Resolution pharmacology and the treatment of infectious diseases.

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Abstract

Inflammation is a physiological response composed by well-defined and overlapping events that can eliminate pathogens and reestablish homeostasis of tissues. Physiological systems have an elastic capacity to deal with numerous perturbations. Infection may lead to inflammation, tissue damage and disease as consequence of breakdown of tissue resilience. The resolutive phase is a sine qua non condition to achieve homeostasis after acute inflammation. Exuberant or chronic inflammation occurs in diverse infectious diseases. Pro-resolving molecules may be useful for the treatment of certain infections, as these molecules modulate the immune response and avoid the exacerbated/misplaced inflammation unleashed by microbes. Some pro-resolving molecules may also favour pathogen clearance, in addition to decreasing tissue damage. In this review, we discuss the endogenous role and the therapeutic potential of the most relevant pro-resolving molecules in the context of bacterial and viral infections.

Resolution pharmacology and the treatment of infectious diseases

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Abstract:

Inflammation is a physiological response composed by well-defined and overlapping events that can eliminate pathogens and reestablish homeostasis of tissues. Physiological systems have an elastic capacity to deal with numerous perturbations. Infection may lead to inflammation, tissue damage and disease as consequence of breakdown of tissue resilience. The resolutive phase is a *sine qua non* condition to achieve homeostasis after acute inflammation. Exuberant or chronic inflammation occurs in diverse infectious diseases. Pro-resolving molecules may be useful for the treatment of certain infections, as these molecules modulate the immune response and avoid the exacerbated/misplaced inflammation unleashed by microbes. Some pro-resolving molecules may also favour pathogen clearance, in addition to decreasing tissue damage. In this review, we discuss the endogenous role and the therapeutic potential of the most relevant pro-resolving molecules in the context of bacterial and viral infections.

Keywords: Inflammation, resolution pharmacology, pathogen-host interactions, infection, virus, bacteria.

Inflammation and host-microbial interactions

Inflammation is elicited by the host in response to microbes and is believed to be essential for protection against infection. This process starts through the activation of innate immune cells expressing pattern recognition receptors (PRR) which recognize molecular patterns expressed by microorganisms (pathogen-associated molecular patterns (PAMPs) or damage associated molecular pattern (DAMPs) released in response to them. An appropriate inflammatory response involves the coordinated production and release of molecules at the site of infection. This response restrains pathogen proliferation and is necessary for the ensuing adaptive immune response. In general, as the infection is controlled, the inflammatory response is followed by a resolution phase and return to homeostasis. However, excessive, or misplaced inflammation can be detrimental to the host, leading to further tissue damage and eventually death (Garcia et al, 2010; Sousa et al., 2020).

Many endogenous mediators have been described whose major function is to drive the resolution of inflammation. The various classes of mediators of resolution and major representatives in each class is given in Table 1. A review of the data that has led to their classification as pro-resolving molecules is beyond the scope of the current review but can be found at other recent reviews on the subject (see Sugimoto et al., 2019, Panigrahy et al, 2021, Feehan and Gilroy, 2019). As it will be discussed here, these so-called mediators of resolution tend to reduce inflammatory responses and to ameliorate the ability of the host to deal with bacterial and viral infections. As a corollary of the latter findings, we argue that the use of pro-resolving molecules or the activation of endogenous pro-resolving pathways during viral and bacterial infections may hold great promise as therapeutic strategies to avoid excessive inflammation without altering the ability of the host to deal infection.

Resolution pharmacology and its potential as a therapy for infection

We have previously hypothesized that inflammation was a major contributor to tissue dysfunction and death associated with viral and bacterial infections (Garcia et al., 2010; Fagundes et al, 2012; Costa et al., 2022; Araujo et al., 2022; Machado et al., 2020; Melo et al., 2021, Tavares et al., 2022a, Boff et al., 2020). Formal demonstration of this hypothesis in humans was brought about by the COVID-19 (Coronavirus Disease 19) pandemic in which studies clearly showed the central contribution of excessive inflammation to end-organ damage and death associated with infection. SARS-CoV-2 infection caused a profound negative impact

worldwide, leading to overwhelmed healthcare systems and numerous human losses. There are now good vaccines that prevent severe disease and a few antiviral treatments, such as Paxlovid®, that clearly impact disease development if started early in the course of infection (Najjar-Debbiny et al, 2022). For COVID-19, anti-inflammatory strategies, such as use of glucocorticoids and anti-IL-6, may provide additional benefit in severely ill patients (Maskin et al, 2022; Du et al, 2021). We have hypothesized that the use of pro-resolving strategies may be beneficial in the context of COVID-19 (Sousa et al, 2020).

For many other severe infections, such as Influenza, Ebola, and dengue, there are few therapeutic options and effective vaccines. Clearly, in addition to microbial-directed strategies (anti-microbials or vaccines), strategies targeting the host may be beneficial as they potentially have the capacity to treat various infections with similar pathogenic mechanisms. It is possible that targeting inflammation resolution may be beneficial for the host during bacterial and viral infections. In the next sections, we summarize the evidence demonstrating the expression, roles and effects of the best described pro-resolving molecules (see Sugimoto et al. 2019 for a comprehensive review of existing pro-resolving molecules) in the context of bacterial and viral infections. We focus on mediators and infections for which there is more significant data or analysis. We discuss the relevance of mediators of resolution in the context of bacterial and viral infections below and in Supplementary Tables 1 and 2. The latter tables also provide references on the role or effects of mediators of resolution beyond viral and bacterial infections.

Lipid Mediators

- Lipoxin A4 (LXA4)

Lipoxin A4 (LXA4) is an endogenous lipid mediator that has been demonstrated to possess anti-inflammatory and pro-resolutive properties in both sterile inflammation (Zhang et al., 2008; Vachier et al., 2005) and infection (Wu et al., 2015) models. In order to exert its effects, LXA4 binds to the Formyl peptide receptor 2 (FPR2), which is expressed on the membranes of various leukocytes, including macrophages and neutrophils. LXA4 is produced by lipoxygenases (LOs) from arachidonic acid, which also produces pro-inflammatory lipids, such as leukotrienes. Several pre-clinical studies have evaluated the impact of LXA4 during infection using 5-LO, 15-LO, and 12-LO genetically ablated mice. However, it is important to note that these enzymes are associated with the induction of various lipid mediators with both pro- and anti-inflammatory properties. Therefore, these genetically ablated mice will also lack pro-inflammatory lipids, which may certainly impact the final outcomes of the findings.

1.2 - LXA4 and viral infections

Shirey and colleagues found that during Respiratory Syncytial Virus (RSV) infection, macrophages from 5-LO or 15-LO knockout mice failed to develop an alternatively activated phenotypic profile (AA-M) both*in vitro* and *in vivo* . Furthermore, 5-LO and 15-LO mice showed increased perivasculitis in the lungs when compared to their wild-type counterparts. Pharmacological inhibition of lipoxygenases in peritoneal-derived macrophages also inhibited AA-M differentiation (Shirey et al., 2014). In addition, infant patients co-infected with RSV and *Mycoplasma pneumoniae* showed lower LXA4/LTB4 ratios, indicating that LXA4 production may be affected during co-infection (Wu et al., 2016). Taken together, these studies suggest that LXA4 plays a role in the alternative activation of macrophages during RSV infection and subsequent resolution of lung pathology.

The role of LXA4 during Influenza infection is somewhat controversial. Morita and colleagues demonstrated that LXA4 treatment during H1N1 infection in mice did not affect survival or alter levels of chemokines (Morita et al., 2013). In contrast, the inhibition of lipoxin production was associated with increased lethality rates in H5N1-infected mice (Cilloniz et al., 2010). These studies suggest that the role of LXA4 may vary depending on the viral strain.

Since the beginning of the COVID-19 pandemic, a wide range of review articles have suggested the potential therapeutic use of bioactive lipids and SPMs in the context of COVID-19 (see, for example, Batiha et al., 2022; Lee, 2021). However, there is currently limited available data on the topic. One study found a

marked increase in LXA4 levels in the BAL fluid of COVID-19 patients when compared to healthy volunteers (Archambault et al., 2021). However, we have not found any studies that evaluated the effect of these lipids in experimental SARS-CoV-2 infection or COVID-19. Therefore, the role of LXA4 during SARS-CoV-2 infection remains unclear.

1.3 - LXA4 and bacterial infections

Various studies suggest that LXA4 plays a protective role in models of pulmonary infection by *Pseudomonas aeruginosa* (*P. aureoginosa*). Treatment with LXA4 was found to decrease bacterial proliferation and increase the efficacy of antibiotics against *P. aeruginosa* biofilms (Wu et al, 2016; Thornton et al, 2021). LXA4 also prevented *P. aeruginosa* invasion by preventing tight junction disruption and stimulating the protein levels of ZO-1 in cultured airway epithelial cells obtained from patients with cystic fibrosis (Higgins et al, 2016). The significance of LXA4 for these bacteria can be highlighted by the ability of *P. aeruginosa* to develop mechanisms to sabotage the lipoxin system. These bacteria may secrete an epoxide hydrolase called conductance regulator inhibitor (Cif), which disrupts the synthesis of 15-Epi-LXA4 by host cells. In the BAL fluid of cystic fibrosis patients, increased levels of Cif were associated with decreased levels of LXA4, augmented concentration of IL-8, and impaired lung function (Flitter et al, 2017). The epoxide hydrolase secreted by these bacteria also decreased mucociliary transport and hindered bacterial clearance from the lung (Hvorecny et al, 2018). These findings provide compelling evidence that LXA4 contributes to bacterial clearance and host protection during *P. aeruginosa* infection, both in pre-clinical models and in humans.

LXA4 has also been found to have beneficial effects during*Porphyromonas gingivalis* (*P. gingivalis*) infection. LXA4 was shown to decrease the activation of integrin CD11b/CD18, reduce ROS generation in whole blood, inhibit cell activation, and prevent *P. gingivalis* aggregation. In a model of periodontitis induced by *P. gingivalis* , treatment with a stable analog of LXA4 limited neutrophil recruitment and tissue injury in the oral cavity (Börgeson et al, 2011). Additionally, both human neutrophils exposed to *P. gingivalis* and a mouse model showed increased COX-2 levels, which were decreased with LXA4 treatment (Pouliot et al, 2000). Furthermore, LXA4 was found to promote autophagy and inhibit the inflammasome in RAW264.7 cells exposed to *P. gingivalis* lipopolysaccharide (PgLPS) (Zhao et al, 2021).

Treatment of mice with 15-Epi-LXA4 during peak lung inflammation led to the clearance of *Escherichia coli* (*E. coli*) and promoted neutrophil apoptosis and efferocytosis (Sekheri et al, 2020). Treatment was effective in reducing the levels of IL-6 and TNF when administered in combination with antibiotics (Ueda et al, 2014). Other studies have also shown the potential therapeutic benefits of LXA4 during lung inflammation (Wu et al, 2014). During UV-killed *E. coli* exposure in human skin, LXA4 and other SPMs were synthesized in a time-dependent manner, which coincided with the expression of the FPR2 receptor and the start of the resolution phase (Motwani et al, 2018). Additionally, stable analogs of LXA4 demonstrated beneficial effects in treating*Salmonella typhimurium* (*S. typhimurium)* infection, pneumococcal pneumonia, LPS-induced lung injury, and cecal ligation and puncture (CLP) in a rat model (see Supplementary Table 1) (Gewirtz et al, 1998; Siegel et al, 2021; Qi et al, 2015; Walker et al, 2011; Wu et al, 2014).

However, in the case of *Klebsiella pneumoniae* (*K. pneumoniae)* pneumosepsis in mice, levels of LXA4 were increased in the early stage of sepsis and were associated with local and systemic infection, leading to high mortality rates. Treatment with LXA4 during early sepsis worsened the infection, while late treatment improved survival by reducing excessive inflammation (Sordi et al, 2013). Moreover, our research group showed that LXA4 treatment hindered the migration of dendritic cells in the joint during *Staphylococcus aureus* (*S. aureus*) infection, which was crucial in reducing bacterial burden (Boff et al, 2020). Overall, these findings suggest that the development of lipoxin-based therapies may not be straightforward, as the type of bacteria and the timing of therapy initiation may significantly impact the effectiveness of LXA4 or its analogues.

2.1 - Resolvin D (RvD), E (RvE) and T (RvT) series

Resolvins are potent mediators that promote resolution of inflammation and are synthesized from the lipids docosahexaenoic acid (DHA), eicosapentaenoic acid (EPA), and n-3 docosapentaenoic acid (n-3DPA) (Serhan

and Levy, 2018). These pro-resolution molecules are synthesized in a coordinated manner by macrophages and neutrophils to counteract inflammation and promote resolution in the affected tissue. Resolvins exert their actions by binding to different membrane receptors, such as FPR2, ERV1, DRV1, and DRV2, expressed by diverse types of cells (Chiang and Serhan, 2017).

2.2 - Resolvins and viral infections

Most studies on resolvins and viruses have focused on respiratory viruses, including SARS-CoV-2 infection. One study found no difference in serum or plasma levels of Resolvins D1 to D5 between healthy volunteers and COVID-19 patients (Regidor et al, 2021). Meanwhile, another study found downregulated levels of RvD1 and RvD3 in the plasma of critically ill COVID-19 patients (Palmas et al, 2021). However, a small sample size may have contributed to the inconsistency between these findings. Decreased systemic levels of RvD1 and RvE4 were linked to poor prognosis and reduced survival of patients with COVID-19 (Palmas et al, 2021). In contrast, levels of all RvD1 to D5 (except RvD3) were higher in the BAL fluid of COVID-19 patients compared to control individuals (Archambault et al, 2021), potentially reflecting an attempt by the host to dampen inflammation in the lungs. Additionally, a RvD6 isomer decreased the expression of ACE2 receptor and pro-inflammatory cytokine levels *in vitro* (Pham et al, 2021). Finally, treatment of macrophages with RvD1 and RvD2 upon SARS-CoV-2 infection reduced levels of TNF, IL-6, IL-8, CCL2, and CCL3 cytokines (Recchiuti et al, 2021). Although data on endogenous levels of these molecules during COVID-19 are still elusive, their exogenous administration may hold great promise against the disease.

During coinfection with *Streptococcus pneumoniae* (*S. pneumoniae*) and influenza A virus (H3N2), treatment with AT-RvD1 during the acute phase of infection ameliorated lung inflammation in mice, reducing neutrophil elastase activity, parenchymal inflammation, infiltrated neutrophils, and monocytes. *In vitro* , RvD1 treatment decreased TNF and IL-8 mRNA during H3N2 infection (Wang et al, 2017). Additionally, BALB/C mice infected with H3N2 and treated with RvD1 had reduced airway inflammation and phosphorylation of NF-ϰB p65 and IkBα (Guo et al, 2020). Importantly, in both studies, RvD1 did not affect viral titers of H3N2. In line with this findings, Morita and colleagues showed that treatment with RvD1 or RvD2 in A549 cells did not decrease viral titers during H1N1 infection (Morita et al, 2013). Similarly, topical treatment with RvD1 in rats infected with herpes simplex virus (HSV) did not decrease viral titers at different time points analyzed, although it decreased parameters of inflammation in the cornea of infected rats (Rajasagi et al, 2017). This suggests that RvD1 modulates the host response without altering its capacity to deal with pathogen replication.

In the context of RSV infection, different subtypes of resolvins may have varying effects on the host. For instance, treatment with RvD1 was found to be associated with increased viral loads in the lungs and a lower antibody response upon reinfection in mice (de Freitas et al., 2021). Conversely, RvE1 was shown to be beneficial against RSV: RvE1 treatment restored the M2 phenotype of macrophages that were infected with RSV (Shirey et al., 2014). Furthermore, RvE1 was found to have beneficial effects against HSV-1. RvE1 treatment decreased inflammation caused by HSV-1 infection in the cornea, reduced the levels of IL-6, IFN-γ, and CXCL-1, and increased the levels of IL-10 (Rajasagi et al., 2011). Taken together, these studies demonstrate that resolvins can alleviate inflammation caused by viruses, in addition to stimulating markers of resolution, such as M2 macrophage polarization. Overall, these molecules show great promise in the fight against viral infections.

2.3 - Resolvins and bacterial infections

A wide range of studies have demonstrated the effects of resolvins in various model of bacterial infections. For example, treatment with RvD1 reduced inflammation and neutrophil infiltrates during *P. aureoginosa* infection in mice (Lee et al., 2022). In the case of*Citrobacter rodentium* (*C. rodentium*) infection, post-infection treatment with RvD1 plus RvD5 decreased bacterial loads, reduced inflammation, and rescued mice from lethality (Diaz et al., 2017). Accordingly, administration of RvD2 limited neutrophil infiltration, enhanced phagocytosis and bacteria clearance, and expedited inflammation resolution in *Escherichia coli* (*E. coli*) and *S. aureus* infections (Chiang et al., 2015). RvD3 treatment improved bacterial clearance, efferocytosis, and

accelerated resolution during peritonitis induced by *E. coli* infection, making it a promising agent against *E. coli* (Norris et al., 2018). Additionally, treatment with approximately 0.1nM concentrations of RvD4 proved effective against *S. aureus* infection in mice (Winkler et al., 2016). *In vitro* studies also demonstrated the immune modulation of RvD1, RvD2, and RvD5 during *E. coli*infection in human macrophages, resulting in a decrease in the production of pro-inflammatory cytokines (Palmer et al., 2011; Werz et al., 2018).

Resolvins have shown efficacy in both sepsis and sepsis-like models. For instance, in a murine model of sepsis induced by cecal ligation and puncture (CLP), delayed systemic treatment with RvD1 increased bacterial clearance, improved mouse survival, and decreased neutrophil influx and cytokine production, such as TNF (Chen et al., 2014). In a model of sepsis induced by D-galactosamine (GalN), mice treated with RvD1 concurrently with D-GalN injection exhibited a lower number of neutrophil accumulations and decreased levels of HMGB1 and CCL2 in serum (Murakami et al., 2011). Other studies have demonstrated the potential of RvD1, RvD2, RvE1, and AT-RvD1 treatment, as well as the protective effect of endogenous levels of these lipids, in various sepsis models. These treatments increased mouse survival, reduced bacterial load, and suppressed pro-inflammatory cytokine production (Chiang et al., 2012; Chen et al., 2020; Silva et al., 2021; Svahn et al., 2016, see Table 1 and Supplementary Table 1). Importantly, administration of RvD1 in conjunction with antibiotics expedited the resolution of peritonitis, indicating the potential of resolvins to be used as adjutants in traditional bacterial infection and septic condition treatments (Chiang et al., 2012).

RvD1 has garnered significant attention in pre-clinical models of lung infection due to its ability to ameliorate lung damage, reduce inflammation, and decrease bacterial loads. Studies conducted in mice have demonstrated the positive effects of RvD1 or AT-RvD1 treatment in response to various pathogens such as *E. coli* , *P. aeruginosa* , and Nontypeable Haemophilus influenzae (NTHi) (Codagnone et al., 2018; Croasdell et al., 2016; Abdulnour et al., 2016; Wang et al., 2017; Sekheri et al., 2020; Isopi et al., 2020; Bhat et al., 2021). These effects of RvD1 were primarily attributed to a significant decrease in neutrophil accumulation. Additionally, RvD1 could accelerate the resolution phase in the lungs, either alone or in combination with antibiotics against *P. aureoginosa* (Gao et al., 2020). Other classes of resolvins, such as RvE1 and RvD2, also demonstrated beneficial effects. RvD2 decreased bacterial load in the lungs during*P. aeruginosa* infection (Walker et al., 2022; Sundarasivarao et al., 2022). Treatment with RvE1 in mice decreased neutrophil accumulation, improved *E. coli* clearance, and dampened cytokine production (Seki et al., 2010).

In summary, these results demonstrate that resolvins, especially RvD1, show promise as therapeutic candidates against a range of bacterial infections, either alone or in combination with antibiotic treatments.

3.1 - Maresins

Maresins are lipid metabolites derived from DHA (docosahexaenoic acid) and are produced by macrophages and neutrophils. They possess potent anti-inflammatory and pro-resolving properties (Serhan et al., 2009). Furthermore, recent research has revealed the existence of different conjugates of maresins that are generated through enzymatic hydrolysis in the tissue. These conjugates are known as maresin conjugates in tissue regeneration (MCTRs) (Levy et al., 2020).

3.2 - Maresins and viral infections

Limited data is currently available regarding the role of maresins during viral infections. In the context of SARS-CoV-2 infection, it has been observed that the levels of maresin-1 and maresin-2 were significantly higher in the serum of severe COVID-19 patients compared to healthy volunteers (Regidor et al., 2021). However, these lipids were not detected in the bronchoalveolar lavage (BAL) fluid of COVID-19 patients, although an increase in other specialized pro-resolving mediators (SPMs) was observed (Archabault et al., 2021). Additionally, in the case of respiratory syncytial virus (RSV) infection, maresin-1 has shown promising effects. It was found that maresin-1 reduced inflammation, viral transcripts, and increased the production of IFN-β during RSV infection by binding to the LGR6 receptor (Krishnamoorthy et al., 2023). However, more comprehensive studies are needed to further investigate the potential of maresins in experimental viral infections and to understand better their role in viral pathogenesis.

3.3 - Maresins and bacterial infections

A study conducted by Jiang et al. (2022) revealed that daily supplementation of *Lactobacillus casei* (*L. casei*) during the intensive phase of tuberculosis led to an upregulation of various bioactive lipids, including Maresin 1. Plasma levels of these lipids showed a strong correlation with the downregulation of pro-inflammatory cytokines. Additionally, supplementation with enriched marine oil increased the levels of different lipids, particularly MaRn-3 DPA, in the plasma of healthy volunteers. Notably, individuals receiving the supplementation exhibited higher phagocytic capacity of *S. aureus*by neutrophils compared to the placebo group, indicating the effectiveness of specialized pro-resolving mediators (SPMs) in modulating peripheral blood cells (Souza et al., 2020). *In vitro*studies have demonstrated that maresin-1 production by M2 macrophages is stimulated during *E. coli* infection. Moreover, maresin-1 has been shown to limit the infection of human macrophages by *M. tuberculosis* , thereby reducing inflammation (Werz et al., 2018; Ruiz et al., 2019). *In vivo* experiments involving coinfection with influenza A virus (IAV) and *Streptococcus pneumoniae* demonstrated that administration of MCTR1 plus MCTR3 or MCTR3 alone resulted in reduced lung inflammation and bacterial load at different time points post-infection (Tavares et al., 2022b). These findings, like those observed with lipoxin A4 (LXA4), indicate a potential beneficial role for maresins in the treatment of bacterial infections. However, further research is needed to fully understand and explore their therapeutic potential in this context. Additional studies are necessary to investigate the mechanisms of action, optimal dosing, and potential synergistic effects of maresins with other treatments.

4.1 - Protectins

Protectins, like other specialized pro-resolving mediators (SPMs), are derived from docosahexaenoic acid (DHA) and are produced by hydrolases. These bioactive lipids exhibit potent pro-resolving actions, even at nanomolar and picomolar concentrations (Hansen et al., 2019; Schwab et al., 2007). They exert their effects on various cell types, including macrophages, neutrophils, and glial cells (Marcheselli et al., 2003; Schwab et al., 2007; Hong et al., 2003). Notably, recently discovered conjugated lipids with similarities to protectins have also been found to possess pro-resolving properties. One example is protectin conjugates in tissue regeneration 1 (PCTR1) (Dalli et al., 2015). These conjugated lipids expand the repertoire of pro-resolving molecules and contribute to the resolution of inflammation and tissue regeneration.

4.2 - Protectins and viral infections

Although there is limited data available, the existing studies suggest a promising role for protectins in viral infections. For instance, during HSV-1 infection, treatment with protectin D1 (PD1) reduced inflammation in stromal keratitis lesions by decreasing pro-inflammatory cytokine levels and increasing IL-10 levels (Rajasagi et al, 2013). In murine models, intranasal therapeutical administration of PD1 or protein conjugates in tissue regeneration 1 (PCTR1), which is also derived from docosahexaenoic acid (DHA), decreased viral load, tissue lesions, and prevented the decrease of IFN-λ caused by RSV in the lungs. Moreover, these lipids increased IFN-λ levels in human bronchial epithelial cells infected with RSV (Walker et al, 2021). PD1 also demonstrated antiviral effects against H1N1 and H5N1 in vitro in A549 cells and improved survival in mice infected with the PR8 strain of H1N1 (Morita et al, 2013). Notably, the levels of PD1 were downregulated in the lungs of mice infected with the pathogenic H5N1 strain of influenza (Morita et al, 2013). These findings collectively indicate that PD1 may modulate a common host antiviral pathway, making it an intriguing molecule for further investigation in the context of viral infections.

4.3 - Protectins and bacterial infections

Bacterial infections have been found to influence PD1 levels. For instance, infection with *Borrelia sp.* was shown to increase PD1 levels in the joints of mice (Blaho et al., 2009). Similarly, in a model of antibiotic-induced dysbiosis in mice, *Clostridium butyricum*(*C. butyricum*) infection led to elevated levels of PD1, resulting in increased concentrations of IL-10, TGF-β1, and IL-4 produced by CD4+ T cells in the intestinal tract (Ariyoshi et al., 2021). These findings suggest that PD1 plays an important endogenous role in these specific contexts. Moreover, PD1 treatment has demonstrated positive effects on bacterial infections. In vitro studies have shown that PD1 treatment improves the uptake of *E. coli* by human macrophages and

neutrophils (Hamidzadeh et al., 2022; Chiang et al., 2012). In a mouse model of peritonitis, activation of the G-protein coupled receptor 37 (GPR37) by PD1 during *Listeria monocytogenes* (*L. monocytogenes*) infection prevented mouse mortality, and PD1 treatment resulted in decreased bacterial load in peritoneal fluids (Bang et al., 2021). Although these studies are preliminary, they suggest a promising role for PD1 and its potential therapeutic effects against bacterial infections.

5.1 - Annexin A1 (AnxA1)

Annexin A1 (AnxA1) is a protein consisting of 346 amino acids that is synthesized by various cell types including macrophages, neutrophils, lung fibroblasts, and epithelial cells. AnxA1 expression is increased upon administration of glucocorticoids. It was initially discovered as an inhibitor of Phospholipase A2. Several pre-clinical studies have provided evidence for both the endogenous pro-resolving role and the therapeutic potential of AnxA1 (Flower et al., 1979; Ernst et al., 1990; Hannon et al., 2002).

5.2 - AnxA1 and viral infections

Annexin-A1 (AnxA1) exhibits a complex relationship with various viruses. In addition to its involvement in resolving inflammation, recent studies have demonstrated its interaction with several processes crucial for the replication of specific viruses and antiviral host responses. For instance, AnxA1 was found to enhance the expression of the cytoplasmic sensor retinoic acid-inducible gene I (RIG-1) both before and after infection with influenza A virus (IAV) in A549 cells (Yap et al., 2020). Furthermore, the overexpression of AnxA1 resulted in an increase in IFN-β levels, while silencing AnxA1 impaired IFN-β and IFN-stimulated responsive element activation. This stimulation of IFN-β expression occurs through a physical interaction between AnxA1 and a cytoplasmic protein known as tank binding kinase 1 (TBK-1) (Bist et al., 2013). Interestingly, Ma et al. demonstrated that the 3A protein of foot and mouth disease virus (FMDV) hinders the formation of the AnxA1-TBK-1 complex, thereby inhibiting the AnxA1-mediated increase in IFN-β (Ma et al., 2022). The inhibitory effect of AnxA1 has also been observed in hepatitis C virus (HCV) infection. *In vitro* studies using human hepatoma cell line Li23-derived D7 cells, which express exogenous AnxA1, showed a significant inhibition of viral RNA replication compared to wild-type cells, demonstrating the inhibitory effect of AnxA1 against HCV (Hiramoto et al., 2015).

Significantly, it has been shown that AnxA1 can facilitate viral binding and/or replication in several viral infections. In the case of reovirus and measles virus infections *in vitro* , AnxA1 promotes the formation of syncytia both within the cytoplasm and in the extracellular space (Ciechonska et al., 2014). Regarding HIV, solid evidence suggests that the FPR2 receptor serves as a co-receptor for viral entry, independent of AnxA1 (Shimizu et al., 2008; Nedellec et al., 2009; Jiang et al., 2011; Cashin et al., 2013). Furthermore, herpes virus and IAV exploit the AnxA1 pathway by utilizing the FPR2 receptor to enhance virus uptake by host cells. Both the glycoprotein E (gE) of herpes virus and the envelope protein of IAV bind to AnxA1 and utilize FPR2 for cell entry (Wang et al., 2022; Arora et al., 2016; Tcherniuk et al., 2016).

In the case of IAV infection, the AnxA1/FPR2 axis triggers specific signaling pathways that favor various steps of viral replication, including endosomal export of the virus, endosomal trafficking to the nucleus, and enhanced autophagy and apoptosis (Rahman et al., 2018; Arora et al., 2016; Cui et al., 2020). Consequently, FPR2 inhibitors have shown antiviral effects against H1N1, H3N2, H6N2, and Influenza B viruses (Courtin et al., 2017). Recent findings indicate that IAV infection stimulates the release of exosomes that downregulate several genes involved in the inflammatory response, including the AnxA1 gene (Zabrodskaya et al., 2022). Additionally, in vitro studies have demonstrated that H1N1 infection upregulates the expression of FPR2 (Ampomah et al., 2018), likely as a strategy to promote disease progression. However, treatment with AnxA1 prior to IAV infection has been shown to expand the population of alveolar macrophages and increase the survival of mice, considering the well-known protective role of these cells against IAV (Schloer et al., 2019). Collectively, these results may appear contradictory, but they highlight that the effect of a particular protein can depend on the timing of treatment initiation. In the latter study, the immunomodulatory role of AnxA1 proved to be beneficial in the context of the infection, despite its known involvement in pathways that facilitate viral replication.

The role of AnxA1 in the context of COVID-19 remains elusive. Canacik and co-workers have demonstrated a decrease in systemic levels of AnxA1 in severe COVID-19 patients compared to healthy volunteers and the moderate disease group. In contrast, Ural and colleagues have shown that patients with severe disease exhibit increased levels of AnxA1 compared to mild COVID-19 individuals or healthy controls (Canacik et al., 2021; Ural et al., 2022). An integrative analysis of multi-platform omics has revealed AnxA1 as a potential therapeutic target against SARS-CoV-2 infection (Li et al., 2021). Indeed, this may reflect the host response during COVID-19, as the levels of AnxA1 were found to be up-regulated in circulating monocytes of convalescent patients (Wen et al., 2020). Future investigations will provide clarity on the potential utilization of AnxA1 or its mimetic peptides as therapeutic agents to mitigate inflammation and accelerate the resolution process in the context of COVID-19.

Recent studies conducted by our group have demonstrated that in murine models of Dengue virus (DENV) and Chikungunya (CHIKV) virus infection, mice lacking AnxA1 (AnxA1KO) and mice lacking the FPR2 receptor (FPR2KO) exhibited increased inflammation without significant differences in viral loads compared to wild-type (WT) mice. Importantly, treatment with $Ac_{2\text{-}26}$ resulted in decreased production of pro-inflammatory cytokines and reduced tissue damage in both DENV and CHIKV infections, while viral titers remained unaffected (Costa et al., 2022; de Araújo et al., 2022). These findings suggest that AnxA1 may hold promise as a therapeutic target against these viruses by suppressing excessive inflammation. Finally, the combination of antiviral agents with AnxA1-based therapies holds great potential as an ideal synergistic strategy for treating these conditions.

Overall, these results demonstrate that the effects of AnxA1 can be either beneficial or detrimental depending on the specific viral type. The potential use of FPR2 inhibitors or AnxA1 monoclonal antibodies shows great promise in the treatment of certain viral infections, such as HSV and IAV. However, it is crucial to conduct clinical trials and human studies to determine whether the findings observed in mouse models can be replicated in human diseases. Additionally, stimulating the AnxA1/FPR2 axis may offer improved prognostic outcomes against certain infections, such as DENV and CHIKV infections.

5.3 - AnxA1 and bacterial infections

To date, most studies on AnxA1 during bacterial infections have focused on its endogenous role and the importance of its receptor in containing inflammation and promoting resolution. Limited data is available regarding the exogenous administration of AnxA1 as a potential therapy. For example, research has shown that mice lacking the FPR2 receptor (FPR2KO) were more susceptible to meningitis induced by *Streptococcus suis* (*S. suis*), while treatment with AnxA1, which binds to FPR2, reduced bacterial burden in the brain, lowered the production of IL-6 and CXCL1, and decreased neutrophil infiltration into the brain (Ni et al., 2021). Beneficial effects of AnxA1 have also been observed in other bacterial infections. The absence of AnxA1 impaired the host response against *Mycobacterium tuberculosis* and resulted in a transient increase in bacterial burden in the spleen (Vanessa et al., 2015). Interestingly, the inhibition of Phosphodiesterase-4 (PDE-4) with Rolipram, combined with antibiotic treatment, reduced bacterial burden and inflammation during pneumococcal pneumonia in mice, and was associated with increased AnxA1 expression levels (Tavares et al., 2016). In a murine model of *S. pneumoniae* infection, $Ac_{2\text{-}26}$ treatment decreased lung lesions and bacterial load in the lungs of wild-type (WT) mice, but this effect was not observed in FPR2KO mice, indicating that the beneficial effects of the AnxA1 mimetic peptide occur through the FPR2 receptor (Machado et al., 2020). AnxA1 has been found to bind to *Vibrio cholerae* (*V. cholerae*) and Lactobacillaceae in the gut, and *V. cholerae* can interfere with AnxA1 dynamics by secreting proteases that cleave AnxA1 into different fragments, suggesting the importance of this molecule for the pathogen (Zoued et al., 2021). While these findings are intriguing, they are not conclusive, and they demonstrate that bacteria can also affect AnxA1 dynamics and modulate the capacity of the host to deal with pathogens through perturbations of the AnxA1/FPR2 signaling pathway.

6. – Other potential pro-resolving molecules

6.1. α-MΣH

α-MSH and its derived peptides have been extensively studied for over 30 years due to their potential anti-inflammatory properties in various microbial infections, including fungal, bacterial, and viral infections (Cutuli et al., 2000; Catania et al., 1998a; Catania et al., 2000). These peptides are part of the melanocortin system, which includes adrenocorticotropic hormone (ACTH), α-, β-, and γ-melanocyte-stimulating hormones (α-, β-, γ-MSHs) (Dinparastisaleh et al., 2021). Despite the presumed potential of α-MSH, only a few studies have explored the role of this molecule during infections. There are different melanocortin receptors (MC1R-MC5R), and most of the anti-inflammatory or pro-resolving effects are attributed to MC1R or MC3R.

6.2 - α-MΣH ανδ ιραλ ινφεστιονς

Limited data is currently available regarding the role of α-MSH in viral infections. Most studies have primarily focused on conducting *in vitro* experiments and analyzing circulating levels of α-MSH in humans during viral infections. However, to date, there have been no studies that definitively demonstrate the pro-resolutive effect of α-MSH treatment in mouse models of viral infections or in human clinical studies. Nevertheless, certain findings have indicated that systemic levels of α-MSH were higher in HIV patients compared to controls. Notably, an association was observed between elevated levels of α-MSH and reduced levels of IL-6, as well as a decrease in disease progression (Catania et al., 1993; Airaghi et al., 1999; Catania et al., 1994). Furthermore, α-MSH-derived peptides were found to decrease HIV replication in monocytic cell lineages (Barcellini et al., 2000). In addition, α-MSH demonstrated a reduction in the production of IL-1β and TNF induced by the viral protein gp120 in whole blood samples obtained from HIV patients (Catania et al., 1998b). However, the specific receptors through which α-MSH mediates these mechanisms remain unknown, despite its promising *in vitro* effects against HIV.

6.3 - α-MΣH ανδ βαστεριαλ ινφεστιονς

Despite viral infections, the literature provides solid evidence demonstrating the antibacterial capacity of α-MSH and its derived peptides. Several derived peptides and analog molecules of α-MSH have shown effectiveness against E. coli, Methicillin-resistant*Staphylococcus aureus* (MRSA), and *S. aureus* (please refer to Supplementary Table 2 for specific references). In terms of the molecule's pro-resolutive effects, research has found that α-MSH treatment leads to a decrease in the phagocytosis of unopsonized*E. coli* and *S. aureus* , inhibition of NO production by RAW 264.7 cells, downregulation of TLR2 expression induced by *S. aureus* , and a reduction in IL-6 levels while mitigating fever induced by LPS in rats (Phan and Taylor, 2013; Star et al., 1995; Ryu et al., 2015; Huang and et al, 1998). In a mouse peritonitis model, administration of the agonist AP214 prior to zymosan injection inhibited cell infiltration via MC3R. *In vitro* experiments also demonstrated that AP214 reduced the release of TNF, IL-6, and IL-1β by primary peritoneal macrophages stimulated with zymosan via MC3R. However, it is important to note that AP214 stimulated the uptake of zymosan particles and apoptotic neutrophils by macrophages (Montero-Melendez et al., 2011). These studies strongly suggest that both α-MSH and its agonist exert pro-resolutive effects against bacterial infections, and these effects may be mediated by MC3R.

7.1. Glucocorticoid-induced leucine zipper (GILZ)

Glucocorticoid-induced leucine zipper (GILZ) is a crucial component of the anti-inflammatory response. It is a protein consisting of 137 amino acids and is rapidly induced by the administration of glucocorticoids in various cell types. GILZ serves dual functions as a transcription factor, activating different genes, and as a cytoplasmic protein, interfering with various signaling pathways (Ronchetti et al., 2015; Bruscoli et al., 2021; Bereshchenko et al., 2019).

7.2 - GILZ and viral infections

To date, no studies have demonstrated the pro-resolutive effect of GILZ during viral infections. In fact, research has shown that GILZ binds to STAT1 and hinders its translocation to the nucleus, thereby reducing the expression of type I interferon-induced genes (Nataraja et al., 2022). This suggests that GILZ may have a detrimental impact on the host during certain viral infections. Additionally, studies have revealed that the infectious bursal disease virus (IBDV) thwarts the ubiquitination and degradation of GILZ in the

cytoplasm through the viral protein VP4, leading to the inhibition of type I interferon production *in vitro* . Knockdown of GILZ using siRNA significantly impeded IBDV replication (He et al., 2018; Li et al., 2013). Further investigations are required to establish the precise role of GILZ during viral infections.

7.3 - GILZ and bacterial infections

Recent findings from our group have shed light on the role of GILZ during bacterial infections. Studies using GILZ knockout (KO) mice have shown that these mice exhibit decreased bacterial clearance and enhanced lung lesions when infected with *Streptococcus pneumoniae* . Conversely, the introduction of a cell-permeable transactivator of transcription (TAT)-GILZ fusion protein increased macrophage phagocytosis and reduced bacterial load in the lungs (Souza et al., 2022). TAT-GILZ treatment also enhanced macrophage influx with a regulatory phenotype in a model of *E. coli* -induced peritonitis in mice, accompanied by increased production of IL-10 and TGF-β levels, efferocytosis and bacterial clearance (Grossi et al, 2023). Intriguingly, monocytes isolated from septic patients displayed lower expression of GILZ. However, when GILZ was overexpressed specifically in macrophages and monocytes, bacterial clearance was enhanced in a cecal ligation and puncture (CLP) mouse model (Ellouze et al., 2020). Supporting these findings, upregulation of GILZ in immune cells was associated with reduced mortality induced by lipopolysaccharide (LPS) in mice (Ng et al., 2020). Conversely, downregulation of GILZ in macrophages led to increased phagocytic activity during *S. typhimurium* infection *in vitro* (Hoppstädter et al., 2019). Therefore, the role of GILZ during bacterial infections appears to be dependent on the specific cell type and bacterial strain. These results suggest the potential for developing targeted treatments tailored to specific bacterial strains in human infections. Drug delivery systems that selectively upregulate GILZ levels in macrophages may be beneficial in certain bacterial infections, rather than increasing its systemic levels across all cell types. Nonetheless, further studies are needed to gain a better understanding of these complex dynamics.

8. Angiotensin-(1-7) - a proof of concept:

8.1 Angiotensin-(1-7) [Ang-(1-7)] and its first finds

Angiotensin-(1-7) (Ang-(1-7)) is an important component of the Renin-Angiotensin System (RAS), which regulates blood pressure and electrolyte balance (Santos et al, 2018). It is a heptapeptide with therapeutic potential demonstrated in the late 1980s by reducing blood pressure in an *in vivo* model (Campagnole-Santos et al., 1989). Ang-(1-7) is generated by the catalysis of Angiotensin I (Ang I) or mostly Angiotensin II (AngII) by the Angiotensin-Converting Enzyme (ACE) 2 anchored in the cytoplasmic membrane of the cell. Ang-(1-7) and AngII usually have opposing effects and act by binding specifically to its Mas receptor (MasR) which is a type of G protein-coupled receptor (GPCR). Activation of this receptor leads to a signaling cascade that triggers the production of nitric oxide. This ACE2/Ang-(1-7)/MasR axis is then called the RAS alternative pathway and is usually referred to as the protective counterpart of the RAS. Counter-regulation of AngII signaling by Ang-(1-7) reduces reactive oxygen species (ROS) generation, cell proliferation, fibrosis, and controls inflammation pathways by decreasing TGF-β/NF-kB signaling and proinflammatory molecules (Sampaio et al, 2007; Gallagher and Tallant, 2004; Ni et al, 2012). As a result, the administration of Ang-(1-7) or MasR agonists has emerged as a potential therapeutic strategy to counteract the negative effects of Ang II in various diseases. Finally, the discovery of Ang-(1-7) and its role as a protective peptide in the RAS alternative pathway has opened new avenues for research and therapeutic interventions. Further studies are needed to fully elucidate the molecular mechanisms and clinical implications of Ang-(1-7), but its therapeutic potential in modulating the RAS and mitigating the detrimental effects of Ang II holds great promise.

In addition to its well-established effects on the cardiovascular and renal systems, numerous studies have now demonstrated the anti-inflammatory and pro-resolving properties of (Ang-(1-7) in various models of chronic and acute non-infectious inflammation. These models include asthma, arthritis, and ischemia. Studies have shown that Ang-(1-7) exerts beneficial effects in these inflammatory conditions. For example, it has been found to reduce airway inflammation and improve lung function in asthma models (El-Hashim et al., 2012; da Silveira et al., 2010). In arthritis models, Ang-(1-7) has been shown to attenuate joint inflammation

and cartilage destruction (Zeng et al., 2009). Additionally, in ischemia models, Ang-(1-7) has demonstrated protective effects by reducing tissue damage and promoting tissue repair (Jiang et al., 2012; Santos et al., 2014).

The underlying mechanisms by which Ang-(1-7) exerts its anti-inflammatory and pro-resolving effects are multifaceted. Figure 1 provides a comprehensive overview of the documented effects of therapeutic administration of Ang-(1-7) in various models of viral and bacterial infections. In mouse models and *in vitro* experiments, Ang-(1-7) has been found to induce apoptosis of neutrophils and eosinophils, promote the clearance of apoptotic cells (efferocytosis), facilitate the migration of macrophages, and induce the polarization of macrophages towards an M2 anti-inflammatory phenotype (de Carvalho Santuchi et al., 2019; Melo et al., 2021; Barroso et al., 2017; Magalhaes et al., 2018; Pan et al., 2021). Cellular and molecular actions contribute to the resolution of inflammation, tissue repair, and the restoration of homeostasis. Findings from these studies highlight the potential therapeutic implications of Ang-(1-7) in the management of various inflammatory conditions. However, further research is still needed to fully understand the precise mechanisms underlying its effects and to explore its therapeutic potential in clinical settings.

8.2 Ang-(1-7) and viral infections

Recent studies have shed light on the involvement of the Renin-Angiotensin System (RAS) in the pathogenesis of various viral infections. Specifically, in models of Influenza A infection caused by strains such as H7N9 and H5N1, the deficiency of angiotensin-converting enzyme 2 (ACE2), which is responsible for converting Angiotensin II (AngII) into Ang-(1-7), has been shown to intensify the pathogenesis and lead to acute lung injury (ALI) associated with increased morbidity. Absence of ACE2 results in an increase in inflammation, primarily due to the activation of the Type 1 receptor (AT1R) by AngII. This dysregulation of the ACE2/Ang-(1-7)/AT1R axis contributes to the exacerbation of lung inflammation and injury in response to Influenza A infection (Zou et al., 2014). Interestingly, administration of ACE2 has been found to improve acute inflammation caused by Influenza A (H5N1) infection, suggesting a potential therapeutic approach (Zou et al., 2014). In patients with severe influenza A (H7N9) infection, an elevation in plasma levels of AngII has been observed and strongly associated with disease progression (Yang et al., 2014). This further supports the notion that dysregulation of the RAS system, specifically an imbalance between AngII and Ang-(1-7), contributes to the severity of viral infections and their associated inflammatory responses. These findings highlight the importance of the RAS system in viral infection pathogenesis and suggest that modulation of this system, such as restoring the balance between AngII and Ang-(1-7), may have therapeutic potential in mitigating the inflammatory response and improving outcomes in severe viral infections. However, further research is needed to fully understand the complex interactions between the RAS system and viral infections and to explore the potential of targeting this system for therapeutic interventions.

In addition to AngII, studies have evaluated the relevance of Ang-(1-7) and its Mas receptor. Our observations revealed that oral administration of Ang-(1-7) reduced mortality and attenuated excessive inflammation by promoting resolution effects such as apoptosis and efferocytosis of neutrophils following Influenza A (H1N1) infection. These effects were associated with a decrease in viral load and lung injury. Importantly, the success of Ang-(1-7) treatment was directly linked to the presence of the Mas receptor, as the absence of this receptor worsened the infection, leading to 100% mortality (Melo et al., 2021).

8.3 Ang-(1-7) and bacterial infections

In the context of bacterial infection, treatment with Ang-(1-7) has shown promising benefits in reducing lung bacterial load, sepsis, and mortality associated with pneumococcal infection following Influenza A virus infection (Melo et al., 2021). Another significant finding of Ang-(1-7) is its ability to restore the phagocytic capacity of neutrophils in mice with experimental Type 2 Diabetes Mellitus, enabling them to effectively phagocytize bacteria such as *Staphylococcus aureus* , which is known to cause lung infections (Soto et al., 2019). In the context of bacterial infection, Ang-(1-7) has also been found to suppress macrophage polarization towards the M1 phenotype and promote a shift towards the M2 phenotype in a model of polymicrobial sepsis induced by cecal ligation and puncture (CLP). This modulation of macrophage phenotype reduces

excessive inflammation (Pan et al., 2021). Additionally, in the same CLP model, Ang-(1-7) has been shown to attenuate mortality by mitigating the exaggerated inflammatory response, oxidative stress, and apoptosis (Tsai et al., 2018). These results highlight the protective effects of Ang-(1-7) against infections and emphasize that modulation of the RAS can be beneficial in promoting the resolution of inflammation associated with infections.

Conclusion

Pro-resolving molecules modulate a range of pathways associated with tissue inflammation and damage during viral and bacterial infections and provide overall beneficial effects and earlier control of infection and restoration of tissue homeostasis. These beneficial effects in inflammation without altering the ability of the host to deal with infection are the basis for the development of pro-resolving molecules or their mimetics as co-adjuvant treatment of infection. In addition, these molecules appear to provide anti-inflammatory, pro-resolving and, at times, anti-infective benefit, without the known undesirable and immunosuppressive effects of glucocorticoids.

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Table 1 - Overall effects for the best studied pro-resolving molecules in the context of bacterial and viral infections.

Mediator	Pathogen class	Overall effects
LXA4	**Bacteria**	In general, beneficial effects against different types of bacteria. Administration of LXA4
Resolvins	**Virus**	Overall, Resolvins display anti-inflammatory and protection from tissue damage without
	Bacteria	Robust evidence demonstrates that different types of resolvins decrease inflammation, en
Maresins	**Bacteria**	Despite little data, evidence suggests pro-resolutive effects, such as decreased inflammati
Protectins	**Bacteria**	Overall, administration of PD1 is associated with decreased bacterial burden and increas
	Virus	PD1 administration decreased both inflammation and viral loads against different viruse
GILZ	**Bacteria**	Evidence points towards to pro-resolutive effects depending on the host cell and bacteria
AnxA1	**Bacteria**	In most of the studies, AnxA1 and Ac2-26 were associated with diminished inflammatio
	Virus	Accelerated resolution and decreased inflammation of endogenous AnxA1 and Ac2-26 tr
Angio (1-7)	**Virus**	Ang-(1-7) reduces exacerbated inflammatory response, increases apoptosis and efferocyt
	Bacteria	Ang-(1-7) prevents sepsis, bacterial burden in the lung, recovers ability of neutrophils to

Supplementary Table 1 - Studies showing the effects of the administration of pro-resolving mediators or their role as assessed by inhibition of their synthesis or results in gene deficient mice or cells.

Mediator	Evidence	Pathogen	Reference
Lipids			
LXA4			
		Virus	

Mediator	Evidence	Pathogen	Reference
	I*n vitro* and *in vivo* (macrophages), 5-LO deficient cells fail to develop M2 macrophage polarization, leading to exuberant pneumonitis and peri bronchiolitis	Respiratory sincicial virus (RSV)	Shirei et al., 2014
	Inhibition of lipoxins production and increased lethality of mice infected with the H5N1 VN/1203 strain	IAV	Cilloniz et al., 2010
		Bacteria	
	Decreased bacterial burden of 5-LO KO mice	*Mycobacterium tuberculosis*	Bafica et al. 2005
	Increased lung bacterial burden and lethality of infected mice associated with inhibition of LXA4 production	*Mycobacterium tuberculosis*	Peres et al., 2007
	LXA4 diminished *P. gingivalis* aggregation via integrins activation	*Porphyromonas gingivalis*	Börgeson et al., 2011
	LXA4 diminished tissue injury and COX-2 levels	*Porphyromonas gingivalis*	Pouliot et al., 2000
	Inhibition of inflamasome and autophagy inR AW264.7 exposed to *P. gingivalis* lipopolysaccharide (PgLPS)	*Porphyromonas gingivalis*	Zhao et al., 2021
	15-Epi-LXA4 treatment enhanced bacterial clearance	*Escherichia coli*	Sekheri et al., 2020
	Decrease of IL-6 and TNF when combined with antibiotic treatment	*Escherichia coli*	Ueda et al., 2014
	Inhibition of pro-inflammatory mediators	*Salmonella typhimurium*	Gewirtz et al., 1998

Mediator	Evidence	Pathogen	Reference
	Pharmacological inhibition of LXA4 receptor resulted in more pulmonary edema and increased bacterial loads in the lungs and systemically	*Pneumococcal pneumonia*	Siegel et al., 2021
	Anti-inflammatory effects during cecal ligation and puncture (CLP) in a rat model	Cecal ligation and puncture (CLP)	Walker et al., 2011; Wu et al., 2014
Resolvins (D, E, and T series)			
		Virus	
	Decreased levels of pro-inflammatory cytokines and ACE2 expression with RvD6 treatment *in vitro*	SARS-CoV-2	Pham et al., 2021
	in vitro, diminished levels of TNF, IL-6, IL-8, CCL2, CCL3 and CCL4 with RvD1 and RvD2 treatment	SARS-CoV-2	Recchiuti e tal, 2021
	AT-RvD1 ameliorates lung inflammation, without altering viral loads	H3N2 and *Streptococcus pneumoniae* co-infection	Wang et al., 2017
	Decreased mRNA levels of TNF and IL-8 in pNHBE cells with RvD1 treatment without affecting viral load	H3N2	Guo et al., 2020
	RvD1 treatment decreased inflammation parameters, although failed to decrease viral laods *in vivo*	Herpes Simplex Virus (HSV)	Rajasagi et al., 2017
	RvE1 decreased inflammation and IL-6, IFN-γ and CXCL-1 levels in the cornea	HSV-1	Rajasagi et al., 2011
	RvE1 restored M2 phenotype of 5-LO macrophages *in vitro*	RSV	Shirey et al., 2014
		Bacteria	

Mediator	Evidence	Pathogen	Reference
	RvD1 promotes resolution of inflammation in a mouse model of bacterial keratitis	*Pseudomonas aureoginosa*	Lee et al., 2022; Carion et al., 2019
	RvD1 and D5 treatment reduced bacterial loads, inflammation and rescued mice from death	*Citrobacter rodentium*	Diaz et al., 2017
	RvD2 promotes the resolution of inflammation and bacterial clearance	*Staphylococcus aureus*	Chiang et al., 2015
	RvD2 promotes the resolution of inflammation and bacterial clearance	*Escherichia coli*	Chiang et al., 2015
	RvD4 enhanced efferocytosis *in vivo*	*Staphylococcus aureus*	Winkler et al., 2016
	Decrease in the production of pro inflammatory cytokines via RvD1 treatment in human macrophages	LPS and *Escherichia coli*	Palmer et al., 2011
	RvD1 and D5 decreased production of inflammatory cytokines and increased phagocytosis of bacteria by human machrophages	*Escherichia coli*	Chiang et al., 2012
	RvD3 decreased pro-inflammatory cytokines production and accelerates resolution	*Escherichia coli*	Norris et al., 2018
	RvD1 treatment decreased inflammation, increased bacterial clearance and survival of mice	CLP	Chen et al., 2014
	RvD1 treatment decreased inflammation in a model of sepsis induced by D-galactosamine (GalN)	of sepsis induced by D-galactosamine (GalN)	Murakami et al., 2011

Mediator	Evidence	Pathogen	Reference
	RvD1 and D5 decreased production of inflammatory cytokines and increased phagocytosis of bacteria by human macrophages and neutrophils	*Escherichia coli*	Chiang et al., 2012
	RvD1 treatment reduced bacterial burden and lung inflammation during infection in mice	*Pseudomonas aureoginosa*	Codagnone et al., 2018
	AT-RvD1 treatment decreased leukocyte influx and production of pro inflammatory cytokines and increased bacterial clearance during Nontypeable Haemophilus influenzae (NTHi) in mice	Nontypeable *Haemophilus influenzae* (NTHi)	Croasdell et al., 2016
	Treatment with AT-RvD1 1h post infection enhanced the clearance of *E. coli* and *Pseudomonas aeruginosa* in a murine model of pneumonia	*Escherichia coli* and *Pseudomonas aeruginosa*	Abdulnour et al., 2016
	AT-RvD1 treatment decreased lung inflammation and lung pneumoccocal load in the lungs	*Streptococcus pneumoniae*	Wang etal, 2017
	17-epi-RvD1 restored human neutrophils apoptosis *in vitro* and decreased bacterial load during *E. coli* infection in the lungs	*Escherichia coli*	Sekheri et al., 2020
	RvD1 treatment decreased lung inflammation and decreased bacterial burden in cystic fibrosis infected mice	*Pseudomonas aeruginosa*	Isopi et al., 2020

Mediator	Evidence	Pathogen	Reference
	RvD1 treatment alone or in combination with ceftazidime accelerate the resolution of inflammation in the lungs	*Pseudomonas aeruginosa*	Gao et al., 2020
	AT-RvD1 treatment attenuated renal inflammation in a model of CLP in BALB/C mice	CLP model	Silva et al., 2021
	RvD1 and RvD2 (individually) treatment diminished bacterial load in the kidneys in a model of *S. aureus* infection	*Staphylococcus aureus*	Svahn et al., 2016
	RvD2 treatment decreased bacterial loads in the lungs during *P. aureoginosa* infection	*Pseudomonas aeruginosa*	Walker et al., 2022; Sundarasivarao et al., 2022
	RvE1 treatment decreased inflammation and increased bacterial loads during *E. coli* infection	*Escherichia coli*	Seki et al., 2010
	RvE1 treatment increased antimicrobial activity and decreased bacterial load against *Aggregatibacter actinomycetemcomitans*	*Aggregatibacter actinomycetemcomitans*	Abdullatif et al., 2022
	decreased inflammation during *P. gingivalis* infection in mice and in rabbit treated with RvE1	*Porphyromonas gingivalis*	Hasturk et al., 2007
	RvE1 attenuated inflammation and reduced bacterial load in a CLP model and diminished the levels of IL-1B, IL-6 and CCL-2 in LPS stimulated bone marrow-derived macrophages (BMDMs)	CLP model	Chen et al., 2020

Mediator	Evidence	Pathogen	Reference
	Resolvins of T series prevented NET formation *in vitro* and decreased bacterial load and neutrophil influx during *S. aureus* infection *in vivo*	*Staphylococcus aureus*	Chiang et al., 2022
Maresins			
		Bacteria	
	Mar-1 decreased bacterial intracellular growth	*Mycobacterium tuberculosis*	Ruiz et al., 2019
	MCTR3 alone or in combination with MCTR1 decreased lung inflammation and bacterial burden during *Streptococcus pneumoniae*	*Streptococcus pneumoniae*	Tavares et al., 2022
		Virus	
	Mar-1 decreased inflammation and viral transcripts during RSV infection	RSV	Krishnamoorthy et al., 2023
Protectin			
		Bacteria	
	Improved levels of IL-10, TGF-β and IL-4 in the intestinal tract via PD1 in a model of gut dysbiosis	Gut dysbiosis	Ariyoshi et al., 2021
	PD1 treatment increased uptake of *E. coli* by human macrophage and neutrophil	*Escherichia coli*	Hamidzadeh et al., 2022; Chiang et al., 2012
	PD1 treatment decreased bacterial burden in mice infecte with *L. monocytogenes*	*Listeria monocytogenes*	Bang et al., 2021
		Virus	
	Topic treatment with PD1 during HSV decreased inflammation in rodent model	RSV	Rajasagi et al., 2013
	Intranasal treatment with PD1 and PCTR1 decreased inflammation and genomic viral load during RSV infection	RSV	Walker et al., 2021

Mediator	Evidence	Pathogen	Reference
	Decreased viral replication of H1N1 and H5N1 in A549 cells	IAV	Morita et al., 2013
	Improved survival rates of mice infected with H1N1	IAV	Morita et al., 2013
α-MΣH			
		Bacteria	
	Decrease in the phagocytosis of unopsonized *E. coli* and *S. aureus* by RAW 264.7	*Escherichia coli* and *Staphylococcus aureus*	Phan and Taylor, 2013
	Downregulation of TLR2 expression induced by*S. aureus* in human keratinocytes	*Staphylococcus aureus*	Ryu et al., 2015
	α-MSH decreased levels of IL-6 induced by LPS in rats	LPS induced model	Huang and Tatro, 1998
		Virus	
	α-MSH reduced the production of pro-inflammatory cytokines in the blood of HIV patients	HIV	Catania et al., 1998
GILZ			
		Bacteria	
	Increased lung lesion and bacterial burden during bacterial infection in GILZ KO mice	*Streptococcus pneumoniae*	Souza et al., 2022
	Enhanced bacterial clearance in CLP model associated with increased expression of GILZ restricted to macrophages	CLP model	Ellouze et al., 2020
	Up-regulation of GILZ associated with reduced mortality induced by LPS in mice	LPS-induced	Ng et al., 2020
AnxA1			
		Bacteria	

Mediator	Evidence	Pathogen	Reference
	AnxA1 treatment decreased bacterial burden and inflammation in a model of meningitis induced by bacteria	*Streptococcus suis*	Ni et al., 2021
	Ac2-26 treatment decreased bacterial load and inflammation in the lungs of infected mice via FPR2 receptor	*Streptococcus pneumoniae*	Machado et al., 2020
		Virus	
	Pro-resolutive effects of Ac2-26 treatment during DENV infection	DENV	Costa et al., 2022
	Pro-resolutive effects of AC 2-26 treatment during CHIKV infection	CHIKV	de Araújo et al., 2022
Ang-(1-7)			
		Virus	
	Ang-(1-7) oral administration reduced lethality, promoted resolution and decreased inflammation associated with Influenza infection	H1N1	Melo et al., 2021
	Mas receptor genetic ablated mice displayed 100% lethality when infected	H1N1	Melo et al., 2021
		Bacteria	
	Ang-(1-7) treatment decreased bacterial load in the lungs and reduced mortality associated with pneumococcal infection following Influenza A virus infection	*Streptococcus pneumoniae*	Melo et al., 2021
	Improved phagocitic capacity of neutrophils from diabetic mice	*Staphylococcus aureus*	Soto et al., 2019
	Ang-(1-7) treatment reduced inflammation associated with infection by promote M2 phenotype polarization in mice	CLP model	Pan et al., 2021

Mediator	Evidence	Pathogen	Reference
	Ang-(1-7) treatment reduced inflammation and lethality associated with infection	CLP model	Tsai et al., 2018

Supplementary Table 2 - The interference of pathogen on the expression of/endogenous role of pro-resolutive molecules .

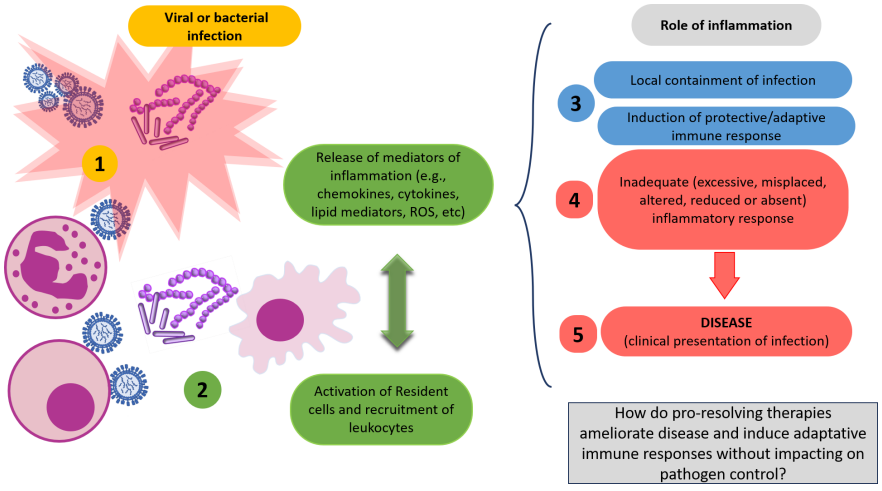
Mediators	Evidence
Lipids	
LXA4	
	Downregulation of LXA4 levels *in vitro*. Exogenous LXA4 reduced the activation of E
	Possible downregulation LXA4 levels to modulate chromatin dynamics and favours vir
	Lower LXA4/LTB4 ratio during co-infection
	Increase in LXA4 levels in human monocytes
	Decreased levels of LXA4 in Gx KO infected mice
	Marked increase in LXA4 levels in the BAL fluid of COVID-19 patients
	Elevated plasma levels of LXA4 in active tuberculosis patients compared with latently
	Virulent strains of M. tuberculosis stimulate production of LXA4, playing a deleteriou
	Increased LXA4 levels and decreased survival and host cell death
	Bacterial epoxide hydrolase decreased the levels of 15-Epi-LXA4 synthesis and enhanc
	Time-dependent production of LXA4 and FPR2 expression in the human skin
	Disturbed levels of LXA4 in the human placenta during infection
	Disturbed levels of LXA4 in nasal polyps
Resolvins (D, E, and T series)	
	Downregulation of RvD1 and RvD3 in the plasma of critically ill COVID-19 patients.
	Higher levels of RvD1, D2, D4 and D5 in the BAL fluid COVID-19 patients when com
	Diminished levels of RvD1 in the plasma in humans
	Diminished levels of RvD1 in the serum of patients with Hansen's disease
Maresins	
	Increased levels of Mar-1 and Mar-2 in the serum of COVID-19 patients when compar
α-MΣH	
	Cleavage of α-MSH by toxins produced by *S. aureus*
	Higher levels of α-MSH in the blood of HIV patients correlated with reduced progressi
GILZ	
	IBDV prevented GILZ degradation
	NS1 protein of RSV decreased the levels of GILZ in A549 cells
	Up-regulation of GILZ levels by Y*ersinia enterocolitica* and *Clostridium difficile in vit*
	Lower expression of GILZ in monocytes from septic patients
	Increased expression of GILZ restricted to macrophages
AnxA1	

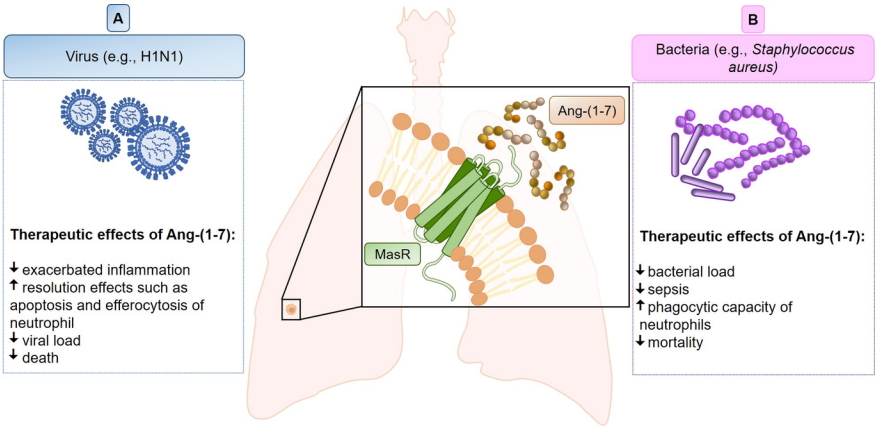
Mediators	Evidence
	Enhanced levels of AnxA1 in the spleen of infected mice Enhanced levels of AnxA1 in the cytoplasm of liver cells of golden hamsters Increased levels of AnxA1 in human neutrophils and RPE cells Up-regulated levels of AnxA1 in both skin and serum of patients Perturbed levels of AnxA1 in MDSCs of infected patients Increase of AnxA1 levels during Rolipram + antibiotics treatment Decreased levels of AnxA1 in the plasma of COVID-19 patients increased levels of severe COVID-19 patients compared to mild patients Increased expression levels of AnxA1 in circulating monocytes of COVID-19 convalesc H1N1 infection up-regulates FPR2 expression *in vitro*

Figure legends:

Figure 1: The double-edge role of inflammation in the context of infection. (1) Pathogens (viruses or bacteria) infect host-cells. Inflammation is needed for pathogen control. (2) Mediators of inflammation recruit and activate leukocytes and resident cells, (3) events that are associated with local containment of infection and induction of protective immune response. (4) When inadequate, the inflammatory response may cause (5) disease. Here, we discuss how mediators pro-resolving therapies contribute to the control of disease during infection.

Figure 2: Therapeutic effects of Ang-(1-7) against infectious diseases . Ang-(1-7) exerts its effects by binding to MasR receptors, leading to the amelioration of inflammation and disease signs. This has been observed in various models of respiratory infection. In both (A) viral (e.g., H1N1) and (B) bacterial (e.g. Staphylococcus aureus) infections, Ang-(1-7) induced pro-resolving effects and decreased viral and bacterial loads. It has been shown to induce pro-resolving effects, meaning it helps resolve the inflammatory response and promotes tissue repair.





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