

SPM Emerging Area

Inflammation resolution and surgery

Research Highlights

- Surgery is an inflammatory event. Higher levels of perioperative inflammation has been associated with increased risk of complications, poorer outcomes in patients with sepsis, and postoperative (postop) cognitive decline.¹⁻⁶
- Patients with many chronic inflammatory conditions have been shown to have lower levels of specialized proresolving mediators (SPMs). This places these individuals in an inflammation resolution deficit before going in for surgery.⁷⁻³³
- Circulating proresolving mediators have been shown to drop immediately postsurgery in humans. Lower levels of these SPMs were linked with higher levels of IL-6, which in this study was higher in individuals who experienced postop complications.³
- Emerging research shows that proresolving mediators impact multiple aspects of surgery recovery including enhance wound healing, reduce postop pain, prevent postop neuroinflammation and cognitive dysfunction, and enhance clearance of bacterial and fungal infection and increase survival in models of sepsis.³⁴⁻⁴⁵

Rationale for perioperative inflammation management

Surgery is an inflammatory event. Surgical incision, IV cannulation, intubation, and catheterization breach skin and epithelial defenses, eliciting an inflammatory response.¹ Potential exposure to infectious pathogens also induces an inflammatory response, and the type of anesthesia can play a role in modulation of the immune response. For example, in a mouse model of infection, isoflurane enhanced, whereas lidocaine delivery dampened immune response and inflammation-resolving activities.⁴⁶

The initial inflammatory response is intended to be robust and protective and evolved to eliminate invading organisms, to promote healing and regeneration of tissues, and in ideal conditions to return the body to homeostasis.¹ However, the initial inflammatory reaction to surgery is followed by a proportionate immune-suppressive phase, as anti-inflammatory mechanisms kick in to counteract the proinflammatory response.¹ The prevalence and severity of inflammation as well as postop complications vary with surgery type and also by comorbidities of the patient undergoing surgery.¹

Managing the magnitude of the initial proinflammatory response may have benefit postoperatively,¹ as:

- Systemic and neuroinflammation that occur in response to surgery are drivers of postop cognitive dysfunction²
- Circulating levels of the proinflammatory cytokine IL-6 were shown to be higher in patients who experienced a range of postop complications³
- Higher levels of inflammatory markers are related to sepsis severity and poorer outcomes for patients with sepsis⁴⁻⁶

- Balanced inflammatory response without excessive inflammation leading to immunosuppression is relevant for risk of infection and wound healing

Clinical conditions associated with a resolution deficit

Human studies have identified several conditions where levels of certain SPMs and/or the balance between proresolving and proinflammatory markers are reduced in circulation or tissues. Many patients with these chronic conditions can be candidates for surgery and are at greater risk of reduced resolution capacity before the challenge of surgery.

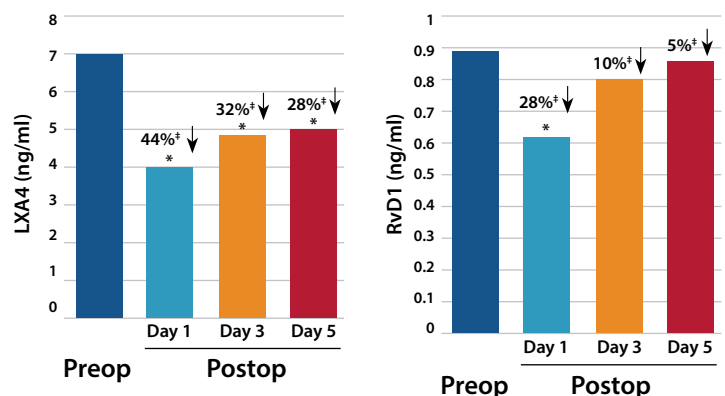
- Obesity⁷⁻⁹
- Endometriosis^{10,11}
- Asthma^{12-18,31}
- Cystic fibrosis¹⁹⁻²¹
- Peripheral arterial disease^{9,22}
- Cardiovascular disease^{23-25,32}
- Arthritis^{26,27}
- Alzheimer's disease^{28,29,33}
- Systemic Lupus Erythematosus (SLE)³⁰

Additionally, emerging data from animal studies shows that aging increases the magnitude of response to an inflammatory challenge, delays resolution, and is associated with dysregulated production of SPMs.⁴⁷

Proresolving mediators are reduced postoperatively in humans³

- In a group of subjects (n=41; 54% men; median age 57 years) undergoing liver resection, circulating levels of proresolving mediators LXA4 and RvD1 were shown to drop immediately postsurgery (Figure 1).
- Levels of the proinflammatory cytokine IL-6 increased significantly on day 1 postop and remained significantly elevated on days 3 and 5.
- Higher IL-6 concentrations were associated with postop complications.
- Higher circulating levels of LXA4 and RvD1 were linked with lower levels of IL-6.

Figure 1: Significant reduction in proresolving mediators in early postop phase.



[†]Percent change from preoperative (preop) values
^{*}Denotes significant differences from preop values

Figure adapted from Cata JP et al. *World J Surg Oncol.* 2017;15(1):152.³

Resolvin production pathways associated with uncomplicated recovery from trauma in humans⁴⁸

- Study subjects who had experienced blunt trauma (n=96) were classified as having complicated (Marshall Score > 6) or uncomplicated recoveries (Marshall Score < 6).
- Those with uncomplicated recoveries had higher expression of genes related to resolvin production in circulating blood leukocytes.
- Expression of genes related to leukotrienes, a group of proinflammatory lipid mediators, was lower in those with uncomplicated recovery
- Additionally, the ratio of leukotriene/resolvin gene expression score was also significantly reduced in the uncomplicated recovery group.

Emerging preclinical animal and cell data highlights the impact of SPMs in aspects of surgery recovery

RvD1 reduced postincisional pain in animal

- RvD1 reduced postincisional pain³⁴
- RvD1^{34,35} and RvD2³⁵ reduced hypersensitivity in a models of persistent postop pain
- SPMs have been shown to have analgesic effects in several models of inflammatory and neuropathic pain³⁶ and modulate TRP channels involved in detecting and inducing pain³⁶

Neuroinflammation and prevention of postop cognitive dysfunction in mice

- MaR1³⁷ or RvD1³⁸ treatment of mice undergoing orthopedic surgery prevented hippocampal memory function reduction that occurred with surgery and reduced markers of neuroinflammation.
- MaR1 treatment in orthopedic surgery mouse model prevented loss of blood brain barrier integrity that occurred with surgery³⁷

Enhanced wound healing in mice

- RvD1 treatment of mice with diabetic wounds reduced time to wound closure³⁹
- RvE1, RvD1, or RvD2 treatment in dermal wound model reduced wound healing time by an average of 6-9 days⁴⁰

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