Addressing Rampant Inflammation

By Steve Myers, Senior Editor

Generally, inflammation is a process that protects against infections and injuries. However, like most body systems, a healthy response requires a balance of pro-inflammatory and anti-inflammatory activities. When inflammation becomes chronic or out of control, ill health can result, including any number of conditions such as vascular disease, bowel dysfunction and cancer. As science continues to expose the plot and perpetrators of unhealthy inflammation, many natural ingredients are stepping up to help bring the inflammatory process back to a healthy equilibrium.

Acute inflammation delivers needed blood and immune cells to the site of infection or injury. This helps curb the problem and promote healing. The five signs of inflammation are redness, heat, swelling, pain and decreased function of the affected area.

Inflammation is activated by various cells already present at the problem site. Mast cells are activated by injury or pathogen (or perceived pathogen), causing them to release hordes of mediators such as granules—histamine, heparin and serine proteases—and lipid mediators—prostaglandins, leukotrienes and cytokines such as tumor necrosis factor-alpha (TNFa), interleukin (IL) and chemokines. These mediators can recruit more immune cells to the problem site and activate immune cells at the site to release more mediators.

The lipid mediators involved have interesting and complex biosynthesis relative to essential fatty acid (EFA) metabolism. The eicosanoids—including leukotrienes, and the prostanoids prostaglandins (PGs) and thromboxanes—are derived from three fatty acids: omega-3 **eicosapentaenoic acid** (EPA), omega-6 **D-gamma linolenic acid** (DGLA) and omega-6 arachidonic acid (AA).

These fatty acids are converted to eicosanoids by enzymes such as cyclooxygenases (COX-1 and -2) and lipoxygenase (LOX), which are released by the immune system to help produce various immune cells. These catalyses occur in different cascades. AA, which is mostly sourced from dietary linoleic acid, heads a cascade that results in eicosanoids (series 2) that generally prompt inflammation. EPA heads the primary competing cascade, which results in eicosanoids (series 3) that are less inflammatory or even anti-inflammatory.

The DGLA cascade also competes with the AA cascade, though the DGLA-derived eicosanoids (series 1), while less inflammatory, have thus far proved less active and relevant than those from EPA. Furthermore, dietary GLA might contribute to both pro- and anti-inflammatory cascades, given dietary linoleic acid atop the AA cascade converts to GLA; however there are subtle differences in how GLA from AA conversion and dietary GLA each interact with the enzymes generating eicosanoids. For these complexities, dietary GLA is not as much a focus as dietary EPA when it comes to inflammation mediation.

All these fatty acids are catalyzed by COX-1 is a constitutive enzyme, and COX-2, an inducible enzyme, into their respective eicosanoids. Competition for these COX enzymes is a big part of inflammation control. The enzyme 5-LOX also affects the two primary cascades, converting AA into

leukotrienes that are generally pro-inflammatory (series 4), while breaking EPA into generally anti-inflammatory leukotrienes (series 5). DGLA produces no leukotrienes via the 5-LOX pathway.

Inhibiting the actions of these COX and LOX enzymes has been the approach of pharmaceutical-based care. NSAIDs (non-steroidal anti-inflammatory drugs), such as ibuprofen, inhibit both COX-1 and -2. However, by inhibiting COX-1, these drugs can result in undesirable side effects, including stomach problems (e.g., bleeding, ulcers). Thus, pharmaceutical companies explored drugs that could inhibit COX-2 more than COX-1 at a much higher ratio (300-to-1). These include Vioxx, Celebrex and a number of other COX-2 inhibitors that were eventually pulled from the market because of increased risk of cardiac events, including heart attack and death.

While these COX-2 inhibitors helped with some areas of pain management, they led to increased production of eicosanoids with vasoconstrictive (narrowing blood vessels) and platelet aggregating (blood clotting) effects, which contributed to the unfortunate cardiac side effects.

On the flipside, aspirin is a well-known inhibitor of COX-1, thus tilting the eicosanoid production to those from COX-2 conversions, including prostacyclin, a vasodilator that prevents blood clotting. As such, prostacyclin can protect the vascular system from high blood pressure and hardening of the arteries, key risk factors for heart attack and stroke.

While aspirin results in fewer unwanted side effects than other NSAIDs, research has focused on more natural management of these inflammatory cascades, attempting to maintain a balanced system in health people and correct chronic inflammation in ill people.

Given the respective cascades start with dietary essential fatty acids (EFAs), addressing the intake ratio of omega-6s to omega-3s has become a popular starting place for natural inflammation control. Western diets have notoriously become overly heavy in omega-6s and deficient in omega-3s. Therefore, the primary effort is increasing intake of omega-3s via diet or dietary supplementation.

EPA tops the omega-3 anti-inflammatory cascade, relative to COX and LOX catalysis; thus increased EPA from eating more fish or taking fish/marine oil supplements is the most touted EFA intervention for inflammation management. Fellow omega-3 **DHA** (docosahexaenoic acid), also very common in fish and marine sources, can retroactively convert back upstream to EPA, but not in huge amounts.

Alpha linolenic acid, found in seed oils, is another omega-3 EFA that can convert in the body to longer-chained EPA; however, these conversions are limited by competition with omega-6 linoleic acid for metabolism by certain desaturase enzymes. Despite this disadvantage, a diet rich alpha linolenic acid has been shown to better lower inflammatory markers then has a linoleic acid-rich diet or the typical American diet.

Lowering levels of such inflammatory markers, including C-reactive protein (CRP) and vascular adhesion molecules (VCAMs), is considered a beneficial step towards lowering cardiovascular diseases, which is amplified by inflammation.

Chapters: