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Editorial

Editorial: **Preventing postoperative ileus with *n*-3 PUFA**

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▶ SEE CORRESPONDING ARTICLE ON PAGE 231

Gastrointestinal ileus is most commonly initiated by direct mechanical disturbances to the bowel during abdominal surgery. These disturbances trigger a classic acute inflammatory response associated with the induction of arachidonic metabolism and the production of prostaglandins and leukotrienes. As outlined in **Figure 1**, these agents induce a vascular response comprised of increased permeability and endothelial expression of selectins and integrins. Proinflammatory cytokines and chemokines released within the inflamed tissue recruit a predominantly PMN infiltrate. The resulting inflammatory cascade produces mediators that impair neuromuscular communication and have direct inhibitory effects on smooth muscle contractility, leading to the typical symptoms of bowel stasis: abdominal distension, nausea/vomiting, and the inability to pass gas or stool. Whereas the mechanisms that induce ileus are fairly well understood, those that drive recovery are less clear [1]. In a recent manuscript, Stein et al. [2] provide evidence that lipid mediators derived from endogenous PUFA metabolism play an active role in the process of resolution. Furthermore, perioperative exposure to exogenous *n*-3 PUFA was found to attenuate dysmotility in a murine POI model.

For many years, resolution of inflammation was considered to be a relatively passive event, occurring as anti-inflammatory mediators and antioxidants, such as IL-10 and heme oxygenase 1, suppress proinflammatory mediator production. Recovery occurs as the initiators of inflammation wane, and chemoattractants are cleared. With the discovery of naturally occurring lipid mediators that have anti-inflammatory and proresolving properties, it has become clear that resolution is an active programmed response [3, 4]. Biosynthesized from dietary ω-3 essential fatty acids, these lipids are generated as structurally distinct families of signaling molecules called resolvins, protectins, and maresins. Collectively termed SPMs, observations from animal models indicate that SPMs function as agonists, activating biologic pathways that inhibit cellular recruitment and enhance scavenging and clearance of apoptotic PMN by macrophages.

With the use of a mouse model of POI, Stein et al. [2] demonstrated that the 3 classes of SPM and their upstream precursors DHA and eicosapentaenoic acid were significantly up-regulated within the intestinal muscularis, 24 h following surgical manipulation. The most abundantly expressed SPMs were the DHA-derived molecules resolvin D2 and PDX. Both were shown to be produced via the activity of 12/15-lipoxygenase expressed in infiltrating monocytes. Preoperative intravenous infusion of DHA-enriched *n*-3 PUFA emulsion significantly reduced cellular inflammation and prevented POI in this model. PDX, delivered intraperitoneally immediately postoperatively, showed a similar effect. These observations promptly beg the question: can these pathways be harnessed to prevent POI in the clinical setting?

As in mice, uncomplicated ileus in humans is generally self limiting, with bowel motility returning in 3–5 d. As such, POI is considered by some to be a normal physiologic response and should be allowed to run its course. Contrary to this premise are observations that induction of ileus is not limited to direct bowel manipulation [5]. Circulating mediators arising from injured tissue following major orthopedic surgery or physical trauma readily traffic to the gastrointestinal tract, where they can induce the inflammatory events that cause bowel stasis. To the degree that ileus can induce mucosal barrier break and bacterial translocation, followed by loss of smooth muscle contractility with static and distended loops of gas- and fluid-filled bowel, this suggests that the tissue is not at rest but rather in distress.

Advances in the management of surgical patients through the use of endoscopic techniques, reduced administration of opioid analgesics, and early ambulation and food intake have reduced the incidence of severe ileus, which in the past, plagued many postoperative patients. Nevertheless, even moderate ileus remains a significant source of patient discomfort. Bowel stasis of more than a few days' duration can contribute to cardiovascular and pulmonary system stress, increase the risk of anastomosis leak, and stimulate bacterial overgrowth of the intestine. Particularly vulnerable are the trauma patient, the elderly, and patients with cardiovascular,

Abbreviations: DHA = dososahexaenoic acid, *n*-3 PUFA = ω-3 polyunsaturated fatty acid, PDX = protectin DX, PMN = polymorphonuclear, POI = postoperative ileus, SPM = specialized proresolving mediator

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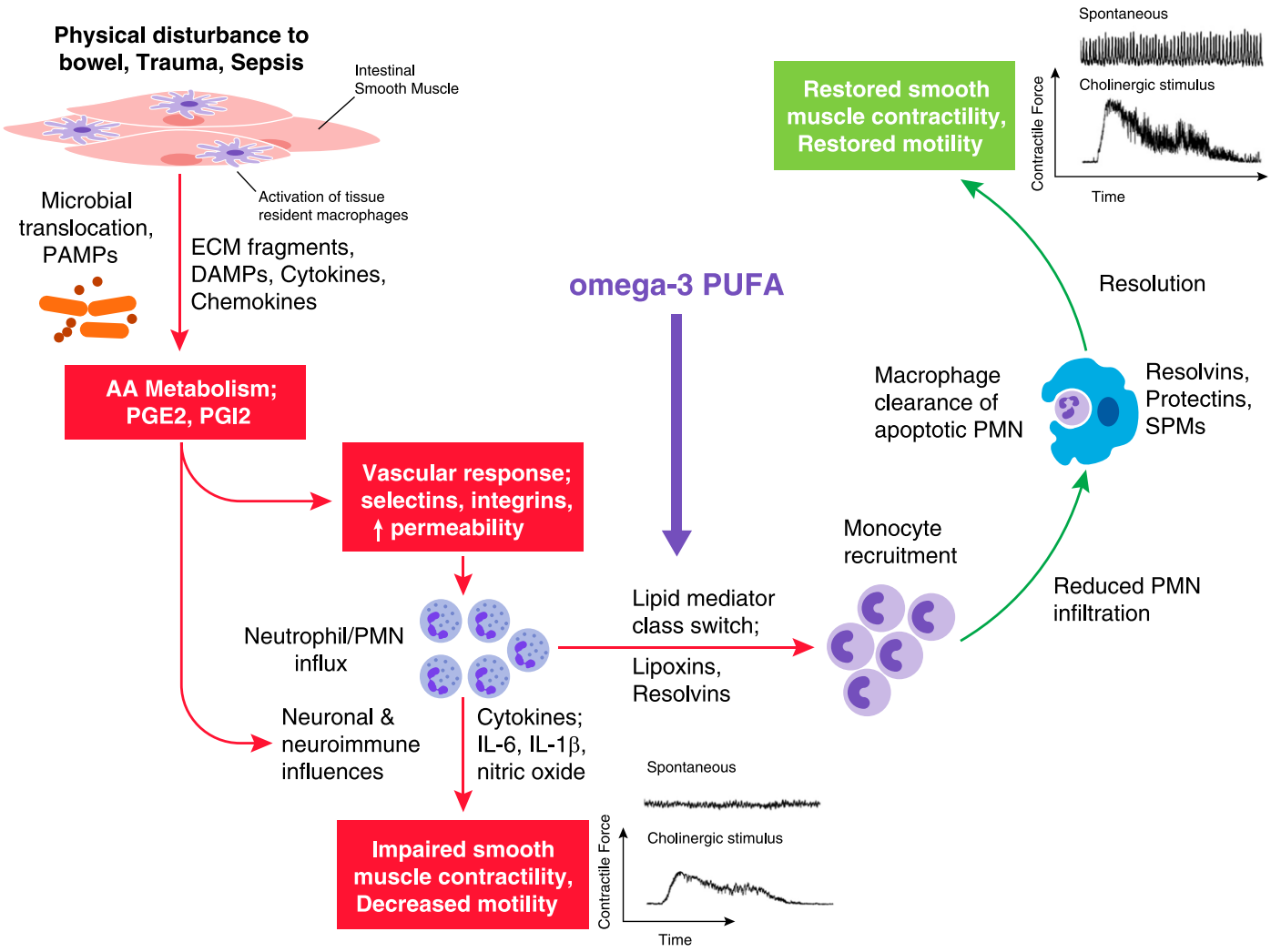

Figure 1. The inflammatory response and proposed mechanism of resolution in POI. Disturbances to the bowel from direct physical contact or from circulating mediators released by trauma or sepsis result in the activation of tissue resident macrophages and induction of an eicosanoid-dependent acute inflammatory response. Initiation of the vascular response, as well as altered neuronal and neuroimmune signaling, culminates in the direct inhibition of intestinal smooth muscle contractility and a reduced capacity to respond to neuronal stimuli, producing the signs and symptoms of ileus. It has been proposed recently that the self-resolution of POI occurs as a result of a lipid mediator class-switch from eicosanoid production to that of lipoxins and resolvins. Derived from *n*-3 lipid stores, these mediators suppress cellular inflammation, induce clearance, and promote restoration of tissues to homeostasis. Administration of exogenous *n*-3 lipids before inflammation is fully advanced has the potential to prime the resolution phase and prevent or reduce the magnitude and duration of ileus. PAMPs, Pathogen-associated molecular patterns; ECM, extracellular matrix; DAMPs, damage-associated molecular patterns, AA, arachidonic acid.

pulmonary, or metabolic comorbidities. The prevention of or minimization of ileus, especially in those at greatest risk, would seem a laudable goal.

It must also be recognized that the reduction of health care costs is a high priority, given the current U.S. economic environment [6]. In all cases of ileus, release from the hospital is dependent on return of bowel function. The reduction of hospital stay by as little as 1 d can provide substantial cost savings. However, the identification of which patients to treat poses considerable challenges. It is well recognized that the severity of ileus correlates with the degree of tissue disturbance. Thus, benchmarks might be identified, depending on the extent of the surgical intervention and the existence of comorbidities. Nevertheless, even "physiologic" ileus can progress in an unpredictable fashion to adopt a pathologic course. With the consideration of the potential for improved patient comfort and cost savings, it could be argued that there is merit in treating patients undergoing surgery for all but the least invasive procedures.

Studies in animal models have shown that inflammation progresses rapidly, within a few hours postoperatively. Therefore, interventions that inhibit the inflammatory response need to be implemented perioperatively to have a maximal effect. This presents a high bar in terms of tolerability and safety for the development of treatment strategies. particularly for POI, where all but the most severe cases are expected to resolve eventually without treatment. Orally administered drugs are less desirable as a result of pre- and perioperative nil per

os protocols, and the risk of inducing pathology or contributing to an existing one must be minimal. Perioperative administration of DHA-enriched *n*-3 PUFA could present a cost-effective way to meet these requirements.

In humans, dietary supplementation with *n*-3 PUFA is regarded as beneficial for the prevention and treatment of atherosclerosis and thrombosis and chronic inflammatory diseases, such as rheumatoid arthritis, metabolic syndrome, and psoriasis. Clinical trials indicate that they are well tolerated and have a good safety profile [7]. Whereas orally administered DHA-enriched *n*-3 PUFA can take several days to weeks to reach maximum effect in more chronic conditions, when taken as an intravenous infusion during acute inflammation, the desired effect can be achieved in a few hours [8, 9]. The efficacy of PDX has not been well studied in humans but shows similar effects in preclinical models. Further study is warranted to determine whether PDX delivered alone in an intravenous formulation would provide equal or better resolving effects.

In conclusion, perioperative intravenous infusion, followed by oral supplementation of DHA-enriched *n*-3 PUFA, may provide benefit in resolving POI with low risk of adverse effects.

DISCLOSURES

The authors declare no conflicts of interest. The views expressed here are those of the author(s) and not necessarily those of the companies or institutions that employ them.

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Editorial: **Fish neutrophils meet proresolving eicosanoids**

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► SEE CORRESPONDING ARTICLE ON PAGE 241

The clearance of pathogens and the initiation of inflammation by neutrophils are 2 well-known biologic processes. However, growing evidence suggests that besides their classically described self-elimination by apoptosis, these cells play an active role in the resolution of inflammation. For example, 3 subpopulations of neutrophils were recognized early in mice infected with *Staphylococcus aureus*, namely PMN-N (normal, no cytokine production), PMN-I (producing IL-12 and CCL3), and PMN-II (producing IL-10 and CCL2) [1]. The polarization of neutrophils, as occurs in macrophages, was later confirmed in the context of infection [2] and tumor [3] immunity. In this issue of *JLB*, with the use of a self-resolving zymosan peritonitis model, Barreda and colleagues [4] show that neutrophils from the teleost fish goldfish (*Carassius auratus*) are actively involved, not only in the proinflammatory phase of the inflammatory process but also in its resolution, suggesting that the complex role of neutrophils in inflammation and their ability to polarize existed before the divergence of fish and tetrapods, >450 million yr ago. Interestingly, goldfish neutrophils are the main source of the proinflammatory eicosanoid LTB_4 during the acute inflammatory phase, as well as of the proresolving eicosanoid LXA_4 during the proresolving phase of the inflammatory process. In mammals, neutrophil-derived LTB_4 is involved in the initial stages of neutrophil recruitment from blood to inflamed tissues [5]. However, the main eicosanoids produced in vitro by human neutrophils after activation by a variety of inflammatory stimuli are proinflammatory TXB_2, the inactive metabolite of TXA_2, and PGE_2 [6]. More recently, it has

Abbreviations: hpi = hours postinfection, LTA/B_4 = leukotriene A/B_4, LXA_4 = lipoxin A_4, PMN = polymorphonuclear leukocyte, ROS = reactive oxygen species, TXA/B_2 = thromboxane A/B_2

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