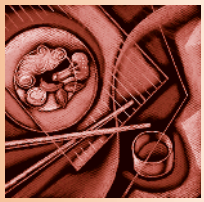

Nutrition and Immunity

Balancing Diet and Immune Function

Susan S. Percival, PhD

Immunity is a complex and redundant system that requires all nutrients for proper functioning. An immune response can be broken into 3 phases: surveillance, the response, and ending the response. Nutrient needs are greater during the response because of the need for cell proliferation and mediator synthesis. Chronic inflammation is the result of not ending the response and can lead to disease. A specific T cell, known as the gamma delta (γδ) T cell, is important as a first line of defense for eradicating pathogen and plays a critical role in ending the immune response when it is no longer needed. Dietary components of plant origin have the ability to prime γδ T cells, making them more effective for pathogen eradication. Some studies have shown that the cells have a greater ability to proliferate after people consume these plant compounds, and in addition, a reduction in the severity of cold and flu symptoms follows. Priming these cells may also help reduce chronic inflammation supporting dual roles for the γδ T cell. The immune system is supported by the classic essential nutrients as well as beneficial, nonessential phytochemicals. Nutr Today. 2011;46(1):12–17

This article briefly reviews the components of the immune system with emphasis on a particular leukocyte, the gamma delta (γδ) T cell. The importance of nutrition in this large and complex system cannot be underestimated. All nutrients, macro and micro, are required in an optimum balance for the proper function of immunity. The issue is that an optimum balance specifically for the role of immunity in humans is not well understood. This article describes some of the consequences of nutrient deficiencies, but more importantly discusses foods that help maintain or balance the immune response by the γδ T cell. The consequences of an immune system that is out of balance are also discussed.

Functional Immunity

Parts and Location

Immune cells originate in the bone marrow. Some cells differentiate there, in the marrow (neutrophils, other granulocytes, and B cells), whereas others travel to the thymus (T cells) to differentiate. Some cells, for example, monocytes, travel through the blood and differentiate into macrophages in the tissues. Whereas the blood cells are the best studied because of their accessibility, many of our immune cells reside in the skin and the epithelial linings of the gut, lung, and reproductive system. The gut, because of its large surface area, is the largest immune organ in the body.

Three Modes of Operation

The first mode of operation is known as surveillance (Figure). To survey their environment, the immune cells migrate in and out of the lymph, blood, and tissues. Some maintain residence in tissues or lymph, whereas others never stop moving. Both static cells and migrating cells can be "samplers," testing their immediate surroundings for evidence of foreign invaders. Surveillance destroys foreign invaders without any symptoms of illness. One particular cell involved in surveillance is the γδ T cell, whose importance is a central focus of this report.

The second mode of operation is the activation or response. If surveillance is not enough to combat the foreign invader, the immune system goes into action, which is known as the response mode. First, signaling molecules such as cytokines (peptides), leukotrienes, and prostaglandins (lipids) are synthesized and secreted, resulting in a complex network of communication signals to other cells of the immune system. Cell numbers

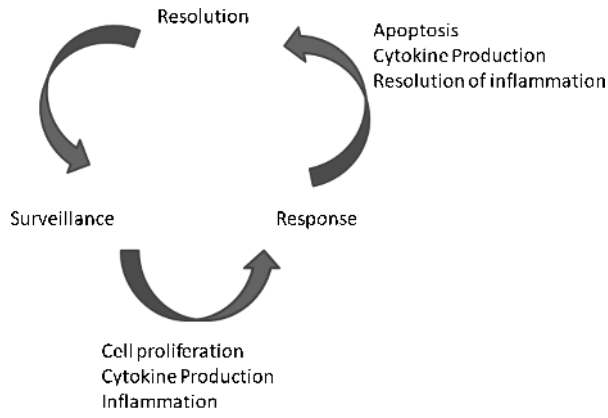

Figure. The cyclic nature of immunity. Surveillance is the nonsymptomatic mode of handling foreign invaders. When surveillance is not enough, activation of the immune response occurs, driven by cytokines and lipid mediators. Once the foreign invader has been disposed of, then an active process operates to resolve inflammation so that it returns to surveillance.

expand greatly, and eventually, the foreigner is destroyed by cytotoxic activity of the immune cells. Symptoms of illness, including inflammation and fever, accompany the response.

To understand the response capacity of immunity, the general organization will be covered first. In most of the literature, immunity is organized into 2 systems, the innate immune system and the adaptive (or acquired) immune system (Table). The cells of our innate immune system react within minutes to a foreign invasion. They kill pathogen using free radicals and other toxic chemicals, and they recognize foreign invaders by their nonspecific patterns. The innate cells express receptors on their cell surfaces that recognize nonspecific patterns known as pathogen-associated molecular patterns (PAMPs). Bacteria, for example, contain unique molecules such as lipopolysaccharide, not found in any other plant or animal. Other PAMPs are derived from viruses, protozoa, and fungi and include molecules such as peptidoglycans, lipoproteins, flagellin, double-stranded and single-stranded RNA from viruses, imidazoquinolines, CpG DNA motifs, and teichoic acids. Our innate immune system uses pattern recognition receptors to detect PAMP, and this recognition results in an immune response. Interaction of the PAMP with the pattern recognition receptors sets off a chain reaction of signaling molecules such as cytokines, prostaglandins, and leukotrienes. These mediators, in turn, cause activation of the adaptive (or acquired) immune cells, the alpha beta (αβ) T cells and the B cells. The adaptive cells may take up to days to fully respond. They get their signals not only from the innate cells' signaling molecules but also from antigen-presenting cells. Each T or B cell of the adaptive immune system produces a unique receptor, and each cell responds to very specific antigens, not just a generalized pattern. Cells of the adaptive immune system have the ability to distinguish between self and nonself. Their mode of killing is by initiating apoptosis or programmed cell death. These cells are influenced by previous exposures to pathogens and thus are said to have memory.

Finally, the third mode is the return to normal surveillance. When the pathogen has been destroyed, the immune system returns to surveillance mode. This return to normal surveillance is an active process utilizing specific cells such as γδ T cells, macrophages, natural killer cells, and $CD8^+$ T cells to destroy activated immune cells to end the response. The consequence of not ending the response is chronic inflammation and is discussed in the following section.

Nutritional Aspects

Nutrient Deficiencies

Many examples exist in the literature of specific nutrient deficiencies that result in impaired immunity and an impaired immune response. Protein-calorie malnutrition, essential lipid deficiency, and vitamin and mineral deficits all result in some aspect of impaired immunity. Nutrients are important for synthesis and secretion of

Table. Origin and Function of Immune Cells

Branch	Cell	Differentiation Location	Specialized Function
Acquired	B cell	Bone marrow	Secret antibodies
	T cell	Thymus	Cytotoxic, helper, regulatory
Innate	Monocyte	Bone marrow	Further differentiates to macrophages
	Macrophage	Tissues (see monocyte)	Phagocytosis, respiratory burst
	Neutrophils	Bone marrow	Phagocytosis, respiratory burst
	Other granulocytes:	Bone marrow	Various: basophils, eosinophils, mast cells
Characteristics of both	γδ T cell	Thymus	Cytotoxic, regulatory
	Natural killer cell	Bone marrow	Cytotoxic

signaling molecules, cell proliferation, free radical generation, and the active process of immune suppression at the end of the response. Lacking any nutrient would impair the response.

Nutrition for Surveillance and for the Response

A healthy, balanced diet provides all nutrients necessary for adequate operation of the surveillance mode because that is the normal condition under which nutrient requirements were determined. However, it is much more difficult to study the increased nutrient requirements during the immune response, but considering that cell proliferation is a major part of the response, all nutrients are required in greater quantity. To determine how much of an increased need occurs during the response, nutrient requirements would have to be studied at the onset of illness. Some of the nutrients for which information is available and that show a greater need in the context of the immune response include conditionally essential amino acids,[1,2] zinc,[3] and magnesium.[4] An exception to the generalized statement that all nutrients are needed in greater amounts is iron, because it appears to be sequestered during an immune response.

Other indirect evidence that suggests initiating an immune response requires more nutrients is due to the nature of the response itself: in addition to the demands for cellular proliferation, the immune response must synthesize and secrete signaling molecules and antibodies. Although it is difficult to pinpoint exactly how much more of a specific nutrient is needed, some research suggests that greater doses of nutrients may reduce the severity of a cold or flu. A meta-analysis[5] suggests that gram quantities of vitamin C taken regularly had no effect on the incidence of common cold symptoms but were beneficial in that they reduced the duration of the cold. However, a subgroup exposed to extreme conditions (exercise and/or cold weather) did have a reduced incidence when supplemented with gram quantities of vitamin C. The mechanism by which vitamin C works to reduce severity of an illness is not clear.

Folic acid and other B vitamins that are involved in 1-carbon metabolism are also considered critical nutrients for the response mode. Because of the rapid proliferation of many immune cell types, the need to synthesize DNA, transcribe message, and translate proteins may require more of these vitamins.

Vitamins A and D, because of their role in cellular differentiation and transcription, are theoretically required in greater amount when mounting an immune response. The stores of nutrients may be enough to handle the increased need without requiring an increased intake, but nonetheless are used by the body to a greater extent for an immune response.

During the response, assessing nutrient requirements is more challenging. Nutrients are required in greater quantity when the immune system is responding, but what ones, and how much, is not known. Studying simple illness in humans is not easy, unless perhaps it is under controlled conditions, such as a viral challenge. Humans are genetically or environmentally dissimilar, but even more challenging is that humans have differences in vaccination histories as well as immunological memories. In other words, different people will respond in different ways to the same challenge.

Consequences of Not Ending an Immune Response

Inflammation is a necessary component of the immune response. What is inflammation, exactly? It is a collection of symptoms described more than 2000 years ago as swelling, due to increased permeability of the capillaries resulting in edema, redness, and heat due to increased blood flow, and pain due to stimulation of nerve endings. Some of these symptoms occur because of the release of reactive oxygen species that are part of the killing mechanism of the innate immune system. Other symptoms are from the effect of the cytokines and lipid mediators that drive the inflammatory process and set the stage for both the eradication of the foreign invader and the repair of damaged tissues. Normally, mechanisms are in place to restore the immune response to its surveillance mode. However, in some circumstances, the immune system inappropriately stays "on" because it is chronically stimulated by some foreign invasion that cannot be eradicated, or the mechanism to turn inflammation off is impaired. Chronic inflammation is thought to be responsible for many diseases.

Conversely, the disease itself might be a cause of chronic inflammation. Heart disease, cancer, rheumatoid arthritis, inflammatory bowel disease, and some neurological disorders have symptoms that suggest chronic inflammation may be involved in the disease process. Reactive oxygen species that are generated during chronic inflammation may cause damage to host macromolecules if not contained or neutralized. For example, oxidized low-density lipoprotein molecules may be viewed as foreign by the immune system and are taken up by macrophages in the arterial vessel walls. Reactive oxygen species may damage cellular DNA, and this damage may have some relationship to cancer, although cancer is much more complex than simple DNA damage. Oxidation of proteins affects the elasticity of cell membranes and may impair function of enzymes.

Some neurological disorders are associated with oxidized proteins in the brain. Damage to carbohydrate moieties, specifically those in the joint fluids such as hyaluronic acid, is thought to be associated with some forms of arthritis. To summarize, inflammation is important for an immune response, but there are circumstances where it may be dysregulated. Can diet help alleviate some of the repercussions of chronic inflammation? And, importantly, can dietary factors be helpful in helping to resolve the inflammation after it is no longer needed for the immune response?

Good evidence has been published that omega-3 fatty acids play a role in resolving inflammation when the response is no longer needed. The omega-3 fatty acids of importance are eicosapentaenoic acid and docosahexaenoic acid, 20:5n-3 and 20:6n-3, respectively. The synthesis of lipid mediators from these fatty acids produces inflammatory products of lower bioactivity compared with those derived from arachidonic acid, 20:4n-6. Moreover, eicosapentaenoic acid and docosahexaenoic acid can produce lipid mediators with anti-inflammatory activity. The potent anti-inflammatory mediators are known as the resolvins and protectins.[6]

Priming as a Means to Optimize Immune Response

The ability to prime our immune cells is poorly defined, mechanistically. B cells are primed as a result of vaccinations. In this sense, B cells are trained to recognize an attenuated foreign invader and forms memory cells that can respond faster and more effectively in the event that foreign invader is encountered again.

Certain molecules prime the immune cell without overtly activating the cell because they interact only weakly. Known as nonmicrobial priming, it is a fairly new concept in relation to dietary compounds and results in upregulation of mRNA transcripts but no translation of protein.[7] The immune cell is primed by certain food ingredients and is now able to respond quicker and more effectively to eradicate the real foreign invader because the building blocks are already present. Some of the molecules that can weakly interact with immune cells and prime them are found in foods of plant origin. The complex molecular structure of some phytochemicals may look similar to a PAMP, but not similar enough to result in activation.

Evidence That Some Food Ingredients Prime Immune Cells

This portion of the article discusses recent research showing evidence of priming of the γδ T cell by food and food components. First, the γδ T cell is briefly described, and then, the food components that prime this cell are briefly reviewed.

The γδ T cell resides mainly in the skin and in the epithelial linings of the gut, lungs, and reproductive tract. There they act as a first line of defense against pathogens that are eaten or inhaled. About 5% to 8% of human T cells in the blood are the γδ T cells, with the remainder circulating T cells the more common αβ T cell. Although they are a T cell, carrying the T-cell receptor (TCR), they behave more like innate cells in that they recognize PAMPs and do not require recognition of the major histocompatibility complex as does the αβ T cell.

Generally, the γδ T cells are studied with those isolated from the blood because acquiring them from tissue, in humans, at least, is not feasible. Some of the γδ T cells may be naive, meaning they have not interacted with pathogen. But some may have already surveyed their environment, have interacted with foreign objects, and are now migrating through the blood to other locations.[8] Thus, some of the γδ T cells isolated from the blood have been exposed to food components in the gut, and the functional changes due to diet can be measured in γδ T cells obtained from blood samples, regardless of whether the food components have been absorbed.

In addition to the ability of γδ T cells to kill pathogen-infected cells and malignant cells, they are also necessary to turn off the immune response. In animal models where the γδ TCR is knocked out, the animals are inflamed.[9,10] Adding another inflammatory stress to γδ-TCR knockout mouse model is fatal. The researchers showed that γδ cells physically interacted with activated macrophages, resulting in macrophage cell death, and were required to end the response. If dietary compounds can enhance the function of γδ T cells, then diet may be instrumental in providing anti-inflammatory activity as well.

The relationship between diet and the γδ T cell was first published in 1999.[11,12] These studies showed that drinking tea beverage compared with coffee resulted in an increased γδ T-cell proliferation and interferon γ synthesis. The mechanism by which tea was thought to work was through a unique amino acid, L-theanine. After L-theanine is consumed, it is hydrolyzed to glutamic acid and ethylamine by the kidney.[13,14] Ethylamine is thought to be the nonmicrobial antigen that interacts with the γδ T cell.

If a compound from tea interacts with the γδ T cell, we asked if other fruits and/or vegetables also interact with this cell. In 2 studies, γδ T-cell numbers were increased in the blood when subjects were fed a fruit and vegetable concentrate[15] or grape juice from Concord grapes (publication in review). The cellular proliferative capacity was not changed, but in 1 study,[15] a reduction in

circulating interferon γ was observed, which suggests lower inflammatory activity.

A capsule containing a standardized mixture of tea components, L-theanine and catechins, showed an ability to functionally change γδ T cells after consumption.[16,17] In these studies, people consumed a defined amount of L-theanine with tea catechins for 10 weeks. White blood cells from the subjects were then incubated ex vivo, with the compound responsible for priming them, ethylamine, and the results showed a greater activation and proliferation of γδ T cells from subjects consuming L-theanine compared with those obtained from people consuming the placebo. A greater concentration of interferon γ was also produced by the cells from the L-theanine consumers. One of the inflammatory biomarkers that were measured was reduced, whereas a second one went unchanged.[16] The subjects taking the tea components experienced fewer cold and flu symptoms during the study.

Results of these studies led to the hypothesis that the phytochemicals found in plants can prime the γδ T cell. Other in vitro research showed that γδ T cells interact with proanthocyanidins and result in increased proliferation and activation.[18] Despite limitations to in vitro cell culture studies, we hypothesize that in vivo the γδ T cells obtained from blood may have interacted with phytochemicals while residing in the gut. γδ T cells migrate out of the gut into the bloodstream where they are isolated and shown to have functional changes. The hypothesis of nonmicrobial priming suggests that the weak interaction of food phytochemicals with the cells does not activate the cell, but only primes it to respond better and faster to a secondary stimulus.[7] Although phytochemicals are not essential for life, as is a classic nutrient, they are beneficial to health.

Summary

All nutrients are important for maintaining immunity and providing appropriate amounts of protein, fat, carbohydrate, vitamins, and minerals for the surveillance mode of keeping us from getting sick. More nutrients are required during pathogen invasion, but it proves more difficult to study exactly what is the "right" balance of nutrients that are required to provide an optimal response when invaded by pathogen.

The food ingredients mentioned in relation to priming of the γδ T cells are plant-derived compounds. Thus, the best advice for a healthy immune system is to consume fruits and vegetables and includes tea. Vitamin C, folic acid and other B vitamins, vitamins A and D, phytochemicals, and food fiber all work to keep the immune system functioning without overresponsiveness (inflammation) or underresponsiveness (illness). These compounds do not appear to be stored in the body; therefore, to maintain a primed state requires daily consumption, to maximize exposure and thus benefits. Priming immune cells promotes a faster and stronger response. γδ T cells are unique cells that are important in surveillance, response, and ending the response. They appear to be supported by dietary compounds in a manner consistent with health benefits.

Susan S. Percival, PhD, is a professor of nutritional sciences in the Department of Food Science and Human Nutrition at the University of Florida, Gainesville. Her educational background includes a master's of science degree from the University of California, Davis, and a PhD from the University of Texas, Austin. She did her postdoctoral research in the Department of Biochemistry and Biophysics at Texas A&M University. From 1978 to 1981, she was tenure track faculty at the University of Rhode Island prior to an educational leave to pursue her doctorate. In 2004, she took an 8-month sabbatical leave at the National Institutes of Health with the Nutritional Sciences Research Group at the National Cancer Institute. She currently teaches courses on current issues in dietary supplements, research planning, and nutrition and immunity. Her current research deals with how dietary components influence immunity. Experimental models in cell culture, mice, and in humans reveal that certain dietary components including bioactive compounds from fruits and vegetables, herbs and spices, red wine, and green tea affect specific branches of immunity. These plant bioactive food components have benefits not only with their protective antioxidant capacity, but also through their ability to affect intracellular signaling pathways and prime immune cells to activate faster and to a greater extent when stimulated to do so.

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