WHY LEAKY GUTS LEAD TO MS?

READERS SUMMARY:
1. What determines our ultimate health fate?
2. What exactly is epigenetics?
3. How does an autoimmune disease begin?
4. Is multiple sclerosis tied to gut inflammation?
5. What is an inflammasome and why is hypomethylation so critical?

My first post on epigenetics seems to have stimulated a lot of talk based upon the emails I received. I think we need to dig a bit deeper into this area because it is now clear scientifically that epigenetics really determines our ultimate health outcomes. In fact, it is the easiest way to alter our genomes by modifying our dietary choices. To begin let's simply define what epigenetics is in 2011. Epigenetics is any mechanism that affects genes without chaining the nucleotide sequence of the DNA. The two major ways epigenetic modification occurs via our diet is via methylation of our DNA or of acetylation of our histone proteins. The amount of methyl and acetyl groups come from our diets. For example, when we have low methylation in our diet, our DNA becomes hypomethylated. Lower levels of methylation correlates with development of higher rates of cancer and with autoimmune conditions. Obviously, none of us wants to get cancer or autoimmune disease so I think we all need to pay attention about how epigenetics can help keep us free of disease.

Cellular functioning determines health and sickness. This is the core of levee one. Many cellular functions also determine how we age. As soon as we are born aging commences. No one really perceives aging that way but they need to because the science of epigenetics is the engine driving that biologic fact. Most aging pathways intersect with many others simultaneously. Their collective summation over time is called the process of aging. All act in an interdependent fashion and epigenetic modification of our genome is one of those powerful forces that shape the fate of our cells. Remember that groups of cells function in unison to make our organs. Our organs form the basis of our physiology. The degree of exposure of an organ to a specific environmental factor can also determine its ability to induce specific alteration within that organ.

In the Paleo community we often hear about the effects of grains that cause autoimmune conditions like celiac disease and Hashimoto's disease. We rarely hear how this really occurs. The answer is epigenetic modifications of our genome by the grains and how they interact with our gut's immune system. That interaction occurs because of the constant assault of our immune system causes hypomethylation of our immune cells in the gut. This process leads to the formation of something called the "inflammasomes". Inflammasomes are triggered by inflammation. This chronic inflammation triggers activation of specific danger associated diseases called (DAMP's). Things you may know about that trigger DAMP's are asbestos, silica, alum, BPA, and grains. These are examples of exogenous stressors. Some examples of endogenous stressors of the "inflammasome" are ATP, uric acid, Mitochondrial dysfunction, obesity,

PUFA's, ceramics, ROS and hyperglycemia. The inflammasome triggers an inflammatory cascade that eventually secretes cytokines IL-1Beta and IL-18. These cytokines eventually lead to the production of IL-6 and TNF alpha that we learned about in our leptin series. IL-6 and TNF alpha activate the 911 system (NF kappa beta) in our cells that signal major cellular suicide or recycling pathways within the cell. (apoptosis or autophagy). It also appears that obesity can produce unchecked activation of the inflammasome to provoke inflammation and cause autoimmune destruction of certain organs. This mechanism is now known to cause autoimmune diseases like type two diabetes, celiac, atherosclerosis, MS, and type one diabetes.

Today I want to talk about one autoimmune disease that I have gotten many questions about. That disease is multiple sclerosis (MS). In the past decade we have learned about new pattern recognition molecules called NOD like receptors (NLR). NLR's recognize both pathogens and DAMP's so they are important sensors of cellular stress that arises from bacteria or from cellular instability as it occurs. Clinical studies have identified an important role of inflammasome derived cytokines in MS pathogenesis. IL- 1 beta levels are correlated with the severity of MS disease a patient could face if they had MS. People with a high ratio of Il-1 beta compared to the IL-1R antagonists are epigenetically predisposed to developing MS. (Huang et al., 2004: Ming et al.,2002.) The correlation of IL 1 cytokines to neurodegenerative disorders is strengthened by the experimental autoimmune encephalomyelitis mouse model of MS disease as well. IL1 produces neuroinflammation by promoting the differentiation and production of IL-17 producing T cells that causes cell death of CNS myelin that characterizes MS plaques. Myelin is the covering of nerve cells. Think of it like the plastic covering on an electrical wire. When the plastic is pulled off the wire is exposed and subject to a "short circuit" and it wont work well.
Research is beginning to show that chronic inflammation from our gut, coupled with low vitamin D levels, and poor VDR receptor function allow for the activation of auto-reactive T cells that destroy cells that make the covering (myelin) of nerve cells. MS is a debilitating neuroinflammatory disease that occurs when auto-reactive T cells gain entry into the CNS and destroy myelin producing oligodendrocytes. It appears the T cells can enter the CNS via a leaky blood brain barrier that comes from a leaky gut or chronic inflammation of any sort. An early finding in MS patients but in all autoimmune disease in evolution is the constant finding of low levels of DHEA. Interestingly, when DHEA is replaced it has been shown to help limit the severity of disease progression. In some cases, the disease can be "pushed" to remission after it has been diagnosed when DHEA levels are treated. The DHEA level is felt to be down regulated because of the constant stress on the adrenal to make cortisol due to the non stop nature of the inflammatory cascade in autoimmune diseases. We call this low DHEA finding pregnenolone steal syndrome. DHEA is known to be a potent inhibitor of IL-6 and TNF alpha too! I am constantly amazed that this hormone is not assayed in all cases of autoimmunity and replaced.

WRAPPING IT UP: Today the treatment of MS revolves around Interferon beta use (IFN-B). IFN-B works because it decreases the production of IL-1beta from the inflammasomes. It does this by limiting the activation of the inflammasome to

begin with. Real advancements in treatment of MS will occur when we figure out precisely what interactions are with the food choices and how they interact in our gut with the bacteria and immune system that lead to the generation of these auto-reactive T cells.

For now, we understand that the likely causation of MS is tied to chronic inflammation from our diet that initiates the irritation of the gut. This gut irritation induces epigenetic changes in our immune cells in the gut associated lymphoid tissue (GALT) to cause DNA hypomethylation sequences that eventually lead to the formation of inflammasomes. These inflammasomes produce inflammatory cytokines that further modify our immune cells to become auto-reactive cells to our own myelin coating of our nerves cells to cause short circuits all over our brain and spinal cord in multiple sclerosis patients. It now appears that any disease that causes chronic inflammation can induce autoimmune reactive cells to form. This is why we see many associations of inflammatory diseases to autoimmune diseases. The factor tying these diseases together is epigenetic modification of certain parts and cells of our immune system so that they can no longer protect our organs and instead begin to slowly destroy them overtime and result in disease propagation.

CITES
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