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REVIEW ARTICLE

Immune mediators of postoperative ileus

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Abstract
Clinical background In all patients undergoing abdominal surgery, a transient phase of interruption of bowel motility, named postoperative ileus (POI) occurs. POI is often accepted as an unavoidable "physiological" response and a self-limiting complication after surgery although it has a significant impact on patient morbidity with prolonged hospitalization and increased costs. Annual economic burden has been estimated as much as US $1.47 billion in the USA (Iyer et al. in J Manag Care Pharm 15 (6):485–494, 2009).
Pathophysiology The pathophysiology has been elucidated within the last decades, demonstrating that both, neurogenic and inflammatory mechanisms are involved in response to the surgical trauma. It is now generally accepted that POI pathogenesis processes in two phases: a first neurogenic phase is accountable for the immediate postoperative impairment of bowel motility. This is followed by a second immunological phase that can last for days and mainly affects strength and length of POI. More recent findings demonstrate a bidirectional interaction between the nervous and the immune system, and this interaction significantly contributed to our present understanding of POI pathophysiology. Although nerval mechanisms have a significant impact in the early phase of POI, the contribution of the immune system and subsequently its manipulation has risen as the most promising strategy in prevention or treatment of the clinically relevant prolonged form of POI.
Aims The present manuscript will give an update on the inflammatory responses, the involved cell types, and participating immune mediators in POI.

Keywords Postoperative ileus · Intestinal inflammation · Macrophages · Mast cells · Dendritic cells

Abbreviations

ACh	Acetylcholine
DAMP	Danger-associated molecular patterns
CO	Carbon monoxide
COX-2	Cyclooxygenase-2
Egr-1	Early growth response protein-1
HO-1	Heme oxygenase-1
iNOS	Inducible nitric oxide synthase
ME	Muscularis externa
MCP-1	Monocyte chemoattractant protein-1
NO	Nitric oxide
POI	Postoperative ileus
PPAR	Peroxisome-proliferator-activated receptor
PUFA	Polyunsaturated fatty acids
TLR	Toll-like receptors

Clinical relevance of POI

Postoperative ileus (POI) has been accepted as a physiological complication after abdominal surgery, and it comes into clinical focus mainly when occurring in its prolonged form. Modern multimodal perioperative approaches like "fast-track" protocols have been developed to improve postoperative morbidity. However, POI occurs still frequently and patients suffer from nausea and vomiting up to the risk of aspiration once POI occurs. Therefore, POI is associated with reduced patients satisfaction and increased length of

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hospital stay. The accompanying cost for patients´ health care has been estimated at US $1.47–1.75 billion in the USA [1, 2]. In a recent study of Iyer et al., 17,000 patients undergoing colectomy were analyzed for occurrence of POI [1]. The length of hospital stay was significantly prolonged (13.8 days) in patients with POI compared with patients without POI (8.9 days). Asgeirsson et al. demonstrated an occurrence of POI in 24% (84% primary POI) in a retrospective analysis of 184 colectomized patients. The total costs were significantly higher for patients with POI (US $16,612 vs. $8,316) [3].

Pathophysiology

Normal bowel motility is a complex regulated interaction between intrinsic and autonomic nerves and individual and coordinated smooth muscle cells activity. The normal motility is mainly determined by the migrating motor complex which regulates bowel motility between meals. Furthermore, hormones play also an important role. Although the complex interactions between all players are still poorly understood, multiple factors have been identified to the pathogenesis of POI. (A) An immediate response is the activation of neurogenic, sympathetic—mostly adrenergic—pathways [4] activated by nociceptive stimuli during surgery (skin incision and bowel manipulation) [5–7]. Additionally, missing parasympathetic innervation was also described. (B) While the twentieth century was mostly dominated by research about inhibitory nerval signaling, first evidence of an immunological response to abdominal surgery was shown by Kalff et al. in an animal model of intestinal manipulation after laparotomy in the late 1990s [8–10]. In 2003, its relevance was also confirmed in humans [11]. Therein, infiltration of leukocytes was shown as a consequence of surgical trauma and linked to the postoperative dysmotility in late phase POI, beginning 3–4 h after surgery and lasting for several days. While the inhibitory adrenergic nerve signaling ends mostly with the end of the operation, this immunological late phase of POI is responsible for sustained clinically relevant gastrointestinal dysmotility. Interestingly, the inflammatory response to the surgical trauma is mostly limited to the tunica muscularis and not the lamina propria mucosae. However, the inflammation also spreads from manipulated to unmanipulated areas of the gastrointestinal tract. (C) A third factor is the intra- and postoperative use of analgesics, primarily of opioids that bind to μ-opioid receptors in the gastrointestinal tract, resulting in a postoperative dysmotility.

While the neurogenic phase (A) and pharmacological factors (C) have been extensively reviewed elsewhere [12–15], the present manuscript focuses on the inflammatory events involved in the genesis of POI.

Classical and non-classical immunocytes in POI development

Resident tissue macrophages

Mikkelsen et al. first identified resident immunocytes within the subserosal and Auberbach's plexus of the intestinal wall. Functionally, these cells were able to ingest FITC dextrane molecules from the circulation but a role in immune defense was not supported at this time. Nearly 10 years later, the group of Bauer and Kalff rediscovered this cells in rats and demonstrated a cell-specific expression of CD163, the macrophage scavenger receptor (ED2) [16]. Although other immunocytes populations could also be identified in the untreated tunica muscularis, ED2-positive macrophages were the most abundant population [17]. Eskandari et al. demonstrated that the resident muscularis macrophages express the CD14 molecule that is necessary for LPS signaling after binding to its receptor [18]. LPS challenge led to cellular activation and production of inducible nitric oxide synthase (iNOS) thereby demonstrating that these cells are able to contribute in immunoresponses [19, 20]. The immunological competence of these normally quiescent macrophages in POI development has been shown 1 year later in 1998 in a rat model of intestinal manipulation. Expression of the leukocytes function-associated antigens (LFA-1) has been localized to the resident muscularis macrophages 1 h after intestinal manipulation. This was the first indication that these cells could play a significant role in the onset of POI. In several rodent studies, Mikkelsen et al. have shown that these macrophages show different phenotypes and numbers depending on mice's age [21, 22], their intramuscular localization [23], and their distribution along the gastrointestinal tract [21]. Pharmacological inhibition and depletion as well as genetically based deficiency in colony stimulating factor-1 mutant mice showed that these cells play a key role in the onset of POI [24]. A follow-up study demonstrated immediate p38 mitogen-activated protein kinase (MAPK) phosphorylation after intestinal manipulation that was absent in mice lacking macrophages within the muscularis externa (CSF-1 mutant mice). As p38 MAPK activation is crucial for induction of many proinflammatory genes, preoperative application of a macrophage specific inhibitor of this pathway, named CNI-1493, consequently prevented mice from POI [25]. Importantly, the resident macrophages also play a significant role in anti-inflammatory responses that are triggered via cholinergic vagus nerve signaling.

Dendritic cells

Flores-Langarica et al. demonstrated that a significant fraction of the resident muscularis macrophages express the

dendritic cell (DC) markers CD11c and DEC-205 and were able to present antigens and stimulate CD4 and CD8 T cells. The expression of classical DC activation molecules like CD80 and CD86 and DEC-205 was upregulated following microbial stimuli. The presence of DC function within the normally quiescent muscularis externa is a hallmark in POI propagation. A present study of our group demonstrates that these DC are involved in T cell activation after intestinal manipulation, subsequently inducing dissemination of the local inflammation along the complete gastrointestinal tract, also to unmanipulated parts [26]. This phenomenon was already described by Schwarz et al., who demonstrated that a selective jejunal manipulation caused a pan-enteric inflammation and dysmotility [27]. The recently illuminated mechanism shows that DC-derived IL-12 activates T helper type 1 memory cells which finally activate resident muscularis macrophages via interferon γ. Interestingly, after becoming activated these specialized T cells leave the manipulated parts of the gut, probably via the portal blood and mesenteric lymph flow and recirculate via an intestine specific receptor (CCR9) into the whole gastrointestinal tract, which includes also unmanipulated areas (Fig. 1). This indicates that DC activation occurs before macrophage activation. However, the initial factor leading to DC activation and a time line within the initial phase has not been shown in this study. Furthermore, in depth analyses of the phenotype and function of the resident macrophages are still missing. Nevertheless, the mixed DC-macrophage phenotype probably completes the immunological competence of the muscularis externa by essential functional properties of both cell populations (i.e., phagocytosis and antigen presentation).

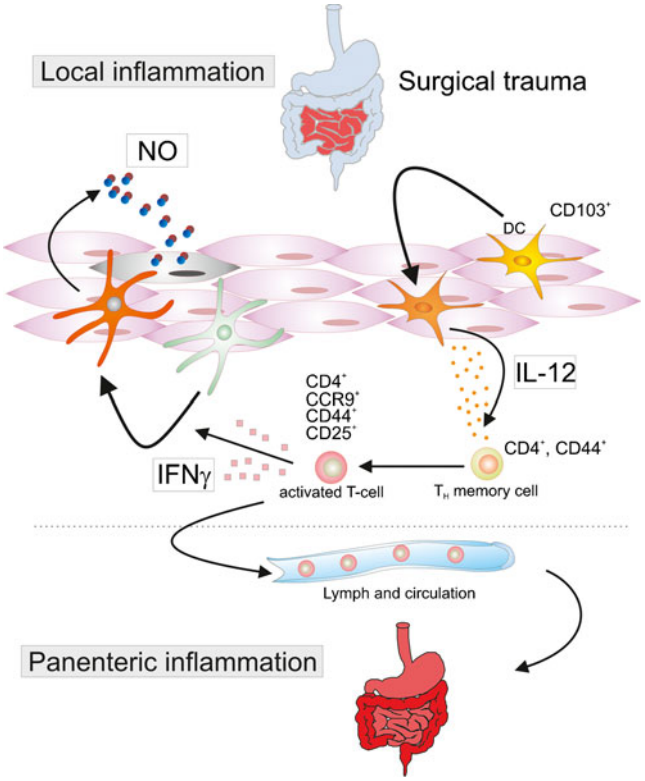

Fig. 1 Dissemination of local surgery-induced inflammation along the entire gastrointestinal tract. Intestinal handling (surgical trauma) induces IL-12 release from resident $CD103^+$ dendritic cells that is able to activate quiescent T_H memory cells. These activated T cells release interferon-γ (*IFN-γ*) that leads to local activation of resident muscularis macrophages and a subsequent vast nitric oxide (*NO*) production. Finally, NO inhibits smooth muscle contractility leading to a local dysmotility. Additionally, the activated T cells are able to enter circulation via lymph and blood vessels and relocate to the intestinal wall in a CCR9-dependent manner. This relocation spreads the locally induced inflammation along the complete gastrointestinal tract (also the unmanipulated bowel), finally leading to a panenteric inflammation and POI

Mast cells

Another important immunocyte population associated with POI are mast cells. In rodents, they are abundant in the lamina propria mucosae, the mesentery and the peritoneal cavity, but cannot be detected in the muscularis externa or submucosa of jejujum, ileum and colon while they are abundant in the stomach wall [9, 28, 29]. In humans, mast cells are present within the lamina propria mucosae (2–3% of all cells) and slightly less in the submucosa (1%) [30]. In the muscularis externa, they appear only sporadically. It is noteworthy to emphasize this mast cells deficiency within the muscularis externa and submucosa of mice's small bowel and colon, as many studies addressing mast cells function in POI have been performed in mice. This indicates that mast cell contribution in POI development originates from mesentery, peritoneal, or lamina propria mucosae mast cells. In comparison, the amelioration of postoperative gastroparesis by mast cell stabilization as shown by de Jonge et al. [31] could be indeed mediated by effects on stomach wall resident mast cells.

Mast cells lay in close proximity to blood vessels and afferent nerve fibers, indicating that liberation of mast cell derived mediators could affect nerval signaling and vascular perfusion as well as translocation of these mediators into the circulation. Their close relation to enteric nerves and afferent nerve fibers is of special interest and there is significant evidence for mast cell nerve interactions in the pathogenesis of functional and inflammatory bowel disorders. In this context some works demonstrated that mast cells are involved in the pathogenesis of postoperative motility dysfunctions, i.e., gastroparesis and POI in mice and humans [31, 32]. The use of the mast cell stabilizer ketotifen accelerated postoperative gastric emptying and significantly reduced neutrophil extravasation into small bowel muscularis externa. Furthermore, mice lacking mast cells due to a mutation in the c-kit receptor gene also demonstrated a reduced postoperative neutrophil infiltration [31]. Reconstitution of bone marrow derived mast cells resulted in regular

neutrophil postoperative infiltration compared with wildtype animals. A recent work also demonstrated that mast cell presence is involved in the increase of postoperative epithelial permeability [33]. The postoperative increase of small particle flux across the intestinal epithelium was abolished in mast cell-deficient W-sh mice. The contributing mast cell-derived mediators have to be identified in future work [34]. Participation of other mast cell-derived (classical) proinflammatory mediators besides the preformed and spontaneously released (proteases and histamine) is also likely [35].

Non-classical immunocytes

Without doubt, classical immunocytes as macrophages, dendritic cells, and mast cells are the most important immunocytes in POI development. However, in the last years there is growing evidence about the contribution of non-classical immunocytes in a variety of inflammatory diseases. With regard to the muscularis externa as the major effector organ in POI, smooth muscle cells, enteric neuronal cells as well as interstitial cells of Cajal have been shown to exert—additionally to their regular functions in intestinal homeostasis—also immunoregulatory responses upon stimulation. Therefore, these cells can be also determined as non-classical immunocytes.

Immunohistochemical stainings identified the Toll-like receptors (TLR) 3, 4, and 7 in enteric neuronal cells from the myenteric plexus [36, 37], indicating a possible role in innate immune response. Functional TLR 4 receptor signaling has further been shown by our group demonstrating an increase of iNOS and IL-1β gene expression in rat intestinal smooth cells cultures [38]. Furthermore, sphingosine-1 phosphate, produced by COX-2 activation during inflammation, demonstrated activation of the early growth response gene transcription factor 1 (Egr-1). Egr-1 has been shown before to contribute in POI development wherein a strong immunoreactivity in smooth muscle and neuronal cell nuclei was shown after intestinal manipulation [39]. Although non-classical immunocytes significance has not been evaluated in regard to their netto effect in the overall inflammatory response, these works demonstrate their functional involvement in innate immune responses. However, further research is needed to address their involvement in POI. With exception of the in vitro models of mechanical alteration [38], the lack of valuable in vitro models for the surgical bowel manipulation is indeed a crucial factor.

Mediators

Adhesion molecules, chemoattractants, and cytokines

After the first evidence for an immunological-driven pathophysiology of POI, many publications demonstrated the roles of individual inflammatory mediators in this disease. All approaches used the standardized model of surgical small or large bowel manipulation. A first focus was set on adhesion molecules and chemoattractant proteins (i.e., ICAM-1, P-selectin, LFA-1, Mac-1, and MCP-1), responsible for the attraction and extravasation of circulation immunocytes into the manipulated muscularis externa [10, 24]. Kalff et al. demonstrated that ICAM-1 transcription is strongly induced within the muscularis externa by surgical manipulation. P-selectin, an adhesion molecule constitutively expressed and stored in endothelial cells' cytoplasm, is rapidly mobilized to the plasma membrane.[10] Inhibition of ICAM-1 by specific antisense oligonucleotides as well as depleting antibody treatment ameliorated postoperative ileus in rodents [10, 40]. Inhibition of these molecules prevented the vast immunocyte infiltration and ameliorated POI. Additionally, MCP-1 significance on altered intestinal motility has been shown in a related model of endotoxemic ileus.

Many of these adhesion molecules are induced by interleukin signaling and contribution of a variety of cytokines has been shown. Most analyses were done on the transcriptional level, demonstrating a rapid induction of several genes immediately after intestinal manipulation. Others presented detailed expression time curves of up to 20 different mediators measured within an ELISA or multiplex protein assay [39, 41] that were detected either in muscularis culture supernatants or lysates. Interestingly, POI development is obviously driven by a T_H1 immunoresponse as alterations of the prototypical T_H2 cytokines IL-4, IL-5, or IL-13 have not been found. [39, 41] While most works solely demonstrated expression profiles of selected cytokines, recent publications pointed out functionally significance of individual cytokines in the pathogenesis of POI. In 2005, our group demonstrated that IL-6 is a major cytokine in POI development that leads to nuclear activation of the STAT3 transcription factor [42] which is involved in counter regulatory anti-inflammatory signaling. In the same year de Jonge and colleagues showed that the Jak2-Stat3 signaling pathway is activated by vagus nerve signaling, which is also known as the cholinergic anti-inflammatory pathway. Together these works depict complex orchestration of proinflammatory and anti-inflammatory reaction, both depending on each other.

Another prominent proinflammatory cytokine is IL-12 that is upregulated after intestinal manipulation [26, 41]. Importantly, IL-12 release from $CD103^+CD11b^+$ dendritic cells promotes activation of macrophages with subsequent IFN-γ release and migration of T_H1 memory which is an early event in POI development and dissemination along the gastrointestinal tract.

The importance of a third major cytokine was shown by the Bauer group, investigating the effect of IL-10 deficiency in a mouse model of POI. IL-10 knockout mice suffered from a prolonged POI persistence with dramatically increased

levels of IL-6, IL-1α, TNF-α, IL-1, and IFN-γ compared with wildtype mice. Besides IL-10 other molecules and cell types play a role in the counter regulation and resolution of POI. This aspect is discussed in detail addressed in a separate chapter below.

Kinetic active effector molecules

While the molecules mentioned above are responsible for induction, maintenance, and regulation of the inflammatory response to the intestinal manipulation, they have mostly indirect effects on intestinal motility. However, other factors are produced affecting POI in a direct manner. Two important molecule classes are gasotransmitters like nitric oxide (NO) as well as prostanoids. NO is produced by NO synthases (NOS) of which three different subtypes exists: endothelial, neuronal, and inducible (iNOS) NOS. In contrast to the constitutively expressed endothelial and neuronal forms, the high-output iNOS form is strongly induced in inflammation and leads to a vast production of NO. Protective properties of NO include antibacterial defense and vasodilatation while it also functions as an important inhibitory neurotransmitter in gastrointestinal motility. Significance of NO in POI has been addressed in rodent models. Kalff et al. showed that iNOS transcription was strongly induced in the muscularis externa and lamina propria mucosae [43]. In the latter, iNOS mRNA levels peaked within the first 60 min and decreased under baseline levels of unmanipulated control animals at 3–24 h. In contrast, iNOS transcription within the muscularis externa continuously increased within 12 h after surgery and slowly set to baseline levels within 24 h after surgery. The immediate response within the lamina propria mucosae, which is highly susceptible to ischemic insults, indicates a rapid perioperative counter regulation of surgery-induced hypoperfusion [44]. In late phase POI, increased NO production probably stabilizes recovered mesenteric perfusion and is even higher as under control condition (laparotomy without intestinal manipulation) in rats [45]. One would expect that NO also contributes to antibacterial defense, especially in late POI when bacterial translocation into mesenteric lymph nodes can be observed. However, the significance of the antibacterial properties has never been investigated in POI.

Another key enzyme in inflammatory responses is COX-2. In contrast to its constitutively expressed isoform COX-1, COX-2 expression and activity is strongly increased during inflammation. Classical COX-2 activation leads to metabolism of inner surface membrane-bound arachidonic acid to prostaglandin H2 which is subsequently processed to different prostanoids (i.e., prostaglandins (PG) and thromboxanes). First effects of prostaglandins on intestinal motility have been described by Bennett and colleagues in the 1960s [46–48]. Three different prostaglandin isoforms stimulated gastrointestinal motility with different degrees in the stomach, the small and the large bowel. One form, PGE2E has been shown by another group to induce strong colonic longitudinal muscle contractions but relaxation of the circular muscle layer [49]. This indicates a complex regulation of gastrointestinal motility. Schwarz et al. demonstrated that COX-2 gene transcription is strongly induced by intestinal manipulation and both, selective COX-pharmacological COX-2 inhibition or gene deficiency, alleviated POI in mice [50]. Pan-prostaglandin levels within the muscularis increased over time and immunohistochemical staining demonstrated a strong COX-2 protein expression in infiltrating monocytes and enteric neurons. This indicates a netto synthesis of intestinal motility inhibiting prostanoids during POI. However, detailed prostanoid profiling has never been performed and therefore distinct effects of single prostanoid subtypes remain to be elucidate.

Transcription factors and other mediators

Regulation of gene expression during inflammation is complexly orchestrated. A variety of transcription factors (TF) act as downstream regulators after binding of inflammatory mediators to their specific receptors and induce de novo synthesis of additional proinflammatory molecules. Typical pleiotropic immunoregulatory TF that have been analyzed in POI are NF-κB, the STAT family of TF, PPARγ, and EGR-1.

The STAT family is composed of seven proteins and interacts upstream with JAK proteins of which four are known. A prominent member is the isoform STAT 3 of which three subforms exist (α,β,γ).Intestinal manipulation in our hands led to a rapid phosphorylation of STAT3 within the muscularis externa and the lamina mucosae which depends on IL-6 signaling [42]. Electromobility gel shift assays demonstrated that STAT3α was the dominant activated isoform within muscularis externa while it was STAT3γ within lamina propria mucosae. As STAT3 principally is a negative regulator of inflammatory responses [51] its downstream phosphorylation via IL-6 receptor leads to a counter regulation within POI. Interestingly, de Jonge et al. demonstrated that the anti-inflammatory vagus nerve signaling is mediated via a Jak2-STAT3-dependent pathway [52] (see below).

Another class of TFs are the peroxisome-proliferator activating receptors (PPARs), which are nuclear receptors. The isoform PPARγ is strongly expressed within the colon and contributes to intestinal inflammation and homeostatis [53]. Preoperative treatment of mice with the synthetic PPARγ agonist rosiglitazone prevented postoperative colonic as well as small bowel inflammation by prevention of Egr-1 expression and downstream target genes [54]. Egr-1 is a pleiotropic TF that plays a critical role in regulation of

several hundred genes, including IL-1β and IL-6, TNF-α, ICAM-1, MCP-1, and MIP-1. Its contribution to manifestation of POI has been described by Schmidt et al. [39]. Interestingly, Egr-1 is abundantly expressed within nuclei of smooth muscle and enteric neurons in the early POI phase. In the late phase, Egr-1 expression switched from the resident non-classical immunocytes to the infiltrating monocytes. As shown within wildtype chimeric mice that received bone marrow transplants from Egr-1-deficient mice, Egr-1 expression in the infiltrating immunocytes is the critical factor in POI manifestation [39].

The closing link between PPARγ and Egr-1 has been found within the degradation of the red blood dye heme by HO-1. The end product of this metabolism is carbon monoxide (CO). In 2003, the Bauer group was first demonstrating a beneficial role of CO in prevention of POI [55]. Following works confirmed that preoperative intraperitoneally or inhaled CO as well as synthetic water-soluble CO-releasing molecules ameliorate POI in rodents and swine. [56–58]. Hoetzel et al. demonstrated that CO exerts its effects via activation of PPARγ [34] which offers a consecutive link between pro- (Egr-1) and counter regulatory (PPARγ and CO) TF in POI.

Initial triggers of the immunoresponse

While activation of sympathetic nervous signaling has been shown to be responsible for the early postoperative nervally mediated dysmotility, the triggers of the immunoresponse remain unknown. However, three possible routes have been discussed and were partially addresses (Fig. 2).

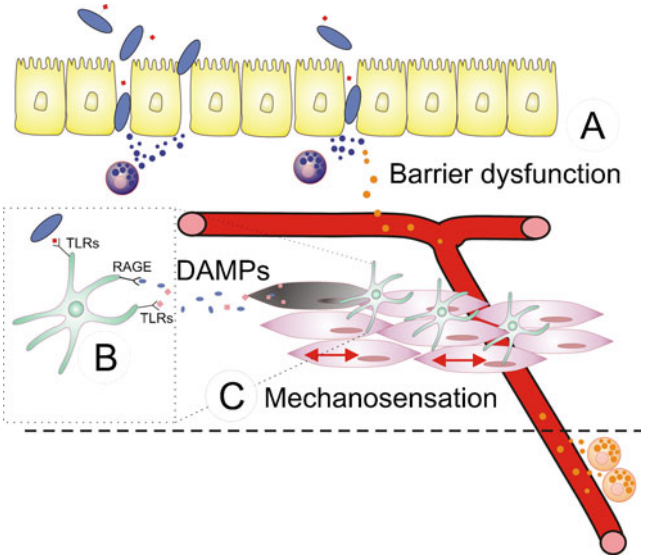

Fig. 2 Intestinal inflammatory responses following abdominal surgery. **A** Intestinal manipulation activates mast cells laying in close proximity to mesenteric blood vessels (*orange round cells*) and within the lamina propria mucosae (*violet round cells*). Vasoactive released substances diffuse into blood vessels and the tissue and increase mucosal permeability leading to translocation of luminal pathogens that can induce innate immune response via Toll-like receptors (*TLRs*) on resident macrophages (*green stellate cells*). **B** Another route is the release of damage associates molecular patterns (*DAMPs*) from damaged cells or degraded extracellular matrix proteins. DAMPs bind to specific receptors on resident macrophages like TLRs or the receptor for advanced glycation end-products (*RAGE*) and activate intracellular innate immune signaling in resident macrophages. **C** Abnormal high surgical (mechanical) strain to the gut wall activates mechanosensitive ion channels and receptors on different cell types (i.e., smooth muscle cells, enteric neurons, or macrophages). Subsequent proinflammatory responses like expression of iNOS and IL-1b gene induction induce and worsen innate an immune response

1. *Barrier dysfunction*

   The first is the translocation of luminal pathogens into the bowel in consequence of an epithelial dysintegrity. Schwarz et al. have verified this transference by detection of luminally applicated fluorescent microspheres [59]. Total numbers of microspheres within the muscularis externa increased within 24 h after intestinal manipulation. By use of a two-loop model, the authors demonstrated that microspheres are taken up by monocytes that become drained via thoracic duct lymph into the circulation. Interestingly, these microspheres-laden cells relocate to the muscularis externa by a still unknown mechanism. Additionally, a recent publication demonstrated that living bacteria translocate after intestinal manipulation [33]. Importantly, mast cell function was recently shown to affect gastrointestinal wall integrity as in mast cell deficient W-sh and W/W-v mice significantly less bacteria were found within the mesenteric lymph nodes.

   Another hint to the involvement of luminal pathogens was also shown by Türler et al. in a model of colonic manipulation [60]. One should note that this model differs from the more commonly used small bowel manipulation as the large bowel contains log numbers more bacteria and bacterial degradation product that can act as innate immune stimuli. The authors demonstrated luminal translocation from intra-colonically applied fluorescent LPS after surgical manipulation. TLR4 deficient mice were protected from postoperative intestinal dysmotility as well as rats treated for six preoperative days with oral antibiotics. Additionally, de Jonge et al. showed that oral antibiotic treatment prevents intestinal dysmotility and ameliorates neutrophil extravasation into the muscularis externa after small bowel manipulation [33]. Although these works clearly indicate that translocation of luminal contents occurs in consequence of surgical manipulation, it remains unknown how and importantly at which time point epithelial dysintegrity and subsequent bacterial translocation occurs. Unpublished data of our group, which are in accordance with the data from Schwarz et al. [59] show that living bacteria occur in mesenteric

lymph nodes and the lung at later time points (12–24 h postoperatively) while they are absent 3 h postoperatively. This indicates that epithelial barrier breakdown occurs in late phase POI and is not an initial trigger in manifestation of POI.

2. *Trauma: danger-associated molecular pattern (DAMP) molecules*

As a second possible trigger of POI, liberation or generation of DAMPs was mentioned before. Most DAMPs are molecules that exist as functional or structural molecules inside of living cells. They become relevant as DAMPs by their presence in the extracellular space. Typically, these molecules do not have a proinflammatory function per se. However, when released from stressed or dying cells, they trigger an immunoresponse via several receptors, including RAGE (receptor for advanced glycation end-products), TLR2, TLR4, and TLR9 [61, 62]. The list of DAMPs is rapidly increasing while the best understood DAMPs are high-mobility group box protein-1, S100A8/S100A9 heat-shock protein, uric acid, DNA and ATP. As POI intensity and duration increases with the strength of the surgical trauma it is a reasonable suspicion that surgery leads to cell stress/damage that finally results in the release of valuable amounts of DAMPs within manipulated intestinal wall. Albeit growing evidence about the contribution of TLR receptors in POI development, contribution of surgery-induced DAMP signaling has not yet been directly addressed. However, accumulation and turnover of extracellular matrix (ECM) components is a hallmark of tissue injury [63] and a recent publication from Moore et al. indicates that ECM degradation during immunocyte infiltration in POI has significant impact on postoperative bowel wall inflammation and motility [64]. Particularly, matrix metalloproteinase 9 (MMP-9) was shown to be a major ECM degrading enzyme in this process. As modified ECM components, like fragmented hyaluronan, stimulate proinflammatory responses via TLR signaling in a variety of damaged tissues [65, 66], alteration (fragmentation) of ECM molecules could be a major trigger in POI. Although, contribution of ECM degradation is a comprehensible mechanism one should be aware that this degradation will not only occur in the initial phase but also in late phase POI during vast immunocytes infiltration. Nevertheless, the present literature still fails to identify initial trigger mechanisms/molecules that are responsible for the induction of the complexly orchestrated postoperative immunoresponse in POI.

3. *Mechanosensation*

The observation that the strength of the surgical trauma is linearly linked to the intensity of postoperative intestinal dysmotility, spawned the hypothesis that mechanosensation could be the initial trigger of POI. As the lung and blood vessels, the intestinal wall underlies a long-life mechanical strain, which is considered as a normal mechanical alteration during propulsive movement. Mechanical forces during abdominal surgery or mechanical lung ventilation or in diseases states like vascular hypotension are abnormally high. However, our current knowledge of mechanically induced inflammatory responses in inflammation-driven diseases is mainly limited to abnormal forces during mechanically lung ventilation and vascular hypotension. This is astonishing as mechanosensation is an important regulatory mechanism of bowel motility.

Within the gut, growing numbers of cell types have been described to express functional mechanoreceptors. Intrinsic and extrinsic sensory nerves are the most prominent. However, also macrophages and smooth muscle cells express mechanosensitive ion channels or react to mechanical forces in a proinflammatory manner [67]. In a recent study, we demonstrated that intestinal smooth muscle cell cultures respond to continuous mechanical stretch by upregulation of typical iNOS and IL-1β upregulation but not IL-6 or COX-2. Surprisingly, peritoneal macrophages demonstrated IL-6 and COX-2 but not iNOS or IL-1β upregulation after mechanical stretch [38]. Furthermore, Schmidt et al. demonstrated an early upregulation of the transcription factor Egr-1 in muscularis externa smooth muscle cells of intestinally manipulated mice [39]. Interestingly, Egr-1 transcripts have been shown to become upregulated by mechanical strain in vascular smooth muscle cell cultures [68]. These results demonstrate that the gastrointestinal tract, despite the continuous peristaltic strain, is able to detect and respond to abnormal (surgical) forces in an inflammatory manner.

Counter regulation/resolution

Antiinflammatory cytokines

Counter regulatory mechanisms are important functions to avoid an excessive and prolonged inflammation. In animal models of POI several counter regulatory strategies have been investigated. As described before, most of them aim at the down regulation, inactivation of inflammatory molecules or silencing of immunocytes in the early phase of POI. In contrast, the literature about direct anti-inflammatory molecules is rare in the field POI. Probably, this imbalance originates from the strategy to favor prevention of POI compared to intervention after it has been manifested. In contrast to the variety of proinflammatory cytokines, IL-10 actively down regulates inflammatory processes. Stoffels et al. demonstrated that IL-10 deficiency leads to a prolonged

postoperative dysmotility and abnormal high levels of proinflammatory mediator expression during resolution of POI in mice [41]. Restoring deficiency with recombinant IL-10 ameliorated this prolonged form. However, the cellular source of IL-10 remains to be identified as monocytes, neutrophils and macrophages—as the major players in late phase POI, all are able to produce IL-10.

Nerve-immune interactions

In the last decade, identification of nerve immune interactions by the Tracey group gave significant insights into endogenous counter regulatory nerval signaling pathways that control peripheral inflammation to avoid overabundant innate immune responses. The so called cholinergic anti-inflammatory pathway (CAIP) led to release of the evolutionary ancient molecule acetylcholine (ACh) which acts via the specific nicotinic α7-ACh receptor subtype on peripheral macrophages and other cytokine producing cells. As POI is based on a peripheral inflammation and cytokine release from resident and infiltrated leukocytes of the gut wall, contribution of CAIP in resolution of POI is likely. The et al. described in 2007 that electrical vagus nerve stimulation and the selective α7-ACh receptor agonist AR-R17779 led to a significant acceleration of postoperative gastric emptying and reduction of neutrophils numbers in the muscularis externa [69]. This effect seems to be at least partially mediated via α7-ACh receptors that are able to induce a downstream STAT3 dependent anti-inflammatory signaling, as shown by the same group before[52]. A recent publication of the Ozaki group identified a new peace of the upstream signaling puzzle involved in the anti-inflammatory effects of acetylcholine. They found that selective 5-HT4 receptor agonists like mosapride citrate effectively ameliorated POI in an α7-nACH receptor dependent manner [70]. Although mosapride has been validated in several gastrointestinal disorders and was also effective in acceleration of the time to first flatus and motility indices of upper gastrointestinal postoperative motility, the particular clinical relevance of its anti-inflammatory potential remains to be evaluated. It is the same with the specific α7-ACh receptor agonists, which has been shown to even worsen experimental colitis [71]. This indicates caution in evaluating subtype specific α7-ACh receptor agonists for treatment of any form of intestinal inflammation. Nevertheless, these data depict a concrete endogenous mechanism of nerve-immune interactions to resolve or prevent overshooting of peripheral inflammation to avoid tissue damage by the inflammatory response.

Immunomodulatory nutrients

The evidence for beneficial effects of perioperative use of immune modulatory nutrition is high, particularly in surgical and critically ill patients [72, 73]. While excellent reviews about the general immunomodulatory capacity of nutrients have been publishes elsewhere, we herein focus on the use of lipids and their effects on postoperative gastrointestinal motility and inflammation. Long-chain fatty acids attract our special attention, as some of them are precursors of a class of kinetic active mediators, the eicosanoids. The subclasses of prostaglandins and leukotriens are of major interest in POI because they affect intestine motility and function as chemoattractants, respectively. Precursors of these molecules are polyunsaturated fatty acids (PUFA) like the ω-6 arachidonic acid, and the ω-3 eicosapentaenoic acid. They are metabolized by COX and lipoxygenase and their products depend on the precursor and have more or less inflammatory potential. ω-3 PUFA have been considered for a long time as "good" PUFA as they are metabolized to less inflammatory eicosanoids. Indeed, cellular eicosanoids profiles differed between patients that were perioperatively treated with different PUFA [74, 75]. In a recent study, our group demonstrated that preoperative intravenous ω-3 PUFA application significantly ameliorated neutrophil influx and intestinal dysmotility after intestinal manipulation [76]. Gas chromatografical analyses confirmed that intestinal tissues as well as bone marrow cells demonstrated significant changes with an increase of supplemented PUFA reflecting the administered lipid emulsions. This short-term intravenous application is of particular interest for malnourished high-risk patients undergoing open abdominal surgery. Several clinical studies also demonstrated that perioperative enteral nutrition improves patients' postoperative outcome and morbidity and was beneficial for critical ill patients. However, one should note that meta-analysis demonstrated no beneficial effect of perioperative immunonutrition on postoperative mortality [77–79].

Lubbers and colleagues found an interesting link between the above mentioned CAIP and enteral lipid administration [80]. They demonstrated that high lipid nutrition stimulated vagal reflexes in a cholecystokinin (CCK)-dependent manner which finally alleviated muscularis externa inflammation and POI in rats. CCK is released during enteral nutrition and normally induces saturation via vagal afferents. Selective CCK receptor antagonist prevented the beneficial effects of the high lipid diet. In this promising approach, the effect of different fatty acid qualities (i.e., fatty acids chain length or saturation) remains to be evaluated.

Anti-inflammatory treatment strategies—lessons to learn

A reliable strategy for prevention or therapy of POI does not exist. Most approaches still use—remarkably without clinical evidence of efficacy—prokinetic drugs like acetyl

choline esterase inhibitors or dopamine antagonists (see Cochrane analysis [14]). In the last decade, special μ-opioid antagonist proved to be efficient in prevention of opioid-induced POI. As none of the current treatments targets the underlying surgery-induced inflammation it is not astonishing that many clinical trials failed to show significant benefits. Hence, with our current knowledge about the inflammatory character of POI more powerful immunomodulatory regimens have to be tested in clinical trials, and it is well accepted that prophylaxis of the initial inflammatory steps is the most promising strategy.

The current literature two immunocyte types are in focus, mast cells and resident macrophages. A mast cell stabilizer (ketotifen) has been tested first in a clinical pilot study. Congruent with the experimental data, postoperative gastric retention was significantly reduced by ketotifen while small bowel and colonic transit were not affected [81]. Inhibition of resident macrophages has been tested in experimental model by pharmacological depletion with clodronate liposomes [24] and inactivation with the tetravalent guanylhydrazone CNI-1493 [25]. The promising results include overall gastrointestinal transit and colonic transit improvement and show that wound healing disturbances do not have to be suspected. However, clinical trials for macrophages inhibition in prevention of POI are still anticipated.

In general, an unsolved problem of clinical trials about POI is the absence of "hard" criteria like a valid biomarker. Present primary endpoints are rather "soft" criteria like time to appearance of first bowel sounds or first defection. Others, like length of hospital stay and discharge from hospital are often more driven by the individual healthcare and reimbursement systems than by valid medical indications. The finding of valuable biomarkers for prediction, occurrence, strength, and duration of POI should be an important goal of future research.

Conclusions

The present literature provides sufficient evidence for a significant role of inflammatory processes in the genesis and maintenance of POI. After decades with little success in the treatment of POI by prokinetic drugs, modern immunomodulatory approaches should now be transferred into clinical testing. Evidence for advantage of prophylactic compared with therapeutical strategies is high and transient inhibition of macrophages or mast cells are momentarily the most promising once. However, evaluation of new drugs strongly depends on the quality of future clinical trials which are currently suffering from the absence of valid biomarkers.

Conflicts of interest None.

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