Immune System Health

Naturopathic Nutrition 2
Learning Outcomes:

On successful completion you will be able to:

• Explain the major pathophysiologies of the immune system
• Describe in detail the functions of different aspects of the immune system
• Evaluate orthodox medical testing and treatment for autoimmune diseases
• Outline nutritional therapy approaches to support optimal immune function
• Show awareness of the importance of referral with ‘Red Flag’ symptoms
Immune System

• The immune systems is a complex integration of **synergistic** segments that are continuously barraged by stimuli - from **both internal and external** sources

• Immunology has continued to be a **rapidly developing field** in which mechanisms are continually being conceptualised and revised

Immune System

• For the therapist interested in assessing and maintaining a patient's health, the development of a thorough understanding of the clinical aspects of the immune system and the many factors that enhance and/or inhibit normal function is essential as immunity is our key to keeping dis-ease at bay.

• The immune system is truly holistic, as evidenced by the close association of psychological, neurologic, nutritional, environmental and hormonal factors with immune function – to study the immune system one must be aware of the interplaying factors.

Immune System

• Many conditions are dependant on the health and integrity of the immune system - from colds and recurrent infections, through to allergies and to severe, debilitating auto-immune conditions

• Supporting the immune system is critical to good health

• The best approach to supporting immune function is a comprehensive plan involving lifestyle, stress management, exercise, diet, nutritional supplementation, and the use of plant-based medicines

Primary roles of a healthy immune system

1. To identify potentially infectious or injurious substances
2. To distinguish self-antigens from non-self antigens
3. An ability to assess the potential level of threat posed by infectious, toxic or non-self
4. To mount a response that is appropriate to the level of threat
5. To repair any damage that ensues from these encounters

The layered defence strategy of immunity

• Physical and mucosal barriers
  • Skin, mucus, enzymes in tears, saliva and skin oils, the cough reflex, genito-urinary, respiratory and gastrointestinal tract mucosa

• Innate (non-specific)
  • Immediate but non-specific response – granulocytes, complement system, non-specific inflammatory reaction
  • Does not require memory to an antigen

• Acquired (specific)
  • Activated by the innate immune system
  • A specific response created then retained after the pathogen has been eliminated therefore allows the adaptive immune system to mount faster and stronger attacks each time this pathogen is encountered Involves B and T cells as well as the previous innate components

The two arms of the immune system

- **Innate** (Nonspecific)
  - 1st line of defense
  - Cellular Components
  - Humoral Components

- **Adaptive** (Specific)
  - 2nd line of defense
  - Protects/re-exposure
  - Cellular Components
  - Humoral Components

Microbiology and immunology online. University of Southern Carolina School of Medicine Dept.  
Innate Immune System

- Genetically based - **Non specific** i.e. all antigens are treated the same way
- **Microflora**
  - We have about $10^{13}$ cells in our bodies and $10^{14}$ bacteria, most of which live in the large intestine but also in the nose, mouth, stomach, small intestine, large bowel, genito-urinary system – bacteria plays a protective role as well as a pathological
- **Cells of the innate immune system**
  - Phagocytes, granulocytes, monocytes, macrophages, natural killer cells
  - Each of the cells in the innate immune system bind to antigens using pattern-recognition receptors
Acquired Immune System (Adaptive)

- Not present at birth - called *adaptive* as the immune system must *adapt itself* to encountered threats
- Also called *specific* immunity
- **Lymphocytes** are the type of white blood cell responsible for acquired immunity:
  - Come in two major types: B cells and T cells
  - The peripheral blood contains 20–50% of circulating lymphocytes; the rest move in the lymph system
  - Roughly 80% of them are T cells, 15% B cells and remainder are undifferentiated cells
  - Lymphocytes constitute 20–40% of the body's WBCs

University of Hartford.
The two responses of the immune system

<table>
<thead>
<tr>
<th>Innate</th>
<th>Acquired</th>
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<tbody>
<tr>
<td>Non-specific</td>
<td>Specific</td>
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<tr>
<td>Response is antigen <strong>independent</strong></td>
<td>Response is antigen dependent</td>
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<tr>
<td>Immediate maximal response</td>
<td><strong>Time lag</strong> in maximal response</td>
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<tr>
<td><strong>Not</strong> antigen specific</td>
<td>Antigen specific</td>
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<tr>
<td>Exposure results in <strong>no</strong> immunological memory</td>
<td>Exposure results in immunological memory</td>
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So what causes immune reactions?

- Most of the time – it is the protein component of the virus, bacteria, food or foreign matter.
- Polysaccharides and lipopolysaccharides (LPS) can often cause immune reactions also. A large number of LPS comes from bacterial cell walls.
- Nucleic acids can cause a reaction in some cases.
- Super antigens are generally chemical toxins produced by bacteria that can cause an immune reaction (such as toxic shock syndrome).
Antibody - Antigen reactions

• Normally, an antibody is specific to one type of antigen (lock and key effect)
• In some cases there is something known as cross-reactivity, which is when an antibody reacts with more than one antigen - this can be one of the aspects responsible for the development and maintenance of auto-immunity
Review of immune system cells

- **Immune System**
  - **Myeloid Cells**
    - Granulocytic
      - Neutrophils
      - Basophils
      - Eosinophils
    - Monocytic
      - Macrophages
      - Kupffer cells
      - Dendritic cells
  - **Lymphoid Cells**
    - T cells
      - Helper cells
      - Suppressor cells
      - Cytotoxic cells
    - B cells
      - Plasma cells
    - NK cells
Phagocytes

• This is a group of immune cells specialized in finding and "eating" bacteria, viruses, and dead or injured body cells. There are three main types:

• the granulocyte
• the macrophage
• the dendritic cell.
Review of immune system cells

- The **granulocytes** often take the first stand during an infection.
- They are phagocytic, they attack any invaders in large numbers, and eat until they die.
- The pus in an infected wound consists chiefly of dead granulocytes.
- Neutrophils - specialise in killing bacteria.
- Basophils - release histamine.
- Eosinophils – specialise in parasites, are antigen presenting.
Review of immune system cells

- The **macrophages** are slower to respond to invaders than the granulocytes, but they are larger, live longer, and have far greater capacities.
- Macrophages also play a key part in alerting the rest of the immune system of invaders.
- Macrophages start out as white blood cells called monocytes.
- **Monocytes** that leave the blood stream turn into macrophages.

"The Immune System - in More Detail". Nobelprize.org. 1 Aug 2012
http://www.nobelprize.org/educational/medicine/immunity/immune-detail.html
Review of immune system cells

• The **dendritic** cells devour intruders, like the granulocytes and the macrophages
• Like the macrophages, the dendritic cells help with the activation of the rest of the immune system
• They are also capable of filtering body fluids to clear them of foreign organisms and particles

"The Immune System - in More Detail". Nobelprize.org. 1 Aug 2012
http://www.nobelprize.org/educational/medicine/immunity/immune-detail.html
Review of immune system cells

Lymphocytes- B and T Cells

• Lymphocytes are made in the bone marrow, but they migrate to the lymphatic system
• Lymphatic cells contain receptor sites that are antigen specific

"The Immune System - in More Detail". Nobelprixe.org. 1 Aug 2012
http://www.nobelprixe.org/educational/medicine/immunity/immune-detail.html
T cells

T- cells - there are different subsets of T cells

T helper cells - (also called CD4+ cells)-

- help to mediate the innate immune response. They do this through the release of chemokines. There are different secretors of chemokines, and they are given different numbers dependant on their secreting pattern e.g. Th1, Th2, Th3, Th17 and Th0 are the most researched cellular patterns

- Their primary task is to activate B cells and killer T cells, however, the helper T cells themselves must be activated

"The Immune System - in More Detail". Nobelprize.org. 1 Aug 2012
http://www.nobelprize.org/educational/medicine/immunity/immune-detail.html
Cytotoxic T cells (Tc) or CD8+ cells
• These cells destroy virally infected cells directly, as well as cancer cells. They are responsible for transplant rejection reactions.

Memory T cells (Tcm or Tem)
• These cells remember an antigen and attack it directly when they become activated.
Regulatory T cells- (Treg) — used to be called T suppressor cells

- The major role of the Treg cells are to shut down a T cell reaction at the end of an immune response, and to kill any T-cells that have become auto-toxic
- They have a very important role of keeping acquired immunity in check.
T Helper cell activation

- Macrophages and/or dendritic cell present information about the captured pathogen to the T helper cells
- When the receptor of a helper T cell recognizes the antigen, the T cell is activated
- Once activated, helper T cells start to divide and to produce proteins that activate B and T cells as well as other immune cells
T Helper cell activation

**Antigen Presentation**

1. A phagocyte "eats" a bacteria.
2. Parts of the bacteria (antigen) goes to the surface of the phagocyte.
3. The phagocyte presents the antigen to a helper T cell.
4. The helper T cell is activated.

"The Immune System - in More Detail". Nobelprize.org. 1 Aug 2012
http://www.nobelprize.org/educational/medicine/immunity/immune-detail.html
B cells

• The B lymphocyte cell searches for antigen matching its receptors
• If it finds such antigen that matches inside the B cell a triggering signal is set off
• To become fully activated, the **B cell needs proteins produced by helper T cells to become fully activated**
• When this happens, the B cell starts to divide to produce clones of itself. During this process, two new cell types are created, **plasma cells** and **B memory cells**
Plasma B cell

- The plasma cell is specialized in producing antibodies (immunoglobulins - Ig) that will respond to the same antigen that matched the B cell receptor.
- Ig are released from the plasma cell so that they can seek out intruders and help destroy them.
- Plasma cells produce Ig’s at an amazing rate and can release tens of thousands of Ig’s per second.
Antibody reaction

- When the Y-shaped antibody finds a matching antigen, it attaches to it
- The attached antibodies attract macrophages
- Antibodies also neutralize toxins and incapacitate viruses, preventing them from infecting new cells
- Bacteria and other pathogens covered with antibodies are also more likely to be attacked by the proteins from the complement system
• The Memory Cells are the second cell type produced by the division of B cells
• These cells have a prolonged life span and can thereby "remember" specific intruders
• T cells can also produce memory cells with an even longer life span than B memory cells
• The second time an intruder tries to invade the body, B and T memory cells help the immune system to activate much faster

"The Immune System - in More Detail". Nobelprize.org. 1 Aug 2012
http://www.nobelprize.org/educational/medicine/immunity/immune-detail.html
The immune system depends upon not only cellular function, but many biochemical and metabolic changes to mediate the immune response.

These differing changes in the body include:

- Cellular proliferation
  - e.g. increase in WBC numbers
- Enhanced protein synthesis
  - e.g. antibody production
Biochemistry and immunity

• Inflammatory mediator production
  • e.g. cytokine, kinins, tumour necrosing factor, interleukin, prostaglandin and nitric oxide production

• Physiological changes
  • e.g. fever, appetite, cortisone release - The adrenal gland releases both cortisol and cortisone (also cortisone is made by peripheral conversion of cortisol). Cortisone is the most active in reducing immune reactions

• Metabolic changes
  • e.g. gluconeogenesis, muscle protein loss, oxidant production

Chemical and protein immune mediators

• There are a number of different chemicals that help to mediate the immune response

**Innate immunity requires:**

• **TNF-α** - tumour necrosis factor alpha-
  – Produced by activated macrophages in response to microbes
  – It is an important mediator of acute inflammation
  – TNF-α also acts on the hypothalamus to produce fever and it promotes the production of acute phase proteins
Chemical and protein immune mediators

- **IL-1 - Interleukin 1**
  - inflammatory cytokine produced by activated macrophages. Its effects are similar to that of TNF-α and it also helps to activate T cells

- **IL-10 - Interleukin 10**
  - produced by activated macrophages and Th2 cells. It is predominantly an inhibitory cytokine
  - It inhibits production of IFN-γ by Th1 cells, which shifts immune responses toward a Th2 type
  - It can also help in dampening of immune responses
Chemical and protein immune mediators

• IL-12 - Interleukin 12
  – produced by activated macrophages and dendritic cells
  – stimulates the production of IFN-γ and induces the differentiation of Th cells to become Th1 cells
  – enhances the cytolytic functions of NK cells

• Type I interferons
  – Type I interferons (IFN-α and IFN-β) are produced by many cell types and they function to inhibit viral replication in cells. They also activate NK cells
Chemical and protein immune mediators

• **INF-γ -Interferon gamma**
  – A cytokine produced by primarily by Th1 cells, although it can also be produced by Tc and NK cells to a lesser extent. It has numerous functions in both the innate and adaptive immune system

• **Chemokines**
  – Chemokines are chemotactic cytokines produced by many kinds of leukocytes and other cell types
  – They represent a large family of molecules that function to recruit leukocytes to sites of infection and play a role in lymphocyte trafficking by determining which cells will cross the epithelium and where they are directed to go
Adaptive immunity also requires:

- **IL-2 - Interleukin 2**
  - is produced by Th cells, although it can also be produced by Tc cells to a lesser extent. It is the major growth factor for T cells. It also promotes the growth of B cells and can activate NK cells and monocytes.

- **IL-4 - Interleukin 4**
  - is produced by macrophages and Th2 cells. It stimulates the development of Th2 cells from naïve Th cells and it promotes the growth of differentiated Th2 cells resulting in the production of an antibody response. It also stimulates Ig class switching to the IgE isotype.
• **IL-5 Interleukin 5**
  – is produced by Th2 cells and it functions to promote the growth and differentiation of B cells and eosinophils

• **TGF-β transforming growth factor beta**
  – is produced by T cells and many other cell types. It is primarily an inhibitory cytokine. It inhibits the proliferation of T cells and the activation of macrophages
  – It also acts to block the effects of pro-inflammatory cytokines
Eicosanoids

• The eicosanoids include prostaglandins, leukotrienes, thromboxanes, and lipoxins
• They are derived from the oxygenation of 20-carbon polyunsaturated essential fatty acids via the enzymes cyclo-oxygenase (COX) and lipoxygenase (LOX)
Eicosanoids

• The eicosanoids are considered local hormones
• They have specific effects on target cells close to their site of formation
• They are rapidly degraded, so they are not transported to distal sites within the body
• But in addition to participating in intercellular signalling, there is evidence for involvement of eicosanoids in intracellular signal cascades
Eicosanoids

- They play a role in:
  - inflammation and pain
  - Th1/Th2/Th17 balance
  - fever
  - regulation of blood pressure
  - blood clotting
  - immune system modulation
  - control of reproductive processes & tissue growth
  - regulation of sleep/wake cycle
Eicosanoid synthesis

- Synthesised from **essentially fatty acids** in the phospholipid bilayer, which are released by the enzyme **phospholipase A2**
- **Arachadonic acid** is the most commonly released EFA from the phospholipid bilayer, with the highest affinity for phospholipase A2
- The enzymes responsible for conversion of arachadonic acid are **cyclo-oxygenase (COX)** and **lipoxygenase (LOX)**
• PGE$_2$, is an essential homeostatic factor, is also a key mediator of immunopathology in chronic infections and cancer

• It suppresses acute inflammatory mediators, resulting in its predominance at late/chronic stages of immune response

• It promotes Th2, Th17, and regulatory T cell responses

• It modulates chemokine production, inhibiting the attraction of proinflammatory cells while enhancing local accumulation of regulatory T cells cells and myeloid-derived suppressor cells

• By targeting the production, degradation, and responsiveness to PGE$_2$ provides tools to modulate the patterns of immunity in a wide range of diseases, from autoimmunity to cancer
PHOSPHOLIPID

Phospholipase A₂ Enzyme

Arachidonate

Cyclooxygenase (COX) enzymes

Prostacyclin (PGI₂)
- Actions:
  - Vasodilation
  - Hyperalgesia
  - Stops Platelet Aggregation

Thromboxane (TXA₂)
- Actions:
  - Thrombotic
  - Vasoconstrictor

Prostaglandin F₂α (PGF₂α)
- Actions:
  - Bronchoconstrictor
  - Myometrial Contraction

Prostaglandin D₂ (PGD₂)
- Actions:
  - Inhibits Platelet Aggregation
  - Vasodilator

Prostaglandin E₂ (PGE₂)
- Actions:
  - Vasodilator
  - Hyperalgesic

Aspirin NSAID
- COX-1/COX-2
- COX-2
  (inhibit cyclooxygenase)

Lyso-glyceryl-phosphorylcholine

Platelet-Activating Factor
- Actions:
  - Vasodilation
  - Increase Vascular Permeability
  - Bronchoconstriction
  - Chemotaxin

Immunoglobulins

Immunoglobulin (Ig)

Immunoglobulins are glycoprotein molecules that are produced by plasma cells in response to an antigen and which function as antibodies.

Functions of Ig

• Antigen binding
• Effector functions
  – Either they activate complement proteins
  – Binding to various immune cell types to activate function

Microbiology and immunology online. University of Southern Carolina School of Medicine
Immunoglobulins

Immunoglobulin classes

The immunoglobulins can be divided into five different classes, based on differences in the amino acid sequences in the chains - IgG, IgM, IgA, IgD, IgE

- Immunoglobulins work by:
  - complement fixation - proteins attach to antigen surface and cause holes to form
  - neutralization - binding to specific sites to prevent attachment
  - agglutination
  - precipitation - forcing insolubility and settling out of solution
Properties of Ig’s

IgG
• the most versatile Ig
• 75% most abundant in the serum
• Is the only Ig that can cross the placental barrier – so is responsible for conferring immunity to the newborn
• Mainly prepares the antigen for phagocytosis by other cells

Microbiology and immunology online. University of Southern Carolina School of Medicine Dept. [http://pathmicro.med.sc.edu/ghaffar/innate.htm](http://pathmicro.med.sc.edu/ghaffar/innate.htm)
Properties of Ig’s

**IgM**

- IgM is the first Ig to be made by the foetus and the first Ig to be made by a virgin B cells when it is stimulated by antigen.
- IgM is physically much larger than the other immunoglobulins
- IgM is the dominant antibody produced in primary immune responses (the first time you have an active infection of that pathogen)
Properties of Ig’s

IgA

• IgA is the major class of Ig in secretions - tears, saliva, colostrum, mucus. Since it is found in secretions secretory IgA is important in local (mucosal) immunity
Properties of Ig’s

IgE

• The least common serum Ig since it binds very tightly to receptors on basophils and mast cells even before interacting with an antigen.
• Involved in allergic reactions - As a consequence of its binding to basophils and mast cells, IgE is involved in allergic reactions.
• Serum IgE levels rise in parasitic diseases, therefore measuring IgE levels is helpful in diagnosing parasitic infections.
Pathogen

Immature, inactive helper and killer T-cells

Pieces of pathogen presented on surface of antigen-presenting cell (macrophage)

Mature, inactive helper and killer T-cells

Helper and killer T-cells are activated by antigen-presenting macrophage, but only if T-cells recognize specific antigen presented by macrophage

Helper T-cell activates B-cell

Active helper and killer T-cells replicate, including formation of memory cells

Active B-cell replicates, and produces antibody molecules that can bind to specific antigens

B-cell is activated by the antigen but only if B-cell recognizes specific antigen. Active helper T-cell is required for B-cell activation

Killer T-cells require helper T-cells for activation

Antibody binds to antigen (“tagging”)

Memory B-cells can respond to subsequent infection by that kind of pathogen

Memory T-cells can respond to subsequent infection by that kind of pathogen

Killer T-cells kill any body cell infected with that specific kind of antigen

Complement system destroys the antigen

Phagocytic cells engulf the tagged antigen

Immature, inactive B-cells

Mature, inactive B-cells

Free antigen in blood
Humoral and Cellular Immunity

**Humoral immunity**
- B cells are produced to produce antibodies and oversee humoral immunity, which is an immunoglobulin driven reaction to the antigen.

**Cell-mediated /cellular immunity**
- T cells are non-antibody producing lymphocytes which are also produced in the bone marrow but sensitised in the thymus and constitute the basis of cell-mediated (cellular) immunity.
- B cells — and antibody production — are not activated.

University of Hartford.
Humoral Immunity

- The focus is prevention of infection: via the production of antibodies by B cells
- Antibodies prevent infection by attaching to the surface of invading pathogens and aiding in their disposal before they can infect cells
- Note that once the pathogen - antigens, viruses, bacteria or toxins - has entered the cell, the B cells are unable to access them
- Antibodies agglutinate, precipitate, neutralise and alter the local environment by stimulating an inflammatory reaction, activating complement or causing cell lysis

Cellular Immunity

Works in 3 main ways:

1. Activates non-specific natural killer cells and macrophages
2. Activates antigen-specific cytotoxic T cells
3. Stimulation of cells to secrete cytokines that direct and regulate the immune response to produce a response which is tailored towards eliminating a specific pathogen

Involves many different types of immune cells

- Natural killer, T helper, monocytes, macrophages, neutrophils, dendritic cells

Immune regulation

• One theory of immune regulation involves homeostasis between T-helper 1 (Th1) and T-helper 2 (Th2) activity

• T helper(Th)cells
  • Secrete cytokines that stimulate the non-specific immune response to continue and co-ordinate the activity of B cells, cytotoxic T cells and other T helper cells


T Helper cells and immune regulation

Once Th cells have been activated they then:
1) Select the appropriate effector mechanisms (e.g., B cell activation or T cell generation)
2) induce proliferation of appropriate effector cells
3) Enhance the functional activities of other cells (e.g., granulocytes, macrophages, NK cells)

There are four subpopulations of Th cells: Th0, Th1, Th2 and Th17 cells
T Helper cells and immune regulation

• When naïve Th0 cells encounter antigen in secondary lymphoid tissues, they are capable of differentiating into inflammatory Th1 cells, helper Th2 cells or pathogenic T17 cells, which are distinguished by the cytokines they produce.

• Whether a Th0 cells becomes a Th1, a Th2 or a T17 cell depends upon the cytokines in the environment, which is influenced by antigen.
Cytokines

• Cytokines produced by Th1 cells activate macrophages and participate in the generation of cytotoxic lymphocytes (CTL), resulting in a cell-mediated immune response.

• In contrast cytokines produced by Th2 cells help to activate B cells, resulting in antibody production.
T helper cell immune regulation

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T helper cells

- **Th1 cells** drive the type-1 pathway (cellular immunity):
  - Fight viruses and other intracellular pathogens
  - Eliminate cancerous cells
  - Stimulate delayed-type hypersensitivity (DTH) skin reactions

- **Th2 cells** drive the type-2 pathway (humoral immunity):
  - **Up-regulate antibody production** to fight extracellular organisms

T helper cells

- Over-activation of either pattern can cause disease
- Either pathway can down-regulate the other, leading to a ‘see-saw’ type effect, referred to as **Th1 / Th2 dominance**
- This hypothesis has an issue - as human cytokine activities rarely fall into exclusive pro- Th1 or -Th2 patterns, therefore it is important to review material constantly as the classification of diseases has been known to change
- The newest research that now involves the role of Th17 seems to complicate this hypothesis a bit more

T helper cells - the ‘see-saw’ effect

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T helper 1 cells (Th1)

- Th1 cell cytokines:
  - Interferon-gamma (IFN-γ), interleukin (IL)-2, interleukin (IL)-12, and tumour necrosis factor (TNF) activate macrophages and are responsible for cell-mediated immunity and phagocyte-dependent protective responses.
  - More pro-inflammatory than the Th2 cytokines.
  - Excessive pro-inflammatory responses can lead to uncontrolled tissue damage seen in organ specific autoimmune disorders – RA, MS, DM1 for example.
  - Th1 cells are also involved in the pathogenesis of Crohn's disease, Helicobacter pylori -induced peptic ulcer, acute kidney allograft rejection and unexplained recurrent abortions.

T helper 2 cells (Th2)

- Associated with the promotion of IgE and eosinophilic responses in atopic condition
- Th2 cells produce IL-4, IL-5, IL-10, and IL-13, which are responsible for strong antibody production, eosinophil activation and inhibition of several macrophage functions
- Allergen-specific Th2 responses are responsible for atopic disorders in genetically susceptible individuals

T helper cells – Th17

- Th17 cells are a fairly new discovery in immunity, they mainly secrete IL-17 (hence their name). They are increased in production by IL-21.
- They may play an essential role in protection against certain extracellular pathogens such as Klebsiella, pneumonia, Bacteroides fragilis, Borrelia burgdorferi, mycobacterium tuberculosis and fungal species.

T helper cells – Th17

- Th17 cells with specificity for self-antigens are highly pathogenic and have been thought to lead to the development of inflammation and severe autoimmunity.
- Recent evidence has also shown though that in some situations Th17 has a regulatory and anti-inflammatory effect.
- Research is still concentrating in this new area.

Balance of Th1 and Th2

- **Measurement of the cytokines** establishes the dominance of either Th1 or Th2 within various disease states.
- The optimal scenario is a well **balanced** Th1 and Th2 response, suited to the immune challenge.
- Balance is regulated via the **T-regulatory cells** and various nutrients to down- or up-regulate the balance.
Testing of Th1/Th2

Cytokine testing - only really used in research

Genovations - Immunogenomic profile
• Tests for genetic susceptibility to a certain immunological cytokine secreting pattern

The ‘Chicago’ test-
• Tests the presence of TH1/Th2 cells and cytokine secreting patterns, plus NK cells. Generally only used in frequent miscarriage and IVF procedures – very expensive
• Most information about Th1/TH2 balance is gathered by symptomology and other testing
T-regulatory cells

- T-regulatory cells
  - Also known as regulatory T-cells or Tr lymphocytes or CD4+ regulatory cells
  - Located primarily in the gut-associated lymphoid tissue (GALT)
  - Probiotic bacteria enhance the effects of Tr lymphocytes.
- The loss of Tr-mediated suppression is implicated in the pathogenesis of the disease.
- Therefore optimal GIT status is imperative for optimal immune status.

T regulatory cells

- Activated Tr dampen the function of a wide range of immune cells including T cells, B cells, Dendritic cells and monocytes
- Activated Tr also affect a broad range of immune contexts including cardiovascular disease and obesity-induced insulin resistance

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PMCID: PMC3376463
T-regulatory cells

Th1/Th2 BALANCE = HEALTH

Th1
IL-12, TNF-α, IFN-γ

Gr

Th2
IL-4, IL-10

Defence against:
- Viruses
- Bacteria
- Fungi
- Tumours

Defence against:
- Allergens
- Chemicals
- Parasites
Gut-associated lymphoid tissue (GALT)

- Approximately 60% of the immune system and more than 80% of the immunoglobulin-producing cells are located within the mucosa of the gastrointestinal tract.
- GALT is intended to provide the **first line** of defence against foreign invaders.
- Comprises **two layers** of defence to a foreign pathogen or antigen:
  1. The localised secretory IgA (sIgA) response
  2. Antigens and foreign substances that escape the sIgA surveillance can enter the mucosal layer, where the GALT provides the second layer of defence.

Gut-associated lymphoid tissue (GALT)

Secretory (sIgA)

- The first line of defence
- Like an ‘antiseptic paint’ on the GIT mucosa
- Can neutralise viruses and remove antigens before they cross the mucosal barrier and reach circulation
- Prevents invaders from entering the system without activating the complement or inflammatory systems
- Low levels of total sIgA in the GIT is associated with altered intestinal permeability and an increased uptake of food antigens
- **sIgA levels drop when someone is under stress, which is an important body-mind connection**

Gut-associated lymphoid tissue (GALT): 

- The largest mass of immuno-competent cells within the human body
- The GALT samples the luminal contents, coordinates host responses and synthesises inflammatory mediators
- It is also required to differentiate between potential pathogens and commensal bacteria
- This is co-ordinated primarily via toll-like receptors (TLRs) which recognise different bacterial components and quickly respond with stimulation of the adaptive immune response

Gut-associated lymphoid tissue (GALT)

- Different bacteria induce different immunologic responses
- Non-pathogenic bacteria elicit different cytokine responses from epithelial cells, inducing differential effects on the GALT and the adaptive immune system
- The dynamic interplay between the gut flora and the GALT plays an important role in the immunologic response system
- This can be modified via dietary changes – prebiotics – and beneficial bacteria – probiotics

Oral tolerance and the ‘hygiene hypothesis’

- Increasing literature suggests that one reason for the increase in atopic, inflammatory bowel disease and autoimmune disease is due to lack of exposure to sufficient amounts of antigens in the first year of life.
- The ‘hygiene hypothesis’ suggests an infant’s immature immune system requires a certain level of inoculation by dietary antigens to become fully competent.
- Neonates are biased toward Th2 dominance. After birth, growth factors in colostrum and breast milk enhance the maturation of digestive flora.
- So in other words, we have become too clean and sterile so the immune system doesn’t have a chance to learn full competence.

The hygiene hypothesis

• Early weaning, or the mother eating allergenic foods throughout pregnancy was always blamed for sensitisation of the immune system of children with IgE allergies

• Recent research is more along the lines of the hygiene hypothesis, that actually exposing children to allergens earlier helps them to learn better immune competence


The hygiene hypothesis

• ‘Does this mean that our children who are growing up in more urban and suburban environments, living in comparatively sterile homes, drinking chlorinated water, bathed and scrubbed daily with antibacterial soap, not allowed to play in the dirt, and given antibiotics every time they have a snuffle are actually being harmed from an immunologic perspective and will carry this dysfunction with them throughout their lives? The answer is yes, probably.’

David Brady ND

David M. Brady (2012) Autoimmune Disease: A Modern Epidemic?
Molecular Mimicry, the Hygiene Hypothesis, Stealth Infections, and Other Examples of Disconnect Between Medical Research and the Practice of Clinical Medicine, Townsend Letter, June 2012 http://www.townsendletter.com/June2012/autoimmune0612.html
Reducing Th1 dominance

• **1,25(OH)2D3** *(biologically active form of vitamin D3)* presents itself as a regulator of T helper cell proliferation.


• **High 25(OH)D levels correlate with an improved Treg function**, and with skewing of the Th1/Th2 balance towards Th2. These findings suggest that vitamin D is an important promoter of T cell regulation in vivo in MS patients. It is tempting to speculate that our results may not only hold for MS, but also for other autoimmune diseases.

Reducing Th2 Dominance

- Plant phytosterols / Beta-sitosterol
  - Increase production of Th1 cytokines IL-2 and IFN-γ and inhibit Th2 cytokine production (IL-4, IL-6, IL-10, IL-15). TNF-α is also inhibited
  - The overall effect is a moderation of immune response, reducing inflammation and allergies and increasing resistance to infection

Reducing Th2 dominance

Quercetin

• Part of the polyphenol flavonoid family
  – It’s effects on nuclear factor-kappa B (NFkB) may reduce production of interleukin-1
  – Inhibits nitric oxide and tyrosine kinase, leading to inhibition of the division and growth of T-cells
  – Other beneficial immuno-stimulatory effects of quercetin may be mediated through the induction of Th-1 derived cytokine, IFNγ, and inhibition of Th-2 derived cytokine, IL-4

Neurotransmitters, stress and Th1/Th2 balance

• Some data is beginning to show that improving neurotransmitter function helps to reduce Th1/Th2 imbalances
• sIgA is also shown to reduce in chronically stressed individuals, increasing the likelihood of GIT reactions
• Actively working to reduce stress and improve neurotransmitter production and function may be prudent

Probiotics and Treg cells

- Probiotics have been shown to improve Treg function, as well as drop circulating IgE levels
- Multiple lactic acid strains have been shown to be helpful

Cheng-Chih Tsai, Po-Chiang Ke, Ten-Ken Hsu and You-Miin Hsieh (2012)
Probiotic strains and immune response

- In a recent study, live cells of lactobacilli and bifidobacteria were evaluated for their immune modulating effects. The strains included:
  - *Lactobacillus casei* Shirota
  - *L. rhamnosus* GG
  - *L. plantarum* NCIMB 8826
  - *L. reuteri* NCIMB 11951
  - *Bifidobacterium longum* SP 07/3
  - *B. bifidum* MF 20/5

Probiotic strains and immune response

- Probiotic strains increased the proportion of CD69+ on lymphocytes, T cells, T cell subsets and natural killer (NK) cells, and increased the proportion of CD25+, mainly on lymphocytes and NK cells
- NK cell activity was significantly increased by all six strains
- Increased production of IL-1β, IL-6, IL-10, TNF-α, granulocyte-macrophage colony-stimulating factor and macrophage inflammatory protein 1α to different extents, but had no effect on the production of IL-2, IL-4, IL-5 or TNF-β
- The *Lactobacillus* strains tended to promote T helper 1 cytokines, whereas bifidobacterial strains tended to produce a more anti-inflammatory profile

Schematic view of the potential mechanism of action by which commensal bacteria and pathogenic bacteria interact with Toll-like receptors (TLRs) and elicit different immune responses.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3382699/?tool=pubmed
Beta-glucans

• β-Glucans are naturally occurring polysaccharides that are produced by bacteria, yeast, fungi, and many plants
• The immunomodulatory activities of β-glucans are usually studied with regard to the activation of macrophages via receptor site binding
  – Has been used for all immune conditions, such as infection prevention, immune enhancing effects and as an antioxidant
  – It has good evidence for use in insulin resistance and high cholesterol (antioxidant function/ as a fibre)

Published online 2011 August 31
http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3202617/?tool=pubmed
Beta-glucans sources

• Medicinal mushrooms such as (but not limited to:
  – Reishi
  – Shiitake – *lentinan*
  – maitake
• Grains such as oats and barley
• Cell wall of baker’s yeast – *saccromyces cerevisae*
Reishi – *ganoderma lucidium*

- Reishi's major benefit appears to be its immunomodulating action, improvement of liver function, and improvement and restoration of the normal functions of the respiratory system as well anti-inflammatory and an adaptogen
- There is research related to its use in cancer, diabetes type 2, chronic hepatitis B and post-herpetic pain
- Dose 2-6g of raw a day (in food) or doses of 600mg-1800mg 3 x day has been used in different clinical trials in adults

Medicinal mushrooms

Shiitake mushrooms (*Lentinula edodes*)

- One main constituent of interest in the fruiting body is the polysaccharide lentinan
- Has been shown to have immunomodulatory effects, especially as an adjuvant in chemotherapy, HIV, and genital herpes
- Dosage - traditional use of 6-16g of the whole, dried shiitake mushroom or 6-8 mushrooms, ingested daily
- Clinical studies have used 4g of powder daily

Medicinal mushrooms

Maitake mushroom (*Grifola frondosa*)

- Immunomodulatory effects, especially from the D-fraction of the beta glucan content
- Trails on diabetes, cancer and immune enhancement have been conducted, and there is reasonable evidence of use
- Dose- Doses of 0.5-1mg/kg daily of beta-glucan from maitake have been taken in divided doses, doses of the raw mushroom have not been established

Medicinal mushrooms

White button mushrooms - Agaricus bisporus

• Increases sIgA in research trials (using 100g of mushrooms)
• Has been shown to activate macrophages in vitro, and there is evidence of effects in vivo
• A therapeutic dosage has not been established, but people often consume between 6-10 mushrooms a day


Sanhong Yu, Veronika Weaver, Keith Martin and Margherita T Cantorna (2009) The effects of whole mushrooms during inflammation, BMC Immunology 2009. This article is available from: http://www.biomedcentral.com/1471-2172/10/12
Inflammation - acute

- External signs of inflammation – pain, redness, heat and swelling – were known long before biologists began to investigate their molecular and cellular mechanisms.
- We now know that the external signs of inflammation are caused by the dilation of blood vessels and action of phagocytes at the site of injury.
- Phagocytes, in turn, produce pro-inflammatory factors such as cytokines and chemokines, which attract leukocytes to deal with the presence of foreign organisms or particles.
- Normally, the inflammatory response ceases within hours or days, once the foreign objects have been removed, and damaged tissue then begins to heal.
Inflammation - chronic

- Chronic inflammation is the continued presence (sometimes over many years) of pro-inflammatory factors at levels higher than baseline.
- Chronically inflamed tissues are characterized by the presence of infiltrating lymphocytes and macrophages, abundant blood vessels, fibrosis, and often, tissue necrosis.
- Chronic inflammation is associated with many diseases, including Alzheimer’s disease, diabetes, atherosclerosis, osteoarthritis and cancer, among others.

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2879478/
Chronic inflammation can lead to:

- Neurodegenerative diseases
  - Alzheimer’s
  - Parkinson’s

- Cardiovascular diseases
  - Cardiomyopathy
  - Atherosclerosis
  - Stroke

- Metabolic disorders
  - Type 2 diabetes
  - Fatty liver disease
  - Sleep apnea

- Musculoskeletal disorders
  - Osteoarthritis
  - Osteoporosis
  - Sarcopenia

- Cancer
  - Gastric, Liver, Lung
  - Gall bladder, Colon
  - Rectal, Pancreatic, Prostate, etc

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC2879478/figure/F1/
Inflammation

• Considered part of both the acquired and innate immune systems
  • An imbalance in the innate system is thought to be the driver of chronic inflammatory conditions

• Understanding the components of the inflammatory cascade is vital to modulating the response:
  • Antigen presenting cells (APCs) including dendritic cells
  • Toll like receptors (TLRs)
  • Chemokines and cytokines
  • Nuclear factor kappa B (NFkB)

Most cells are capable of mounting an inflammatory response as their nucleus contains the genes that code for the enzymes that create inflammation.

When an inflammatory response is required to defend the cell, the appropriate genes are transcribed by a molecule called a transcription factor.

There are several of these, the major one being Nuclear Factor Kappa B (NF-KB).

NF-KB transcribes the genes that code for the production of inflammatory proteins (enzymes) such as cyclo-oxygenase (COX) and lipoxygenase (LOX).

These enzymes then produce the inflammatory mediators such as TNF-α, cytokines (IL-1, IL-6, IL-8) and eicosanoids (prostaglandins, leukotrienes).
The Inflammatory Cascade- NFkB

- Activated by:
- Reactive oxygen species (ROS) – esp. oxidised lipids and reactive nitrogen species
- Glycated proteins
- Homocysteine
- Arsenic, lead, iron or nickel
- Polycyclic aromatic hydrocarbons
- Polychlorinated biphenyls
- Cigarette smoke
- TNF-a, IL-1, IL-18, interferon, activated B and T cells
- Angiotensin II

The Inflammatory Cascade
Nuclear factor kappa B (NFkB)

Downregulated by:
• Alpha-lipoic acid
• Vitamin C and E
• N-acetyl cysteine
• Flavonoids from citrus – kaemperferol and quercetin
• Resveratrol from red grapes and wine
• Green and black tea polyphenols - epicatechin gallate
• Curcumin from turmeric
• Silymarin from milk thistle
• Ginkgolides from Gingko biloba
• Boswellic acid from Boswellia serrata

The Inflammatory Cascade
Nuclear factor kappa B (NFkB)

Downregulated by:

• **Glucocorticoids**
  • They increase the intracellular synthesis of I-Kappa B which binds to and inhibits NFkB
  • Yet many unwanted side effects
    • Diabetes, osteoporosis, muscle wasting, peptic ulceration and perforation
    • Gastro-intestinal, musculoskeletal, endocrine, neuropsychiatric, ophthalmic effects also impaired healing, petechiae, ecchymoses, facial erythema, suppression of skin test reactions, urticaria, hyperhidrosis, skin atrophy, bruising, telangiectasia, myocardial rupture following recent myocardial infarction, congestive heart failure, leucocytosis, hyperglycaemia, hypersensitivity reactions (including anaphylaxis), thromboembolism, nausea, malaise, hiccups, headache, vertigo

The Inflammatory Cascade
Arachidonic Acid

- Arachidonic acid is an important component of mammalian cell membranes
- During the early stages of inflammation arachidonic acid is released from the cell membrane, through the activation of phospholipase A2
- It serves as a substrate for the synthesis of bioactive eicosanoids:
  - e.g., prostaglandins, leukotrienes, thromboxane
- Food sources – meat, eggs and poultry

The Inflammatory Cascade

Fish oils are an excellent source of long-chain n-3 PUFAs, such as eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA).

n-3 PUFAs can be incorporated into cell membranes and reduce the amount of arachidonic acid available for the synthesis of proinflammatory eicosanoids.

- e.g. prostaglandins, leukotrienes

n-3 PUFAs can also reduce the production of inflammatory cytokines, such as tumor necrosis factor alpha (TNFα), interleukin-1, and interleukin-6.
Long-chain N-3 PUFA

• Both human and animal studies have reported that diets high in DHA and EPA increase the proportion of these PUFAs in the membranes of inflammatory cells, white blood cells, and lymphocytes and reduce levels of arachidonic acid.

• Considerable research has been conducted to evaluate the potential therapeutic effects of fish oils in numerous conditions:
  • Including arthritis, coronary artery disease, inflammatory bowel disease, asthma, and sepsis, all of which have inflammation as a key component of their pathology.

Long-chain N-3 PUFA

- Long-chain n-3 PUFAs act:
  - **Directly** (e.g. by replacing arachidonic acid as an eicosanoid substrate and inhibiting arachidonic acid metabolism)
  - **Indirectly** (e.g. by altering the expression of inflammatory genes through effects on transcription factor activation)
- Long-chain n-3 PUFAs also give rise to a family of anti-inflammatory mediators termed resolvins (resolution-phase interaction product)
- Thus, n-3 PUFAs are potentially potent anti-inflammatory agents

Omega-3 fatty acids

• Dietary omega-3 fatty acids are associated with plasma biomarker levels, reflecting lower levels of inflammation and endothelial activation in cardiovascular disease and other chronic and acute diseases, including chronic renal disease, sepsis and acute pancreatitis

Quercetin

- Highly anti-inflammatory due to:
  - **Direct inhibition** of several of the initial processes of inflammation via interaction with calcium channels or calmodulin (the intracellular calcium-binding protein), or both
    - Mast cell and basophil degranulation is an active process that requires calcium influx
    - Quercetin inhibits receptor-mediated calcium influx, thereby inhibiting the primary signal for degranulation
  - Inhibition of mast cell and basophil degranulation, neutrophil and monocyte lysosomal secretion, prostaglandin (most notably, leukotriene) formation, lipid peroxidation

Quercetin

- Inhibition of **phospholipase A2** and **lipoxygenase** enzymes
- Inhibition of the enzyme **hyaluronidase** therefore preventing the breakdown of the collagen matrix of connective tissue and ground substance
- **Membrane-stabilising** action
  - Inhibiting mast cell and basophil degranulation
- Exerts potent **antioxidant** activity and **vitamin C-sparing** action
- **Antiviral** - herpes virus type I, para-influenzae 3, polio virus type I, and respiratory syncytial virus
- Inhibits **tumour** formation
Turmeric – *Curcuma longa*

- **Direct anti-inflammatory effects via:**
  - Inhibition of leukotriene formation
  - Inhibition of platelet aggregation
  - Promotion of fibrinolysis
  - Inhibition of neutrophil response to various stimuli involved in the inflammatory process
  - Stabilisation of lysosomal membranes
  - Inhibition of NfkB – therefore anti-inflammatory
  - There are many research trials on the use of curcumin for inflammation and pain

Turmeric – *Curcuma longa*

- Curcumin is as **effective as cortisone or phenylbutazone** in models of acute inflammation but only half as effective in chronic models.
- However, while phenylbutazone and cortisone are associated with significant toxicity, curcumin displays virtually no toxicity.
- Turmeric extracts exert **significant antioxidant** activity.
- Comparable to standard antioxidants like vitamins C and E.
- **Anti-microbial** - alcohol extracts and the essential oil of *C. longa* were shown in one study to inhibit the growth of *Staphylococcus*, *Streptococcus*, *Bacillus*, *Entamoeba histolytica*, and several pathogenic fungi.

Zingiber officinale (ginger)

- Inhibition of prostaglandin, thromboxane and leukotriene synthesis through the blocking of the cyclooxygenase enzymes
- Also has strong antioxidant activities
- Fresh ginger contains a protease with actions that may be similar to that of other plant proteases such as bromelain, ficin and papain
- Shown to be strongly inhibitory against *Salmonella typhi*, *Vibrio cholerae* and *Trichophyton violaceum*.
- Significant antifungal activity against pathogenic yeast

Contraindications

- High doses of ginger (especially fresh) have been known to cause gastric irritation
- Turmeric and ginger both have anti-platelet activity. Use with caution with individuals with bleeding problems or on anticoagulant medication. Do not give before surgery
- Turmeric and ginger both have a very high organic salicylate content. This preparation may cause reactions (e.g. hives) in salicylate-sensitive patients

Resveratrol

- Resveratrol is a polyphenol that has been shown to reduce Th17 cellular lines therefore giving both anti-inflammatory and immune regulation properties.
- Interacts with both innate and adaptive immunity, such as macrophages, lymphocytes, and dendritic cells.
- There has been minimum reports of adverse effects (unless of course you are sourcing it by drinking wine 😊).
- Sources of resveratrol – red wine grapes especially the skins, seeds and stems (hence why it is high in red wine which uses the whole part of the fruit), but also in pine bark and other herbs.


http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3398412/?tool=pubmed

RESVERATROL

LONGEVITY
- Increase in Sir2 and SIRT1 expression
- Inhibition in the expression of INK4a
- Induction of oxidative phosphorylation
- Mitochondrial biogenesis

NEURODEGENERATIVE DISEASES
- Plaque formation
- Motor and cognitive functions
- Spinal cord injuries
- Amyloid-beta levels

CANCER
- Cancer related transcription factors
- Cell cycle regulation and induction of apoptosis
- Cell differentiation and proliferation
- Immune response and chemical metabolism

CARDIOPROTECTIVE EFFECTS
- VSMC migration and proliferation
- Proliferation of pulmonary artery endothelial cells
- Cardiac fibroblast differentiation
- Platelet aggregation
- Ischemia-reperfusion induced arrhythmia

DIABETES
- Obesity, insulin resistance
- Glucose homeostasis
- Polyphagia, polydipsia, weight loss
- Renal dysfunction

INFLAMMATION
- Aryl hydrocarbon and COX-2
- Synovial inflammation
- iNOS and NO inhibition
- NFkB inhibition

http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3398412/?tool=pubmed – this link provides the additional notes to explain this diagram – students you can do this as an at-home exercise
Anti-inflammatory Diet

- Avoid
  - Excess PUFAs & Trans-fats - foods labelled “No Trans Fats”
  - Avoid processed meats that have sodium nitrate or nitrites
  - Artificial colourings, diet beverages with aspartame, MSG or hidden MSG
- If not vegetarian or vegan
  - Minimise large fish such as tuna and swordfish because of mercury. Avoid farm-raised salmon because of PCBs.
  - Limit red meat or eliminate it unless it is free-range, grass-fed beef or lamb. Choose leaner cuts of meat

Anti-inflammatory Diet

- Include:
- Organic fruits, vegetables, milk products and free-range eggs and meats whenever possible
- Olive or coconut oil for cooking
- Sources of omega-3 fats, including flax seeds and oil (don’t heat flax), sardines, ocean salmon and walnuts
- Daily intake of healthy and colourful fruits (berries, pomegranate, apples, pears and citrus fruits) and vegetables for fibre and beneficial phytochemicals to help your body quench free radicals and biotransform (detoxify) toxins

Inflammation Overview

- Cell Membranes
  - Quercetin
  - Vitamin E
  - Turmeric

- Arachidonic acid

- NFkB
  - COX
    - COX-1
      - Thromboxane
        - Platelet aggregation
        - Vasoconstriction
      - Prostaglandins
        - Gastroprotective
        - Platelet inhibition
        - Vasoconstriction
    - COX-2
      - Prostaglandins
        - Inflammatory
        - Prostaglandins
        - Inflammation
        - Pain
  - LOX
    - COX-2 Inhibitors
      - HETEs
        - Inflammation
      - Leukotrienes
        - Inflammation

- Turmeric
  - Ginger
  - Boswellia
  - Quercetin
  - Vitamin E
  - EPA
  - DHA

- Rosemary
  - Olive leaf
  - Hops

Autoimmune Disease

- Autoimmune disorders are conditions caused by an immune response against the body's own tissues
- The immune system mistakes its own cells for antigens
- Autoimmunity is present in all healthy individuals, to some extent
- However, healthy individuals are able to suppress defective lymphocytes (immune system cells) that mistakenly destroy body cells

Auto-immunity

• Autoimmunity can be defined as breakdown of mechanisms responsible for self tolerance and induction of an immune response against components of the self

• Such an immune response may not always be harmful - but in numerous autoimmune diseases it is well recognized that products of the immune system cause damage to the self
Autoimmune development

• Both antibodies and effector T cells can be involved in the damage in autoimmune diseases.
• HLA (human leukocyte antigen) is a histology complex which helps the immune system to recognize self from non-self
• Association has been found between certain HLA types and autoimmune diseases such as HLA: B8, B27, DR2, DR3, DR4, DR5
• This is the ‘genetic’ component of auto-immunity
Theories of development of auto-immunity

- **Sequestered antigen** – some lymphoid cells may not have been exposed to various self-antigens as they matured, hence when they get into the wrong place in the body, they may not recognise self
- **Escape of auto-reactive clones** – T cells in the training ground of the thymus may not be fully trained enough before they are released into the system
- **Lack of regulatory T cells** - There are fewer regulatory T-cells in many autoimmune diseases, and an imbalance in the Th1/Th2 ratio
- **Cross reactive antigens** - Antigens on certain pathogens may have determinants which cross react with self antigens and an immune response against these determinants may lead to effector cell or antibodies against tissue antigens. Post streptococcal nephritis and carditis, anticardiolipin antibodies during syphilis and association between *Klebsiella* and ankylosing spondylitis are examples of such cross reactivity
### Known associations of cross-reactivity

<table>
<thead>
<tr>
<th>Microbe species</th>
<th>Autoimmune disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Klebsiella</td>
<td>Ankylosing spondylitis</td>
</tr>
<tr>
<td><em>Citrobacter, Klebsiella, Proteus, Porphyromonas</em></td>
<td>Rheumatoid arthritis</td>
</tr>
<tr>
<td>Yersinia</td>
<td>Graves' disease &amp; Hashimoto's disease</td>
</tr>
<tr>
<td>S. Pyogenes</td>
<td>Rheumatic fever</td>
</tr>
<tr>
<td>Campylobacter</td>
<td>Guillain-Barré syndrome</td>
</tr>
<tr>
<td>Chlamydia</td>
<td>Multiple sclerosis</td>
</tr>
<tr>
<td>E. coli, Proteus</td>
<td>Autoimmunity in general</td>
</tr>
</tbody>
</table>

Pathogens and AI

• The proposed mechanisms of how microbes in the GIT or UT cause an auto-immune response
  1. An antigen protein cross reaction
  2. Mouse models have shown that in some bacteria/pathogens in the GIT induces Th17, which increases the inflammatory response

David M. Brady (2012) Autoimmune Disease: A Modern Epidemic?
Molecular Mimicry, the Hygiene Hypothesis, Stealth Infections, and Other Examples of Disconnect Between Medical Research and the Practice of Clinical Medicine, Townsend Letter, June 2012 http://www.townsendletter.com/June2012/autoimmune0612.html
Autoimmune Disease

A person may experience more than one autoimmune disorder at the same time.
The most prominent autoimmune disorders include:

- Hashimoto's thyroiditis
- Pernicious anaemia
- Addison's disease
- Grave's disease
- Celiac disease
- Type I diabetes
- Rheumatoid arthritis
- Systemic lupus erythematosus
- Sjögren's syndrome
- Multiple sclerosis (MS)

There are over 80 autoimmune disorders all presenting with unique symptoms.
## Examples of autoimmune classification

<table>
<thead>
<tr>
<th>Disease</th>
<th>Antibody Action on</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myasthenia gravis</td>
<td>Acetylcholine receptors</td>
</tr>
<tr>
<td>Graves's disease</td>
<td>Thyroid-stimulating hormone receptor</td>
</tr>
<tr>
<td>Thyroiditis</td>
<td>Thyroid</td>
</tr>
<tr>
<td>Insulin-resistant diabetes</td>
<td>Insulin receptor</td>
</tr>
<tr>
<td>Asthma</td>
<td>Beta-2 adrenergic receptors</td>
</tr>
<tr>
<td>Juvenile insulin-dependent diabetes</td>
<td>Pancreatic islet cells</td>
</tr>
<tr>
<td>Pernicious anemia</td>
<td>Gastric parietal cells</td>
</tr>
<tr>
<td>Addison's disease</td>
<td>Adrenal cells</td>
</tr>
<tr>
<td>Idiopathic hypoparathyroidism</td>
<td>Parathyroid cells</td>
</tr>
<tr>
<td>Spontaneous infertility</td>
<td>Sperm</td>
</tr>
<tr>
<td>Premature ovarian failure</td>
<td>Interstitial cells, corpus luteum cells</td>
</tr>
<tr>
<td>Pemphigus</td>
<td>Intercellular substance of skin</td>
</tr>
<tr>
<td>Primary biliary cirrhosis</td>
<td>Mitochondria</td>
</tr>
<tr>
<td>Autoimmune hemolytic anemia</td>
<td>Erythrocytes</td>
</tr>
<tr>
<td>Idiopathic thrombocytopenic purpura</td>
<td>Platelets</td>
</tr>
<tr>
<td>Idiopathic neutropenia</td>
<td>Neutrophils</td>
</tr>
<tr>
<td>Vitiligo</td>
<td>Melanocytes</td>
</tr>
<tr>
<td>Osteosclerosis and Meniere’s disease</td>
<td>Type-II collagen</td>
</tr>
<tr>
<td>Chronic active hepatitis</td>
<td>Nuclei of hepatocytes</td>
</tr>
<tr>
<td>Goodpasture's syndrome</td>
<td>Basement membranes</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>Gamma globulin, virus-related antigens</td>
</tr>
<tr>
<td>Sjogren's syndrome</td>
<td>Nuclei and centromeres</td>
</tr>
</tbody>
</table>
Autoimmune disease

Dual signal hypothesis:
   The primary lesion – viral or bacteria infection
   AND
   Immune dysregulation

Example
   “We report evidence that a ‘local’ inflammatory process occurring in the CNS along with a concomitant, but possibly unrelated, peripheral inflammatory event may trigger a CNS specific autoimmune reaction cascade sustaining the multiple sclerosis pathogenesis”

Autoimmune disease: the primary lesion

- This is the drive to react to self and can be caused by:
  - Infection and infestation
    - Mycoplasmas
    - Klebsiella and Chlamydia (AS)
    - Proteus mirabilis and Epstein-Barr virus (RA)
    - Saccharomyces cerevisiae (Crohns)
    - Cytomegalovirus (Ulcerative Colitis)
  - Chronic tissue destruction or excessive apoptosis
    - As seen in type 1 diabetes

Mycoplasmas are a genus of bacteria that lack a cell wall and:

- They can pass through bacteria retaining filters
- They are not affected by antibiotics

Their role in autoimmune disease could be:

- Providing the causing primary lesion
- Contributing to the immune dysregulation by provoked a broad range of immune responses
- Being the actual pathogenic agents which directly infect the target tissue causing inflammation

The immune and bowel connection

• Protective factors are:
  • Intestinal wall integrity
  • Liver integrity
  • Phagocytic function in the liver
Bowel Connection

• Potential causes of pathological increase in gut permeability:
  • Disturbance of normal intestinal flora by antibiotics
  • Endotoxaemia
  • Inflammation and infection
  • Non-steroidal anti-inflammatory drugs
  • Prolonged exercise
  • Ischaemia and oxidative stress
  • Genetic components or other diseases (coeliac disease or IBD)
Autoimmune Disease: Immune System Dysregulation

This is a state of hyper-reactivity or imbalance in the immune response and can be caused by:

- Infection and infestation
- Endotoxaemia
- Allergy or chemical sensitivity
- Genetic factors
- Food intake
- Injury or foreign body
- Stress
- Cancer
- Vaccinations?

Diagnosis and testing of AI

- The C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) tests can be used to monitor inflammation, which is associated with autoimmune disorders
  - Not specific enough to diagnose a particular disease
  - But useful to monitor treatment and degree of inflammation
Diagnosis

- The **fluorescent antinuclear antibody** test (FANA) is considered a reliable first step for identifying autoantibodies.
- The FANA test is a blood test used to detect abnormal antibodies, called **autoantibodies**.
- The autoantibodies bind to components of an individual's own cells and cause the immune system to attack the body.

Examples of Autoantibodies

Systemic autoantibodies
The list below includes some of the autoantibody tests that are used to identify systemic autoimmune disorders. (often includes arthritic Sx)

- Antinuclear Antibodies (ANA)
- Anti-Neutrophil Cytoplasmic (ANCA)
- Anti-Sjögren Syndrome A (Anti-SS-A) (Ro)
- Anti-Sjögren Syndrome B (Anti-SS-B) (La)
- Anti-Double Stranded DNA (Anti-dsDNA)
- Rheumatoid Factor (RF)
- Anti-Jo-1
- Anti-Ribonucleoprotein (Anti-RNP)
- Scleroderma Antibody (SCL-70)
- Anti-Smith (Anti-Sm)
- Cyclic Citrullinated Peptide Antibody (CCP)
Organ-specific autoantibodies

- **Thyroid**
  - Thyroid Stimulating Immunoglobulins (TSI)
  - Anti-Thyroid Peroxidase (anti-TPO)
- **Gastrointestinal tract**
  - Anti-Tissue Transglutaminase (anti-tTG)
  - Anti-Gliadin Antibodies (AGA)
  - Intrinsic Factor Antibodies
- **Liver**
  - Smooth Muscle Antibody (SMA)
  - Anti-Mitochondrial (AMA)
  - Liver-Kidney Microsomal autoantibodies
- **Kidney**
  - Anti-Glomerular Basement Membrane (GBM)
  - Clotting (coagulation) system
  - Cardiolipin Antibodies
Autoimmune disease: Orthodox Treatment

- **Corticosteroids and immunosuppressant** medications (including cyclosporine and azathioprine) are commonly used to reduce the immune response.
- Side effects of **immunosuppressants** may lead to severe infections because they weaken the immune system.
- Non-steroidal anti-inflammatory drugs like ibuprofen have been used to relieve pain and reduce inflammation.
- **Intravenous Immunoglobulin Transfusion** (IVIG) containing immunoglobulins are administered to boost the body's immune response and decrease the risk of infections.
- Other medications are specific for each system that is being affected.

Autoimmune Disease : Treatment

- **Low antigenic diet**
  - Remove possible antigens from the diet. Gluten, casien and grains are often a problem, but food intolerance testing or allergy testing may be helpful for others
- **Avoid processed foods**
- **Optimise fibre** intake – psyllium, oat bran, germinated barley
  - Especially soluble fibre to encourage SCFA production via probiotics
- **Omega 3 oils** – fish oil, flaxseed oil, borage oil
- **Dairy free** and low starch may help anklyosing spondylitis
- **Low sulphur** diet may help ulcerative colitis

Nutritional management goals

- Optimise gut and liver function
  - support membrane integrity
  - Address any dysbiosis
  - Increase phase 2 biotransformation
- Remove any infections
- Address any food intolerances or allergies
- Reduce oxidative load
- Reduce inflammatory load
- Balance Th1/Th2/Th17 levels
- Remove smoking
  - Smoking is consistently found to be a risk factor for developing rheumatoid arthritis and multiple sclerosis
- Introduce stress management techniques
Key factors in immune dysregulation are probably:

- Chronic sinus disease
- Exposure to solvents or mercury
- Stress
- Antigenic factors in diet – esp. cows milk
- General poor immunity
- Vitamin D
- Vitamin B12
- Cigarette smoking
- Bowel flora dysbiosis

• Deficiency of vitamin D is common among patients with inflammatory and autoimmune disorders and those with prolonged critical illness
• Especially seen in MS, but there is also evidence in a large percentage of patients with Grave’s disease, ankylosing spondylitis, systemic lupus erythematosus, and rheumatoid arthritis
• A recent trial of vitamin D supplementation in patients with prolonged critical illness showed a significant and dose-dependent “anti-inflammatory effect” evidenced by reductions in IL-6 and CRP
Vitamin D

Vitamin D

- A careful examination of the vitamin D toxicity literature found that the consumption of more than 4000 IU a day of vitamin D$_3$ caused no harm but raised 25(OH)D to high-normal concentrations in practically all adults.

- For individuals living in northern latitudes, daily vitamin D$_3$ supplementation is indicated to overcome the decline in 25(OH)D and to control parathyroid hormone levels in postmenopausal women.

• Green tea’s antioxidant and anti-inflammatory effects have led to the proposition that it may have a role in fighting autoimmune diseases — such as type I diabetes, rheumatoid arthritis, lupus and Sjogren’s syndrome
• In the laboratory, green tea catechins stimulated changes in human cells that made them less susceptible to autoimmune attack by the immune system. Additionally, green tea dramatically decreased inflammation in healthy tissues, another change indicative of decreased autoimmune activity. These exciting findings suggest that green tea polyphenols may help reduce the incidence and severity of autoimmune diseases

Vitamin E

• In a study conducted at the University of Texas Health Sciences Centre, it was found that fish oil containing vitamin E delayed the onset of autoimmune diseases in autoimmune-prone mice (Venkatraman et al. 1994)

• Another study on the effects of vitamin E deficiency was conducted in the United Kingdom and reported in Inflammation Research (1995). It was found that dietary components that provide antioxidant effects may contribute to the treatment of inflammatory/autoimmune diseases (Amarakoon et al. 1995)

Systemic lupus erythematosus (SLE)

- Systemic lupus erythematosus (SLE) is a chronic inflammatory disease that has many manifestations and follows a relapsing and remitting course.
- It is characterized by an autoantibody response to nuclear and cytoplasmic antigens.
- SLE can affect any organ system, but mainly involves the skin, joints, kidneys, blood cells, and nervous system.
SLE - pathophysiology

- There is multisystem microvascular inflammation with the generation of autoantibodies.
- Many immune disturbances, both innate and acquired, occur in SLE.
- Serum antinuclear antibodies (ANAs) are found in nearly all individuals with active SLE.
- Antibodies to native double-stranded DNA (dsDNA) are relatively specific for the diagnosis of SLE.
SLE - causes

INNATE SUSCEPTIBILITY
- HLA type (DR3/2)
- Immunoregulatory genes (multiple)
- Complement levels
- Hormonal levels

ENVIRONMENTAL STIMULI
- UV exposure
- Microbial response
- Drugs

AUTOIMMUNE PROLIFERATION
- Hyperactive B-cell/T-cell activation
  - High ratio of CD4:CD8 T-cells
- Defective immune complex clearance
  - Impaired tolerance

AUTOANTIBODY PRODUCTION
- Apoptosis & self-exposure
  - Self-recognition
- Foreign-Ab cross-reaction
SLE- causes

- Patients have higher levels of AB’s to EBV and other retroviruses
- Chronic bacterial infections are common pre-diagnosis
- Silica dust and cigarette smoking may increase the risk of developing SLE
- Adverse drug reactions are responsible for 5% of cases
- Higher oestrogen levels (e.g. HRT) have been linked to onset – breastfeeding decreases risk
- The results of one study suggest that low vitamin D levels increase autoantibody production in healthy individuals; vitamin D deficiency was also linked to B-cell hyperactivity and interferon-alpha activity in patients with SLE
SLE- prognosis

• Relapsing and remitting course
• Dependant on the system effected, it can range from mild to life threatening symptoms
• People with SLE have a higher risk of CVD and frequent infections, so preventative plans should be put in place
• Photosensitivity is common in SLE, to take preventative measures with UV sunlight
SLE- symptoms

- Constitutional – fatigue, arthritis pain, fever, weight loss or gain
- Musculoskeletal – arthritis, fibromyalgia
- Dermatologic – butterfly skin rash, photosensitivity and other diseases
- Renal – glomurelalar damage
- Neuropsychiatric - seizures, tics, headaches
- Pulmonary – Pleursy, SOB, chest pain and other infections
- Gastrointestinal – nausea and dyspepsia
- Cardiac – chest pain, increased risk of endocarditis and CVD
- Hematologic - multiple cytopenias such as leukopenia, lymphopenia, anemia, or thrombocytopenia
Diagnosis

• Diagnosis is made via exclusion of other symptoms, and is dependant on the systems involved. Due to it’s diversity, it is often hard to pin down, so the diagnostic criteria is broad, and 4 out of 11 Sx needs to be present

• Presence of antibodies are screened for and may include a large number of different antibodies, but in most cases the predominant Ab anti nuclear antibody (ANA) is present

Medical treatment

• There is currently no cure for lupus. Instead, treatment focuses on alleviating the symptoms of the disease
• **Corticosteroids**: suppress the body's immune system and decrease inflammation
• **Immunosuppressants**: Immunosuppressants like methotrexate, cyclophosphamide or azathioprine
• **Nonsteroidal anti-inflammatory drugs (NSAIDs)**: used for pain and inflammation
• **Antimalarial drugs**: The mechanism of action of antimalarial agents in systemic lupus erythematosus (SLE) remains unknown but seems to alleviate some symptoms
• **Sunscreen**: To reduce rash from UV light
Naturopathic findings in SLE

- DHEA levels are often low in people with lupus, and some clinical trials have supported the use of it as a supplement (not available in UK). Stress often causes relapses.

- We can extrapolate these findings to deduce that supporting adrenal function and stress reduction techniques may be helpful in preventing relapses of SLE.
SLE and Vitamin D3

- Patients with systemic lupus erythematosus (SLE) have a high prevalence of abnormal bone metabolism and vitamin D deficiency
- Vitamin D also exerts protective effects against SLE through non-genomic factors, such as ultraviolet radiation (UV) exposure, matrix metalloproteinase, heme oxygenase-1, the prostaglandins, cyclooxygenase-2, and oxidative stress
- Thus, vitamin D may play a beneficial role in SLE

Patients with diagnosed celiac’s disease are 3x more likely as a risk factor to get SLE than the general population. We can extrapolate that the gut-immune-microbiota connection is something to be aware of in SLE.

SLE – metabolic differences

• The SLE metabolome exhibited profound lipid peroxidation, reflective of oxidative damage

• Deficiencies were noted in the cellular anti-oxidant, glutathione, and all methyl group donors, including cysteine, methionine, and choline, as well as phosphocholines

SLE – metabolic differences

- evidence of heightened oxidative stress, inflammation, reduced energy generation, altered lipid profiles and a prothrombotic state

- Resetting the SLE metabolome, either by targeting selected molecules or by supplementing the diet with essential fatty acids, vitamins and methyl group donors offers novel opportunities for disease modulation

Colds and ‘Flu’

• The U.S. population experiences nearly a billion colds annually. Children usually have about 6-10 colds per year. Adolescents and adults have about 2-4. Adults over 60 typically have less than one cold per year.

• Influenza, more commonly called "the flu", is much more serious and much less common than the common cold. Each year 35-50 million people in the US get the flu. Most people recover. But the flu still causes complications which lead to 100,000 hospitalisations and more than 50,000 deaths each year.

Natural medicines comprehensive database. *Natural medicines in the clinical management of cold and flu.*
Common Colds

- More than 200 different viruses can cause the common cold
- The rhinovirus is the most common.
  - Responsible for 30% to 50% of all colds and is spread both by physical contact, like shaking hands and touching door knobs, and through airborne transmission

<table>
<thead>
<tr>
<th>Virus</th>
<th>% of cases</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhinovirus</td>
<td>30 to 50</td>
</tr>
<tr>
<td>Coronavirus</td>
<td>10 to 15</td>
</tr>
<tr>
<td>Parainfluenza virus</td>
<td>5</td>
</tr>
<tr>
<td>Respiratory syncytial virus (RSV)</td>
<td>5</td>
</tr>
<tr>
<td>Adenovirus</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Enterovirus</td>
<td>&lt;5</td>
</tr>
<tr>
<td>Unknown</td>
<td>20 to 30</td>
</tr>
</tbody>
</table>

Natural medicines comprehensive database. *Natural medicines in the clinical management of cold and flu.*
Influenza

- The ‘flu’ is caused by 3 types of viruses:
  - Influenza A, influenza B, and influenza C
- Two proteins on the surface of the virus facilitate viral spread in the respiratory tract
- These proteins can change and the changes produce, what looks like a new virus, to the immune system
- This means the influenza virus reinvents itself to some degree every year or every few years
- The greater the changes, the greater the risk for a pandemic
## Symptoms of Colds and Influenza

<table>
<thead>
<tr>
<th>Symptom</th>
<th>Common Cold</th>
<th>Influenza</th>
</tr>
</thead>
<tbody>
<tr>
<td>Onset</td>
<td>more gradual</td>
<td>abrupt</td>
</tr>
<tr>
<td>Headache</td>
<td>mild, uncommon</td>
<td>severe, common</td>
</tr>
<tr>
<td>Fever</td>
<td>uncommon or 0.5° C (1° F) increase</td>
<td>common 37.7 to 40° C (100 to 104° F)</td>
</tr>
<tr>
<td>Myalgia, arthralgia</td>
<td>uncommon</td>
<td>common</td>
</tr>
<tr>
<td>Malaise</td>
<td>mild</td>
<td>severe</td>
</tr>
<tr>
<td>Fatigue, weakness</td>
<td>very mild, short duration</td>
<td>common, lasts 2 to 3 weeks</td>
</tr>
<tr>
<td>Cough (dry)</td>
<td>mild to moderate</td>
<td>common, severe</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>mild to moderate</td>
<td>common, severe</td>
</tr>
<tr>
<td>Anorexia</td>
<td>uncommon</td>
<td>common</td>
</tr>
<tr>
<td>Nasal congestion</td>
<td>common</td>
<td>occasional</td>
</tr>
<tr>
<td>Sneezing</td>
<td>common</td>
<td>occasional</td>
</tr>
<tr>
<td>Sore throat</td>
<td>common</td>
<td>occasional</td>
</tr>
</tbody>
</table>

Natural medicines comprehensive database. *Natural medicines in the clinical management of cold and flu.*
Garlic

• Supplementation with aged garlic extract improves both NK and γδ-T cell function and reduces the severity of cold and flu symptoms
• In a RCT, aged garlic given as a supplement reduced the duration of cold and flu symptoms and improved immune competence. The number of days missed from work were fewer in the garlic group
• No difference was seen between 45 days compared to 90 days supplementation
• The dose used in the trail was 2.56g a day of aged garlic extract

Herpes Simplex

• Recurrent viral infection of the skin or mucous membranes
  • Single or multiple clusters of small vesicles on an erythematous base frequently occurring about the mouth (herpes gingivostomatitis), lips (herpes labialis), genitals (herpes genitalis), and conjunctiva and cornea (herpes keratoconjunctivitis)

• Incubation period 2 to 12 days, averaging 6 to 7 days
• Regional lymph nodes may be tender and swollen
• Outbreak may follow minor infections, trauma, stress (emotional, dietary, and environmental) and sun exposure

Herpes Simplex

- **Zinc – 25 mg bid**
  - Effective inhibitor of HSV replication in vitro, its effect in vivo is probably related to its role in enhancing cell-mediated immunity
- **A lysine-rich/arginine-poor diet**
  - HSV replication requires the synthesis of arginine-rich proteins
  - Lysine has antiviral activity in vitro due to antagonism of arginine metabolism
  - 1 g tid along with dietary restriction of nuts, chocolate, and gelatin
Immune support

• Garlic (*Allium sativum*)
  • Direct antibacterial, antiviral, antiparasitic and antifungal affects via the constituent allicin
  • Use in both acute and preventatively
  • Please note high dose contraindications with certain medications

• Larch arabinogalactan (*Larix occidentalis*)
  • May enhance the action of NK cells and may increase the production of lactobacillus acidophilus
  • 1,000 - 4,000 mg per day in two equally-divided doses

References:

Natural medicines comprehensive database. *Natural medicines in the clinical management of cold and flu.*
Nutrient Immune Support

- Selenium
  - Deficiency increases COX-2 expression and higher PGE2 levels and may decrease leukotriene production

- Vitamin C
  - Modulates lymphocytes and phagocytes, regulates NK cells, and can modulate cytokine and antibody production
  - Anti-histamine
  - Ascorbic acid or mineral ascorbates with bioflavonoids
  - 1-2 gram per day

Natural medicines comprehensive database. *Natural medicines in the clinical management of cold and flu.*
Nutrient Immune Support

• **Vitamin E**
  • Increases humoral antibody production, resistance to bacterial infections, T-lymphocyte response, TNF productions, NK cell activity
  • 200 mg per day

• **Zinc**
  • Normal development and function of immune cells
  • Deficiency rapidly diminishes antibody and cell mediated responses leading to increased opportunistic infections.
  • Inhibits rhinovirus replication in vitro
  • Zinc gluconate lozenges

Natural medicines comprehensive database. *Natural medicines in the clinical management of cold and flu.*
Lactobacillus Rhamnosus GG

• Promotes antigen-specific immune responses, particularly in the IgA class, prevents intestinal permeability/defects, and promotes controlled antigen transport across Peyer's patches – important in the generation of the local secretory immune response


• Increases serum levels of interleukin-10
  • IL-10 is an immunomodulating cytokine that inhibits synthesis of cytokines involved in inflammation, including IL-2, IL-4, IL-6, IL-12, TNF-a and interferon-gamma (IFN-g)
  • It upregulates the growth of B cells and downregulates IgE synthesis

Healthworld Australia (2009). Lactobacillus rhamnosus GG. Brisbane.
Antioxidants

• Be aware that oxidation always accompanies inflammation and therefore optimising antioxidant status would be considered beneficial
• Key nutrients to assist:
  • *Vitis vinifera* (*Grape seed*)
  • Quercetin
  • d-alpha-tocopherol
  • Ascorbic acid
  • *Camellia sinensis* (*Green Tea*)
  • Beta-carotene from *Dunaliella salina*
  • *Silybum marianum* (*St Mary’s Thistle, providing Silymarin*)
Herbal Immune Support

- Andrographis (*Andrographis paniculata*)
- Boneset (*Eupatorium perfoliatum*)
- Echinacea (*Echinacea angustifolia, Echinacea purpurea*)
- Astragalus (*Astragalus membranaceus*)
- Elderberry (*Sambucus nigra*)
- Siberian ginseng (*Eleutherococcus senticosus*)

Natural medicines comprehensive database. *Natural medicines in the clinical management of cold and flu.*