Dr. Rath Health Alliance – International Webinar

The role of micronutrients in controlling inflammation

Presented by John Cha, June 12, 2012

1) What is Inflammation? Inflammation is a reaction of an organism to irritation, injury, or infection. In each of these cases, the body must respond to either repair damage or to call upon the cellular or humoral immune system to launch an attack on a dangerous particle. In response to these circumstances, the body intends to remove or neutralize the irritant by calling upon immune cells to engulf and take apart the pathogenic substance or organism and/or remove the debris of damage to allow for healthy cells and tissue structures to take the place of the destroyed cells and tissue components. The body may also take portions of the pathogen and generate antibodies to them when called to do so by the inflammatory response. In a relay system to the brain, these mediators of local vascular change and cell signaling trigger pain and discomfort through local nerves. Pain, Redness, Immobility, Swelling, and Heat (PRISH) are the umbrella of symptoms caused by acute inflammation, that inflammatory response that occurs immediately after irritation, injury, or infection. To illustrate, there are policeman cells called mast cells that reside in the connective tissue surrounding cells. When they are primed against a pathogen with something called IgE and encounter it, they release histamine, responsible for the allergic symptoms people have for pollen, a respiratory tract irritant. The histamine functions to cause capillaries to become permeable and for blood vessels to dilate. This not only serves the useful purpose of allowing immune cells such as neutrophils which engulf and destroy infectious organisms and response proteins such as complement and fibrinogen to be able to access the site of action, but also causes the discomfort of inflammation. Thus the swelling and redness of inflammation both serves a useful purpose and an annoyance to the person suffering it. It is in this way that inflammation not only triggers the healing process, but also notifies a person that he or she has incurred something injurious. By design of evolution, inflammation serves to both initiate a repair response and also inform us that there is something wrong and that we should take action to this pathological condition.

2) In addition to the tangible manifestations of inflammation involved in combating infection and the healing response, referred to as PRISH, there are many signals that cells emit in response to various pathogenic stimuli called cytokines. These various cytokines draw components of the immune system to the site emitting this homing beacon or distress signal. Here in this graphic, we see the interplay of immune cells responding to cytokines. For example, IL-1 and TNF emitted by damaged cells causes more immune cells such as macrophages to home to the site of secretion, while these same cytokines also cause fever by activating the hypothalamus of the brain to do so. There are many inflammatory cytokines which call on different portions of the immune response in different ways.

3) Inflammation is both good policeman and bad policeman in the human body. In the best case scenario, inflammation prevents further aggravation and damage, successfully calls on the immune system to prevent or stop further infection or reaction to a toxin, and removes debris to allow for the surrounding healthy cells to rebuild and replace damaged tissues. As with angiogenesis and cell division, a dynamic balance of inflammation occurs in the body which maintains health. When this balance is disturbed and there is too much inflammation, we have the body's own healing mechanisms causing unintended damage which is involved in various diseases. When there is too little inflammation, literally nothing happens where it should and infection takes root and runs amok or pathological conditions remain unrepaired. In some cases, the body does the best it can but cannot replace tissue quickly enough without first addressing more urgent tasks such as fighting overt infection or preventing blood loss. In this case, or when too much of the original tissue is destroyed, the body utilizes fibroblasts to repair what it can, leaving a scar. This is known as fibrosis. While this is not the best scenario, it is certainly better than bleeding to death. When the acute inflammatory response is very intense, and the immune system has launched a very robust response at the irritant, and the irritant whether it is of an infectious or toxic nature cannot be removed, collateral damage occurs to the surrounding tissues. The proteolytic activity of the immune cells combined with the oxidative and chemical damage from the immune activity and the irritant cause lesions to worsen as is the case of this inflamed appendix.

4) This inflamed appendix is a severe example of what occurs when a disease condition is not resolved. This also may occur after decades of low level chronic inflammation that eventually

results in severe lesions. Chronic inflammation occurs as a result of an insult to a tissue that does not resolve over time but continues. This may be constant repeated mechanical injuries, constant low level infections, constant oxidation, chronic intoxication of a tissue, or constant exposure to an allergic or toxic substance. When the reparative processes of the body cannot fully account for the amount of damage that occurs over a span of time such as decades in the case of atherosclerosis, the balance is tilted in favor of cumulative degeneration. Wherever there is a site that is chronically insulted, the irritated cells will send out a steady stream of local inflammatory mediators as well as systemic homing cytokines for the immune cells such as neutrophils, monocytes, macrophages, T-cells, natural killer cells, and basophils. These all participate in attempting to remove the insulting stimulus, whether it is an infectious organism, a virally infected cell, an oxidized lipoprotein, cellular debris, or other noxious molecule. However, without removing the inflammatory matter from an area that is calling on the immune system, the immune system over time actually causes unintentional damage to the area as it attempts to resolve the inflammation. This is the nexus of all inflammatory origin of disease. The well-meaning immune system, not being able to remove the cause of the cytokine homing beacon simply continues to surround the area and keeps trying to remove the source of inflammation. The immune system does not pay attention to healthy tissues as they do not secrete the signals for it to move in and act.

5) Chronic inflammation participates in causing or aggravating many diseases. Cardiovascular disease, Cancer, Chronic infections, Arthritis, Allergy, Alzheimer's disease, Parkinson's disease, and Multiple Sclerosis are among the diseases that could not occur without chronic inflammation. Cardiovascular disease, the initial focus of Dr. Rath is very much a chronic inflammatory disorder. The so-called clogged arteries that cause heart attack do not occur overnight, over several months, or over several years, but after decades of chronic inflammation, and not because quote unquote cholesterol sticks to the inside of an artery. Cholesterol is not even soluble in blood without actively being delivered via a solubilizing protein that together with cholesterol becomes LDL or Lp(a). During this span of time, mechanical and oxidative damage that does not go repaired by the arteries themselves cause the cells of the arteries to initiate the inflammatory cascade and to release homing cytokines into the bloodstream. These cytokines cause immune system cells to swoop into the site of damage where they attempt to remove the debris by burrowing into the artery. As oxidized

matter is toxic to these cells, they become trapped inside the artery and die, liberating more inflammatory substances and another cycle of immune cell activity. Additionally, cytokines liberated by the inflamed artery such as IL-6 cause the liver to generate more Lipoprotein(a) which binds to wounded tissues. As this cascade continues over time, a grave yard of cells and a waste dump of material accumulates at the original site of inflammation. This is the plaque of atherosclerosis and coronary artery disease. When the inflammation is not resolved or otherwise quenched with anti-inflammatory substances, the plaque of cells and cellular debris brought by a well-intentioned immune response continues to build, squeezing off the space inside the artery and obstructing blood flow. These plaques may burst open, causing immediate blood clotting or thrombosis which precedes and causes ischemic infarct or heart attack. Ironically, had the immune system ignored these inflammatory signals, plaque formation would not occur. In cancer, constant inflammation contributes to cancer formation by accelerating all facets of carcinogenesis. Excessive, chronic inflammation in and of itself is carcinogenic. In a very recent paper, "Molecular Link Mechanisms between Inflammation and Cancer," the authors cite epidemiological studies that relate 25% of all cases of cancer to unresolved inflammation and chronic infections. Additionally, the utilization of anti-inflammatories is associated with fewer incidences of many types of cancers. Chronic infections cause chronic inflammation, and one amplifies the effects of the other in a cycle that does not resolve. Arthritis too is a disorder in which the well-meaning immune system inadvertently causes further damage to the joints by responding to inflammation. Allergy can be potentiated and amplified through the IgE component of inflammation recognizing normal day to day environmental exposures as pathogenic and in an excessive manner. Alzheimer's Disease can be aggravated by inflammation in the brain which increases the risk for dementia, the loss of mental function. Multiple sclerosis also involves the incorrect activity of the immune system, in this case T cells, which in their attempt to resolve inflammation attack the nervous system and cause more inflammation, attracting other sets of immune system cells.

6) While the approach by conventional medicine to treat chronic inflammation is a series of synthetic anti-inflammatories, anti-histamine drugs, and corticosteroids, over time these have been demonstrated to exhibit side effects, some severe such as heart disease. On the other hand, it is has been known for some time that vitamins A, B, C, D, and E all exhibit anti-inflammatory qualities in various aspects and through different mechanisms. Amino acids

Proline, Lysine, and Arginine derived from dietary proteins exhibit anti-inflammatory effects. Omega-3 fatty acids have demonstrated their ability to modulate the lipid eicosanoid mediators of inflammation from a pro-inflammatory profile to an anti-inflammatory profile. Phytochemicals from food plants have attracted a lot of attention in the recent years with their potent polyphenol anti-inflammatory components. Green Tea, Citrus, Ginger, Pomegranate, Chokeberry, Cabbage, Turmeric, and Walnut are just a few of those foods containing naturally occurring anti-inflammatory compounds. As of yet, organic chemists haven't been able to generate anything close to this natural armamentarium through rational drug design. Yet we can learn lessons from nature and employ its medicines against our most common and lethal maladies such as coronary heart disease.

7) Here we see an illustration of an artery that has released inflammatory cytokines into the bloodstream in response to oxidized lipid that has made its way into the damaged artery. While normal lipids are not inflammatory, the oxidized or rusted variants are toxic and irritate the artery. The cytokines attract monocytes out of the circulation which attach to the site of cytokine secretion and burrow into the artery as macrophages in an attempt to remove the oxidized matter. If they do not successfully remove this and transport it back to the liver in reverse cholesterol transport, they become trapped and lodged inside the artery as foam cells. Foam cell lesions are the first atherosclerotic lesions seen in humans and are not comprised of cholesterol sticking to the artery, but living cells. When these foam cell lesions die, they liberate their components which include the oxidized lipid. The immune cells in fact contribute to arterial lesions. The rational would be then to prevent the inflammatory cytokine signaling that attracts monocytes to the region.

8) In studies conducted here by Dr. Ivanov, the rationally designed mix of micronutrients including citrus and green tea polyphenols was able to minimize the secretion of cytokines that attract the immune system response to the artery. In particular, a dose of 100mg per Liter of the nutrient mix brought down Monocyte Chemoattractant Protein (MCP-1) secreted in response to TNF-a, an inflammatory mediator to nearly normal levels. The MCP-1 protein as its name suggests brings to bear the macrophages on the artery, which actually create atherosclerotic lesions in their attempt to clear out the offensive material in the artery.

9) Where there is inflammation, there is COX-2 induced. Under normal circumstances COX-1 is present, but under inflammation where there is IL-1B, COX-2 is generated. COX-2 is an enzyme that in turn produces a vasoactive compound called ProstaglandinE2 or PGE2 for short. PGE2 not only participates in changing the microenvironment of wounded areas by causing vasodilation and fluid stasis, but also drives cell growth which is necessary to regenerate damaged areas. In the microenvironment around a tumor, PGE2 secretion enhances the growth of cancer cells.

10) When we added an escalating dose of this nutrient mix up to 100 milligrams per Liter, the secretion of PGE2 by stimulated white blood cells was decreased in a dose dependent manner.

11) Inflammatory cytokine release and PGE2 release both amplify each other in a feed forward loop, with one augmenting the other. At the hub of this cycle is a protein called NF-kappa Beta, which is involved in both response to inflammation and generating inflammatory mediators.

12) So we also took a look at the effect of the nutrient mixture upon this critical molecular hub of inflammation and found that NF-kappaB activation is decreased in a dose dependent manner as well.

13) Synthetic PGE2 inhibitors such as ibuprofen or other cox selective drugs have various mechanisms by which they function. We asked the question whether this nutrient mixture was acting by decreasing the actual genetic production of COX-2 enzyme by a technique called Real Time PCR with relative expression against a gene known not to vary much in cells regardless of their situation. We observed that the COX-2 enzyme gene code itself, called mRNA decreased with nutrient mix, indicating that the compounds had an effect at the transcriptional level. Of course, if there is less enzyme, there is less enzymatic product generated, which means less PGE2.

14) We also asked whether this decrease in genetic transcripts of COX-2 translated to less actual COX-2 protein, and this western blot which detects proteins shows that there is less actual enzyme. In summary, the nutrient mixture lowered PGE2 formation in inflamed cells by decreasing the production of COX-2 itself.