

# MSM Immune Health Science Brief

*Oral Application*



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## Introduction

The immune system, as it protects and maintains the health of the body, involves a complex series of interrelated cellular and metabolic activities. Many of the identified mechanisms of immune function can foster both a positive and negative role. For example, an initial stress response to external events may be immune enhancing. The immune system activates the hypothalamus and sympathetic nervous system in a coordinated support effort to neutralize the stressor. But the same condition, if prolonged (“chronic stress”) will suppress the immune system, over-producing pro-inflammatory markers that exhaust the immune system leading to various disease states. As with many facets of the immune system, a delicate balance must be achieved. This balance begins with the innate immune system.

The innate immune system provides everyday protection. It is the first line of defense, challenged with maintaining equilibrium between the body and the environment. Broadly, the innate immune system (including the inflammatory response), maintains physical barriers in the skin, lungs, stomach, and urinary tract and is sufficient to maintain homeostasis. The adaptive (acquired) immune system, which is much slower to respond, will be recruited for action with significant threats within the body, typically when a pathogenic threat is imminent. With a healthy and primed innate immune system, a coordinated response can be effective to prevent against foreign invaders.

Various research indicates MSM (methylsulfonylmethane / OptiMSM®) may play an important role in support of the innate immune system. MSM is strongly correlated with positive effects upon inflammation and conditions of oxidative stress such as arthritis, neurodegenerative disease, and allergies. This review serves to explore the various influences MSM has upon the immune system and how such influences serve to mitigate negative outcomes resulting from chronic stressing of immune system function.

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## MSM modulates a healthy immune response

The immune response involves a multitude of different cells and active molecules, but the key messenger molecules that coordinate efforts are the cytokines, which include both pro-inflammatory and anti-inflammatory molecules. IL-1, IL-6, and TNF- $\alpha$  are the primary cytokines involved in the innate immune response and are predominately produced by macrophages. But many others are involved in the process including NF- $\kappa$ B, PGE-2, and NLRP3, which activate a pro-inflammatory response. A key factor in MSM supporting a healthy immune response is in the modulation of how often these response modifiers “activate” the immune response.

In a recent study examining the effect of OptiMSM and exercise on inflammatory markers, blood collected at various time points from five subjects after exercise was analyzed for various immune-stimulated cytokines associated with inflammation. The study was performed to determine if MSM could modulate a healthy immune response even after a typical stressor, such as exercise to exhaustion. Results showed consistent MSM modulation of inflammatory cytokines IL-1 $\beta$ , IL-6, and TNF- $\alpha$ , supporting an anti-inflammatory action immediately after exercise. MSM was also able to promote the production of inflammatory cytokines following LPS stimulation, something not observed in the non-MSM group. This finding indicates MSM may preserve the immune system even in an over-stressed state, possibly by preventing immune cells from becoming exhausted and unable to regulate properly a normal immune response (Godwin, 2015).

Other in vitro research has confirmed the effect of MSM on other inflammatory markers, specifically, MSM has shown the capacity to inhibit the release of nitric oxide (NO) and PGE2 by reducing expression of inducible nitric oxide (iNOS) and cyclooxygenase-2 (COX2) in LPS\* stimulated macrophages (Kim, 2009). The cytokines IL-6 and TNF- $\alpha$  were also decreased. Translocation of the p65 subunit of NF- $\kappa$ B to the nucleus was inhibited. Collectively, these results suggest that MSM inhibits LPS-induced release of pro-inflammatory mediators in murine macrophages through down-regulation of NF- $\kappa$ B signaling.

MSM's ability to modulate the stress response may be most evident by its effect on the expression of IL-6. MSM has been shown to inhibit strongly IL-6 production (Kim, 2009) without limiting its acute functions to normal stress (Godwin, 2015). In many cases, the expression of various inflammatory markers serves primarily in defense of the body. The cytokine IL-6 is rapidly increased in acute inflammatory responses associated with infection, injury, trauma and other stresses. The over-expression of IL-6 produces an undesirable inflammatory state, such as in chronic stress or other chronic immune-suppressing conditions. It was also shown that MSM reduces plasma or local levels of IL-6 in TPA-induced inflammation in mice, suggesting a different mechanism in which MSM modulates the expression of this cytokine (Kim, 2009).

MSM may also help protect cells against cellular death (apoptosis). In a study examining other possible mechanisms of MSM, researchers observed that MSM reversed apoptosis of cells, presumably through the modulation of apoptotic proteins. Since excess NO production causes apoptosis of macrophages, anti-apoptotic effects of MSM are thought to be mediated by its inhibitor effects on inducible NO synthase protein and NO levels (Karabay, 2013).

Other research suggests that sulfur-donating compounds can bolster the strength of the immune system. The immune response makes large demands on sulfur amino acid metabolism, and sulfur-donating compounds contribute to the effectiveness of the antioxidant defense system. This action indirectly influences immune function by modulating the actions of oxidant stress in transcription factor activation (Grimble, 2006).

Other in vitro and in-vivo research has confirmed the capacity of MSM to modulate the expression of cytokines IL-1 $\beta$ , IL-6, IL-8, IL-10, NF- $\kappa$ B, PGE-2 and TNF- $\alpha$  (Kim, 2009; Kloesch, 2011; Amirshahrokhi, 2011, 2013; Oshima, 2007; Ahn, 2014; Godwin, 2015; Hasegawa, 2004; Kamel, 2013).

*\* A compound form of gram-negative bacterium used in laboratory research to elicit a strong immune response.*

## IMMUNE SUPPORT\*\*

Inflammatory Markers	Oxidative Markers
TNF- $\alpha$	MDA
IL-1	PC
IL-6	GSA
IL-8	TEAC
IL-10	CAT
NF- $\kappa$ B	MPO
PGE-2	SOD
NO	NO
iNOS	
COX-2	

*\*\* Research on MSM has shown an effect on various inflammatory and oxidative markers, possibly through modulation of the priming steps involved in their expression. Such effects may serve to reduce the total oxidative and inflammatory burden upon the body.*

## MSM mitigates inflammation by reducing inflammatory markers

A normal inflammatory response is self-limiting and involves down-regulation of pro-inflammatory protein expression and increased expression of anti-inflammatory proteins. Macrophages play a salient role in the inflammatory response and serve as an essential interface between innate and adaptive immunity. Macrophages play a role in immune function/infection after 24 hours, or later, gradually replacing neutrophils. They migrate to the site after neutrophils because they move more sluggishly and cause many of the chemotactic factors that attract them, such as macrophage chemotactic factor, which must first be

released by neutrophils. In research evaluation, the immune activator LPS can trigger macrophages to activate NF- $\kappa$ B, which induces the expression of various inflammatory factors such as nitric oxide (NO), prostaglandins and cytokines. The inhibition of NF- $\kappa$ B occurs through I $\kappa$ B; without phosphorylation and degradation of this protein, NF- $\kappa$ B is unable to move from cytoplasm to the nucleus where it binds to DNA and induces transcription (the instructions to inflammatory markers to exert their effects). Interruption of this translocation may be how MSM modulates the inflammatory response (Kim, 2009). NF- $\kappa$ B is the link between many of the pro-inflammatory cytokines and is known to be activated in chronic inflammatory events.

Kim et al. demonstrated that MSM decreases inflammatory mediators such as TNF- $\alpha$ , IL-6, NO and prostaglandin E2 production in LPS stimulated murine macrophages (Kim, 2009). Another study showed that MSM can ameliorate experimental colitis by reducing the level of IL-1 $\beta$  (Amirshahrokhi, 2011). MSM pre-treatment also was shown to protect against hepatic liver injury by reducing TNF- $\alpha$  and IL-6 levels (Kamel, 2013).

Inflammasomes are molecular platforms activated upon cellular infection or stress that trigger maturation of proinflammatory cytokines such as IL-1 $\beta$ . Some of the best-identified inflammasomes include NLRP1, NLRP3, IPAF, and AIM2, with NLRP3 currently the most fully characterized. NLRP3 plays an important role in the innate response, but its over-expression has also been linked with various pathogenic and metabolic diseases including T2D, obesity, gout and CVD, making it a new target for therapeutic interventions (Ozaki, 2015).

In a study including human and mouse macrophages, MSM significantly attenuated NLRP3 activation with no effect on NLRP4 or AIM 2. MSM also attenuated the transcriptional expression of IL-1 $\alpha$ , IL-1 $\beta$ , IL-6 and NLRP3 and inhibited mitochondrial production of reactive oxygen species. MSM was shown to attenuate NLRP3 during the priming step, a step in which NLRP3 and pro-IL-1 $\beta$  are up-regulated through the NF- $\kappa$ B signaling pathway. By modulating the initial pro-inflammatory instructions, it is thought that down-regulated processes guiding associated pathogenic or metabolic diseases could be altered. Without priming, there is no inflammasome assembly and thus no secretion of pro-IL-1 $\beta$  and pro-IL-18 cytokines (Ahn, 2015).

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## MSM reduces oxidative stress and improves oxidative status

MSM has a very pronounced effect on oxidative status. Free radical and reactive oxygen species (ROS) pairing cellular components such as glutathione (GSH), catalase (CAT), myeloperoxidase (MPO) and superoxide dismutase (SOD) are all elevated in the presence of MSM (Amirshahrokhi, 2011, 2013; Kamel, 2013; Bohlooli, 2013; DiSilvestro, 2008), indicating the strengthening of anti-oxidative capacity.

One of MSM's most important roles in improving oxidative status is in the sparing of endogenous antioxidant glutathione (GSH). Glutathione is the major antioxidant produced by cells, participating directly in the neutralization of free radicals and ROS, as well as maintaining vitamins C and E in their active forms. It plays a major role in repairing DNA, protein synthesis, prostaglandin synthesis, enzyme activation, and has a major role in supporting the immune system. GSH is also known to increase the production of T lymphocytes, and cellular concentrations of GSH have been linked to T-cell numbers in healthy subjects (Kinscherf, 1994). In a study assessing acute lung and liver injury in mice, MSM increased tissue SOD and CAT activity in the presence of a toxic pro-oxidant threat, presumably by mitigating ROS. MSM also increased the synthesis of GSH (glutathione), which could indicate improved cell survival. Depletion of GSH from the cell renders it more susceptible to the effects of oxidants (Amirshahrokhi, 2013). Other research studies on animals have shown that MSM elevates glutathione levels (DeSilvestro, 2008; Maranon, 2008; Mohammadi, 2012).

When endogenous antioxidant levels are reduced, components related to cell-mediated immunity are increased, such as NF- $\kappa$ B. Changes to the body's level of antioxidants can trigger NF- $\kappa$ B, which turns on a host of oxidant respondents. GSH is inversely proportional to IL-1 $\beta$ , IL-8, and TNF- $\alpha$  (Grimble, 2013). Thus, it can be hypothesized that antioxidants exert an immune-enhancing effect by activating transcription factors that strongly associated with cell proliferation and an anti-inflammatory effect by preventing activation of NF- $\kappa$ B by oxidants produced during the inflammatory response. Cellular concentrations of GSH have also been linked to T-cell numbers in healthy subjects (Kinscherf, 1994).

Nuclear factor erythroid 2-related factor (Nrf2) has also been observed as having an emerging role in the regulation of oxidative stress. Nrf2 controls the basal and induced expression of an array of antioxidant response element-dependent genes to regulate the physiological and pathophysiological outcomes of oxidant exposure. Nrf2 exhibits multiple protective effects against chronic disease and has been the subject of major drug development (Ma, 2015). Knockout of Nrf2 in mice substantially increased the susceptibility of mice to a broad range of chemical toxicity and disease conditions associated with oxidative pathology (Kensler, 2007; Motohashi, 2004). In one study evaluating whether MSM would decrease HIV-1 Tat-induced oxidative stress in mouse neuronal cells, it was observed that MSM increased the translocation of Nrf2 to the nucleus in the presence of the Tat protein, suggesting that MSM may reverse the oxidative stress effects of this protein (Kim, 2015).

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## MSM may reduce seasonal allergies

In a multi-centered open-label trial on the efficacy of MSM for the treatment of seasonal allergic rhinitis (SAR), fifty subjects taking 2.6 grams of MSM per day for 30 days experienced a significant reduction in upper and total respiratory symptoms after seven days and lower respiratory symptoms at 21 days. At fourteen days, energy levels significantly increased, which continued through the duration of the trial (Barrager, 2002). It is hypothesized the efficacy of MSM for mitigating SAR may be due to its influence upon inflammatory cytokines, particularly IL-1 and TNF- $\alpha$ . Although histamine levels remained unchanged in the small subset analyzed, interruption in the chronic production of histamine is not ruled out as a possible mechanism. Most allergic responses are mediated by antigen-specific IgE and the products of tissue mast cells (e.g. histamine, which is the most potent mediator of IgE-mediated hypersensitivity). While some evidence indicates high, acute dosages of MSM may ameliorate allergy symptoms, it is the chronic supplementation of MSM which has yielded the greatest benefits, further qualifying MSM's role in fostering a healthy immune response to immune-triggering antibodies.

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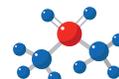
## About OptiMSM®

OptiMSM is the world's premier MSM and the only GRAS-affirmed source available in the world. Manufactured exclusively by Bergstrom Nutrition at a dedicated facility in Vancouver, Washington, OptiMSM is the result of a proprietary distillation process that guarantees an ultra-pure product. Bergstrom's stringent quality control ensures batch-to-batch consistency, a fully traceable production process, and includes independent third-party validation of identity and purity.

### OptiMSM is:

- The only U.S. made MSM
- GRAS-affirmed with FDA Notification and Letter of "No Objection"
- Kosher and Halal certified, Non-GMO, Non-BSE, gluten-free, allergen free, non-shellfish derived, and vegan
- Backed by extensive toxicology data and ongoing research
- Extremely safe; LD-50 > 17,000mg/kg BW
- Distributed internationally
- Backed by unmatched technical/manufacturing support

For more information and science updates, visit us at [www.bergstromnutrition.com](http://www.bergstromnutrition.com)



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