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STATE-OF-THE-ART REVIEW

Specialized pro-resolving mediators: biosynthesis and biological role in bacterial infections

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Keywords
bacteria; inflammation; leukotriene; lipoxin; lipoxygenase; macrophages; neutrophils; resolution; specialized pro-resolving mediators

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Acute inflammation caused by bacterial infections is an essential biological defence mechanism of the host in order to neutralize and clear the invaders and to return to homeostasis. Despite its protective function, inflammation may become persistent and uncontrolled, resulting in chronic diseases and tissue destruction as consequence of the unresolved inflammatory process. Therefore, spatiotemporal induction of endogenous inflammation resolution programs that govern bacterial clearance as well as tissue repair and regeneration, are of major importance in order to enable tissues to restore functions. Lipid mediators that are *de-novo* biosynthesized from polyunsaturated fatty acids (PUFAs) mainly by lipoxygenases and cyclooxygenases, critically regulate the initiation, the maintenance but also the resolution of infectious inflammation and tissue regeneration. The discovery of specialized pro-resolving mediators (SPMs) generated from omega-3 PUFAs stimulated intensive research in inflammation resolution, especially in infectious inflammation elicited by bacteria. SPMs are immunoresolvents that actively terminate inflammation by limiting neutrophil influx, stimulating phagocytosis, bacterial killing and clearance as well as efferocytosis of apoptotic neutrophils and cellular debris by macrophages. Moreover, SPMs prevent collateral tissue damage, promote tissue repair and regeneration and lower antibiotic requirement. Here, we review the biosynthesis of SPMs in bacterial infections and cover specific mechanisms of SPMs that govern the resolution of bacteria-initiated inflammation.

Introduction

The innate immune system orchestrates host defence during acute infectious inflammation with the aim to clear the microbial invaders and cellular debris and to return to homeostasis [1,2]. Pathogen invasion rapidly triggers the release of arachidonic acid (AA) from membrane phospholipids especially in monocytes, macrophages and neutrophils for conversion to leukotrienes and prostaglandins by 5-lipoxygenase (LOX) and cyclooxygenases respectively (Fig. 1) [3,4]. These pro-inflammatory lipid mediators mount the inflammatory

Abbreviations
AA, arachidonic acid; AT-LX, aspirin-triggered lipoxin; AT-Rv, aspirin-triggered resolvin; BPI, bacterial permeability-inducing protein; CF, cystic fibrosis; CLP, caecal ligation and puncture; CREB, cAMP response element-binding protein; CTR, peptido-conjugates in tissue regeneration; DHA, docosahexaenoic acid; DPA, docosapentaenoic acid; EPA, eicosapentaenoic acid; ERK, extracellular signal-regulated protein kinase; FLAP, 5-lipoxygenase-activating protein; FPR2, formyl peptide receptor 2; ICAM, intercellular adhesion molecule; IFN, interferon; IL, interleukin; KC, keratinocyte chemoattractant; LOX, lipoxygenase; LPS, lipopolysaccharide; LX, lipoxin; MAPK, mitogen-activated protein kinase; MCP-1, monocyte chemoattractant protein-1; NF-κB, nuclear factor-κB; PK, protein kinase; PPAR, peroxisome proliferator-activated receptor; PUFA, polyunsaturated fatty acid; RvD, RvE, D-series or E-series of resolvins; SPM, specialized pro-resolving mediators; TLR, toll-like receptor; VCAM, vascular cell adhesion molecule.

response and mediate typical symptoms of inflammation, such as swelling, redness, pain and fever and maintain the inflammatory process [1,5,6]. However, structurally related lipid mediators produced by enzymatic oxygenation of AA but also of eicosapentaenoic acid (EPA), docosapentaenoic acid (DPA) and docosahexaenoic acid (DHA) yield specialized pro-resolving mediators (SPMs) (Figs 1 and 2) with inflammation-resolving properties. SPMs regulate acute inflammation by facilitating pathogen killing and clearance, prevent collateral tissue damage and promote tissue regeneration [7,8]. In analogy to leukotrienes, also the SPMs are enzymatically formed mainly by LOXs [9], where the concerted action of 12/15-LOXs and 5-LOX is apparently key for generation of several SPM members in leucocytes [10]. SPMs act as immunoresolvents in microbial infections by blocking excessive neutrophil influx and activation, promoting recruitment of regenerative macrophages, stimulating phagocytosis of microorganisms and by enhancing the efferocytosis of cellular debris [1,8,11] (Fig. 3). Individual members of the SPM family include lipoxins (LX), resolvins of the E-series (RvE) and D-series (RvD), maresins, protectins as well as their peptido-conjugates in tissue regeneration (CTRs) (Table 1). Importantly, specific high-affinity G-protein-coupled receptors for SPMs have been discovered on a variety of target cells that help to explain the versatile pro-resolving features [12,13]. By acting on these specific receptors at picomolar concentrations, SPMs and CTRs regulate acute inflammatory responses and prevent hyperinflammatory host damage [9,14–17]. Moreover, recent research progress now also sheds light on how SPM biosynthesis is spatiotemporally regulated on the cellular level and which enzymatic pathways are involved in generation of each SPM member. In this State-of-the-Art review, we focus on the cellular biosynthesis of SPM in response to bacterial infections as well as on the immunoregulatory and immunoresolving effects of SPMs related to infectious diseases caused by bacteria.

SPM biosynthetic pathways

Specialized pro-resolving mediators have been documented to be biosynthesized in mammals, including humans and several other organisms, and were detected in various organs and tissues (e.g., brain, spleen, liver, lung, colon, lymph nodes, bone marrow etc.) as well as in body liquids (e.g., plasma/serum, cerebrospinal fluid, synovial fluid, sputum, breast milk and tears) [13]. SPM biosynthesis (Fig. 1) first requires the release of free polyunsaturated fatty acid (PUFA) substrates, mainly by various phospholipases A_2: AA for formation of lipoxins, EPA for E-series resolvins and DHA (or DPA) for generation of protectins, maresins and D-series resolvins [12]. Note that AA and EPA are proposed to be concomitantly released mainly by cytosolic phospholipase $A_2\alpha$, whereas DHA is liberated by a pro-resolving phospholipase, seemingly a secreted phospholipase A_2 isoform [18,19]. The DHA metabolome is the most complex pathway in SPM biosynthesis with a plethora of SPMs from one single PUFA and is exemplarily shown in Fig. 2; for details on the biosynthetic pathways of the AA and EPA metabolomes, the interested reader is referred to excellent reviews [20,21]. Early studies on lipoxin biosynthesis revealed that three types of LOXs are involved: a 15-LOX, a 12-LOX and also 5-LOX [22]. Several lines of evidence propose that for SPM formation from AA and DHA (Figs 1 and 2), the PUFAs are first oxygenated by 12- or 15-LOXs or by acetylated cyclooxygenase-2 in C15 or C17 position to generate 15-hydroxyeicosatetraenoic acid or 17-hydroxy-DHA that are either *S*- or *R*-configurated; those with *R*-configuration are designated as epimers or aspirin-triggered isomers of respective SPMs (e.g., 15-epi-LXA_4 *syn*. AT-LXA_4 or 17-epi-RvD1 *syn*. AT-RvD1) [23]. For conversion of EPA to SPMs, monooxygenation by CYP enzymes is anticipated, leading to 18-hydroxyeicosapentaenoic acid or by 15-LOX leading to 15-hydroxyeicosapentaenoic acid. In a second step, yielding lipoxins and resolvins (Fig. 2), 5-LOX catalyses the hydroperoxidation of C5 or C7 of the PUFAs where the hydroperoxide is subsequently dehydrated to an epoxide by 5-LOX. Hydrolysis of this epoxide and double bond rearrangement leads then to the trihydroxylated LXA_4 and LXB_4 as well as RvD1, RvD2, RvD3, RvD4 and RvE1. Alternatively, the hydroperoxide is reduced to a hydroxy moiety resulting in the dihydroxylated SPMs RvD5, RvD6, RvE2 and RvE4. In contrast, 5-LOX is not required for the formation of the dihydroxylated protectins and maresins from DHA; it seems that the 12/15-LOXs alone fulfil their biosynthesis via generation of an epoxide and its subsequent hydrolysis with double bond rearrangement (Fig. 2). Another option for the epoxide to react, is the conjugation with glutathione catalysed by glutathione transferases or leukotriene C_4 synthase yielding the peptido-conjugated cys-SPM, which undergo consecutive cleavage of the glutathione moiety by gamma-glutamyl transferase and by a dipeptidase. These cys-SPMs include RCTR1-3 derived from resolvins, MCTR1-3 derived from maresins and PCTR1-3 made from protectins (Fig. 2), which at pico- to low nanomolar concentrations stimulate tissue regeneration and are organ protective [14].

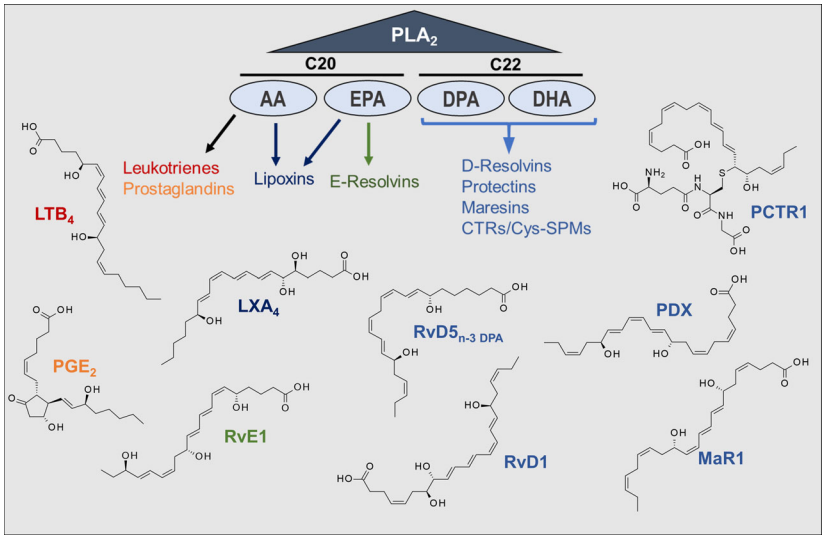

Fig. 1. Overview on different lipid mediator groups, given by a prominent representative each, derived from ω-6 (AA) and ω-3 (EPA, DPA and DHA) PUFAs released by phospholipase A_2 (PLA_2) enzymes. The chemical structures of pro-inflammatory AA-derived leukotriene B_4 (LTB_4) and prostaglandin E_2 (PGE_2) as well as pro-resolving AA-derived LXA_4, EPA-derived RvE1, DPA-derived $RvD5_{n\text{-}3\ DPA}$ and DHA-derived RvD1, maresin 1 (MaR1), protectin DX (PDX) and PCTR1 are shown.

Among the multiple enzymes involved in SPM biosynthesis, the 15-LOX-1 isoform may play a superior role [24–27] as it catalyses at least the first step in the formation of lipoxins, D-series resolvins, protectins and maresins (Fig. 2), yielding the monohydroxylated precursors 15-hydroxyeicosatetraenoic acid (for lipoxins), 17-hydroxy-DHA (for resolvins and protectins) and 14-hydroxy-DHA (for maresins). Interestingly, 15-LOX-1 seems sufficient for the complete generation of LXA_4, protectins and maresins [13]. It should be noted that 15-LOX-1 orthologs from different species vary in their regiospecificity acting as 12- or 15-lipoxygenating enzyme: human 15-LOX-1 preferably oxygenates C15 versus C12 in AA and C17 versus C14 in DHA, while for murine 15-LOX-1 oxygenation at C12 and C14 of AA and DHA, respectively, clearly predominates [28,29]. Moreover, the tissue/cell type distribution of 15-LOX-1 differs between the human and murine ortholog: 15-LOX-1 in humans is constitutively expressed at high levels in airway epithelial cells, immature red blood cells and eosinophils, and can be markedly induced in monocytes/macrophages by interleukin (IL)-4 or IL-13 [30], explaining its high abundance in IL-4-polarized human macrophages [24]. In mice, however, the major cellular source are resident peritoneal macrophages. In addition, also human 15-LOX-2, expressed in macrophages, neutrophils and epithelium, is involved in SPM biosynthesis but exclusively generates 15-hydroxyeicosatetraenoic acid from AA and 17-hydroxy-DHA from DHA [31,32]. Note that the mouse 15-LOX-2 ortholog is an 8-lipoxygenating enzyme, producing 8-hydroxyeicosatetraenoic acid from AA. Together, based on these discrepancies related to 15-LOX-1 and -2, the SPM biosynthetic pathways and (tissue-)specific SPM profiles might differ between mice and humans.

It is obvious that the role of 5-LOX in lipid mediator formation is complex: 5-LOX is essential for leukotriene biosynthesis but also contributes to lipoxin and resolvin formation [33]. Such dual and even opposite function of 5-LOX, that is, catalysis of the formation of pro-inflammatory leukotrienes and of inflammation-resolving SPMs, implies detrimental and beneficial roles of 5-LOX for the host, which is of relevance in terms of the development of 5-LOX inhibitors as therapeutic agents. Several lines of experimental evidence suggest that the interaction of 5-LOX with its activating protein (FLAP) determines if leukotrienes or lipoxins/resolvins are produced by 5-LOX in the cell. Thus, when 5-LOX is distant from FLAP, due to lack of 5-LOX Serine271 phosphorylation [34] or due to FLAP antagonists [25], leukotriene production is reduced in favour of lipoxins and resolvins.

SPMs are biosynthesized during bacterial infections

Accumulating evidence suggests that lipid mediator signature profiles of pro-inflammatory eicosanoids (prostaglandins and leukotrienes) and SPMs in human plasma can be potential biomarkers that correlate with survival and severity in patients with sepsis [35] and, for example also with active tuberculosis disease [36,37]. Severe microbial infections such as sepsis are a major public health concern with high mortality and morbidity mainly caused by dysregulated host responses to systemic bacterial and/or fungal invasion [38]. Although it is now well

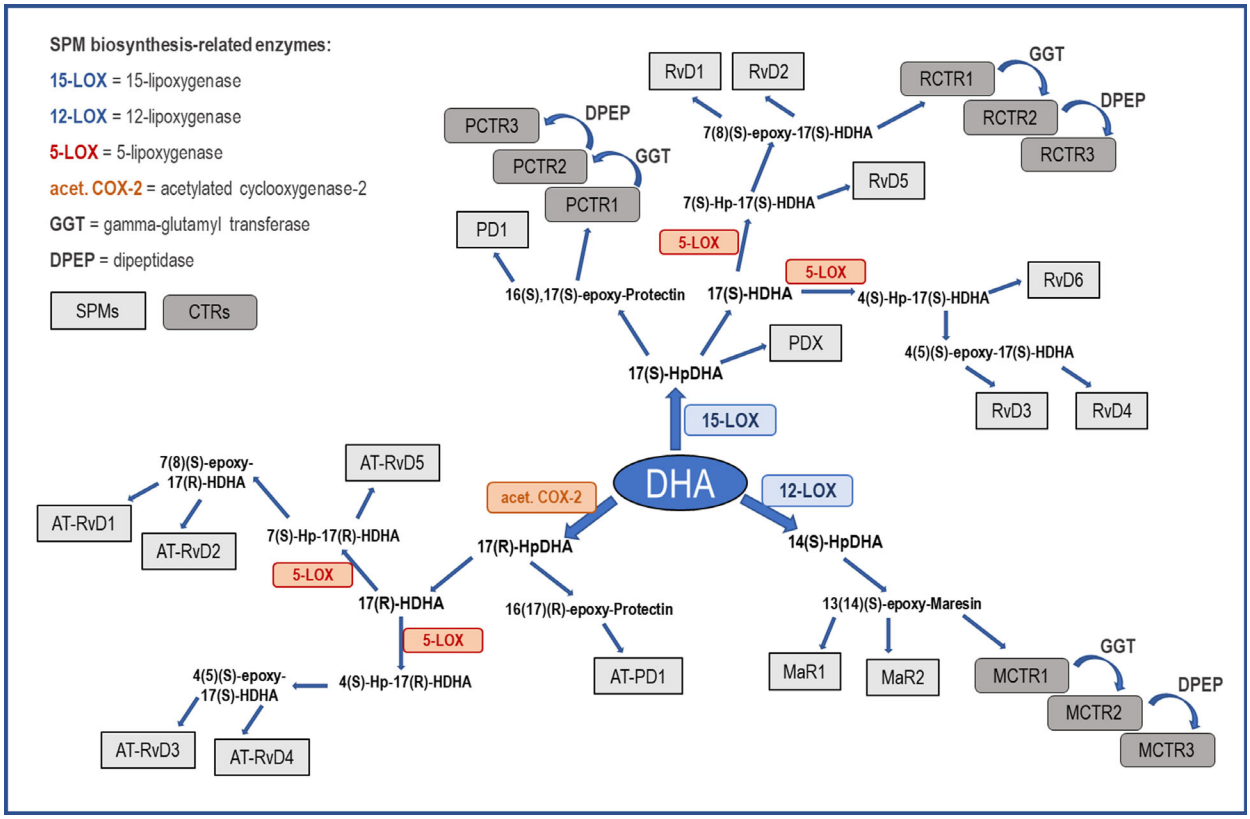

Fig. 2. Biosynthetic pathway of the DHA metabolome. 12-LOX, 15-LOX and acetylated cyclooxygenase-2 initiate the formation of monohydroxylated precursors 17(S)-hydroperoxy-DHA (17(S)-HpDHA), 17(R)-hydroperoxy-DHA (17(R)-HpDHA) and 14(S)-hydroperoxy-DHA (14(S)-HpDHA). Further conversion of these precursors, either via 5-LOX or via generation of an epoxide as intermediate, yield resolvins (RV), maresins (MaR) and protectins (PD) and their related peptido-conjugates (CTRs) via specific mechanisms including epoxide hydrolysis, stereo-controlled oxygenation and glutathione conjugation.

established that pro-resolving processes in infectious inflammation are regulated by the SPM superfamily, how their biosynthetic pathways are spatiotemporally orchestrated in the host during bacterial infections is still elusive. Many animal models that were conducted in order to study SPM biosynthesis and function in infectious inflammation and its resolution employed polymicrobial infections using caecal ligation and puncture (CLP) [39–48]. For example in a murine polymicrobial sepsis model, omega-3-enriched lipid emulsions were shown to elevate biosynthesis of SPMs in a 5-LOX- and 12/15-LOX-dependent manner to orchestrate resolution mechanisms such as tissue regeneration and efferocytosis actions [49]. But also several experimental studies, where defined bacteria such as pathogenic *Escherichia coli*, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Mycobacterium tuberculosis* or *Streptococcus pneumoniae* had been used to infect rodents, reported on increased levels of SPMs [50–59] as well as their cysteinyl-conjugates (CTRs) [15–17,60–63] in exudates and organs during infections. Also in humans, infected with *M. tuberculosis*, the levels of RvD1, AT-RvD1 and RvD2 were reported to be increased [36], while another study found mainly lipoxins and maresins as upregulated SPMs in individuals with tuberculosis [37]. Notably, also probiotic bacteria such as *Clostridium butyricum* elevated protectin D1, in parallel to formation of the anti-inflammatory lipid mediator 15-deoxy-delta-12,14-prostaglandin J_2, thereby preventing antibiotic-associated diarrhoea and providing new insights into gut epithelial barrier protection under conditions of antibiotic-induced dysbiosis [64]. Many studies also used lipopolysaccharide (LPS) as bacterial stimulus to elicit SPM formation in mice, mainly in the acute lung injury model [65–70].

Host cells responding with SPM formation upon bacterial challenge

But which host cell types are primarily responsible for the biosynthesis of SPMs upon bacterial challenge?

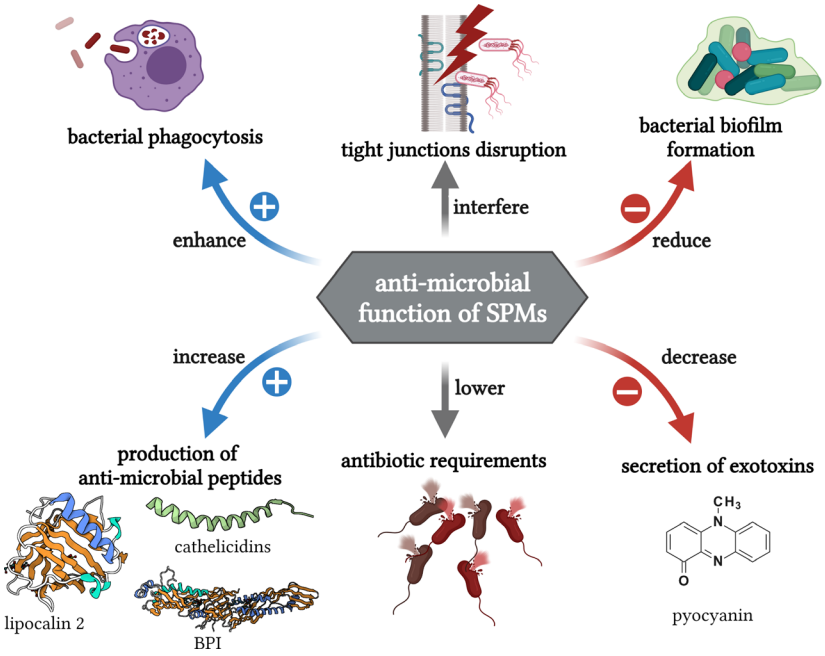

Fig. 3. Summary of the major anti-microbial functions of SPMs leading to better outcome of bacteria-induced inflammation. SPMs can directly act on bacteria thereby reducing biofilm formation and decreasing the secretion of exotoxins, but also act via host cells to enhance phagocytosis, to increase the production of anti-microbial peptides, and to interfere with tight junction disruption. Moreover, and as a consequence of these actions, SPMs lower the antibiotic requirement.

Numerous studies with primary innate immune cells, such as neutrophils, eosinophils, peritoneal macrophages, monocytes and monocyte-derived macrophages or leucocytic cell lines from humans or rodents have been used to study SPM formation at the cellular level. A prerequisite for a given cell to produce SPMs is the expression of the respective biosynthetic key enzymes, that is mainly 12- and 15-LOXs but also 5-LOX and, at least for E-series resolvins, certain CYP 450 enzymes. As mentioned above, the 15-LOX-1 is strongly connected to SPM formation, since the capacity to produce SPMs clearly correlates to 15-LOX-1 expression [24–27]. However, in contrast to 5-LOX or platelet-type 12-LOX that commonly generate substantial products from endogenous fatty acids in cell-based assays, stimuli able to evoke substantial formation of 15-LOX-derived products including SPM from endogenous substrates have long been elusive.

Dalli and Serhan [71] presented different lipid mediator profiles produced by human macrophages during polarization: acquiring an pro-inflammatory M1-like phenotype resulted mainly in pro-inflammatory lipid mediators such as leukotrienes and prostaglandins, while polarization towards M2-like macrophages led to superior amounts of SPMs in their culture medium due to IL-4-induced 15-LOX-1 enzyme expression. We recently showed that such distinct human macrophage phenotypes biosynthesize unique lipid mediator signatures when challenged with pathogenic *E. coli* or *S. aureus* [24–26]. The pathogenicity of these bacteria was mandatory to stimulate macrophages of an M2-like phenotype to produce SPMs including RvD2, RvD5, protectins and maresin 1 [24]. Of note, typical agonists inducing leukotriene/prostaglandin biosynthesis like zymosan, *N*-formyl-methionyl-leucyl-phenylalanine, LPS or Ca^{2+}-ionophore A23187 were hardly active to evoke SPM formation [24,26]. The bacteria-induced 15-LOX-1 activation in M2-like macrophages depended on intracellular Ca^{2+} and correlated with 15-LOX translocation from a soluble to a membranous cell compartment [24]. Importantly, SPM formation was seemingly independent of FLAP, despite the requirement of 5-LOX, suggesting FLAP as an attractive target for inflammation-resolution pharmacotherapy suppressing pro-inflammatory leukotrienes but maintaining SPM formation [25].

Besides exposure of M2-like macrophages to intact *S. aureus*, also *S. aureus*-conditioned medium containing secreted bacterial factors efficiently induced SPM biosynthetic pathways, and in fact, the main exotoxin of *S. aureus*, namely α-haemolysin was revealed as a specific elicitor of SPM biosynthesis [26]. Thus, exogenous addition of α-haemolysin caused the massive formation of SPM in mouse peritoneum and human M2-like macrophages without substantial formation of leukotrienes and prostaglandins. The α-haemolysin receptor ADAM10 on M2-like macrophages mediated α-haemolysin-induced 15-LOX-1 translocation and enzyme activation along with SPM production; other *S. aureus*-derived exotoxins such as phenol-soluble modulins or δ-toxin were inactive in this respect [26]. Of interest, phenol-soluble modulins caused 5-LOX

Table 1. Biological actions of SPM in experimental models of bacterial infection. Overview on the target cells, protein and signalling events that are impacted by SPM and the functional effect and outcome in various animal models of bacterial infections.

SPM	Model	Target cell/target/ signalling	Effect/outcome	Ref.
LXA_4	CLP	Neutrophils	Migration↓, bacteria clearing function↑	[41,42]
		NF-κB	Phosphorylation↓, production of IL-6/MCP1/IL-10↓	[47]
	S. aureus-induced septic arthritis	Dendritic cells	Migration↓	[53]
	LPS-induced acute lung injury	p38MAPK, JNK	Phosphorylation↓	[70]
		Alveolar fluid clearance	Ameliorates AFC disturbance, cytokine release↓	[70]
LXA_4 analogues	Intratracheal injection of *E. coli*	Caspase-3	Activity↑, enhanced neutrophil apoptosis	[89]
		Myeloperoxidase	Tissue expression↓, animal survival↑	[89]
	LPS-induced acute lung injury	TNF-α, nitric oxide	Pulmonary oedema↓, lipid peroxidation↓, neutrophil infiltration↓	[68]
RvD1, AT-RvD1	*E. coli*-induced pneumonia	Macrophages	Phagocytosis↑, efferocytosis↑	[53]
	LPS-induced acute kidney injury	NF-κB	Activation↓	[66]
		Endothelial cells	ICAM-1↓, VCAM-1↓	[66]
		IL-6	STAT3 and ERK phosphorylation↓	[66]
	Intratracheal injection of *P. aeruginosa*	Endothelial cells	ICAM-1↓, VCAM-1↓	[80]
		Leucocytes	Infiltration↓	[84,85]
		Macrophages	Phagocytosis↑, Toll-like receptor (TLR) expression↓	[84]
	Intranasal co-infection of influenza A and *Str. pneumoniae*	Leucocytes	Infiltration↓	[95]
		Neutrophil elastase	Activity↓	[95]
	LPS-induced cardiac injury model	M1-like macrophages	Cardiac infiltration↓	[102]
		NF-κB and MAPK	Phosphorylation↓	[102]
	Oropharyngeal aspiration of non-typeable *H. influenzae*	Cytokines	KC↓, IL-6↓, TNF-α↓	[108]
		Cyclooxygenase-2	Expression↓	[108]
		Macrophages	Bacterial clearance↑	[108]
		Cytokines	IL-6↓, TNF-α↓, IL-10↓, MCP-1↓	[109]
	LPS/D-GalN endotoxin shock model	High mobility group box-1 (HMGB1)	Release↓	[109]
RvD2	CLP	Entire animal	Bacterial titres↓, hypothermia↓	[40]
		CREB, ERK1/2, STAT3	Phosphorylation↑	[40]
		Neutrophils	Trafficking↓	[45]
		Nitric oxide	Production↑	[45]
		Cytokines	IL-1β↓, IL-6↓, IL-10↓, IL-17↓, KC↓, IL-23↓, TNF-α↓	[45]
		Lipid mediators	ProstaglandinE_2↓, leukotrieneB_4↓	[45]
	E. coli-induced peritonitis	Neutrophils	Infiltration↓	[56]
		Leucocytes	Phagocytosis↑, efferocytosis↑	[56]
maresin1	CLP	Cytokines	IL-6↓, TNFα↓, IL-1β↓	[43,44]
		NF-κB	Phosphorylation↓	[43]
		Inflammation marker	Alanine transaminase↓, aspartate transaminase↓, creatinine↓, blood urea nitrogen↓	[43]
		Mitochondria	Damage↓	[44]
	LPS-induced acute lung injury	Cytokines	IL-6↓, TNF-α↓, IL-1β↓	[67]
		Neutrophils	Infiltration↓	[67]
		ICAM-1	Expression↓	[67]
		Caspase-3	Neutrophil apoptosis↑	[87]
Protectin DX	CLP	Macrophages	Phagocytosis↑, M2-like phenotype↑	[48]
RvE1	Acid and *E. coli*- induced acute lung injury	Neutrophils	Accumulation↓	[96]
		Cytokines and chemokines	IL-1β↓, IL-6↓, HMGB-1↓, MIP-1α↓, MIP-1β↓, MCP-1↓	[96]
	Porphyromonas gingivalis-induced periodontitis	Inflammatory marker	C-reactive protein↓, IL-1β↓	[110]

activation for leukotriene biosynthesis in human neutrophils, while α-haemolysin was inactive in these cells to induce lipid mediator formation [72]. It, therefore, appears that inflammatory signalling components in host cells critically affect the balance of pro-inflammatory lipid mediator versus SPM formation.

Host- and bacteria-derived factors manipulate SPM biosynthesis during bacterial infection

Specialized pro-resolving mediator production during bacterial infections is the key for regulating the inflammatory process and for promoting the return to homeostasis, however, several studies showed that diverse host- as well as bacteria-derived factors can manipulate SPM product formation. For instance, Lee *et al.* [73] reported that genetic deficiency of the nucleotide-binding domain, leucine-rich repeat-containing receptor, pyrin domain-containing-3 (NLRP3) reduced proinflammatory lipid mediators but increased LXB_4 in septic mice and in LPS/ATP-activated macrophages along with enhanced survival. On the other hand, bacteria may also limit SPM formation and pro-resolving actions by secretion of virulence factors. Thus, *P. aeruginosa*, a common cause for cystic fibrosis (CF), secretes the conductance regulator inhibitory factor, an epoxide hydrolase that disrupts 14-epi LXA_4 transcellular biosynthesis and is associated with prolonged loss of function in patients with CF [74]. Of interest, a host protective mechanism mediated by vagus nerve stimulation of SPM biosynthesis was identified which regulates antimicrobial functions and resolution of *E. coli* infection; electrical stimulation of human vagus *in vitro* enhanced SPM formation and reduced prostaglandin and leukotriene levels [75]. Together, these insights reflect the complexity of the regulatory processes in the biosynthesis of SPM that are crucial as chemical signals for return to homeostasis and host defence against bacterial invaders.

SPMs regulate and resolve bacterial infection and improve the efficacy of antibiotics

After detection of increased amounts of SPMs in infectious exudates, the connections to the better outcome of infections with various disease-relevant bacteria due to SPMs were intensively investigated (Fig. 3). In particular, LXA_4 or RvD1 as well as their epimers 15-epi-LXA_4 and AT-RvD1 have been applied in several experimental studies (Table 1). LXA_4 interfered with tight junction disruption in bronchial epithelium during *P. aeruginosa* inoculation and consequently delayed and reduced bacterial invasion in CF bronchial epithelial cells [76]. In a mouse CLP model of sepsis, LXA_4 increased Fcg receptor I-mediated neutrophil phagocytic ability but did not directly increase the expression of the receptor [41]. The same study showed that LXA_4 also inhibits the quorum-sensing receptor LasR and thereby decreases the release of pyocyanin exotoxin from *P. aeruginosa* [41]. Of interest, administration of LXA_4 reduced the biofilm and virulence gene expression of *P. aeruginosa* which was observed also with RvD2 [77]. Strikingly, in a pneumococcal pneumonia model, blockade of ALX/FPR2, the receptor for LXA_4 and RvD1, with the antagonist WRW4 enhanced pulmonary oedema and increased bacteria accumulation in the air spaces as well as in the blood [59]. In *M. tuberculosis*-infected human monocyte-derived macrophages, RvD1 and maresin 1 significantly reduced intracellular bacterial growth and heightened antimicrobial properties of the macrophages [78].

Host-directed SPMs can enhance bacterial containment and improve antibiotic efficacy, which was demonstrated for ciprofloxacin in systemic *E. coli* infections as well as for vancomycin in local *S. aureus* skin infections which lowered the antibiotic requirements in both cases [50]. Among various promising antibiotic/SPM combinations, exogenous 15-epi-LXA_4 and ceftazidime attenuated systemic inflammation and inhibited bacteria dissemination in *E. coli*-induced peritonitis in mice with improved survival of infected animals [79]. In LPS-challenged murine lungs, 15-epi-LXA_4 increased the expression of the bacterial permeability-inducing protein (BPI) and of the antimicrobial peptide cathelicidin (LL-37) [65]. Moreover, 15-epi-LXA_4 combined with antibiotics synergistically reduced TNF-α and IL-6 in *E. coli*-activated murine peritoneal macrophages [79]. It was suggested that LXA_4 has direct effects on *P. aeruginosa* biofilm formation and can increase antibiotic efficacy directly [77]. Smart approaches were developed for directed delivery of SPM/antibiotic combinations towards infectious sites of *P. aeruginosa*-treated murine lungs. Thus, neutrophil-membrane-derived nanovesicles that contained RvD1 and ceftazidime effectively alleviated both inflammation and bacterial growth in mouse lungs [80]. Also, the epimer AT-RvD1 enhanced clearance of *P. aeruginosa* and *E. coli* as well as of neutrophils *in vivo*, lung macrophage phagocytosis of bacterial particles *ex vivo*, and efferocytosis by infiltrating macrophages and exudative macrophages *in vivo*; these anti-bacterial and pro-resolving actions of AT-RvD1 were additive to antibiotic therapy [53,81].

Antimicrobial actions of SPMs and involved signalling mechanism

The mechanisms and signalling pathways behind the antimicrobial actions of SPMs (summarized in Table 1),

particularly in the clearance and killing of bacterial invaders, are of great interest and of potential therapeutic value. Aside from their individual G-protein-coupled receptors on the outer cell membrane [12,13], the SPMs have been reported to signal via (a) the protein kinase (PK)A/STAT3 pathway [40,56,66], (b) the Toll-like receptor (TLR)4 [69,82,83], (c) genes associated with nuclear factor-κB (NF-κB) activation [43,45,47,50,65,66,69,84,85], (d) NADPH-oxidase and caspase-3/-8 [86,87], (e) mannose-scavenger receptor and phosphoinositide 3-kinases [88,89] and (f) via extracellular signal-regulated protein kinase (ERK) and cAMP response element-binding protein (CREB) [40,66,86,90,91] (Table 1).

Recent studies demonstrated that RvD2 enhances phagocytosis of *E. coli* and apoptotic neutrophils (efferocytosis) via its receptor GPR18/DRV2 in a protein kinase A- and STAT3-dependent manner to control bacterial infections and to promote organ protection in sepsis [40,56]. Treatment of primary human macrophages incubated with *E. coli* and AT-RvD1 modulated TLR4-mediated production of TNF-α along with increased bacterial internalization and killing [82]. AT-RvD1 also increased the lung levels of anti-microbial peptide lipocalin 2 in a self-resolving murine model of *E. coli* pneumonia, which limits bacterial growth by sequestrating iron [53,81]. In primary leucocytes and epithelial cells of CF patients, RvD1 carries multipronged actions which include reduction in genes associated with NF-κB activation that boost host-defensive phagocytic activity against *P. aeruginosa* [84,85]. In neutrophil-mediated pulmonary injury evoked by intratracheal instillation of live *E. coli*, RvE1 acted through the leukotriene B_4 receptor 1 for enhancing the generation of NADPH oxidase-derived oxygen species and activation of caspase-3 and -8 in order to accelerate neutrophil apoptosis and their removal by macrophages [86]. 15-Epi-LXA_4 acts via the formyl peptide receptor 2 (FPR2) to increase phagocytosis of *E. coli* in a mannose-scavenger receptor- and phosphoinositide 3-kinase-dependent manner [88]. Moreover, treatment of human blood with an endogenous occurrent SPM cluster including RvE1, RvD1, RvD5, LXB_4 and maresin 1 induced ERK and CREB signalling in neutrophils and $CD14^+$ monocytes connected to improved phagocytosis and killing of *E. coli* [90].

SPMs regulate infectious inflammation via different mechanisms

Neutrophil infiltration

One important anti-inflammatory action of SPMs, especially of LXA_4 and its epimer 15-epi-LXA_4, is the cessation of excessive neutrophil influx and activation to limit tissue injury without compromising immune responses and bacterial clearance [92]. For example LXA_4 given 1 h after inducing sepsis in a rat CLP model decreased neutrophil migration to the peritoneum and promoted neutrophil apoptosis, but it increased the bacteria clearing function of neutrophils, without excessive free radical production, concomitant to reduced blood bacterial load at 24 h [42]. LXA_4 also inhibited the ability of bacteria-infected epithelia to direct polymorphonuclear leucocyte movement, reflecting downregulatory functions of acute inflammation at mucosal surfaces [93]. Similarly, 15-epi-LXA_4 dampened leucocyte/endothelial cell interaction and extravascular polymorphonuclear leucocyte migration seemingly by triggering anti-adhesive nitric oxide [94]. Besides infiltration of neutrophils, LXA_4 also impairs dendritic cell migration which was found to be crucial for a protective response in *S. aureus*-induced septic arthritis [58].

In addition to lipoxins, also resolvins and maresin 1 limit excessive swarming of neutrophils without compromising bacterial clearance. Thus, RvD1 significantly diminished bacterial growth and neutrophil infiltration during acute pneumonia caused by *P. aeruginosa* [80,84,85]. In mice with microbial sepsis initiated by CLP, RvD2 decreased neutrophil recruitment [45]. With respect to the leucocyte/endothelial cell interaction, AT-RvD1 inhibited the expression of intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1, along with impaired neutrophil infiltration in endotoxin-induced acute kidney injury [66]. AT-RvD1 also significantly reduced neutrophil elastase activity in the bronchoalveolar lavage of mice coinfected with *Str. pneumoniae* and influenza A virus, accompanied by reduced numbers of infiltrating lung neutrophils and monocytes/macrophages [95]. In LPS-induced models of acute lung injury, maresin 1 downregulated neutrophil adhesion along with lower expression of ICAM-1 and P-selectin [67] and neutrophil survival along with accelerated resolution [67,87]. Also, RvE1 upon i.v. administration prior to acid-induced injury selectively decreased murine lung neutrophil accumulation by 55% [96], and DPA-derived $RvD5_{n\text{-}3\ DPA}$ regulated neutrophil trafficking to the site of inflammation through GPR101 during *E. coli*-initiated inflammation in mice [97]. Finally, various cys-SPM limited neutrophil infiltration in *E. coli*-elicited mice [16,61,98].

Nuclear factor-κB

The NF-κB plays a central role as transcription factor in the host response to bacterial infection by

orchestrating cellular innate and adaptive immune responses through regulation of the expression of proinflammatory cytokines, chemokines and adhesion molecules [99]. Microbial pathogens and pathogen-associated molecular patterns act via the NF-κB signalling pathway to modulate host cell events [100,101]. Several studies revealed modulating functions of SPMs of the NF-κB signalling pathway in bacterial-induced inflammation. For example, SPMs increased the expression of the NF-κB regulators A20 and single immunoglobulin and toll-interleukin 1 receptor domain (SIGIRR) in LPS-activated human epithelial cells to ameliorate pathogen-mediated inflammation [65]. In a sepsis-induced cardiac injury model, RvD1 attenuated deteriorated cardiac functions along with impaired infiltration of pro-inflammatory M1-like macrophages and expression of inflammatory cytokines in the heart, which was traced back to reduced activation of NK-κB and mitogen-activated protein kinase (MAPK) signalling [102]. In a murine CLP model, also maresin 1 inhibited activation of NF-κB with markedly improved survival rate and impaired levels of pro-inflammatory IL-6, TNF-α and IL-1β. In parallel, maresin 1 decreased levels of alanine transaminase, aspartate transaminase, creatinine and blood urea nitrogen in the serum of mice after CLP injury, suggesting improved vital organ functions [43]. In peritoneal macrophages of rats, also LXA_4 blocked NF-κB, as it reduced phosphorylation of the p65 subunit [47], and LXA_4 suppressed inflammation in periodontal ligament cells via the TLR4/MyD88/NF-κB pathway [69].

Cytokines and chemokines

Cytokine and chemokine families mediate both immune cell recruitment and complex mechanisms that characterize infectious inflammation, and dysregulation of the release of cytokines can cause chronic diseases and tissue destruction [1,103]. A number of studies have reported that SPMs interfere with pro-inflammatory cytokines and chemokines [15,43–46,48,51,65–70,79,80,83,85,87,88,93,95,96,102,104–109]. Several studies focused on RvE1 in this respect. For example, in mice with *E. coli*-induced pneumonia, RvE1 inhibited lung tissue levels of pro-inflammatory IL-1β, IL-6, high-mobility-group-protein B1, macrophage inflammatory protein-1α and -β as well as monocyte chemoattractant protein-1 (MCP-1), and was thus suggested as a potential candidate for pneumonia therapy [96]. RvE1 was also effective in the treatment of periodontitis in rats, where it reduced expression of inflammation-related genes and osteoclast activity, and it reversed bone loss in ligature-induced periodontitis [39]. Notably, the rat subgingival microbiota revealed marked changes after RvE1 administration, in both prevention and treatment experiments, suggesting that modulation of local inflammation plays a major role in shaping the composition of the subgingival microbiota [39]. Also in rabbits, RvE1 restored local lesions in established periodontitis and diminished inflammatory markers such as C-reactive protein and IL-1 [110].

Besides RvE1 also DHA-derived SPMs displayed potent anti-inflammatory functions via modulation of cytokines. For example, maresin 1 exerted organ-protective effects in CLP-induced murine sepsis with markedly reduced levels of pro-inflammatory TNF-α and IL-6 as well as with better overall survival rate and attenuated lung and liver injuries [44]. Similarly, in mice with LPS-induced lung injury, maresin 1 attenuated the elevated levels of TNF-α, IL-1β and IL-6, chemokines, ICAM-1, P-selectin and CD24 as well as neutrophil infiltration in lung tissues [67]. Along these lines, maresin 1 impaired LPS-induced secretion of TNF-α, IL-1β and IL-6 in RAW264.7 macrophages and in human peripheral blood mononuclear cells and reverted the suppression of sirtuin1, peroxisome proliferator-activated receptor (PPAR)-γ coactivator 1α and PPAR-γ expression [104]. Using primary monocytes and THP-1 monocytic cells it was shown that suppression of LPS-induced cytokines by RvD2 correlates to impaired expression of TLR4, lymphocyte antigen 96 and downstream signals (MyD88, TRIF and TAK1) seemingly mediated through induction of microRNA-146a [83]. In a D-galactosamine-sensitized mouse endotoxin shock model RvD1 administration significantly reduced the elevated levels of high-mobility-group-protein B1, decreased the peritoneal neutrophil population and the apoptosis of hepatocytes, slightly reduced TNF-α, IL-6 and IL-10 levels and further lowered MCP-1 levels [109]. In mice that had been infected with live non-typeable *Haemophilus influenzae*, AT-RvD1 reduced neutrophil numbers in bronchoalveolar lavage fluid but accelerated influx of macrophages that reduced bacterial load which was accompanied by decreased keratinocyte chemoattractant (KC), IL-6 and TNF-α [108]. Notably, these non-typeable *H. influenzae*-infected mice were protected by AT-RvD1 from weight loss, hypothermia, hypoxemia and respiratory compromise [108].

SPMs promote resolution and survival in infectious inflammation

The resolution of the inflammatory process in general (sterile and non-sterile inflammation) is an active

endogenous program regulated by coordinated temporal and spatial production of SPMs [1,105,111]. Typical features of inflammation resolution include cessation of excessive neutrophil infiltration, accelerated neutrophil apoptosis and their efferocytosis, and tissue regeneration, culminating in increased survival [8]. A large number of experimental studies with rodents have investigated the outcome of various SPMs in resolution of infectious inflammation, mainly by treatment with single SPM representatives such as LXA_4 [47,98], RvD1 [46], AT-RvD1 and AT-LXA_4 [53,89,112], RvD2 [45,56], protectin DX [48], maresin 1 [87,98] or cys-SPM [15–17,61,62] (Table 1). The models frequently consisted of CLP-induced sepsis (peritonitis) or *E. coli*- and *P. aeruginosa*-induced acute lung injury. The most significant outcome of a successful resolution in microbial-induced severe sepsis and septic shock is the survival of individuals. Indeed, increased survival from CLP-induced sepsis by multi-level pro-resolving actions were the major obvious features of resolvins and lipoxins as reported above [45–47]. Pioneer studies identified RvD2 to critically control microbial sepsis, where its multi-level pro-resolving actions, when given exogenously to mice, translated into increased survival from sepsis induced by CLP and surgery [45]. Similarly, after treatment with RvD1, the survival rate and bacterial clearance of mice with CLP-induced sepsis were improved, along with markedly reduced inflammatory reactions compared with the vehicle control group [46]. Also, the administration of LXA_4 increased 8-day survival of rats after CLP, which lived longer than 48 h and simultaneously reduced systemic inflammation as well as bacterial spread [47]. Finally, protectin DX increased the overall survival rate within 8 days and attenuated multiple organ injuries in septic mice upon CLP [48].

Another mean to characterize pro-resolving events in self-limited bacterial infections is the resolution interval (R_i), a key term that describes the duration for neutrophil numbers to reach half the maximum during the inflammatory process [106,113]. Recent studies found that SPMs and their peptido-conjugates accelerate resolution by shortening R_i in self-limited *E. coli* peritonitis infections [15,50,51,61,97,114] and in *P. aeruginosa* lung infections [80].

Apoptosis of infiltrating neutrophils and efferocytosis of apoptotic cells and cellular debris are crucial processes during the resolution of inflammation [2]. Apoptotic cells, especially neutrophils, are removed by macrophages after they have phagocytized invading microbes [2]. Promotion of neutrophil apoptosis by SPMs was found in the resolution phase of *E. coli*-evoked lung injury in mice. Thus, treatment of mice with 15-epi-LXA_4 and AT-RvD1 at the peak of inflammation accelerated clearance of bacteria, blunted neutrophil accumulation and promoted neutrophil apoptosis and efferocytosis mediated through the receptor ALX/FPR2 [112]. AT-RvD1 accelerated neutrophil clearance and increased efferocytosis in the alveolar compartment of mice during *E. coli*- and *P. aeruginosa*-induced pneumonia by infiltrating macrophages and exudative macrophages, actions that were additive to antibiotic therapy [53]. Also during acute lung injury induced by intratracheal instillation of LPS, i.v. injection of maresin 1 at the peak of inflammation attenuated neutrophil accumulation and accelerated caspase-dependent neutrophil apoptosis, while treatment with the pan-caspase inhibitor z-VAD-fmk inhibited the proapoptotic action of maresin 1 and attenuated its protective effects [87]. In human neutrophils cultured with myeloperoxidase, 15-epi-LXA_4 promoted apoptosis by attenuating myeloperoxidase-induced activation of ERK and Akt-mediated phosphorylation of Bad, and by reducing expression of the antiapoptotic protein Mcl-1, thereby aggravating mitochondrial dysfunction [89]. In the same study, 15-epi-LXA_4 administration to mice accelerated the resolution of neutrophil-dependent pulmonary inflammation evoked by carrageenan/myeloperoxidase or by *E. coli*, through redirecting neutrophils to caspase-mediated cell death and facilitating their removal by macrophages [89]. Maresin 1 potently enhanced uptake of apoptotic neutrophils by human macrophages being slightly more potent than RvD1 [98]. Moreover, RvD3 at pico- to low nanomolar concentrations enhanced human macrophage efferocytosis and bacterial phagocytosis, in parallel to increased intracellular reactive oxygen species generation, and reduced human platelet-neutrophil aggregation [51]. Finally, cys-SPMs resolved *E. coli* infections in mice by limiting neutrophil infiltration and stimulating bacterial phagocytosis and clearance as well as removal of apoptotic cells [17,61], shown for MCTRs [16], RCTRs [15] and PCTRs [62] that all stimulated also human macrophage phagocytosis and efferocytosis. RvD2-enhanced efferocytosis of apoptotic neutrophils by human macrophages was further increased by GPR18 overexpression [56], while knockdown of GPR101 limited the ability of $RvD5_{n\text{-}3\ DPA}$ to upregulate phagocytosis of bacteria and efferocytosis [97].

Specialized pro-resolving mediators are also well known for their ability to promote tissue repair and regeneration upon damage during infectious inflammation as part of wound healing and return to homeostasis [1,7,9,14–16,61]. To characterize the effects of SPMs on tissue regeneration, the planarian tissue self-

repair model was mainly used as well as wound healing scratch models. Recent studies showed that SPMs, and especially their peptido-conjugates, potently enhance tissue regeneration and wound healing in planarians [15,26,61,62,115]. Recently, PCTR1 was found to accelerate wound closure which contemporaneously coincided with decreased bacterial burden [63]. Interestingly, RvE1 that is locally produced in response to intestinal mucosal injury, was crucial for intestinal wound repair by promoting cellular proliferation and migration due to activation of pathways including CREB, mTOR and Src-FAK [91].

Conclusions

Infectious diseases are a major cause of global morbidity and mortality, where besides viruses, fungi or parasites, certain bacteria are the causative pathogens that elicit acute inflammation as a host-protective innate immune response. Due to the current antibiotic crisis that will certainly further exacerbate in the future, new therapeutic host-directed approaches besides antibiotics are needed to improve therapy of infectious diseases and to maintain public health. It is obvious that both initiation and resolution of infectious inflammation are tightly regulated by lipid mediators with deleterious (leukotrienes and prostaglandins) or beneficial (SPMs) bioactions that can lead to either persistently inflammatory or self-resolving microenvironments [8]. The identification of multiple beneficial functions of SPMs in bacterial infections (Fig. 3) [13], culminating in resolution of infectious inflammation along with increased survival, opened new avenues for potential treatment of bacterial diseases [116]. In fact, SPMs have emerged as physiologic immunoresolvents that promote the resolution of infectious inflammation, clearance of microbes and tissue regeneration. There is accumulating evidence from numerous experimental studies with various bacterial pathogens that SPMs enhance pathogen containment, lower antibiotic requirement that may possibly reduce also the potential for increasing antibiotic resistance, and increase the survival rate in life-threatening infectious diseases [116]. Such pro-resolution pharmacology with SPMs as agonists of resolution may enhance the host innate response to expedite microbial clearance, limit collateral tissue damage and stimulate tissue regeneration without evoking unwanted side effects, such as immunosuppression [117].

The technical bioanalytical advancements have further facilitated lipid mediator metabolipidomic-based profiling of infected and diseased tissues. Yet, the mechanistic basis for the spatiotemporal induction of lipid mediators by bacteria during infectious inflammation is still incomplete. For example which are the cell types that produce SPMs at the site of infection, acting as single cell or by cell–cell interactions via transcellular biosynthesis, and what are the molecular mechanisms that govern the enzymatic pathways involved? Moreover, which are the bacterial virulence factors that dictate the formation of pro-inflammatory leukotrienes and prostaglandins on one hand and SPMs on the other? Recent studies assigned human anti-inflammatory M2-like macrophages as a major cellular source for SPMs [24,25], and bacterial exotoxins (e.g. from *S. aureus* or *E. coli*) emerged as factors that are exploited by the host to generate SPMs via activation of 15-LOX-1 with the minor formation of leukotrienes and prostaglandins [26]. SPM profiles during bacterial infection in mice *in vivo* are well established. However, a major issue in deciphering SPM biosynthetic pathways is the varying regiospecificity of 15-LOX-1 orthologs from different species [118], with the murine ortholog mainly oxygenating AA and DHA in 12- and 14-position, while the human enzyme mainly acts at C15 and C17 respectively [29]. Therefore, SPM profiles obtained in mice might not be readily transferable to humans.

Resolution of infectious inflammation is an active biosynthetic process that connects the first response of the innate immune system to active immunity with various SPMs. The identification of the (G-protein-coupled) receptors of SPMs opens up the possibility for resolution physiology and pharmacology. We are optimistic that the development of SPM mimetics as agonists of SPM receptors or of drugs able to enhance SPM biosynthesis by smart manipulation of lipid mediator networks or of concrete SPM-biosynthetic enzymes may become therapeutic useful agents that may act alone or in combination with antibiotics to better intervene with bacterial life-threatening diseases by targeting the host.

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Conflict of interest

The authors declare no conflict of interest.

Author contributions

PMJ and OW wrote the manuscript.

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