

## **Specialized Pro-Resolving Mediators: 21<sup>st</sup> Century Inflammation Fighters**

By Robert Silverman, DC, MS, CCN, CSCS

Specialized pro-resolving mediators, or SPMs, are a portion of the omega-3 fatty-acid spectrum that have been shown to have a powerful effect on reducing inflammation. In fact, SPMs represent a paradigm shift in how we regulate the inflammatory response in our patients. SPMs are poised to be the most effective inflammation treatment of the 21<sup>st</sup> century. Evidence suggests they resolve inflammation effectively without compromising the immune response and without risky side effects.

### **Stopping the Inflammatory Process**

Helping a patient resolve a chronic inflammatory condition is one of the biggest challenges a holistic practitioner faces. Even when patients are compliant with dietary and lifestyle changes, and take all the recommended supplements and medications, inflammation can stubbornly persist. We know now resolving inflammation is not a passive process; instead, it's complex and highly active, and can sometimes happen slowly or even stall.<sup>1</sup> Inflammation can linger long after the acute phase of the injury or illness has passed. Without resolution, the body never truly returns to homeostasis and inflammation becomes chronic.

A super-family of naturally occurring lipid mediators called specialized pro-resolving mediators (SPMs) plays a crucial role in switching off the inflammatory response.<sup>2</sup> SPMs don't block the initial inflammation – a desirable natural response to injury and illness. Instead, when the immune response has served its purpose, SPMs down-regulate the process to resolve the inflammation.



Produced in the tissues around the affected area, SPMs

function as "resolution agonists," targeting the immune cells that mediate the inflammatory response. By binding to specific cellular receptors, particularly the types known as "G-protein coupled receptors," SPMs modify cell behavior to promote resolution.<sup>3</sup>

The SPMs (lipoxins, resolvins, protectins and maresins) are derived from arachidonic acid and omega-3 fatty acids. (Arachidonic acid is often seen as an undesirable pro-inflammatory metabolite of omega-6 fatty acid, but as in many other aspects of the immune system, push and pull both have their place.) SPMs in effect signal the immune system to stop actively responding and instead to accelerate the return to homeostasis.

SPMs play a unique role in helping the body finally shut down the immune response, inhibit additional inflammation, clear away the damaging byproducts of the inflammatory process, and aid tissue remodeling. SPMs can facilitate the resolution even of prolonged or chronic inflammation. And once the SPMs have done their job, the body naturally breaks them down and eliminates them.

### **The Limits of SPM Production**

For decades, we thought EPA and DHA from fish oil helped relieve inflammation by competing with pro-inflammatory omega-6 fatty-acid metabolites.<sup>4</sup> This isn't the whole story. In fact, fish oil probably helps relieve inflammation by providing the raw material to build specialized pro-resolving mediators.

SPMs are the end result of a multi-step conversion process in the body that begins with dietary omega-3 fatty acids. This is converted to EPA and DHA; numerous steps farther downstream, EPA and DHA are then converted to a number of different SPMs metabolites. Two that have been carefully studied and shown to have therapeutic value are known as 17-HDHA and 18-HEPE.

Unfortunately, the complex conversion process that ultimately leads to the production of SPMs in the inflamed area is slow and inefficient, even in the healthiest individuals.<sup>5</sup> Normal genetic variation means some people will convert even more slowly than average. For occasional inflammation from an injury or illness, a healthy individual may be able to produce enough SPMs to resolve the inflammation in a timely way. But what about more serious or ongoing inflammation? What about people with suboptimum health?

If the body can't produce enough SPMs, the inflammation will be slow to resolve. It may linger on and become chronic. The protective effect of inflammation becomes destructive instead.

SPM production in amounts large enough to help with resolving inflammation relies on good nutrition and a healthy lifestyle. These fundamental factors aren't always sufficient to help an individual naturally produce enough endogenous SPMs to overcome and resolve an inflammatory condition. Factors that can limit SPM production include:

- Environmental irritant overload
- High intake of low-quality dietary fats
- High intake of processed carbohydrates
- Too little exercise or overexertion
- Other physical stressors, such as poor-quality sleep
- The aging process

While lifestyle and dietary changes can help improve SPM production somewhat, they don't have large effects. The aging process continues every moment and SPM production naturally decreases with age. Simply increasing intake of fish oil or DHA and EPA, even to high levels, isn't sufficient to significantly increase SPM production. Even when intake is high, the conversion process simply remains too complex and inefficient to be improved.

### **The Value of Supplementing**

A more direct and targeted way to raise SPM levels is to supplement with them directly. Currently available supplements are made from fish oil using a fractionation process to create an SPM-enriched product. Recent research has shown that daily dosing with two to six soft gels over six weeks produces reductions in standard inflammation blood markers such as hs-CRP, interleukins, fibrinogen and TNF-alpha.

Because SPMs are naturally produced as a normal part of resolving inflammation, the supplements don't suppress immunity. This makes them much safer than anti-inflammatory drugs such as glucocorticoids, methotrexate or even aspirin. SPM supplements can be taken indefinitely. They have no known side effects or interactions with other supplements or drugs.

### **Clinical Uses for SPMs**

The potential clinical uses for SPMs are basically any condition related to chronic inflammation. Research suggests SPMs can be particularly valuable for asthma, arthritis, diabetes, atherosclerosis and cognitive decline. SPMs also have been used quite effectively to treat gut problems, particularly leaky gut syndrome and irritable bowel disease, and to aid recovery in bone and muscle injuries.

SPMs are a valuable addition to the "Five Rs" protocol used in integrative medicine for healing the gut:

- Remove chemicals (artificial sweeteners, for example), allergens, processed foods, gluten, lactose, sugar, and bad bacteria.
- Replace what was removed with an improved diet and lifestyle, and the addition of digestive enzymes and stomach acid.
- Reinoculate the gut with probiotics to restore balance of good bacteria.
- Regenerate and repair the damage to the intestinal lining with supplements, including natural anti-inflammatories such as bioavailable curcumin, rosemary, ginger, quercetin, and omega-3 fatty acids.
- Retain the gains with ongoing careful attention to diet and the microbiome.

SPMs can be helpful at every stage of the protocol, but they are particularly useful for regeneration and repair because they reduce inflammation and promote healing. Clinicians often find this step in the protocol can be extremely slow and discouraging for the patient. Symptoms such as bloating and pain continue, even when the patient is completely compliant. This is where SPMs can make a big difference by filling the gap in our treatment of inflammation. SPM supplements can give the patient's immune system the final element it needs to calm the inflammation and move on to healing and a return to homeostasis.

After the protocol is complete, daily SPM supplementation helps retain the gains by controlling any inflammation that may develop from illness, lapses in diet, stress and other unavoidable factors.

## Healing Bones and Muscles

SPMs also may be a highly effective treatment for preventing bone loss and stimulating bone regeneration. In particular, the resolvins found in SPMs may mediate bone preservation by direct inhibitory action on osteoclasts.<sup>6</sup> For treating bone injuries, SPMs may be helpful by improving bone regeneration and remodeling. For treating osteopenia and osteoporosis, SPMs offer a significant improvement in safety and patient comfort.

Bisphosphonate drugs such as alendronate (Fosamax) and ibandronate (Boniva) for osteoporosis inhibit osteoclast-mediated bone resorption. However, these drugs can cause dangerous side effects, such as osteonecrosis of the jaw. Selective estrogen receptor modifiers (SERMs) such as raloxifene (Evista) slow bone loss, but carry a high risk of dangerous blood clots and stroke.

In addition, SPMs may be valuable for treating unresolved inflammation in muscle injuries. When inflammation lingers on in damaged muscles, it leads to inefficient tissue repair, which in turn leads to long-term loss of muscle mass and function. The tightly choreographed inflammatory response to muscle injuries can be thrown out of step by a wide range of factors, such as reinjury or dietary deficiencies. The final step in resolution isn't reached and the inflammation continues at a low level, preventing a full return of normal function. Supplementing with SPMs as the injury heals can reduce or eliminate lingering inflammation and speed tissue remodeling.

## References

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