Immunity and Inflammation

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Immunity, Inflammation and Nutrition

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Medicine recognizes two arms of immunity – innate and adaptive. This is an expression of genetic and epigenetic influences. The latter plays out as influences due to nutrition or lifestyle including the use of drug medicaments and supplements.

Orthomolecular and functional medicine approaches have long focused on practical applications of such things for therapeutic benefit.

The prevalence of chronic inflammatory diseases have been increasing. These diseases include allergic conditions (asthma, eczema) as well as autoimmune diseases. It is now well established that the development of clinical phenotypes is the result of an intimate interaction between genetic predisposition and environmental exposures. The adaptive immune system plays an important role in orchestrating the inflammatory response.

The intestinal immune system has two arms of adaptive anti-inflammatory defense which normally preserve the epithelial barrier: (i) immune exclusion performed by secretory IgA (SIgA) and SIgM antibodies to control surface colonization of micro-organisms and dampen penetration of potentially harmful antigens; and (ii) suppressive mechanisms to avoid hypersensitivity to innocuous antigens, particularly food proteins and the commensal microbiota.

The intestinal microbiota and some probiotics are known to interact with the host immune system, thereby influencing both health status and disease risk. These interactions contribute to immune response activation against dangerous stimuli, as well as to the activation of regulatory mechanisms that avoid uncontrolled inflammation and chronic pathologies. To date, most of the applications of probiotics with immunomodulatory traits have been focused on prevention and treatment of different clinical conditions, including infections, chronic inflammatory bowel disorders and allergies.

The gut associated lymphoid tissue is the largest in the body, and mature lymphocytes in the gut mucosa vastly outnumber those in the bone marrow. Large amounts of antigens pass through the gut daily, making the gut mucosa the major site of lymphocyte contact with antigens in the entire body. There is coordinated cross talk between the gut microbiota and the immune system, allowing the host to tolerate the large amount of antigens present in the gut. The importance of perturbations in the gut microbiota and the subsequent impact on the development of inflammation has only recently been recognized. Gut microbiota dysbiosis is related to inflammatory disorders, although whether the microbiota change first, leading to disease development, or respond to another factor is unclear; this is a “chicken and egg” problem.

Certain species of gut commensal microbiota are required for the regulation of immune responses and that perturbations in the microbiota could result in a lack of immune regulation, the outgrowth of more pathogenic microbes, and the promotion of inflammation. A diet enriched in fiber affects the immune system has been elucidated. Prebiotics are non-digestible food ingredients that are selectively fermented in the gut resulting in specific changes in the composition or activity of the gastrointestinal microbiota, thus conferring benefits upon host health. Inulin-type fructans and galactooligosaccharides are the most extensively studied prebiotics. They are fermented in the colon to short-chain fatty acids, and selectively stimulate the growth of bifidobacteria. In addition to increasing the production of SCFAs, such as acetate, propionate, and butyrate, other protective mechanisms of prebiotic activity have been proposed. Prebiotics can also provide resistance to colonization by pathogenic bacteria by inhibiting the adherence of pathogens to the gut epithelium.

Mushroom-derived dietary β-glucans have been shown to elicit diverse immunomodulatory effects in human and animal tissues, including the blood, gastrointestinal tract and spleen. In controlled human trials, β-glucan intake stimulated the immune system in the blood of healthy adults, dampened the allergic response to a respiratory inflammatory agent and improved survival in cancer patients. Additional randomized controlled trials are warranted to enable a more complete understanding of the immunomodulatory effects and specific applications of orally administered β-glucans.

Short-chain fatty acids (SCFAs) are the main metabolic products of anaerobic bacterial fermentation in the intestine. In addition to their important role as fuel for intestinal epithelial cells, SCFAs modulate different processes in the gastrointestinal (GI) tract and in other tissues such as adipose and immune tissues. These fatty acids have been recognized as potential mediators involved in the effects of gut microbiota on intestinal immune function. SCFAs modify the recruitment of circulating leukocytes to the inflammatory site. SCFAs modulate the production of inflammatory mediators by
macrophages. The production of prostaglandin E2 (PGE2) is also modified by SCFAs. Anti-inflammatory actions of SCFAs have been also observed in neutrophils. Vitamin C is a highly effective antioxidant that protects the body's cells against reactive oxygen species that are generated by immune cells to kill pathogens. Primarily through this role, the vitamin affects several components of innate and adaptive immunity; for example, vitamin C has been shown to stimulate both the production and function of leukocytes, neutrophils, lymphocytes, and phagocytes7.

Glutamine is the most abundant free amino acid in the human body. Glutamine has cell- and immune-modulating properties and affects lymphocyte and monocyte metabolism. Moreover glutamine is one of the precursors of glutathione, stimulates the expression of heat shock proteins and influences gene expression. Glutamine starvation activates adenosine 5'-monophosphate-activated protein kinase (AMPK) and is possibly involved in the metabolism of temporal hibernation. Glutamine is used as a nutritional substrate for enteral and parenteral nutrition (mainly in the form of a stable dipeptide) and has a positive effect on the immune response. Glutamine is utilised at a high rate by cells of the immune system in culture and is required to support optimal lymphocyte proliferation and production of cytokines by lymphocytes and macrophages. Macrophage-mediated phagocytosis is influenced by glutamine availability8.

Immune dysfunction and inflammation are intimately related. There is a wealth of nutritional tools that may be applied for benefit. Practically, the biggest problem is there are so many. But good Health Canada approved natural health products are available so determining practical protocols for qualifying patients can be achieved.

References
1. Diet, Immunity and Inflammation
   A volume in Woodhead Publishing Series in Food Science, Technology and Nutrition
2. Immune system stimulation by probiotic microorganisms.
5. Figure 3: Immune modulation by fibres and short-chain fatty acids. From The impact of diet on asthma and allergic diseases Nature Reviews Immunology doi:10.1038/nri3830
8. Glutamine and the immune system; doi: https://doi.org/10.1007/BF01366922
here are a lot of developments regarding supplementation during a pregnancy. As cited below, these pertain to the forms of the ingredients presented in actual consumer end use products. Being aware of the options available allows a practitioner to make better recommendations.

The Folate Matter
It is well established that the presence of folate in the diet of a mother-to-be (MTB) is important to the welfare of the newborn. Until recently reference to “folate” was identical to “folic acid”, a synthetic substance held to have some folate activity. Folic acid has been universally used in supplements because it is cheap and stable. Yet, it is also well known that folic acid can provoke serious side effects for many users, pregnant or not. Nothing raises blood histamine levels like even small amounts of folic acid. This pushes consumers towards a state of histadelia with its many unpleasant attendant symptoms.

Finally, a much safer and more effective form of supplemental folate has emerged for common use. This is methyltetrahydrofolate, aka L-5-MTHF, folinic acid. Mostly now just referred to as MTFH. Many manufacturers of natural health products have adopted MTFH. It provides the benefits of folate without the histamine disturbances of folic acid one of which is to make its users grumpy, cranky and depressed1,2.

There is a lot more to the larger folate debates with the focus on methylation.

The Cobalamin Matter
It is also well established that there is a synergistic relationship between Vitamin B12 (cobalamin) and folate. As with folate, the forms of cobalamin employed in supplements are generally inferior. These being cyanocobalamin or hydroxycobalamin. Cyanocobalamin is a synthetic form and the most widely used. Hydroxycobalamin may convert by stages to active cobalamin. Methylcobalamin is fully active from the get-go and has that handy methyl group built in3. Supplement manufacturers have finally wised up and methylcobalamin B12 products are readily available, many in a sublingual delivery form to better ensure their effects. Also, there is an almighty raging debate over folate, cobalamin and autism risk during pregnancy4,5.

The DHA, EPA Matter
The use of long-chain, generally fish oil sourced fatty acids during pregnancy is routinely recommended. Whether EPA (eicosapentaenoic acid) or DHA (docosahexaenoic acid) the common practice is ‘the more the merrier’. Maybe not. Consider this from the eminent Emily Deans, MD writing in Psychology Today:

“The tricky thing about omega-3 supplementation is that even though DHA is the major omega-3 in the brain, DHA supplementation on its own is a total bust. EPA needs to be at least twice as high as DHA in any supplement for there to be a positive effect in depression trials. For this reason I don’t recommend DHA algae products; there’s just no data to show they are helpful.6”

An emerging opinion then is that pre-formed DHA “is a bust” or at least must be heavily counterbalanced with EPA which remains the deliverer of benefits.

A second concern regarding fish oils regards the form of them presented as a result of their method of manufacture. For many years, manufacturers have favoured a cheap and stable method referred to as ‘ethyl esters’. Effectively, in ethyl ester products the natural glycerol backbone of the triglyceride is swapped out for ethanol. The resulting products are thus synthetic. Objections to the safety of ethyl ester fish oils have been raised at the level of international regulators7.

As with folate and cobalamin, manufacturers have woken up to this matter. Many now make fish oil fatty acids as true natural triglycerides which better conforms with scientific and regulatory standards.

The Iron Matter
The benefits of supplementary iron during pregnancy and otherwise for many women does not need to be made. However again, the form of the supplement used is critical. The traditional form has been ferrous fumerate which is flatly ineffective and inflicts users with constipation. More beneficial forms of iron supplementation have emerged and manufacturers have taken them up.

Iron bisglycinate is a true amino acid chelate which has been pioneered by Albion Laboratories8. The advantage of the bisglycinate is that it has a very low molecular weight and passes out of the gut by passive diffusion. All other forms of iron have to be dissociated, require active transport and then have to be re-associated which attenuates their effectiveness. Plenty of published studies attest to the safety and benefit of iron bisglycinate9. Other manufacturers of this ingredient form have emerged so there are plenty enough products available.

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Baby & Me™ Multivitamin

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Are your patients thinking about specific vitamin and mineral gaps in their diet? The majority of the time the answer is probably no. They may want to eat more fruits and vegetables, or cut down on their sugar intake, but most people are not coming in for an office visit telling us, “I don’t think I’m getting enough folate in my diet.” It’s our job as clinicians to help patients address the inevitable nutritional deficits that occur, and this responsibility takes on extra significance when working with women of reproductive age. By addressing gaps in the diet through appropriate nutrition and supplement recommendations, we have a unique opportunity to influence the health and well-being of both current, and future generations.

Although often overlooked, comprehensive preconception nutrition counseling is of vital importance, since it has been demonstrated that key nutrient deficiencies often exist. A study measuring a functional biomarker of riboflavin status in women of childbearing age living in Vancouver, Canada, demonstrated high rates of riboflavin deficiency. Riboflavin plays a key role as an antioxidant, and is necessary for a healthy liver, skin, hair and eyes. Another example involves a nutrient many people associate with pregnancy; folate. A study published in Obstetrics and Gynecology found that women who had low levels of folate prior to receiving preconception counseling showed a significant increase in red cell folate levels four months afterward. This demonstrates that when educated properly, women are empowered to make positive health changes.

Additional evidence that nutritional deficiencies are quite common is found in the United States, where the CDC's 2nd National Report on Biochemical Indicators of Diet and Nutrition demonstrated that 32% of women were at risk for deficiency in iron and all seven vitamins. Women 20-39 years old were also shown to border on having iodine insufficiency. This is of particular concern for women of reproductive age, due to the important role that iodine has in brain development, as well as being a crucial building block of thyroid hormones.* It’s essential to note that some prenatal multivitamins do not contain this crucial mineral.

Even with the healthiest diet, nutrient deficiencies are clearly prevalent among women of childbearing age. Ideally, these gaps in the diet should be filled before conception to ensure the healthiest start to pregnancy. This is best accomplished by taking a prenatal multivitamin as early as possible, ideally at least six months prior to conception. There are several specific nutrients that warrant additional attention listed below:

**Folate.**

As practitioners, we’ve been educated extensively on the importance of folate, and know that folate needs to be present at sufficient amounts right at the onset of pregnancy.* The U.S. Preventive Services Task Force recommends that all women planning or capable of pregnancy take a daily supplement containing 0.4 to 0.8 mg (400 to 800 mcg) of folic acid. Ideally, folate should be delivered in the methylated form (5-MTHF) which is more readily utilized by many women.*

**Iron.**

It’s estimated that during pregnancy a woman’s need for iron essentially doubles. Therefore it is vital to take a gentle, well-absorbed form of iron daily in a prenatal multivitamin.

**Choline.**

An essential nutrient that is part of the B vitamin family. Choline is needed for healthy fetal development, particularly in the third trimester.* Choline is also required to make phosphatidylcholine, a key component of cell membranes. This vital nutrient is not well known by most women, and is not routinely included in all prenatal multivitamins.

**Iodine.**

As mentioned earlier, it was found by the CDC that young women (20-39) bordered on having iodine insufficiency. All prenatal multivitamins should contain this essential mineral.

Foundational supplements for preconception, pregnancy and postpartum include a multivitamin, essential fatty acids (EFAs), and a probiotic formula. While all of these significantly contribute to the health of mom and baby, a prenatal multivitamin rises to the top as the most critical supplement to begin as early as possible to address nutritional gaps.

References

1. High rates of riboflavin deficiency in women of childbearing age in Cambodia and Canada. April 2014 The FASEB Journal vol. 28 no. 1 Supplement
In every case, the form of the nutrient makes a great difference as regards benefits and safety. For a long time there was a disconnect between the science and the products manufactured. Now, that gap has closed. If the reader needs advice as to specific brands and products, Nature's Source will be pleased to give good advice.

1. Neonatal and Fetal Methylene tetrahydrofolate Reductase Genetic Polymorphisms: An Examination of C677T and A1298C Mutations; https://doi.org/10.1086/303082

Continued from page 4

5 Ways to Stand Up to GMOs

1. Educate friends and family about their right to know.
2. Choose Non-GMO or Non-GMO Project Verified products.
4. Support mandatory GMO labeling efforts.
5. Engage a young friend.

“At Nature’s Source we are pursuing the non-GMO movement with thousands of like-minded consumers and brands to press forward for truthful GMO labeling.”

Sanjiv Jagota
Founder & President

The matter of Genetically Modified Organisms (GMOs) is a major public policy issue that is being fought across the globe on many fronts. There is no middle ground when it comes to GMOs. The contenders are polarized. The stakes are high. The natural health community – industry, consumers and health professionals are firmly aligned in the anti-GMO camps. NHP organizations are leading the fight. Read more about the Non-GMO movement in our Non-GMO Guide.
Regulatory blank cheque for untested GM potatoes?

Thirty-three organisations including farmers, scientists, retailers, caterers and environmentalists, have lodged a formal objection to a proposed open air field trial of experimental GM potatoes, describing them as untested, unwanted and unnecessary. A trial will see experimental potatoes planted in an open field at the Sainsbury Laboratory in Norwich, despite the fact they have not been tested under controlled conditions. Applications for a “deliberate release” of genetically modified organisms usually include a molecular analysis of the plants or micro-organisms involved to demonstrate that the DNA changes that have occurred are the ones that were intended. However, the Sainsbury Laboratory stated in its application that “most of the transgenic plants described in this application are currently in the transformation pipeline”, ie they do not yet exist. Liz O’Neill, Director of umbrella campaign GM Freeze, which coordinated the formal multi-agency objection said: This application is premature at best. The Sainsbury Lab is asking Defra to sign a regulatory blank cheque by asking for consent to plant experimental potatoes which have not even been analysed in a test tube, much less properly studied under controlled greenhouse conditions.

Canada Report: There will be no commercial plantings of genetically modified (GM or genetically engineered) potatoes in Canada in 2017 due to market rejection. The GM potato was approved in Canada in March 2016. The company Simplot says they have only put the GM potato on hold until the market is ready.


A trove of internal documents from Monsanto, recently unsealed in a lawsuit against the agricultural biotech giant, has revealed the firm’s role in the knotty tale of a paper from the lab of a scientist known for his stance against genetically modified organisms (GMOs). That paper is “Long term toxicity of a Roundup herbicide and a Roundup-tolerant genetically modified maize,” published in September 2012 in the journal Food and Chemical Toxicology (FCT) and retracted in January 2014. Gilles Seralini, a scientist known for an adversarial stance towards GMOs, was first author. The documents, posted last week by the law firm of Baum, Hedlund, Aristei and Goldman, show Monsanto engaged with a network of scientists and other commentators to spread the message that the Seralini paper was bad science and should be retracted.

The New Food Fights: U.S. Public Divides Over GMOs

From the Pew Research Center: Key findings from a new Pew Research Center survey conducted from May 10 to June 6, 2016, with a nationally representative survey of 1,480 adults.

A new survey finds that 55% of Americans believe organically grown produce is healthier than conventionally grown varieties, while 41% say there is no difference between organic and conventionally grown produce and 3% say that conventionally grown produce is better. Four-in-ten Americans (40%) say that most (6%) or some (34%) of the foods they eat are organic. Fully three-quarters of these Americans (75%) are convinced that organic foods are healthier than conventionally grown foods.

At the same time, there is a sizable minority – 39% – of Americans who consider genetically modified foods worse for a person’s health than other foods. This compares with 48% of adults who say GM foods are no different from non-GM foods and 10% who say GM foods are better for health.

http://www.pewinternet.org/2016/12/01/the-new-food-fights/

Conflicts of interest in GMO research: study

Financial conflicts of interest were found in 40 percent of published research articles on the genetically modified crops, also known as GMO crops, French researchers claim. The findings in the Dec. 15 edition of the U.S. journal PLOS ONE focused on hundreds of research articles published in international scientific journals.

“We found that ties between researchers and the GM crop industry were common, with 40 percent of the articles considered displaying conflicts of interest,” said the study. Researchers also found that studies that had a conflict of interest were far more likely to be favorable to GM crop companies than studies that were free of financial interference.

Thomas Guillemaud, director of research at France’s National Institute for Agricultural Research (INRA), told AFP that the team originally looked at 672 studies before narrowing down to the pool to 579 that showed clearly whether there was or was not a financial conflict of interest.

“Of this total, 404 were American studies and S3 were Chinese,” he said. “The most important point was how we also showed there is a statistical link between the presence of conflicts of interest and a study that comes to a favorable conclusion for GMO crops,” Guillemaud said.

Conflicts of Interest in GM Bt Crop Efficacy and Durability Studies; https://doi.org/10.1371/journal.pone.0167777
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