

How Do We Attain Inflammation Modulation?

Author: Dr. Joseph Pizzorno, ND

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Co-authored by Joseph Katzinger, ND

Dr. Joe Katzinger consults as medical researcher and health writer with SaluGenencists, Inc. He earned his ND degree from Bastyr University, and graduated summacum laude with a bachelors of science in honor's biochemistry from Michigan State University.

Inflammation is playing an ever-increasing role in many of today's chronic diseases, and, at first glance, its bad reputation seems well-deserved. For example, chronic (sometimes called non-resolving) inflammation is thought to significantly contribute to the pathogenesis of many modern illnesses, such as atherosclerosis, diabetes, obesity, cancer, chronic respiratory and digestive diseases, neurodegenerative diseases and even the process of aging itself. In fact, in an article published in the reputable journal *Cell*, the authors claim that "... perhaps no single phenomenon contributes more to the medical burden in industrialized societies than non-resolving inflammation."⁽¹⁾

However, a closer look at the cellular mechanisms that drive an inflammatory response (as well as the evolutionary gains associated with this process) paints a different picture. Inflammation is best viewed as an adaptive response to a noxious environment.⁽²⁾ In controlled amounts, it is both necessary and beneficial for maintaining homeostasis (a balance within the body) by eliminating infectious agents and performing a general housekeeping role of removing damaged and injured tissues. Thus, rather than viewing all inflammation as harmful, it would be more accurate to view it along a spectrum, with particular attention to what drives the more chronic and non-resolving processes, which adds fuel to the fire of so many diseases. This viewpoint should also be informed by an understanding of how both our individual and collective genomes influence inflammatory pathways, and how different today's Western lifestyle is from the environment our genes have evolved in. This contrast helps explain why inflammation's detrimental role today is due to a "...mismatch between the current environment and the evolutionary pressures of the past."⁽²⁾

In this month's article, we'll try to concisely review what drives inflammation, and suggest some clinically relevant interventions.

Physiology of Inflammation and Cellular Dysfunction

Scientific understanding of acute (i.e., short-term) inflammation is quite extensive and is characterized by four overlapping phases: recognition of some type of infection or tissue damage, recruitment of specific cells to the trouble spot, eliminating the source of the damage followed finally by resolution of inflammation.⁽³⁾ The triggers for chronic inflammation are not as well defined (and may not always be due to infection or tissue damage), yet recent research points to two factors that may lead to its persistence: inhibition of the resolution of inflammation and disturbed cellular function.

Of course, much attention has been given to the anti-inflammatory benefits of omega-3 (n-3) fatty acids, but only recently has their role in resolving inflammation been better

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characterized. While once thought of as a passive process, the resolution phase of inflammation is now known to be a very active, preprogrammed and tightly controlled process.⁽⁴⁾ Furthermore, the mediators of inflammation primarily belong to a class of compounds known as lipoxins, protectins and resolvins, which are derived from the n-3 fatty acids DHA and EPA. The Western diet is typically not only low in these n-3 fatty acids, it is also rich in both arachidonic acid from animal products and n-6 fatty acids from corn and vegetable oils (which are precursors for inflammatory mediators). A nearly 1:1 ratio of n-6 to n-3 fatty acids was probably common throughout most of our evolutionary history, while a Western diet is at least 15:1. This much higher ratio has been linked to numerous diseases, most likely because it drives inflammatory pathways, while simultaneously preventing their resolution.^(5,6) Total fatty acid intake is probably not as important as the ratio between n-6 and n-3's.^(7,8) Genetic factors also play a role here. For example, individuals with a polymorphism (genetic variant) in the 5-lipoxygenase gene are more likely to develop atherosclerosis. However, if their dietary ratio of n-3 to n-6 is balanced, this risk is neutralized.⁽⁹⁾

The second factor gaining greater recognition is the importance of healthy cellular function to preventing chronic inflammation. Known as both "parainflammation" and "meta-inflammation," these terms refer to chronic low-grade inflammation that is either metabolically triggered or initiated in response to impaired cellular function. For example, when exposed to a surplus of nutrients (such as glucose, typical for a Western diet), inflammatory molecules and pathways are engaged which are very similar to those found in classic inflammation.⁽¹⁰⁾ This may also help to explain why a high fiber and low glycemic index diet are associated with lower production of inflammatory markers.⁽¹¹⁻¹³⁾

Metabolically triggered inflammation also recognizes a close overlap between immune and metabolic functions, as well as how dysfunction in cellular organelles (such as mitochondria and the endoplasmic reticulum) can induce production of inflammatory mediators. This last point may be particularly important—it's possible that improving cellular function and creating a more optimal cellular environment may protect us from the damages of inflammation. A recent animal-based study also suggests that up-regulating cellular protective enzymes may protect a cell from inflammation, while at the same time not limiting the benefits of inflammation.⁽¹⁴⁾ This cytoprotective effect was mimicked by administering N-acetylcysteine (NAC), supporting the role of this and other antioxidants in quenching inflammatory processes.

Gut Microbiota

The role of the gastrointestinal tract in inflammation deserves special mention, partly because of the critical interaction between gut flora (microbiota) and the immune system, as well as the influence of excessive intestinal permeability on systemic inflammation. A healthy microbiota helps not only to prevent overgrowth of toxic bacteria, but also helps to induce immunotolerance and integrity of the intestinal wall.⁽¹⁵⁾ Again, a Western diet has been associated with an altered microbiota composition, one which is more likely to be inflammatory. Lack of breastfeeding and antibiotic use are also risk factors.⁽¹⁶⁾

Conclusion

A Mediterranean diet rich in plant-based whole foods, particularly fruits and vegetables,
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as well as magnesium, fiber and other phytonutrients has been consistently shown in the research to inflammation.^(17,18) It should also be rich in n-3 fatty acids, particularly in comparison to n-6 fatty acids, have a low glycemic index, and ideally be organic.⁽¹⁹⁾ Ensuring optimal vitamins A and D intake is also necessary for modulating a number of immune and inflammatory functions.⁽²⁰⁾ Physical activity (not excessive) is also important, and helps to maintain a healthy body weight, a critical factor for reducing inflammation.⁽²¹⁻²³⁾ Consideration of food allergens, intestinal permeability, as well as dysbiosis is important, and the use of antioxidants and other nutrients which enhance cellular function may both reduce inflammation and protect cells from its damage. Curcumin and resveratrol are two compounds that may be particularly effective, especially when used together.^(24,25) Ultimately, “matching our environment to our genetic uniqueness may be the most advantageous approach.”⁽²⁶⁾

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