NK-cell activation and proliferation; B-cell proliferation
Interleukin 4 (IL-4)	Th2 cells, mast cells	Promotes Th2 differentiation; isotype switch to IgE
Interleukin 5 (IL-5)	Th2 cells	Eosinophil activation and generation
Transforming growth factor β (TGF-β)	T cells, macrophages, other cell types	Inhibits T-cell proliferation and effector functions; inhibits B-cell proliferation; promotes isotype switch to IgA; inhibits macrophages
Interferon γ (IFN-γ)	Th1 cells, $CD8^+$ cells, NK cells	Activates macrophages; increases expression MHC class I and class II molecules; increases antigen presentation

* Many cytokines play roles in more than one functional category.
† Only the major cell types providing cytokines for the indicated activity are listed; other cell types may also have the capacity to synthesize the given cytokine.
‡ Also note that activated cells generally secrete greater amounts of cytokine than unactivated cells.

Table 2: Functional Groups of Selected Cytokines of the Innate and Adaptive Immune Systems.

Mitochondrial Function and Supporting the Immune System

Mitochondria are indispensable DNA-containing organelles within the cell, responsible for providing the vast majority of a cell's energy, in the form of ATP production. The cell uses this energy to perform a wide range of critical metabolic functions, including the ability to mature, proliferate and divide. However, within immune system cells, mitochondria have been implicated as key regulators of both innate and adaptive immune functions through metabolic and cell-signaling mechanisms.

The innate immune system is triggered and mediated through a host of pattern recognition receptors (PRRs) expressed on and within innate immune cells and the cells of other tissues (see page 24 for details). Research shows mitochondria play a vital role in regulating PRR expression and signaling, allowing immune cells to respond to both pathogenic organisms as well as damaged or stressed host cells.[4] In recent years, researchers have identified a novel mitochondrial receptor that interacts with certain soluble members of the PRR family known generally as Rig-1-Like Receptors (RLRs). These particular RLRs recognize double-stranded viral RNA. This mitochondrial receptor, known as mitochondrial antiviral signaling protein (MAVS); when triggered, sends a complex set of secondary signals that activate the NF-κB inflammatory pathways and induces type 1 interferon production. Other research has identified mitochondrial interactions with other PRRs, such as Toll-like receptors (TLRs) and Nod-like receptors (NLRs), that involve the recognition of viral, bacterial, and fungal or damaged-cell patterns requiring innate immune responses.[5,6] These signaling pathways rely on intact healthy mitochondria that maintain the ability to alter their metabolism and their morphology (linking into elongated chains).

Upon activation, innate and adaptive immune cells alter their metabolic activity in order to adapt to the increased demands of cell growth, proliferation and effector functions. In the case of T cells, metabolism changes over the course of an immune response.[7] Prior to antigen encounter, the naïve T cell is in a steady state that is basically metabolically quiescent, requiring little in the way of nutrient intake. When these cells encounter an antigen and become active "effector" T cells, a shift in metabolism occurs, favoring glycolysis and requiring increased nutrient intake. While many of these cells die after an antigen encounter, a small number of these cells become memory T cells and once again return to a steady state of quiescence. However, these cells are now metabolically primed and have an increase in spare respiratory capacity due to increased mitochondrial mass compared to naïve T cells. This spare respiratory capacity (i.e., metabolic reserve, see page 9) allows for a quicker and more robust response when these cells encounter an antigen on a subsequent occasion, an important part of the memory function of the adaptive immune response.

When we combine the growing information about how important mitochondria are for regulating basic immune functions with the fact that mitochondria are severely compromised by both HPA-axis and metabolic stressors, it is clear that mitochondrial support plays a critical part in an overall immune-supporting strategy.[8] In fact, mitochondrial dysfunction and chronic inflammatory signaling may be a key link connecting a number of chronic diseases previously considered unrelated.[9]

Improving Immune Function Through Mitochondrial Support

The published research looking into specific immune outcomes related to treatments targeting mitochondrial support is sparse, primarily because this area of research is relatively new and the biomarkers needed to establish the link between these two phenomena are not clinically established. What is clear, however, is those lifestyle-related inputs that promote a strong and resilient immune system are almost always associated with improved mitochondrial function. Some of those signals include moderate exercise; appropriate macronutrient, micronutrient and antioxidant intake; moderate and intermittent cellular and HPA axis stress (via hormesis, not major acute or chronic stressors); proper circadian rhythm; and toxin avoidance.

Mitochondrial dysfunction has long been speculated to be part of the mechanisms related to aging, immunosenescence and chronic disease, leading to numerous theories for how supporting mitochondrial function may prevent these conditions.

Dr. Bruce Ames has been one of the leading proponents of the mitochondrial theory of aging and chronic disease. He has researched and published a number of studies focused on the use of micronutrients and functionally essential nutrients such as lipoic acid, N-acetyl-cysteine (NAC) and carnitine.[10] The use of micronutrients for immune support is covered in detail elsewhere (page 50), where we review some of the animal models and clinical research done by Ames.

Pattern-Recognition Receptors and the Innate Immune System

While the innate immune system is often characterized as being "nonspecific," the past several decades have uncovered several highly coordinated signaling pathways within innate immune cells that allows the immune response to be appropriate (if not specific) for the invading pathogen. Generally speaking, these signaling pathways are triggered by a host of receptors known as pattern-recognition receptors (PRRs). Unlike the highly specific antigen-binding regions found on antibodies and T cell receptors, these receptors recognize general "patterns" that may signal the need for an immune response, as their name implies.

The two basic types of molecular patterns these PRRs are designed to recognize are either associated with pathogens (PAMPs: pathogen-associated molecular patterns) or tissue damage (DAMPs: damage-associated molecular patterns or sometimes, danger-associated molecular patterns). PRRs are expressed mainly on innate immune cells, such as monocytes, macrophages, dendritic cells and neutrophils; although they are also expressed in B cells and non-immune cells like endothelial cells, epithelial cells and fibroblasts.

The first PRRs identified were the toll-like receptors (TLRs). Today there are at least 10 different human TLRs known to be expressed in immune cells that mediate the signaling response of pathogen encounters with the immune system. Each TLR recognizes different PAMPS expressed on bacteria, viruses, mycobacteria, fungi and parasites (see Figure B). While the majority of the TLRs are expressed on the cell surface (as transmembrane receptors) and recognize pathogen surface molecular patterns such as lipopolysaccharides (LPS), flagellin, glucans, structural proteins or lipoproteins; other TLRs are expressed within intracellular vesicles and mostly recognize pathogen DNA and RNA. Upon recognition of a particular PAMP, TLRs trigger intracellular signaling pathways that direct a specific immune response, appropriate for the particular pathogen. Most TLR-signaling is mediated through a closely associated adaptor protein called MyD88 (myeloid differentiation primary response gene -88), and one of several TRAF (TNF receptor associated factor) proteins (see Figure B). These signals are made even more nuanced by the fact that there are some redundancies in the recognition of TLRs and other PRRs and because many pathogens trigger more than one TLR or PRR. For instance, *Salmonella typhimurium* PAMPs can be recognized by TLR2 (lipoprotein), TLR4 (LPS), TLR5 (flagellin) and TLR9 (unmethylated CpG DNA).[1]

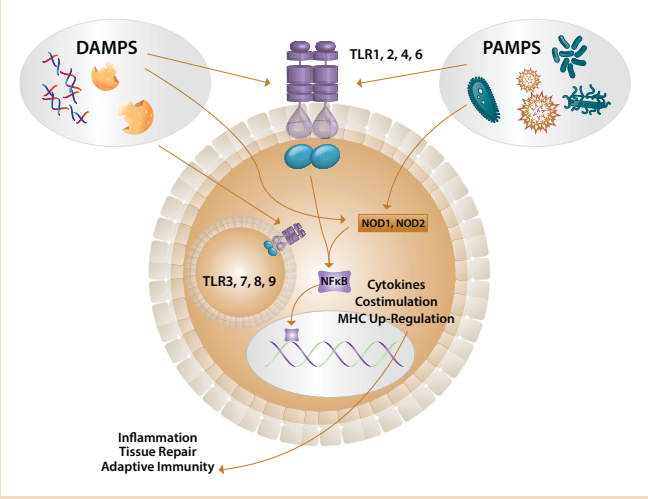


Figure A: Basic Signaling of Pattern Recognition Receptors. See text for explanation.

While TLRs are the best-characterized and studied PRRs, a number of other classes of receptors perform similar functions in innate immune cells. C-type lectin receptors (CLRs) are surface receptors similar to TLRs that recognize a wide range of pathogenic patterns, including those of helminthes,

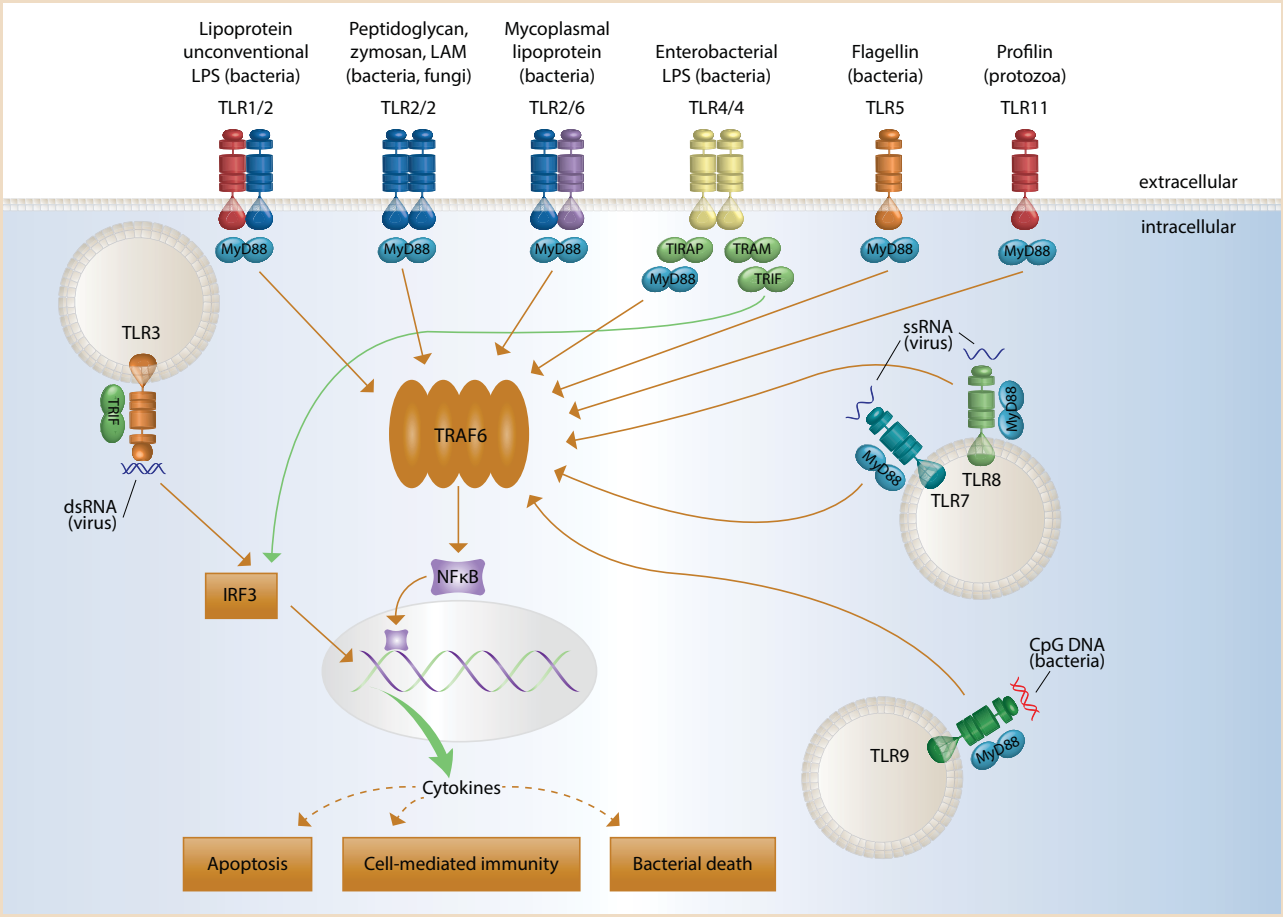


Figure B: Toll-like receptor (TLR) signaling. This diagram shows the different types of TLRs, their locations and the patterns they recognize. See text for more details about the signaling pathways. Image adapted from Minireview: Toll-like Receptors (TLR)-www.abdserotec.com.

fungi and mycobacterium. Dectin-1, a member of CLR family of receptors, recognizes β-1,3-linked glucans on both pathogenic fungi and fungal-derived immunomodulating agents. Retinoic acid-inducible gene 1 (RIG-1) is a member of the RIG-1-like receptors (RLRs), located within the cytoplasm where they mostly recognize viral RNA and signal antiviral responses. Also expressed in the cytoplasm are NOD-like receptors (NOD- nucleotide-binding and oligomerization domain), which recognize a variety of PAMPs and DAMPs and are important regulators of the inflammatory response.[2]

PRRs and the Inflammatory Response

When one or more PRRs recognize a pathogenic or dangerous molecular pattern, a cascade of intracellular signals is triggered. Consistent among these signals is an upregulation of inflammatory cytokines (usually by activating NF-κB and/or MAPK), as well as other notable signals include the upregulation of type-1 interferon (through one of several interferon regulatory factors-IRFs), and changes leading to dendritic cell maturation. The differential nature of the diverse PRR signals also helps inform the way innate immune cells (especially macrophages, monocytes and dendritic cells) condition the adaptive immune response. PRR signaling during antigen presentation helps naïve T cells differentiate into Th1, Th2, Th17 or Treg cells; it also may influence the type of immunoglobulin class produced by B cells.[3]

Besides the near ubiquitous activation of the NF-kB by all PRRs, a particular class of NOD-like receptors (NLRs) produce large intracellular multiprotein complexes called inflammasomes when

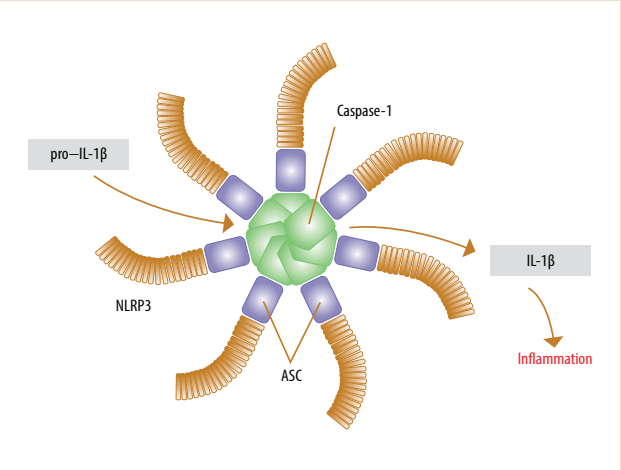


Figure C: Inflammasome (NLRP3) molecule. See text for details. Adapted from *Nature Medicine* 17, 790–791 (2011)

activated.[4] The typical inflammasome is comprised of a complex of seven NLRP3-receptor molecules surrounding a core of seven caspase-1 protease molecules, connected via small adapter proteins (see Figure C). The main function of the inflammasome complex appears to be the activation of caspase-1, which functions to cleave the inactive precursors of the proinflammatory IL-1β and pre-IL-18 into their respective active forms. The activities of the inflammasome also appear to facilitate pyroptosis and programmed cell death triggered by inflammation. Besides traditional PAMPs, NLRP3 inflammasomes may also be triggered by a number of metabolic inflammatory signals like modified LDL particles, high glucose, cholesterol crystals and certain fatty acids. Therefore, PRRs and inflammasomes may be critical mediators in the chronic low-level inflammation related to cardiometabolic dysfunction.[5] Inflammasome complexes are also formed by NLRP1, NLRP6 and NLRC4. There is now some evidence certain inflammasomes may be secreted out of the cell to perpetuate the inflammatory response in a cytokine-like fashion.

Modulating PRRs with Exogenous Signals

If one of the keys to supporting immune function is the appropriate modulation of inflammatory activity, then modulation of PRR activation within innate immune cells is vital. As our understanding of the mechanisms of PRR-signaling increases, so does our hope of finding ways to modulate their activity. In fact, a number of the phytochemicals already considered to be anti-inflammatory appear to have some ability to affect PRR function or signaling.[6,7]

PRR activation is dependent on the receptor's ability to form dimers (homodimers or heterodimers). Several recent studies have shown a number of phytochemicals, such as curcumin, sulforaphane, and cinnamaldehyde, are able to interfere with PRR dimerization, accounting for reduced TLR-signaling. Other bioactive plant compounds, like resveratrol, EGCG, luteolin, quercetin and chrysin, have been shown to inhibit downstream-signaling triggered by PRR activation (apart from NF-kB inhibition). Finally, curcumin and parthenolide (from *Tanacetum parthenium,* feverfew) have been shown to inhibit signaling from the intracellular PRRs NOD1 and NOD2. These mechanisms, along with the other anti-inflammatory mechanisms described for these phytochemicals, help explain their role in preventing and treating inflammatory-mediated chronic diseases.

References

1. Gerold G1, Zychlinsky A, de Diego JL. What is the role of Toll-like receptors in bacterial infections? *Semin Immunol.* 2007 Feb;19(1):41-7.
2. Saxena M, Yeretssian G. NOD-Like Receptors: Master Regulators of Inflammation and Cancer. *Front Immunol.* 2014 Jul 14;5:327.
3. Pone EJ, Xu Z, White CA, Zan H, Casali P. B cell TLRs and induction of immunoglobulin class-switch DNA recombination. *Front Biosci* (Landmark Ed). 2012 Jun 1;17:2594-615.
4. Franchi L, Muñoz-Planillo R, Núñez G. Sensing and reacting to microbes through the inflammasomes. *Nat Immunol.* 2012 Mar 19;13(4):325-32.
5. Takahashi M. Role of the inflammasome in myocardial infarction. *Trends Cardiovasc Med.* 2011 Feb;21(2):37-41.
6. Zhao L, Lee JY, Hwang DH. Inhibition of pattern recognition receptor-mediated inflammation by bioactive phytochemicals. *Nutr Rev.* 2011 Jun;69(6):310-20.
7. Jeong E, Lee JY. Intrinsic and extrinsic regulation of innate immune receptors. *Yonsei Med J.* 2011 May;52(3):379-92.

Immunosenescence

Newborns have an immature immune system and are vulnerable to infectious agents. The immune system begins to mature with appropriate interaction with antigens and is enhanced by the changing microflora of the gut throughout adolescence and adulthood. Of course, aging affects all the systems of the body, and the immune system is no exception. The changes in immune system function that result from aging have been well characterized and are known as immunosenescence.[11]

In essence, this can be described as a loss of immune "reserve" on the one hand and a loss of immune discretion on the other. Meaning that while most measurable features of the immune system decline over time, some may actually increase, such as autoantibody production or inflammatory upregulation. These changes create increased susceptibility to infectious diseases, poor immunization response, and an increased risk for cancer and several autoimmune conditions. Likewise, the increased level of inflammation, sometimes called "inflammaging," mediates a number of well-known chronic diseases.

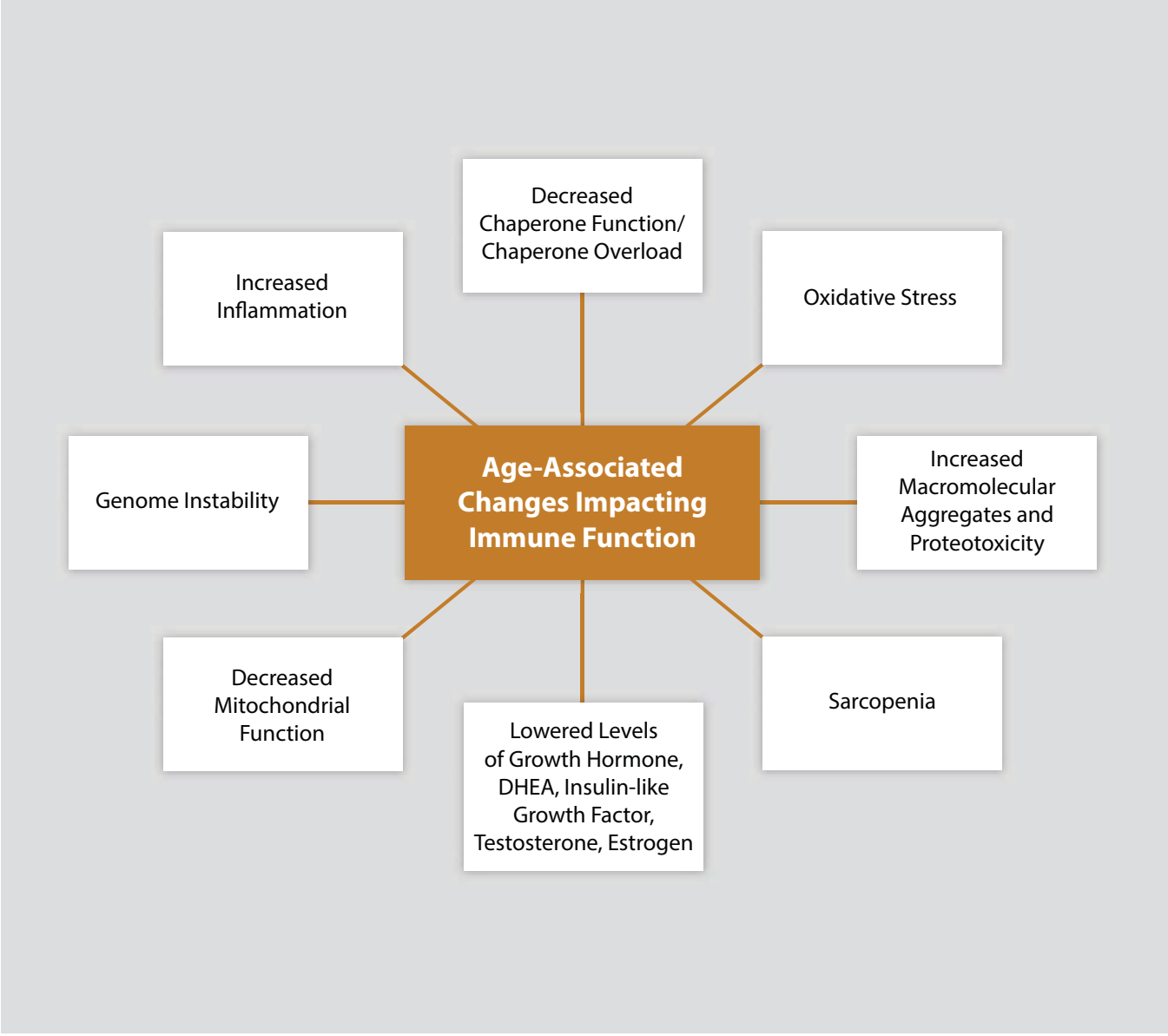


Figure 8: Age-Associated Factors that drive Immunosenescence. Adapted from *Antioxid Redox Signal*. Apr 15, 2011; 14(8): 1551–1585.

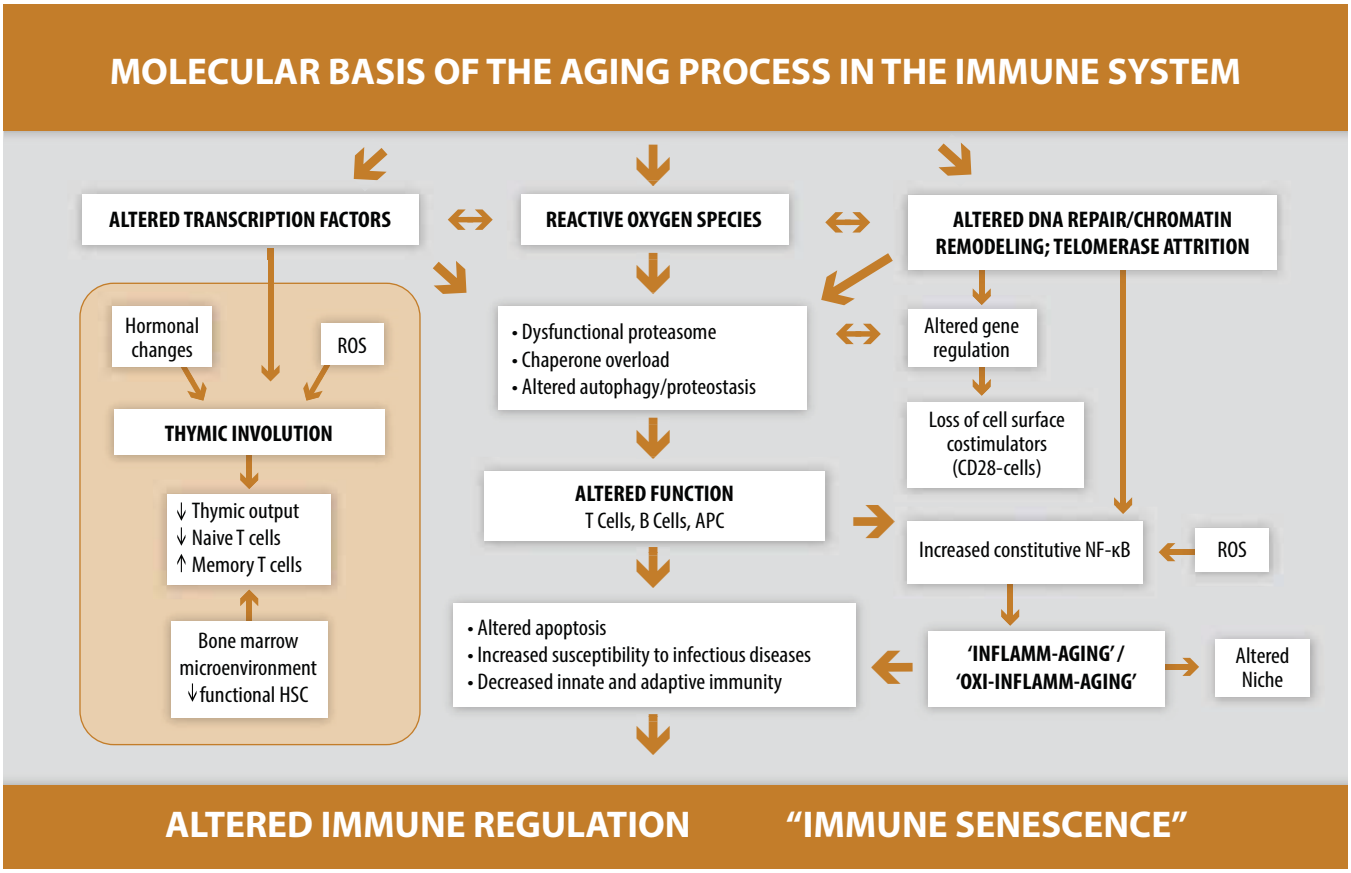


Figure 9: The Mechanisms of Immunosenescence. ROS- reactive oxygen species. HSC- hematopoietic stem cells. Adapted from *Antioxid Redox Signal.* Apr 15, 2011; 14(8): 1551–1585.

Aging cells of all kinds are burdened with a number of functional disruptions: decreased mitochondrial function, increased DNA instability, higher amounts of unquenched reactive oxygen species (ROS), inefficient protein folding and a build-up of cellular toxins (See Figures 8 and 9). Since the lifespan of many immune cells is quite long, especially B and T cells, these disruptions can be cumulative.[12] Furthermore, the result of fewer memory B and T cells combined with diminished bone marrow and thymus function (to provide naïve lymphocytes) adds to the loss of adaptive immune functions.[13,14] After decades of dysfunction and cell apoptosis, the immune system is depleted in specificity, diversity and appropriate regulatory control.

While experienced by everyone, the consequence and impact of immunosenescence is highly dependent on the interplay of genetics, epigenetics, environmental factors and lifestyle-related signals from diet, physical activity, sleep and stress management. The relative ratio of cortisol to DHEA levels (typically higher as one ages), growth hormone expression, thyroid function and antioxidant reserve capacity are critical in determining the rate and severity of age-related immune dysfunction.

Healthy lifestyle choices over many decades will strengthen and build the metabolic reserve that allows immune cells and organs to function well into the eighth and ninth decades of life. Supporting immune function in the aging patient requires understanding, assessing and supporting each of these important parameters, and is the focus of the rest of this handbook.

The Role of the GI Tract in Immune Function

The gastrointestinal (GI) tract is designed to break down and absorb large amounts of nutrients in a relatively short time. To accomplish this, an architectural feature of folds and fingers, called villi, greatly expands the surface area of the GI tract, especially the small intestines, where most nutrient absorption happens (Figure 10). However, this expansive surface area, about the size of a tennis court, is only one cell-layer thin, and therefore represents a highly vulnerable interface with the antigen-rich external environment of the gut lumen. This vulnerability requires a highly coordinated cooperation between GI cells and the immune system. In fact, as is often pointed out, 70–80% of immune cells reside in the GI tract.[15]

The first of our 10 principles for overall immune support is the ability to maintain barrier functions. Nowhere is this more critical than the gut. Both the innate and adaptive immune systems are critical components of the barrier function of the gut. Approximately 100 to 150 mesenteric lymph nodes are distributed throughout the gut to create numerous "stations" for concentrated interactions between antigens, antigen-presenting cells, regulatory cells and effector cells. This specialized feature of the immune system is often referred to as the gut-associated lymphoid tissue (GALT-Figure 11), a subcategory of the mucosa-associated lymphoid tissues (MALT) found throughout other mucosal barriers: eyes, mouth, lungs, breast, vagina, skin, etc.

Another special feature of the GALT is the 30 or so Peyer's patches found primarily along the mucosa of the ilium. These Peyer's patches include a concentration of T cells, B cells and antigen-presenting cells—mostly dendritic cells—that interface directly with the gut lumen through the activities of special gut epithelial cells called M cells (microfold cells). These

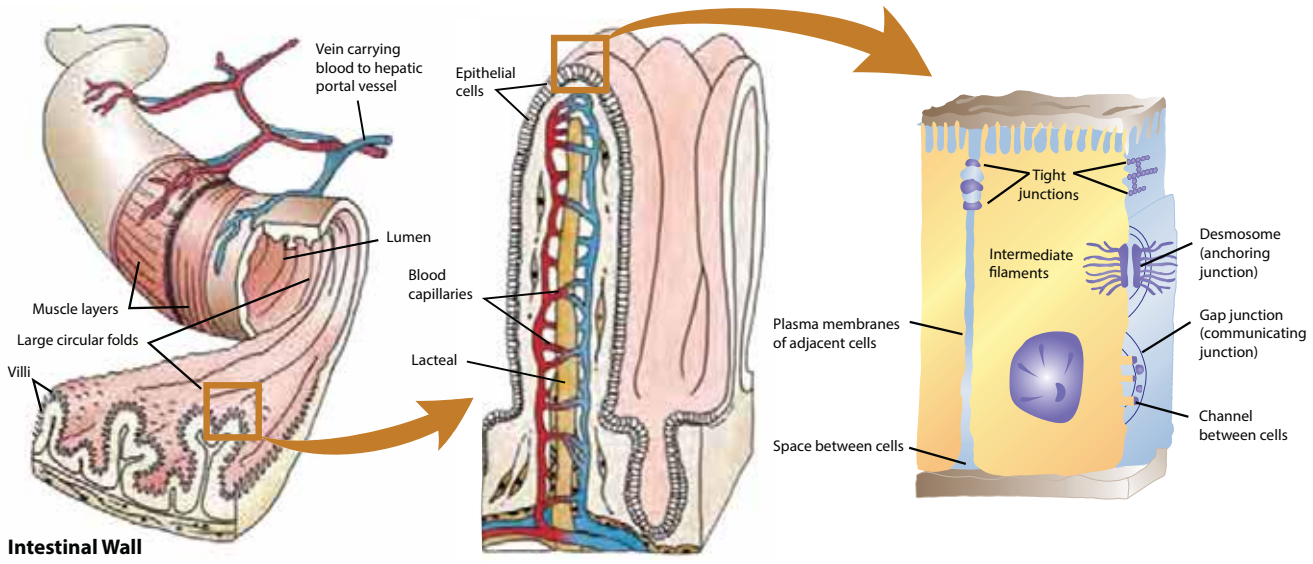


Figure 10: Expanding Surface Area of the GI tract. The intestinal wall uses large folded surfaces containing many individual villi (center). These villi are lined with a single layer of epithelial cells with access to both the blood supply (capillaries) and the lymphatic system (lacteal). Each epithelial cell is joined to the adjacent cell by the formation of tight junctions, preventing particles from the gut lumen from passing between the epithelial cells.

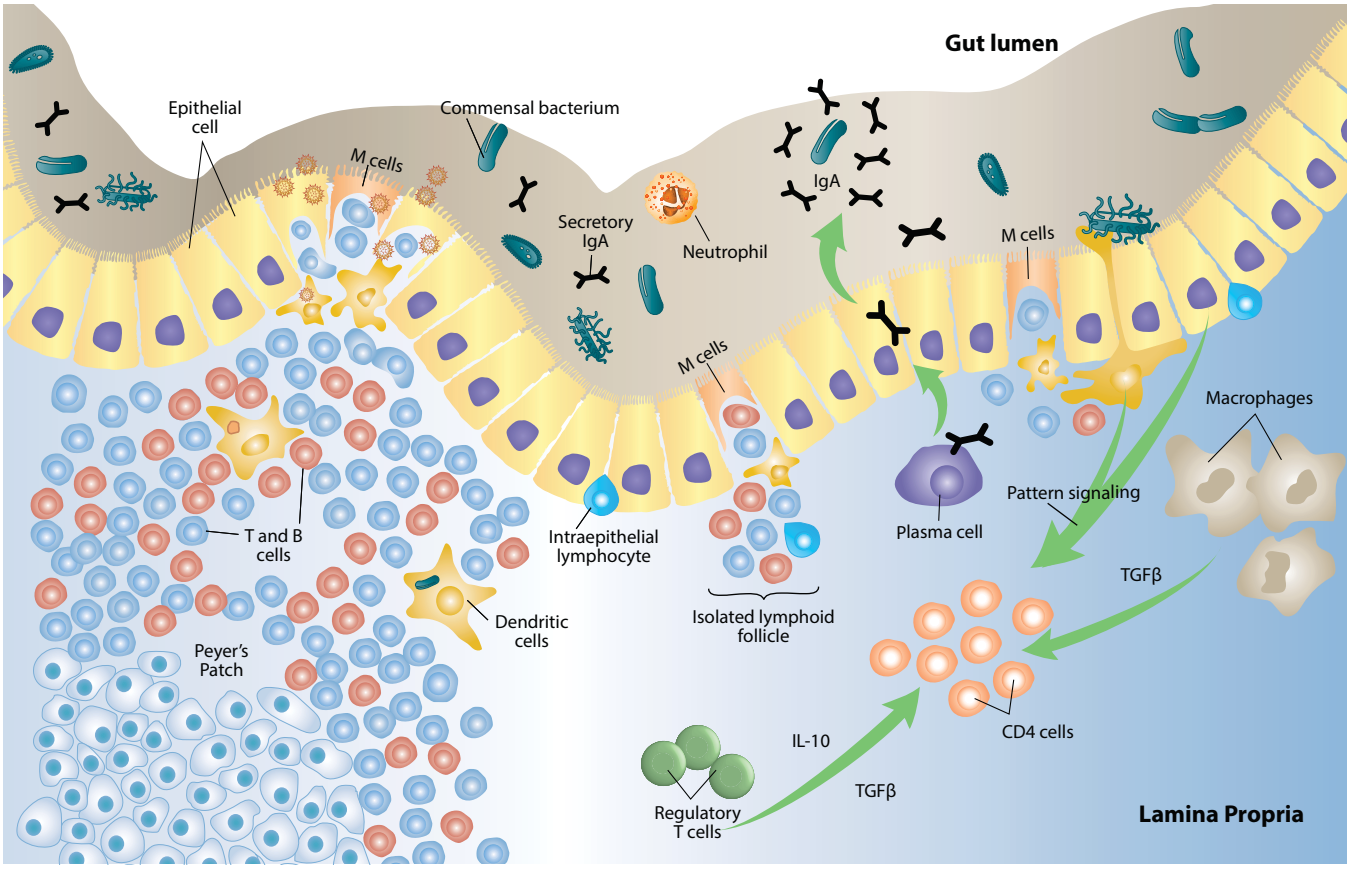


Figure 11: Basic Structures of the Gastrointestinal-Associated Lymphoid Tissue (GALT). See the text for detailed explanation.

M cells are designed to allow the controlled passage of antigens (commensal bacteria, pathogenic bacteria, viruses, fungi, food particles, etc.) into the gut lumen, where they can be delivered safely to antigen-presenting cells that, in turn, present them to both mature and naïve T cells.[16]

In addition to the M cell-mediated antigen sampling, specialized dendritic cells are capable of changing their morphology to permit direct surveillance of the gut lumen by an extension protruding between the gut epithelial cells. This allows the dendritic cell to use its many pattern-recognition receptors to begin reacting to changes within the "pattern" of pathogens in the gut before specific antigens are presented to the adaptive immune cells. This process of immune surveillance is considered to be an important part of the "education" and maturation of the immune system, and also provides an early warning of a potential pathogenic agent in the gut, allowing for a preemptive response. The ultimate goal is to mount appropriate and timely immune responses to harmful and foreign antigens, while creating an active tolerance against harmless or self-antigens.

One of the unique features of the adaptive immune response within the GALT, as in most other mucosal tissues, is the abundance of antibody-secreting B cells, called plasma cells, which produce antibodies of the secretory IgA class (sIgA). This form of antibody is capable of passing into the lumen of the gut, as it does in breast milk, saliva, tears, etc., to interact with antigens while they are still "outside" the body. Antigens sampled via the M cells are presented to T-helper cells and B cells in the mesenteric lymph nodes and, when an appropriate cross-reactivity is triggered, B cells are activated to secrete the corresponding sIgA. Research now shows sIgA expression against both pathogenic and commensal organisms is a key regulatory feature of the intestinal barrier itself.[17,18] Also, there is a well-documented relationship between increased HPA-axis stress and reduced sIgA levels.[19] Laboratory

measurements of sIgA levels are often used as one of many markers of mucosal immune health and/or HPA axis stress-induced immune suppression; and specific sIgA levels measured in a stool or saliva sample can indicate a particular antigenic challenge.[20]

Intestinal Permeability: a Breach in the Barrier

Breaches in the gut barrier function are one of the most potent immune challenges. Intestinal permeability (leaky gut) may permit unprocessed antigens, or even intact organisms from the gut lumen, entry to the lamina propria by passing between, rather than being processed through, GI epithelial cells. These unprocessed antigens are capable of triggering immune responses that can then increase the susceptibility to autoimmune cross-reactivity. In fact, one of the leading theories for the genesis of autoimmune diseases is the immune exposure to unprocessed non-self-antigens that have breached the intestinal barrier.[21]

Using gluten and celiac disease as a model, Fasano et al. have shown a zonulin-mediated loosening of the tight junction proteins, which are intended to prevent intestinal permeability, a model they believe defines a role for intestinal permeability in other immune system conditions such as type 1 diabetes, asthma, multiple sclerosis and inflammatory bowel disease. Although this model is being hailed as a groundbreaking advance to our understanding on how GI disturbances of any kind can trigger an autoimmune response, it is still under considerable debate within the larger world of immunology.

Commensal-Friendly Environment

It is now universally understood in the medical community that GI function and health are strongly correlated with the commensal organisms living within the GI tract (our second basic principle for immune support). The hundreds of subspecies of bacteria that reside in the gut function in close relationship with both the barrier and immune-modulating functions of the gut, protecting the host from immune disturbances in the gut and elsewhere. As mentioned previously, the "training" and maturation of immune system cells is partially dependent on continuous sampling of commensal organisms from within the gut by the GALT. The past several decades have seen rapid advances in our ability to define the nature of the GI microbiota and understand the important role it plays in nearly every health condition.

Research looking into the interrelationship between specific commensal organisms and specific immune outcomes is ongoing. While these types of relationships are well-known for disease-causing organisms, it is now recognized that certain families and species of friendly commensal organisms are responsible for modulating the tight junctions, upregulating sIgA, hindering the growth of harmful organisms, promoting an anti-inflammatory environment, detoxifying harmful metabolites, and liberating or producing several important nutrients (see Figure 12). The use of foods or supplements to deliver probiotics or prebiotics for immune support will be covered in the section on the use of immunomodulators. For a comprehensive review of the use of probiotics or strategies to address other GI health concerns, see our guide "*Gastrointestinal Health: A Lifestyle and Nutrient Approach*," available 2015.

Heal the Gut First

Even from this simple overview of the GI's role in modulating immune function, it is easy to understand why "heal the gut first" became a major principle in the naturopathic medical model. When the basic functions of the GI tract—digestion, elimination, microbial balance and mucosal integrity—are considered in each patient, they will always lead to therapies that strengthen the foundation of the immune system. The most common functional-medicine approach to healing the gut mucosa and improving the barrier function of the gut is generally referred to as the 4-R approach.[22] This approach is explained in detail, along with a host of other GI-related protocols, in a different handbook called, "*Gastrointestinal Health: A Lifestyle and Nutrient Approach*," and we will only summarize the first and last "R" here.

The four Rs stand for Remove, Replace, Re-inoculate and Repair. Some describe a fifth R- Rebalance, which generally corresponds with modulating the regulatory and immune functions of the gut. Removing agents that damage or aggravate intestinal cells or the immune system in the GI tract is absolutely critical to barrier function. When the GALT is challenged by the need to constantly respond to food

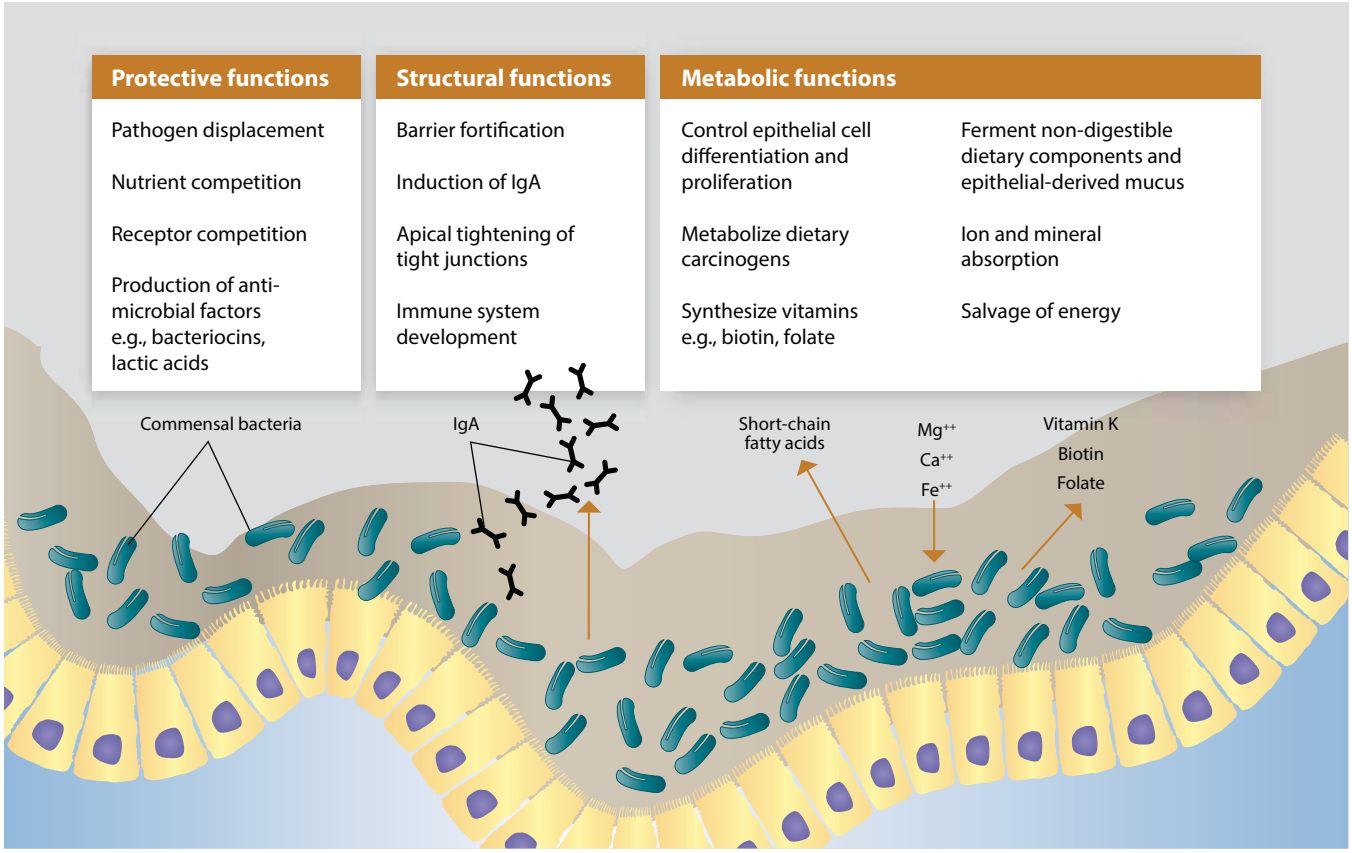


Figure 12: Multiple Benefits from Healthy Commensal Organisms.

antigens, pathogenic bacteria, toxins or other harmful agents, chronic inflammation will result.

Ongoing inflammation can lead to intestinal permeability (leaky gut), allowing antigens entry into the body (lamina propria) while avoiding the highly regulated process of M-cell sampling, further adding to immune activation (inflammation). This is one of the key reasons many functional-medicine clinicians encourage patients with chronic immune issues to use elimination diets, sometimes in coordination with detoxification protocols, to discover allergenic or antigenic (or toxic) burden on the GI system, sometimes even as a first step in chronic disease management. In some cases, like gluten for celiac disease patients, certain immune-challenging substances will need to be permanently removed from the diet. In other cases, some offending substances may be added back to the diet in moderation once the patient's GI tract has been repaired.

Skipping over *Replace* and *Re-inoculate*, the last component of the 4R program is *Repair*. Essentially this involves therapeutic strategies for healing of the mucosal lining of the gut, repairing any gut permeability issues and quieting any over-excitement of the GALT. Again, while more detailed protocol recommendations are available in our other resources, the three keys to repairing the integrity of the gut include reducing inflammation, providing nutrients for specific GI cell growth, and providing strength to immune and liver function.

Reducing Inflammation

One of the most important initial steps to heal the gut is reducing chronic and uncontrolled inflammation. The common mediator of most gut disorders, especially those that destroy the integrity of the mucosal lining (IBD, food allergies, parasitic infections, etc.), is inflammation. Reducing the inflammatory burden can be accomplished naturally by:

- **Diet**: An anti-inflammatory diet is key to promoting proper gut integrity. Diets that increase inflammation will not only increase GI complaints, but will also increase cardiovascular risk, joint diseases, cancer and nearly every other chronic disease mediated by inflammation. A basic list of foods that are proinflammatory (avoid) and anti-inflammatory (increase) is listed on page 124. See pages 46–51 for a complete discussion of immune-related dietary considerations, many of which function through anti-inflammatory mechanism.
- **Reducing obesity/fat mass**: Adipose tissue produces many inflammatory cytokines with destructive consequences in the surrounding tissues. Weight reduction, especially fat-mass reduction, and improving glycemic control will reduce the inflammatory burden on the GI. The relationship between obesity and the relative abundance of certain gut microflora also suggests a direct GI mediation of obesity-related inflammation.[23]
- **Anti-inflammatory herbs**: Many botanicals and their extracts have been shown to be powerful anti-inflammatory agents and clinically useful in managing GI inflammation. Curcumin, concentrated from turmeric root, is considered one of the most potent natural anti-inflammatory agents. This bright orange extract is widely used in inflammatory bowel disorders. Along with curcumin, other natural anti-inflammatory agents include quercetin (also a mast cell stabilizer), boswellic acid, ginger root, bromelain (pineapple enzyme), devil's claw and licorice root. See section on controlling inflammation (page 76), for mechanisms related to these and other natural anti-inflammatory agents.

GI-Specific Nutrients

Like most cells in the body, the cells lining the GI tract need proper nutrients to maintain healthy function. These cells have specific nutrient needs that allow for targeted therapy.[24] Enterocytes, and to a much lesser extent colonocytes, use the amino acid glutamine as a major source of energy; this is true of many cells within the immune system.[25] Glutamine deficiency causes gut dysfunction and, consequently, muscle wasting because the body will remove glutamine from muscle tissue to attempt to bolster gut glutamine levels.[26] Oral glutamine has been shown to protect and/or repair gut morphology and intestinal permeability triggered by numerous assaults.[27]

The need to produce mucin/mucus within the GI tract is also a specialized function of these cells. Supplementation with mucus precursors, such as glucosamine or N-acetyl glucosamine, provides cells with the necessary building blocks to produce appropriate mucin levels. The availability of butyrate, a short-chain fatty acid produced by bacterial fermentation of certain fibers, also promotes mucin production in colonocytes.[28] Addition of fermentable fibers such as FOS (fructooligosaccharides) or inulin along with adequate probiotics will ensure proper butyrate levels.

Needless to say, it is impossible to have a properly functioning immune system while the gut is burdened with dysfunction or imbalance. The barrier function and the environment to host commensal organisms are vital for training and regulating a healthy immune system. Clinicians should always consider GI function as integrated and related to any immune-related dysfunction in the patient and, therefore, part of the prevention and intervention strategy of any immune-related disorder.

References

1. Bellavance MA, Rivest S. The HPA - Immune Axis and the Immunomodulatory Actions of Glucocorticoids in the Brain. *Front Immunol.* 2014 Mar 31;5:136.
2. Bellinger DL, Lubahn C, Lorton D. Maternal and early life stress effects on immune function: relevance to immunotoxicology. *J Immunotoxicol.* 2008 Oct;5(4):419-44.
3. Prokopakis E1, Vardouniotis A. et al. The pathophysiology of the hygiene hypothesis. *Int J Pediatr Otorhinolaryngol.* 2013 Jul;77(7):1065-71.
4. West AP, Shadel GS, Ghosh S. Mitochondria in innate immune responses. *Nat Rev Immunol.* 2011 Jun;11(6):389-402.
5. Lartigue L, Faustin B. Mitochondria: metabolic regulators of innate immune responses to pathogens and cell stress. *Int J Biochem Cell Biol.* 2013 Sep;45(9):2052-6.
6. Cloonan SM, Choi AM. Mitochondria: sensors and mediators of innate immune receptor signaling. *Curr Opin Microbiol.* 2013 Jun;16(3):327-38.
7. Pearce EL, Poffenberger MC, Chang CH, Jones RG. Fueling immunity: insights into metabolism and lymphocyte function. *Science.* 2013 Oct 11;342(6155):1242454.
8. Manoli I, Alesci S, Blackman MR, Su YA, Rennert OM, Chrousos GP. Mitochondria as key components of the stress response. *Trends Endocrinol Metab.* 2007 Jul;18(5):190-8.
9. De Felice FG, Ferreira ST. Inflammation, defective insulin signaling, and mitochondrial dysfunction as common molecular denominators connecting type 2 diabetes to Alzheimer disease. *Diabetes.* 2014 Jul;63(7):2262-72
10. Ames BN. Optimal micronutrients delay mitochondrial decay and age-associated diseases. *Mech Ageing Dev.* 2010 Jul-Aug;131(7-8):473-9.
11. Ponnappan S, Ponnappan U. Aging and immune function: molecular mechanisms to interventions. *Antioxid Redox Signal.* 2011 Apr 15;14(8):1551-85.
12. Fulop T, Le Page A, Fortin C, Witkowski JM, Dupuis G, Larbi A. Cellular signaling in the aging immune system. *Curr Opin Immunol.* 2014 Jun 13;29C:105-111.
13. Pritz T, Weinberger B, Grubeck-Loebenstein B. The aging bone marrow and its impact on immune responses in old age. *Immunol Lett.* 2014 Jul 8. pii: S0165-2478(14)00129-1.
14. Chinn IK, Blackburn CC, Manley NR, Sempowski GD. Changes in primary lymphoid organs with aging. *Semin Immunol.* 2012 Oct;24(5):309-20
15. Mason KL, Huffnagle GB, Noverr MC, Kao JY. Overview of gut immunology. *Adv Exp Med Biol.* 2008;635:1-14.
16. Mabbott NA, Donaldson DS, Ohno H, Williams IR, Mahajan A. Microfold (M) cells: important immunosurveillance posts in the intestinal epithelium. *Mucosal Immunol.* 2013 Jul;6(4):666-77.
17. Mantis NJ, Rol N, Corthésy B. Secretory IgA's complex roles in immunity and mucosal homeostasis in the gut. *Mucosal Immunol.* 2011 Nov;4(6):603-11.
18. Brandtzaeg P. Gate-keeper function of the intestinal epithelium. *Benef Microbes*. 2013 Mar 1;4(1):67-82.
19. Campos-Rodríguez R, Godínez-Victoria M et al. Stress modulates intestinal secretory immunoglobulin A. *Front Integr Neurosci.* 2013 Dec 2;7:86.
20. Cole MF. Detection and quantitation of antifungal sIgA antibodies in body fluids. *Methods Mol Biol.* 2009;499:9-16.
21. Fasano A. Leaky gut and autoimmune diseases. *Clin Rev Allergy Immunol.* 2012 Feb;42(1):71-8.
22. The 4R approach has been championed by the Institute for Functional Medicine (IFM) and is outlined in their *Text Book of Functional Medicine*. Updates to this model (sometimes called the 5R model) are available through IFM material and seminars.
23. Musso G1, Gambino R, Cassader M. Interactions between gut microbiota and host metabolism predisposing to obesity and diabetes. *Annu Rev Med.* 2011;62:361-80.
24. Hering NA, Schulzke JD. Therapeutic options to modulate barrier defects in inflammatory bowel disease. *Dig Dis.* 2009;27(4):450-4.
25. Kim H. Glutamine as an immunonutrient. *Yonsei Med J.* 2011 Nov;52(6):892-7.
26. Gleeson M. Dosing and efficacy of glutamine supplementation in human exercise and sport training. *J Nutr.* 2008 Oct;138(10):2045S-2049S.
27. Wang B, Wu G, Zhou Z et al. Glutamine and intestinal barrier function. *Amino Acids.* 2014 Jun 26. [Epub ahead of print.]
28. Meijer K, de Vos P, Priebe MG. Butyrate and other short-chain fatty acids as modulators of immunity: what relevance for health? *Curr Opin Clin Nutr Metab Care.* 2010 Nov;13(6):715-21.