

Supporting Immune Function

A Lifestyle and Nutrient Approach

Principles and Protocols for Healthcare Professionals

Lifestyle Interventions for Immune Health • Basic Principles of Autoimmunity and Autoinflammation
Slowing Immunosenescence • The GI and Immune Function • Mitochondrial Function and Immune Health
Immunology and Autoimmune Testing • Diminishing Stress and Cortisol-Induced Immune Suppression
Circadian Control of Immune Function • Solutions for Allergies and Inflammation
Overview of Natural Immunomodulators • Protocol and Formulary Suggestions • And much more...

THE STANDARD
ROAD MAP SERIES

Thomas G. Guilliams Ph.D.



POINT INSTITUTE



Supporting Immune Function A Lifestyle and Nutrient Approach

Principles and Protocols for Healthcare Professionals

By Thomas G. Guilliams Ph.D.



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.

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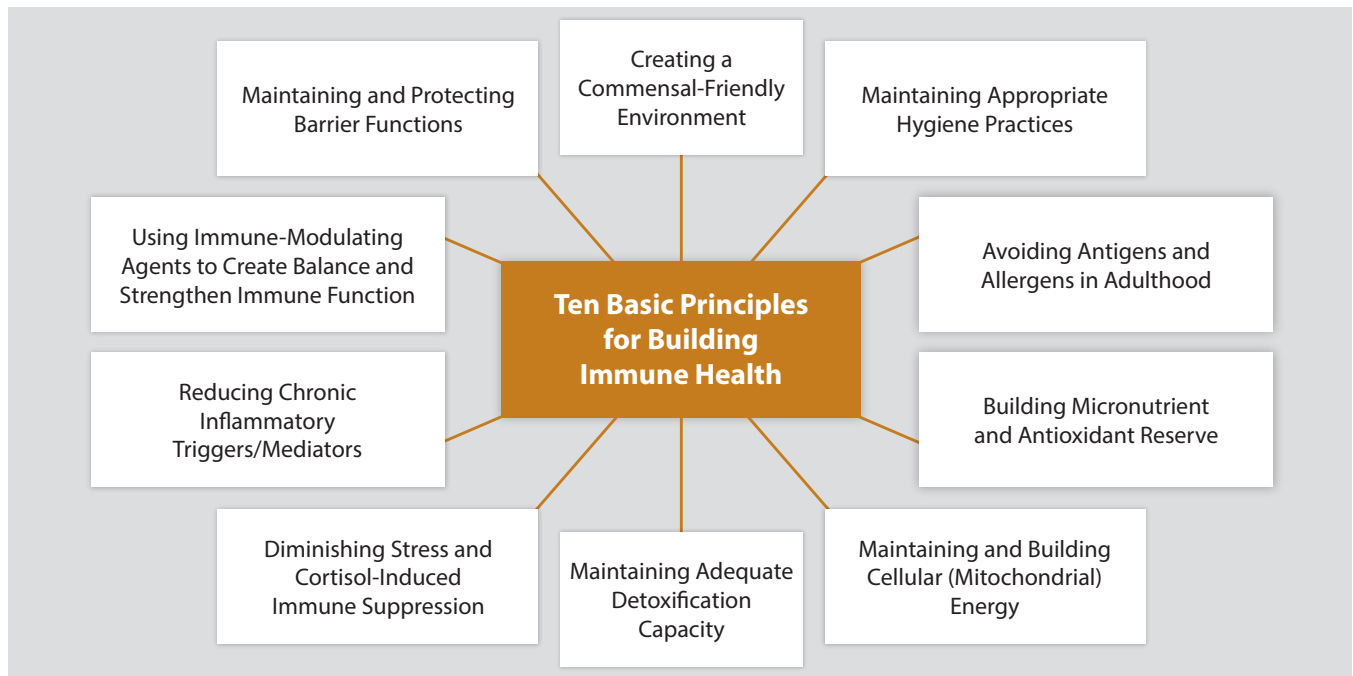
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Basic Principles for Building Immune Health

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.

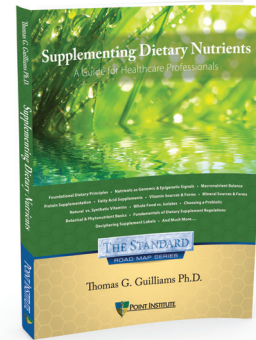
Throughout this guidebook, we will outline specific micronutrients known to be depleted during immune challenges or shown to affect immune- or illness-related outcomes when used as therapeutic agents.

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.



Supplementing Dietary Nutrients A Guide for Healthcare Professionals Thomas G. Guilliams Ph.D.

Written from an industry insider's perspective, this up-to-date reference guide answers challenging questions related to nutrition and dietary supplement use in clinical practice:

- How can nutrients serve as genomic and epigenetic signals?
- What are proven dietary patterns?
- Natural versus synthetic vitamins?
- Whole food versus isolates?
- What is the regulatory climate of dietary supplements?
- How are USRDAs determined and are they adequate?



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).

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- κ B 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

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,

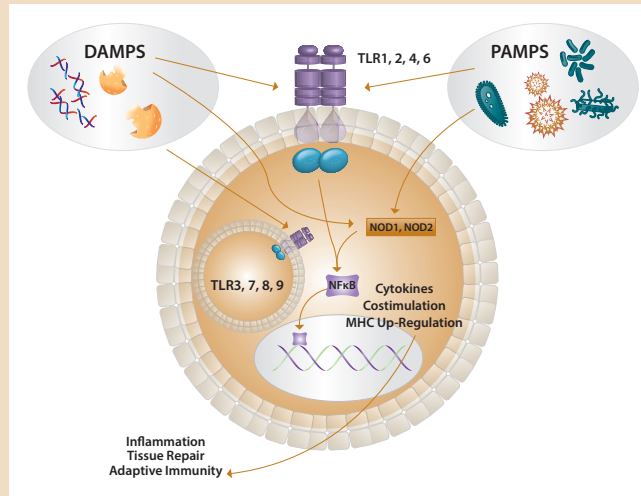


Figure A: Basic Signaling of Pattern Recognition Receptors. See text for explanation.

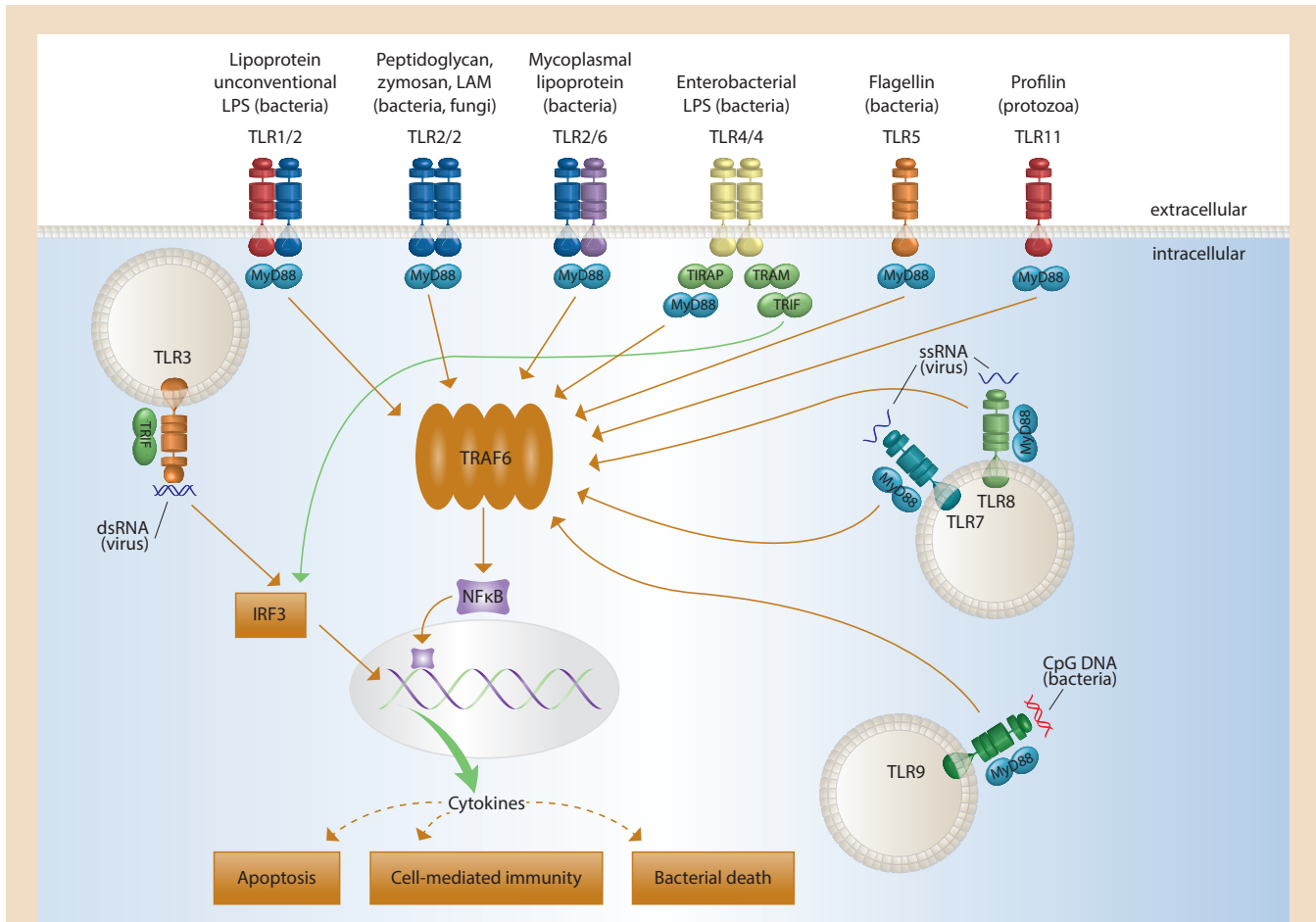


Figure B: Toll-like receptor (TLR) signaling. This diagram shows the different types of TLRs, their locations and the patterns they recognize. See text for more details about the signaling pathways. Image adapted from Minireview: Toll-like Receptors (TLR)—www.abdserotec.com.

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- κ B 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- κ B by all PRRs, a particular class of NOD-like receptors (NLRs) produce large intracellular multiprotein complexes called inflammasomes when

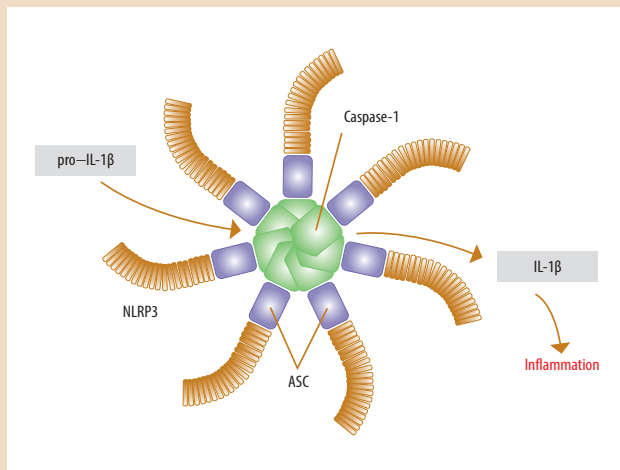


Figure C: Inflammasome (NLRP3) molecule. See text for details. Adapted from *Nature Medicine* 17, 790–791 (2011)

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-1 β 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- κ B 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.

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Autoinflammatory Diseases

While the fundamental understanding of autoimmune mechanisms is focused mainly on the lack of self-tolerance in the adaptive immune system, an ongoing wave of research is showing that many chronic autoimmune challenges may be defined as “autoinflammatory” and are mediated by cells within the innate immune system. In some cases, traditional autoimmune diseases are even being reclassified as having

autoinflammatory components.³ Figure 15 displays a range of autoimmune and autoinflammatory conditions, showing the relative overlap in the distinctions between the triggers and mediators of these different conditions. While these distinctions may not have immediate clinical applications, in many cases implementing an overall anti-inflammatory lifestyle and diet may be one of the best ways to reduce the mediation of these conditions.

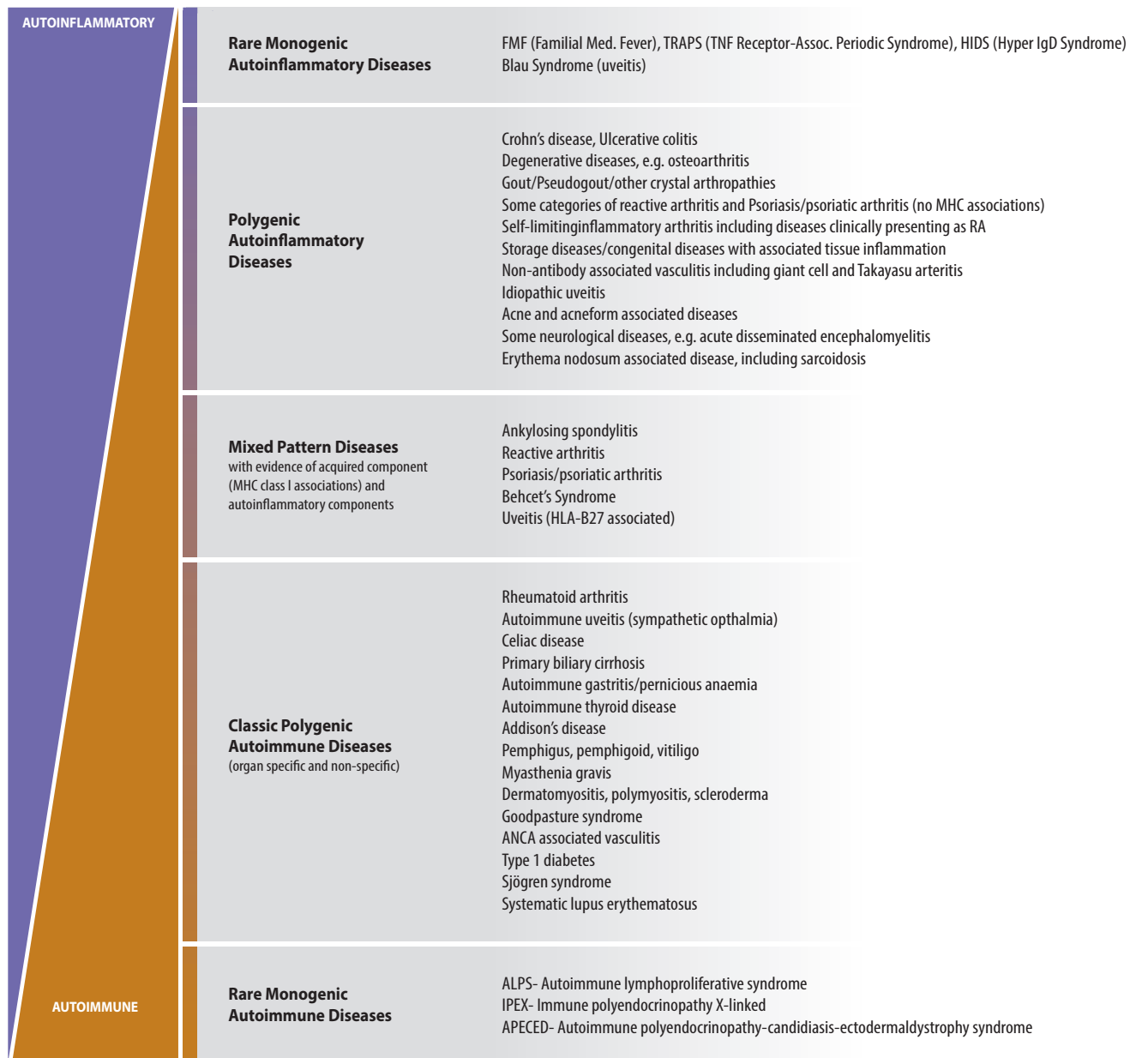


Figure 15: The Autoimmune/Autoinflammatory Disease Continuum. The monogenic “autoinflammatory” diseases may be exclusively determined by local tissue-specific factors. For rare monogenic “autoimmune” conditions, the disease localization appears to be determined predominantly by the adaptive immune response. The clinical heterogeneity within the immunological diseases, both among patients and between populations, may reflect the variable expression of autoinflammatory and autoimmune factors in disease causation. From McGonagle D, McDermott MF (2006) A Proposed Classification of the Immunological Diseases. *PLoS Med* 3(8): e297.

Commonalities of Autoimmune Diseases

While many of the conditions classified as having an autoimmune/autoinflammatory component affect different tissues and appear to be triggered by different stimuli, there are some key commonalities between these different diseases.⁴

1. *A Higher Prevalence in Women:* Depending on the diagnostic criteria used, upwards of 80% of the worldwide sufferers of an autoimmune condition are women.⁵ Sex-linked genetics and differences in immune regulation related to hormone secretion are speculated to drive this distinction (See Figure 16 below).
2. *A Similar Pathophysiology:* While various autoimmune conditions attack different tissues and result in different outcomes, the underlying mechanisms involving both adaptive and innate immune systems are nearly identical. In some cases, as with the presence of anti-nuclear antibodies, the pathophysiology is remarkably similar and only differs by the cell-type being affected. This similarity has negative consequences, such as autoimmune clustering (see below), but also may allow for similarities in positive treatment outcomes across multiple categories of autoimmune diseases.
3. *Genetic Predisposition:* Genetic studies have identified a number of loci that increase the risk for specific autoimmune conditions. These genes may encode loci for genes encoding HLA molecules, pattern-recognition receptor molecules, immunoglobulin or T cell receptors, or in any of the immune-regulating proteins within the cell.⁷ Beyond this, new studies are emerging that show how various epigenetic factors create a protective or susceptible pattern for autoimmune diseases.⁸
4. *Common Environmental Triggers:* As with immune dysfunction and chronic disease generally, many of the same lifestyle and environmental triggers that deplete immune metabolic reserve or trigger

inappropriate immune signaling will increase the risk for, or exacerbate, multiple autoimmune conditions.⁹ These triggers might be infectious organisms, vaccinations, environmental chemicals, tobacco smoke, drugs or food peptides.¹⁰ As with beneficial immune reactions, autoimmune reactions stimulated by environmental triggers can increase in intensity with repeated exposure.

5. *Autoimmune Clustering:* Due to the similarities in genetic predisposition and environmental triggers, it is common to see a clustering of autoimmune diseases in patients. One of the most common clusters is composed of four different autoimmune diseases: AITD- autoimmune thyroid disease (including thyroiditis, Hashimoto’s disease, Graves’ disease), SLE-systemic lupus erythematosus, SS-Sjögren’s syndrome and APS- antiphospholipid syndrome.
6. *A Cycle of Relapse/Recovery:* Many of the common features already described partially account for another feature of many autoimmune/autoinflammatory conditions, a cycle of relapse and recovery. While some of the relapses can be linked with specific environmental triggers, unrelated immune challenge or HPA axis-related stress; many of the relapse (and recovery) episodes often seem to have no known trigger. Most studies attempting to evaluate therapeutic interventions for autoimmune

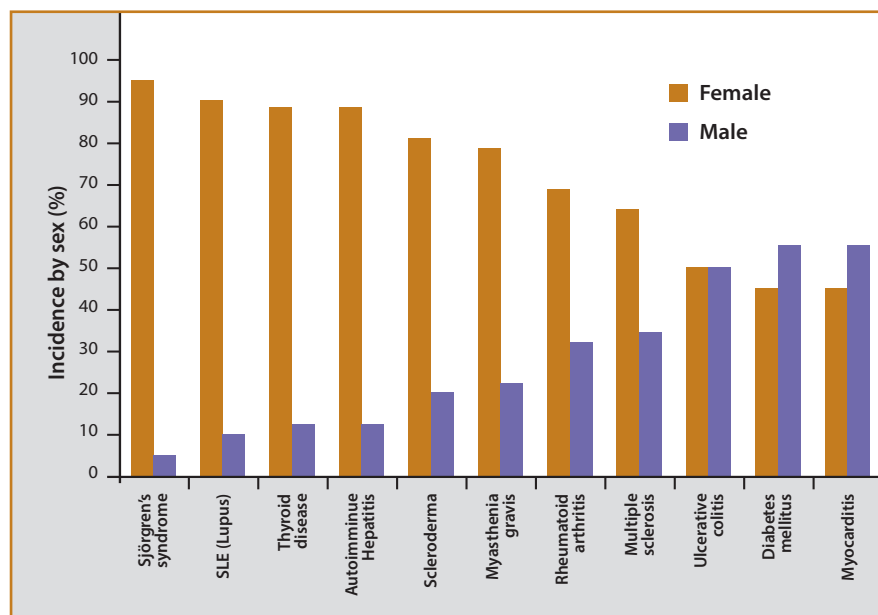


Figure 16. Relative incidence (by percent) by sex for autoimmune disorders. Notice that nearly all show a much higher incidence among women.⁶

conditions choose the number of episodes over time, or time to relapse, in addition to disease severity to evaluate the efficacy of the intervention.

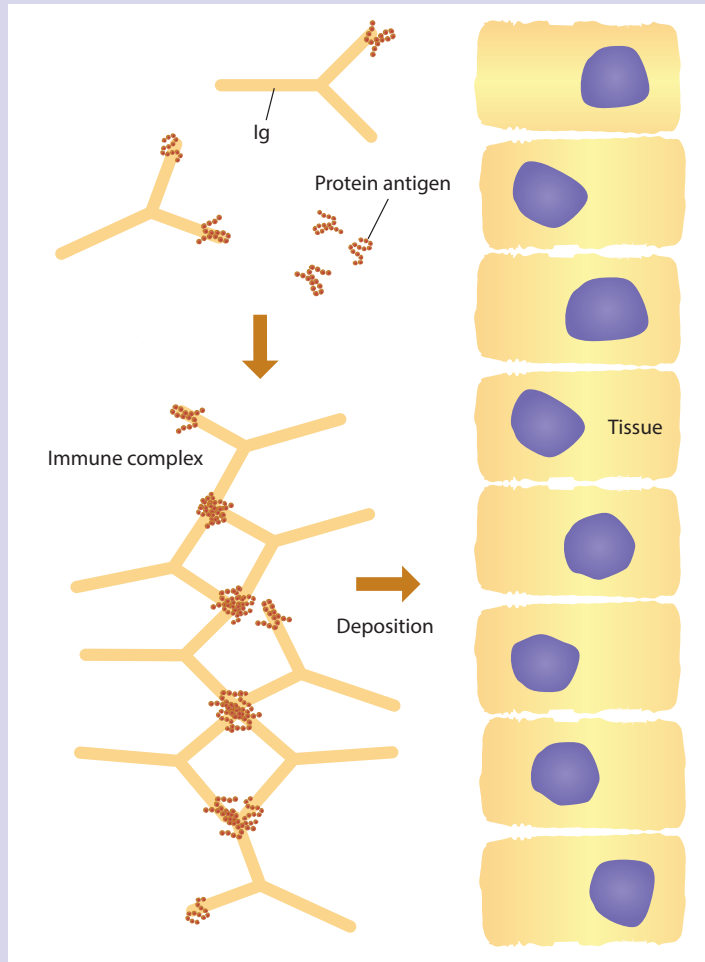
By understanding the similarities linking many different autoimmune conditions, a clinician can leverage the common pathways of risk susceptibility and therapeutic intervention these similarities provide. In subjects with multiple autoimmune syndromes

(polyautoimmunity), this may allow the creation of a single strategy to deal with the underlying drivers of immune dysregulation, helping to discover and avoid those triggers that are precursors to more than one autoimmune outcome. By seeing beyond the “disease” toward the overall support structure of a patient immune health (physiological, emotional, spiritual), a clinician may be able to anticipate and avert an immune system-mediated attack on another organ system.

The Immune Complex

When certain soluble antigens combine with cross-reactive antibodies, an immune complex is able to form. Depending on the type of antibody class involved (typically IgM or IgG) and the sizes of the immune complex, various potential outcomes are possible. In many cases, the immune complex can simply be removed by other immune processes (phagocytosis, complement). However, these immune complexes can also be deposited into tissues, especially the connective tissues of the kidney, skin and joints, where they can trigger chronic inflammatory processes that lead to further tissue damage (a type III hypersensitivity reaction). Some common immune conditions known to have immune complex involvement include glomerulonephritis, rheumatoid arthritis, serum sickness, malaria, subacute bacterial endocarditis and systemic lupus erythematosus (SLE).

Treatments intended to target immune complexes include agents directed at the antigen (if it is known), anti-inflammatory agents or immunosuppressant drugs. In the 1980's and early 90's, several studies using oral enzyme therapy (bromelain, trypsin, chymotrypsin, etc.) to reduce immune complexes in patients with rheumatoid arthritis were published (in German).^{1,2} While these reports showed promise and these types of products are still often used for immune complex-related phenomenon by many clinicians, these studies have not been repeated in the past few decades.



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Immune Support Through Lifestyle Interventions

The best immune-building strategies, both preventative and intervention, are those that provide the metabolic building blocks and regular modulating signals to trigger the intrinsic healing capacity of the body. Under perfect circumstances, all of these signals could be provided by regular inputs from a prudent lifestyle alone. However, in today’s patient population these signals often need to be accomplished through intensive lifestyle changes, augmented lifestyle therapies or even rescue interventions (For more on the prevention-to-intervention hierarchy see pages 11–12).

This section will outline available evidence and proposed mechanisms related to the seven spheres of the lifestyle synergy model discussed in section one of this guidebook. Some additional and more specific lifestyle-related recommendations will be covered in the therapeutic sections of this guidebook. Augmented lifestyle remedies, such as herbal remedies, probiotics and other dietary supplement immunomodulators, will be covered in their own sections.



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Natural Immune-Modulating Agents

Herbs & Botanical Extracts

The use of herbs and botanical extracts for immune enhancement has ancient roots in nearly every culture across the globe. For some cultures, this is still the primary medicinal choice for prevention and treatment of common illnesses. Even in the West, where pharmaceutical drugs have dominated the medical landscape, the use of herbal therapies is still popular. Many of these herbs and botanical extracts have been studied using modern research techniques—methods that are not always suitable to describe the historical benefits seen with these compounds. Even so, we have learned surprising things about the mechanisms and clinical efficacy of many traditional herbal preparations, though some clinical trials have had less than favorable outcomes.

Echinacea

Products containing various forms of Echinacea are among the top-selling herbal preparations every year in the United States. These products are consumed most often to prevent or treat common illnesses, especially for cold and flu prevention.¹ The general term Echinacea describes preparations of three species of purple coneflowers: *E. purpurea*, *E. angustifolia* and *E. pallida*. The roots and rhizomes of each species are used for medicinal purposes, while the whole plant (flower, leaf and root) is also used in the case of *E. purpurea*. Dried roots, liquid extracts, tinctures, dried extracts and standardized extract preparations of each species are available as single-ingredient preparations or mixed with other herbs, vitamins or nutrients.

The constituents with potential immunomodulatory activity within Echinacea species are many, including arabanogalactan polysaccharides, alkamides, caffeic acid esters, echinacoside (not in *E.*

purpurea), volatile oils, polyacetylenes and flavonoids.² Rather than a single active component, most researchers consider Echinacea's activities to be derived from a combination of these constituents. Various preparations and components of *E. purpurea* have been shown to stimulate macrophage activation, a key initiator of the immune response, as well as NK cell activity in both human and animal models^{3,4,5,6,7} These activities, in many cases, are linked directly to increased cytokine expression.^{8,9} Preparations of *E. purpurea* root appear to modulate antigen presenting cells and T-reg cells.¹⁰ Other Echinacea preparations also show limited antiviral,¹¹ antifungal^{12,13} and antibacterial activities.¹⁴

Clinical trials involving preparations of Echinacea have been frequently performed and numerous reviews are available.¹ Comparing these trials is difficult because most study designs differ in the type, dose and method of delivery of the Echinacea preparations, and the length of the study and the primary outcome (prophylaxis vs. treatment). The most common studies are for the prevention or treatment of upper respiratory tract infections where Echinacea preparations have been shown to reduce the frequency, severity and/or duration of common cold symptoms in several trials, particularly in children.¹⁵ One study showed *E. purpurea* attenuated the mucosal-immunity suppression caused by exercise as measured by secretory IgA (sIgA).¹⁶

Many trials have been conducted on multi-herb/nutrient formulas containing Echinacea preparations.^{17,18} One such trial showed children aged 1 to 5, given a liquid herbal blend (containing *E. angustifolia* and *E. purpurea*, propolis, and vitamin C) had 50% fewer upper-respiratory tract infections, 68% fewer incidents of otitis media, and 66% fewer incidence of pneumonia compared to children given a placebo syrup over a 12-week winter season. When

Caution with Immune-Modulating Therapies

There is a general precaution within the medical community that anything that modulates the immune system could possibly trigger or exacerbate autoimmune conditions, aggravate inflammatory conditions or intensify IgE-related allergic reactions (immune overstimulation), or prevent proper response to a pathogen (immune suppression). The published scientific literature is limited in addressing these issues; with little more than a few case reports or speculations based on proposed mechanisms. Therefore, only a general precaution can be given; that aggressive use of ingredients that stimulate or suppress either the innate or adaptive immune systems may not be advisable in patients with a known autoimmune disease or active infection.

Many herbal traditions also recommend using immune-stimulating therapies for short periods of time (weeks or months depending on the tradition), followed by a removal of the therapy for weeks or months before starting the therapy again. Once more, the scientific literature is mostly silent on this approach. In general, it is most effective to stimulate the immune system when there is a “live” target. This is especially true of the adaptive immune system that is best upregulated in the presence of a memory-stimulating antigen. The use of immune-enhancing protocols is therefore advised when a patient is infected, or during the season or situation (indoors, daycare, nursing home, confined travel, etc.) where they have a higher likelihood of contacting pathogens. Clinicians should consider focusing on things that build immune-system reserve (macronutrient balance, micronutrient repletion, overall stress reduction, sleep/chronicity, etc.) rather than relying solely on immune modulators, for general immune support.

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Supporting Immune Challenges

Candidiasis

Candidiasis is the overgrowth of the yeast *Candida albicans* and similar species. *Candida albicans* is a normal inhabitant of the GI tract in humans, as well as the mucus membranes of other orifices such as the mouth, nose and vagina. During immune-system stress or specific GI imbalances, *Candida* can become an opportunistic pathogen and result in harm to the host. The most ancient description of a *Candida* infection is oral thrush, which is common in immune-compromised individuals. Anytime the immune system is under stress, opportunistic organisms within the gut can flourish, this is especially true if beneficial commensal organisms are depleted or reduced. Candidemia, the invasion of live *Candida* in the blood, is rare, severe and should result in immediate hospitalization (although the patient is likely to already be hospitalized as this is frequently a nosocomial infection).

Candida overgrowth is commonly related to the following:

- Long-term antibiotic use (acne, otitis media, sinusitis, etc.)
- High-dose (short-term) antibiotic use (surgery, UTI, etc.)
- Use of alcohol or fermented beverages
- Irritable Bowel Syndrome
- High consumption of sugars, white flour, pastries, etc.
- Compromised immune system (long-term or short-term)
- Chronic stress (which suppresses the immune system)

While *Candida* overgrowth is a common cause of vaginal yeast infections, overgrowth within the GI tract is often unrecognized. This is because *Candida* overgrowth does not always cause overt GI symptoms. These diverse symptoms include mental fog, muscle/joint weakness or pain, general fatigue, and skin irritations, to name a few. These symptoms are a result of the growth of the yeast (and their subsequent metabolites) as well as the death of yeast organisms. These processes put additional burden upon the liver's detoxification capacity, which is responsible for transforming yeast metabolites into harmless substances for elimination.

Once an individual has *Candida* overgrowth, reoccurrence is quite common. Patients will need to maintain a consistent and vigilant lifestyle management program to prevent repeated incidence of Candidiasis. Likewise, strategies to increase immune system and GI barrier function should be considered as an ongoing strategy after a *Candida* elimination protocol.

Stool analysis reports (often part of a comprehensive digestive stool analysis-CDSA) will often enumerate relative *Candida albicans* levels in the mycology section (see your lab for more details). When this is elevated, it suggests (along with history and symptom questionnaires) that *Candida* overgrowth may be contributing to the patient's poor health. There are times when additional, more specific, tests for *Candida* can be performed. These can be utilized if the stool culture within the CDSA shows only modest *Candida* growth but symptoms and history (past or concomitant yeast infections) suggest *Candida* involvement.

These tests typically look in the blood (or saliva) for either antibodies (IgA, IgG, or IgM) to *Candida* peptides or for peptides that cross-react to prepared anti-*Candida* antibodies. Positive reactivity to these tests suggests that the gut-associated immune system has had frequent encounters with invasive *Candida* organisms within the GI mucosa (it does not indicate live *Candida* within the blood). Ask your lab for specific *Candida* test information if you suspect *Candida* that is not confirmed by the CDSA results.

A Balanced and Evidence-Based Approach

From the muscles of the heart to the lymph nodes in the neck to the lining of the gut, the human immune system affects every function of the body. This far-reaching system plays an active role in helping patients achieve and maintain optimal health. In an age of escalating chronic disease and stress-induced illness, unraveling immune system dysfunction is one of the most challenging endeavors that healthcare providers face. Years of research have greatly advanced our knowledge and understanding of the immune system, providing innovative avenues for effective immunity support strategies. While many infectious diseases of the past have ceased to be major threats in Western societies, new immune system challenges have emerged on the battleground of patient care.

Supporting Immune Function: A Lifestyle and Nutrient Approach goes beyond ordinary academic textbooks to deliver practical insights on a complex topic. This beautifully illustrated reference guide discusses clinically-relevant advances in immune system understanding and provides strategies to put these principles into action. Written by a natural products expert with a Ph.D. in molecular immunology, this guide will help healthcare providers better navigate the nuances of the immune system and provide clinical solutions through lifestyle intervention strategies and targeted nutrient support protocols.

This guide is intended to be an indispensable resource for anyone making lifestyle, nutritional or dietary supplement recommendations within a healthcare setting:

- Clinicians
- Pharmacists
- Nutritionists
- Dietitians
- Nurses/Nurse Practitioners
- Medical Technicians
- Nutritional Researchers and Educators
- Health Coaches
- Medical/Health Journalist and Writers
- Students of Health Professions
- Manufacturers/ Distributors of Food and Dietary Supplements

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About the Author:



Thomas G. Guilliams Ph.D. earned his doctorate from the Medical College of Wisconsin (Milwaukee) where he studied molecular immunology in the Microbiology Department. Since 1996, he has spent his time studying the mechanisms and actions of natural-based therapies, and is an expert in the therapeutic uses of nutritional supplements. As the Vice President of Scientific Affairs for Ortho Molecular Products, he has developed a wide array of products and programs which allow clinicians to use nutritional supplements and lifestyle interventions as safe, evidence-based and effective tools for a variety of patients. Tom teaches at the University of Wisconsin-School of Pharmacy, where he holds an appointment as a Clinical Instructor; at the University of Minnesota School of Pharmacy and is a faculty member of the Fellowship in Anti-aging Regenerative and Functional Medicine. He lives outside of Stevens Point, Wisconsin with his wife and children.

Dr. Guilliams' other writings can be found at The Point Institute at www.pointinstitute.org



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