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### LEARNING OBJECTIVES

- Understand the basic physiology and pathology of inflammation.
- Recognize the two different types of feedback loops and identify how chronic inflammation may disrupt homeostatic set points.
- Correlate the impact of yoga therapy on cytokine levels, gene expression, and inflammatory response in research subjects.

## From Cytokine Storms to Feedback Loops: An Overview of Inflammation for Yoga Therapists

By Lilith Bailey-Kroll

A key element of yoga therapy is helping clients develop resilience practices to alleviate pain, reduce the effects of stress, and maintain health. The science and neurophysiology of pain and disease correlate with inflammation and thus, inflammation has traditionally been seen as the enemy, even though it is a natural part of the healing process. Inflammation precipitates a cascade of biomolecular events that cause cellular responses and sometimes ongoing damage that results in life-altering issues.

This article explores the roles of biology, immunology, neuroscience, and biotechnology to examine the inflammatory response and how biomedical science views the potential of yoga. Understanding the basic physiology and pathology of inflammation offers yoga therapists an increased ability to utilize scientific research to inform their practices, communicate and work with other clinicians, and support clients in advocating for their care.

## Stages of Inflammation

The inflammatory response was described by the Roman medical writer Aulus Cornelius Celsus more than 2,000 years ago as the signs of pain (*dolor*), redness (*rubor*), heat (*calor*), swelling (*tumor*), and loss of function (*functio laesa*). Since then, biomedical science has continued to unveil the complicated and fascinating process of inflammation. Inflammation is part of the immune system's response to harmful stimuli such as pathogens and damaged cells. Simply put, the immune system has two parts:

1. the innate immune system, which relies on physical and chemical barriers as well as white blood cells; and
2. the adaptive immune system, made up of lymphocytes that differentiate into B cells, T cells, and antigens.

If something gets beyond our first line of defense (the skin, other epithelial surfaces, and mucous membranes), the immune system kicks into high gear, chemical alarms are released, and the inflammatory response begins.

This response happens via a coordinated system or network between immune cells and blood vessels; inflammation works through a cascade of molecular signals that can be broken down into four phases<sup>1</sup>:

1. activation (induced by infection or tissue damage);
2. identification by pattern recognition receptors (PRR);
3. mediation (by cytokines, discussed below); and
4. restoration (repair or attempted repair of tissues affected by the mediators).

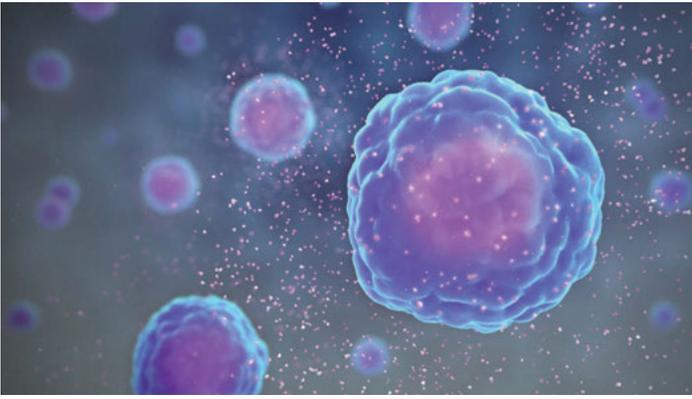
When an inflammatory inducer gets beyond protective barriers (activation), it is picked up by inflammatory sensors, the PRRs, on the surface of specialized cells (identification). PRRs recognize two subclasses of molecular activators:

1. pathogen-associated molecular patterns (PAMP), which respond to various pathogens; and
2. damage-associated molecular patterns (DAMP), which respond to tissue injury and cell damage.

When PAMPs/DAMPs activate the PRRs, they send alarm signals to both the innate and adaptive immune systems to initiate the production of inflammatory mediators.

Proinflammatory mediators are many and varied, but some can be generally classified as autacoids. These molecules act like hormones and can be derived from peptides (bradykinin), lipids (prostaglandins), endothelial cells (nitric oxide), or amino acids (histamine, serotonin). Additionally, mediators can be proteins such as cytokines (chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors). Cytokines are the broadcast system that cells use to communicate to the extracellular environment to say that either things are functioning normally or, in the case of injury or invasion, that a defense must be mounted.

Cytokines also play a role in promoting an overactive immune response, as seen with a cytokine storm, which occurs when white blood cells, specifically T-cells, become dysregulated and hyperresponsive. A prolonged cytokine storm in the lungs will flood the airways with immune-response cells and fluids causing, essentially, death by drowning. Since the early 2000s, infectious disease research has been looking at cytokine storms, but this is a relatively new



Cytokines being released from immune cells.

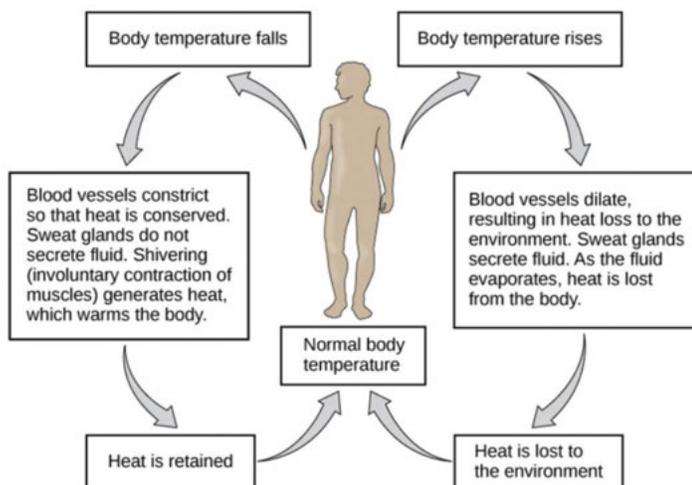
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focus in scientific research, and its complexity is still being clarified.<sup>2</sup> A cytokine storm, or cytokine cascade, is an important aspect of what we are currently seeing in more severe responses to COVID-19 (SARS-CoV-2) as well as in past epidemics, from the sudden acute respiratory syndrome (SARS-CoV-1) outbreak in 2002 to the H1N1 influenza A that caused the pandemic of 1918–1920.

## Feedback Loops and Their Roles in the Immune Response and Homeostasis

Like many processes in the body, inflammation ideally resolves once the inducer is eliminated, the infection is cleared, and damaged tissue is repaired. Once resolved, the body can move back into a state of homeostasis.

The idea of homeostasis in the biological sciences has changed since physiologist Claude Bernard first described it in 1849 as a “condition of free and independent life.” Currently, we understand the metabolic process of homeostasis as a set of regulatory points that respond to feedback loops and regularly reset to keep the composition of the internal environment constant. Specific set points include such processes as temperature; pH; and osmolality in terms of the concentrations of sodium, potassium, glucose, carbon dioxide, and oxygen in body fluids. A feedback loop is a biological occurrence where the system upregulates (positive feedback) or



Example of a homeostatic process: body temperature regulation

Image credit: Homeostasis: Figure 4 by OpenStax College, Biology, CC BY 4.0  
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downregulates (negative feedback). A common example used to illustrate a negative feedback loop is the way in which the body regulates temperature by such responses as sweating or shivering to return to homeostasis.\*

Current theories postulate that chronic low-grade inflammation is a result of functional alterations of the sensors and mediators leading to a disruption in the homeostatic set points or feedback loops. When there is insufficient clearance of the stimulus or pathogen—or a failure to eliminate the inducer—homeostatic disruption triggers proinflammatory events. Over long periods, failure to reset homeostasis creates a low-grade chronic inflammation that has been linked to chronic pain, obesity, type 2 diabetes, atherosclerosis, neurodegenerative diseases, and even cancers.

Additionally, a large and increasing volume of research suggests that microglia-neuron signaling is implicated in neuroinflammation and chronic pain hypersensitivity and is associated with depression, anxiety, schizophrenia, Alzheimer’s disease, Parkinson’s disease, and multiple sclerosis.<sup>3</sup> Microglia are a type of glial cell located in the brain and spinal cord. They are macrophages that act as the first and main form of defense in the central nervous system. As a white blood cell of the immune system, they are particularly ravenous actors, engulfing and digesting debris, microbes, cancer cells, and other foreign substances in a process called phagocytosis. Microglia act in a continuum between two presentations, or phenotypes:

- M1, classically activated macrophages that produce proinflammatory cytokines, and
- M2, alternatively activated macrophages that produce anti-inflammatory cytokines.

Current theory follows a two-hit hypothesis. In the first hit, microglial cells are primed through cellular injury, stress, early-life adversity, psychosocial stress, age, and infection. When a painful injury or event occurs, microglial cells move into the M1 phase and, rather than resolving the injury, play a role in what is called central sensitization. The International Association for the Study of Pain describes central sensitization as increased responsiveness of nociceptive neurons in the central nervous system to their normal or subthreshold afferent input. Thus, central sensitization reduces pain threshold, amplifies pain responses, and spreads pain sensitivity to noninjured areas. Studies have demonstrated the direct induction of macrophage central sensitization by the proinflammatory cytokines.<sup>4</sup> This is of particular interest in yoga therapy and may help to explain why some clients have difficult-to-resolve chronic pain or heightened sensitivity to pain.

## A Few Major Cytokines and What they Do

There are many cytokines, but the ones we will focus on are the three most commonly studied cytokines in chronic low-grade inflammation and neuroinflammation:

1. interleukin-1 beta (IL-1 $\beta$ ),
2. interleukin-6 (IL-6), and
3. tumor necrosis factor alpha (TNF- $\alpha$ ).

It often happens in science that the areas most frequently investigated are chosen simply because they were discovered first, and this is true of IL-1 $\beta$ , which was first purified in 1977. As a key mediator of inflammation, it is essential in immune resistance and response to

pathogens, but it also exacerbates damage in chronic disease. Recent studies indicate that IL-1 $\beta$  plays a pivotal role in many chronic low-grade inflammatory conditions such as atherosclerosis, cancer, and neuroinflammatory disease.<sup>5</sup> Additionally, spinal IL-1 $\beta$  contributes to central sensitization and inflammatory pain hypersensitivity due to its increased presence in the cerebrospinal fluid and rapid modulation of neurotransmitter receptors.<sup>4</sup>

IL-6 is of particular importance to yoga therapists because it is a myokine, a cytokine that can be produced from muscle tissue and significantly increase, in response to muscle contraction during exercise. When IL-6 is produced in muscles, it is anti-inflammatory and plays a role in the activation/inhibition of metabolic genes, induction of lipolysis (the breakdown of fat), and inhibition of insulin resistance as well as suppression of TNF- $\alpha$  production.<sup>6</sup> When IL-6 comes from monocytes or macrophages in response to infection, however, it creates a proinflammatory response as part of a feedback loop with TNF- $\alpha$  or with nuclear factor kappa B (NF- $\kappa$ B) activation.

**Understanding the basic physiology and pathology of inflammation offers yoga therapists an increased ability to utilize scientific research to inform their practices, communicate and work with other clinicians, and support clients in advocating for their care.**

TNF- $\alpha$  has a wide range of inflammatory actions. In the acute phase of inflammation it regulates immune cell response, can induce fever, cause severe weight loss (cachexia), and act as mediator in sepsis. It often acts in combination with IL-1 $\beta$  and IL-6. For example, in the liver TNF- $\alpha$  can increase the production of C-reactive protein, a common blood test that is often run in annual medical exams to determine the presence of inflammation. High levels lead to the skin plaques of psoriasis and the joint inflammation and swelling in rheumatoid arthritis. Additionally, a paracrine feedback loop mediated by TNF- $\alpha$  is closely associated with obesity and can increase insulin resistance as part of type 2 diabetes.<sup>7</sup> (Paracrine signaling is a type of intercellular communication that alters the chemistry and actions of nearby cells.)

TNF- $\alpha$  and IL-1 $\beta$  can act as inducers in a feedback loop with the activation of the NF- $\kappa$ B pathway. NF- $\kappa$ B controls transcription of DNA, cell survival, and inflammatory responses of proinflammatory mediators. It is well accepted that dysregulated NF- $\kappa$ B activation is a hallmark in chronic inflammatory diseases and that targeting the NF- $\kappa$ B-signaling pathway represents an attractive approach for anti-inflammatory therapies.<sup>8</sup> Yoga and other mind-body practices have the potential to encourage negative feedback loops, down-regulating the proinflammatory cytokines TNF- $\alpha$ , IL-1 $\beta$ , and IL-6 through decreased expression of inflammation-related genes and reduction of signaling through the proinflammatory transcription factor NF- $\kappa$ B.<sup>9</sup>

### How Does Yoga Therapy Fit into the Process?

The potential of yoga to reduce proinflammatory cytokines has

been established in three randomized controlled trials. The first, “Effects of 8-Week Hatha Yoga Training on Metabolic and Inflammatory Markers in Healthy Female Chinese Subjects: A Randomized Clinical Trial,” looked at participants on Day 1 and then again 2 days after the conclusion of the study.<sup>10</sup> The researchers found reduced IL-6 and IL-1 $\beta$  levels and hypothesized that, long term, a decrease in response may suppress whole-body chronic inflammation. Unfortunately, they did not have a follow-up at 3 months, which is when more significant changes were noted in the other studies. As yoga therapists, we are well aware that the benefits of yoga are often cumulative over the long term and not usually observable immediately, a factor that needs more consideration in yoga studies.

Another study, “Yoga’s Impact on Inflammation, Mood, and Fatigue in Breast Cancer Survivors: A Randomized Controlled Trial,”<sup>11</sup> involved a 3-month trial with testing done at baseline, immediately posttreatment, and 3 months posttreatment. In regard to TNF- $\alpha$ , IL-1 $\beta$ , and IL-6, immediate posttreatment testing showed no significant group differences; by 3 months posttreatment, however, the yoga group had significantly reduced cytokine levels, fatigue was lower, and vitality was higher. The results showed that “more frequent practice produced greater benefits in fatigue, vitality, and inflammation.”<sup>11</sup>

The final study, “Yoga Reduces Inflammatory Signaling in Fatigued Breast Cancer Survivors: A Randomized Controlled Trial,”<sup>12</sup> followed a 12-week Iyengar Yoga intervention and went deeper into testing by looking at gene expression through bioinformatic analysis.\*\* When the researchers evaluated circulating inflammatory activity, they found IL-1 $\beta$  and TNF- $\alpha$  levels were stable in the yoga group but significantly increased for the control group. No difference was noted for IL-6. The researchers proposed two potential pathways of how yoga might influence inflammatory processes: through increased sensitivity of the glucocorticoid receptors and through reduced sympathetic nervous system signaling. These ideas were echoed in a meta-analysis that concluded, “[Y]oga appears to be associated with improved regulation of the sympathetic nervous system and hypothalamic-pituitary-adrenal system in various populations.”<sup>13</sup>

### The Charge for Yoga Therapists

There’s an old African proverb that says, “If you want to go quickly, go alone. If you want to go far, go together.” None of us alone is ever as smart as all of us are together. For our communities to thrive and not merely survive, it is this author’s opinion that we must individually and collectively study, understand, and be able to communicate in the language of basic and clinical science. Becoming more knowledgeable and fluent in the pathways of inflammation, chronic pain, and disease will allow us to advocate more effectively with and for clients. This ability will

1. expand our skill set,
2. allow us to act as even better bridges between clients and their doctors,
3. improve our marketing, and
4. grow our businesses.

Our profession of yoga therapy is evolving. As a community, we have an opportunity to learn and grow together. I welcome you to

## Additional Resources

British Society for Immunology. *Bite sized immunology*. ([www.immunology.org/public-information/bitesized-immunology](http://www.immunology.org/public-information/bitesized-immunology))

Crash Course. *Immune system, part 1: Innate defenses*. (<https://youtu.be/GIJK3dwCWCw>)

ICU Advantage. *The COVID-19 cytokine storm explained*. ([https://youtu.be/AXP9qQ\\_a0fw](https://youtu.be/AXP9qQ_a0fw))

Khan Academy. *Inflammatory response (human anatomy and physiology, health & medicine)*. (<https://youtu.be/FXSuEIMrPQk>)

Kurzgesagt. *The immune system explained I—Bacteria infection*. (<https://youtu.be/zQGOCouBi6s>)



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\*Unlike a negative feedback loop, the processes of a positive feedback loop (e.g., the neurological and hormonal responses that result in childbirth) do not result in a return to homeostasis but rather a change in status.

\*\*Bioinformatics is a multidisciplinary analysis tool that combines biology, computer science, information engineering, mathematics, and statistics to interpret data.

contact me to continue the conversation and build the sangha (yogic community) that will support this work. [YTT](#)

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