Harnessing resolving-based therapeutics to treat pulmonary viral infections: What can the future offer to COVID-19?

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Abstract

Inflammation is generally believed to be a protective response in the context of infectious diseases. However, altered inflammatory responses can contribute to disease in infected individuals. Multiple mediators that drive the resolution of inflammation have been described. Overall, mediators of resolution tend to decrease inflammatory responses and provide normal or greater ability of the host to deal with infection. In the lung, it seems that pro-resolving molecules or strategies that promote their increase tend to decrease inflammation and lung injury and facilitate control of bacterial or viral burden. Here, we argue that the demonstrated anti-inflammatory, pro-resolving, anti-thrombogenic and anti-microbial effects of pro-resolution mediators may be useful in the treatment of the late stages of disease in patients with COVID-19.

Key words:

Inflammation, resolution, COVID-19, cytokines, thrombosis

General considerations

Inflammation is generally believed to be a protective response in the context of infectious diseases (Tavares et al., 2017). Indeed, inflammatory responses are necessary to contain microorganisms and to provide the adequate co-stimulatory stimuli to adaptive immune responses. Clear examples of these roles are seen in neutropenic individuals who usually die of disseminated bacterial infections (Gustinetti & Mikulska, 2016). Individuals unable to mount an inflammatory response, such as elderly individuals and those undergoing cancer treatment, frequently fail to respond to vaccines. However, it is clear that an altered (decreased, misplaced, excessive, systemic or modified) inflammatory response can contribute to disease in infected individuals (Tavares et al., 2016). As described above, absent or decreased inflammatory responses may lead to microbial spread and death. Bacterial sepsis is a good example of a syndrome where misplaced (systemic rather than at the site of infection), excessive (large amounts of mediators in the circulation) and altered (mediators found in severe disease may be different from those found in less severe patients) inflammatory responses occurs. We have argued previously that taming this altered inflammatory response may be beneficial in individuals with severe infectious diseases (Costa, et al., 2013; Garcia et al., 2010). In this review, we will argue for the potential of harnessing mediators of resolution of inflammation as a means to provide adjunct treatment (to antimicrobial drugs) for severe infectious diseases.

Resolution of inflammation, in a simplified way, is defined as the period between the peak of granulocyte accumulation in the tissue and the complete clearance of recruited inflammatory cells (Sugimoto, et al.,2019) (see Figure 1). Fundamentally, resolution of inflammation will contribute to reverse the accumulation of granulocytes in the inflammatory site and reprogram the cellular and molecular response within the tissue, impacting further in tissue regeneration and repair. Tissues tend not to reverse back to their pre-inflamed state in

terms of cellular composition and phenotype, as previously thought, but achieve a state of 'adapted homeostasis', which impacts the severity of subsequent inflammatory responses (Feehan & Gilroy, 2019). Resolution of inflammation is mediated by the so-called mediators of resolution. These are molecules with very diverse chemical nature that by acting on their receptors will induce a cascade of events that will lead to inflammation resolution and adapted homeostasis of tissues (Sugimoto et al., 2019) (Figure 1).

The possibility of using mediators of resolution to treat inflammation has led to the concept of 'resolution pharmacology', based on correcting and 'pushing the resolution back on track' as a new strategy for fighting complicated and often chronic, inflammatory diseases, such as rheumatoid arthritis (Perretti et al., 2015). There have been a few studies evaluating the role and effects of mediators of resolution of inflammation in the context of bacterial, viral and fungal infection. Overall, most studies have suggested that mediators of resolution tend to decrease inflammatory responses during infection and provide normal or greater ability of the host to deal with infection. For example, in the context of infection with the protozoan parasite *Leishmania brasiliensis*, the pro-resolving molecule annexinA1 (AnxA1) was actively expressed during infection and its absence is associated with more intense inflammatory responses and delayed ability to resolve the lesion (Oliveira et al., 2017). Similarly, FPR2/ALX, the receptor for AnxA1, LXA4 and RvD1, was found to have non-redundant roles in sepsis with exacerbated disease severity in the absence of the receptor (Gobbetti et al., 2014). Below, we review the effects of mediators of inflammation in the context of experimental models simulating inflammation and infection in the lungs.

Effect of pro-resolving-based strategies during lung infection

Several pro-resolving molecules have been shown to decrease effectively inflammation and injury in models simulating pulmonary disease, including asthma, fibrosis and infection.

In the context of asthma, local or systemic administration of hydrogen peroxide (Reis et al., 2015), angiotensin-(1-7) (Magalhaes et al., 2018), AnxA1(Bandeira-Melo et al., 2005) and lipoxin A4 (Levy et al., 2007) have been shown to decrease infiltration of eosinophils in the lung and, in general, changes in airway function. Similarly, mediators of resolution decrease inflammation, injury and fibrosis in bleomycin-induced pulmonary fibrosis (Damazo et al., 2011; Rago et al., 2019) and silicosis (Trentin et al., 2015).

A few studies have examined the effects of the administration of mediators of pro-resolution or their genetic absence in the context of ***bacterial infection*** in the lung. For example, administration of the PDE4 inhibitor rolipram decreased neutrophil recruitment into the lungs and airways and reduced lung injury in a model of pneumococcal pneumonia. There were also decreased cytokine levels in the airways, but bacterial burden was not reduced (Tavares et al., 2016). Noteworthy, the combined administration of rolipram and ceftriaxone improved survival in pneumococcal pneumonia by decreasing inflammation, lung injury, bacterial burden, and phagocytosis. The effects of rolipram appeared to be due to the increase in local levels of AnxA1 (Tavares et al., 2016). This is in agreement with our studies suggesting that AnxA1 mediated the pro-resolving properties of cyclic AMP-elevating agents and cyclic AMP-mimetic drugs (Lima et al., 2017). Interestingly, AnxA1 and Fpr2KO mice were highly susceptible to pneumococcal infection pneumonia, displaying uncontrolled inflammation, increased bacterial dissemination, loss of lung barrier integrity and pulmonary dysfunction. Moreover, treatment with the AnxA1 peptidomimetic Annexin 1-(2-26) decreased inflammation, lung damage, and bacterial burden in the airways by increasing macrophage phagocytosis (Machado et al., 2020). Similarly, absence of FFA2 receptor (a receptor for short chain fatty acids - SCFA) led to increased susceptibility to *Klebsiella pneumoniae* infection, which was associated to both uncontrolled proliferation of bacteria and increased inflammatory response. Treatment with the GPR43 ligand, acetate, was protective during bacterial lung

infection (Galvão et al., 2018). Early treatment with AT-RvD1 enhanced clearance of *Escherichia coli* and *Pseudomonas aeruginosa in vivo*. This was associated with enhanced phagocytosis of bacterial particles and accelerated neutrophil clearance during pneumonia *in vivo* (Abdulnour et al., 2016). Therefore, it seems that treatment with pro-resolving molecules or strategies that promote their increase (such as cyclic AMP elevating agents) tend to decrease inflammation and lung injury and facilitate microbial control following bacterial infection. It remains to be determined whether this is valid for all pro-resolving molecules, their comparative efficacy and whether there is synergy when one or more agent is used.

A few studies have also evaluated the relevance of pro-resolving molecules and pathways in the context of ***viral infections*** of the lung, especially influenza. In an elegant study, Morita and colleagues (2013) found that the lipid mediator protectin D1 (PD1) was suppressed during severe influenza, and PD1 levels inversely correlated with the pathogenicity of H5N1 viruses (Morita et al., 2013). PD1 treatment improved the survival and pulmonary injury of severe influenza in mice and markedly attenuated influenza virus replication via the RNA export machinery. This is consistent with an earlier finding showing that a strain of H5N1 (VN/1203) was more pathogenic in mice than H1N1 (1918 pandemic virus), in part due to early and sustained up-regulation of the components of pro-inflammatory molecules along with inhibition of lipoxin-mediated anti-inflammatory responses (Cilloniz et al., 2010). It has been shown that influenza A virus (IAV) H1N1 (strain PR8) enhanced its replication and propagation through the use of the AnxA1/FPR2 axis (Ampomah et al., 2018; Arora et al., 2016). Indeed, the latter studies clearly show that regulation of ANXA1 and FPR2 expression during IAV infection may be a viral strategy to enhance its infectivity. However, administration of AnxA1 to mice prior to IAV H1N1 infection (strain PR8) significantly attenuated pulmonary injury induced by IAV, with significantly improved survival, impaired viral replication in the

respiratory tract, and less severe lung damage, which were associated with expansion of alveolar macrophages in AnxA1 pre-treated animals (Schloer et al., 2019).

At least one study has evaluated the role of pro-resolving molecules in the context of pulmonary viral infections other than influenza. Infection of 5-lipoxygenase (5-LOX)-deficient mice with respiratory Respiratory Syncytial Virus (RSV) resulted in enhanced lung pathology. The 5-LOX pathway, likely via production of lipoxin A4 and resolvin E1, appeared to be necessary for the induction of alternatively activated macrophages and induction of bronchiolitis (Shirey et al., 2014). Interestingly, the specialized pro-resolving lipid mediator (SPM) 17-HDHA was found to increase the humoral response and provide greater protective effect against live H1N1 influenza infection in mice, hence providing a biological link between pro-resolution signals and the adaptive immune system (Ramon et al., 2014). Indeed, LXB4 was shown to boost memory B cell activation through COX-2 to serve as a potential vaccine adjuvant (Kim et al., 2018).

A previous influenza infection is known to increase the risk to a subsequent pulmonary bacterial infection, such as that caused by *S. pneumoniae*. Indeed, post-influenza bacterial infections seem to account for a significant number of deaths following annual flu epidemics. In a model of pulmonary co-infection with influenza H3N2 (strain A/HKx31) and *S. pneumoniae*, Wang et al. (2017) showed that administration of exogenous aspirin-triggered RvD1 facilitated more rapid clearance of pneumococci in the lungs, while concurrently reducing the severity of pneumonia by limiting excessive leukocyte chemotaxis from the infected bronchioles to distal areas of the lungs (Wang et al., 2017). More recently, we showed that perturbation of the gut microbiota during influenza A virus infection favored respiratory bacterial superinfection with *S. pneumoniae*. In mechanistic terms, reduced production of the predominant short-chain fatty acid (SCFA) acetate appeared to account for the facilitating effects of Influenza infection. Indeed, treatment with acetate reduced bacterial loads, lung

pathology and improved survival rates of double-infected mice (Sencio et al., 2020). It is clear that the overall effects of mediators of resolution in the context of pulmonary infection is enhancement of anti-bacterial and anti-viral defenses and inhibition of inflammatory responses without interfering with the ability of the host to deal with the infection. A note of caution must be given here. At least one study has shown that resolution can trigger a prolonged phase of localized immunosuppression which could predispose the host to secondary infectious (Newson et al., 2017).

Covid-19 and resolvers of inflammation

Since the end of 2019, the world has been swept by the pandemic caused by SARS-CoV2, a new coronavirus first detected in China. SARS-CoV2 infection causes a disease named COVID-19, whose major clinical presentation is pulmonary inflammation and injury. As with most viral infections, the disease is characterized by an initial phase with significant viral replication that is followed by an inflammatory phase. In contrast to many viral infections of the lung, COVID-19 disease is characterized by significant systemic inflammation (cytokine storm) and damage to organs other than the lung, including the heart and kidney. There is also a significant coagulopathy (Moore et al., 2020). While targeting the virus is the rational approach during the first stage of COVID-19, regulating the host response during the phase of overexuberant inflammation and excessive coagulation may offer new therapeutic opportunities. Because of their known protective roles in the context of other pulmonary infections, we argue that harnessing pro-resolving based therapeutics may provide unique new therapeutic strategies in the context of COVID-19.

As shown in Figure 2, there are many demonstrated effects of mediators of pro-resolution that may be useful in the context of COVID-19, including the decrease of neutrophil recruitment and activation, enhancement of pathogen clearance and prevention of excessive

coagulation. Patients who recovered from disease had upregulation of AnxA1 in peripheral blood monocytes (Wen et al., 2020), suggesting a counter regulation of the inflammatory response in well responders. Although these data remain to be validated in bigger cohorts by measuring the AnxA1 levels in those patients, these initial data suggest that decreased expression of AnxA1, and potentially other pro-resolving molecules, may have contributed to worse outcomes in patients with severe COVID-19. Three molecules with demonstrated pro-resolving activity may be especially useful in the context of COVID-19 – AnxA1, angiotensin-(1-7) and plasmin.

As discussed above, ***AnxA1*** expression was increased in recovering mice (Tavares et al., 2016) and administration of the AnxA1 peptidomimetic improved severe pneumococcal pneumonia (Machado et al., 2020) and severe influenza. Together with data showing increased expression in recovered COVID-19 patients, these data suggest that restoration of AnxA1 levels may be useful to treat severe COVID-19 patients.

ACE2 appears to be the most important receptor for SARS-CoV-2 to enter cells. This enzyme generates ***angiotensin-(1-7)***, an endogenous pro-resolving mediator (Barroso et al., 2017; Magalhaes et al., 2018). We have shown that Ang-(1-7) presented pro-resolving actions during lung inflammation (Magalhaes et al., 2018), and was protective in kidney, heart and lung diseases (reviewed by (Simões E Silva, Silveira, Ferreira, & Teixeira, 2013). Indeed, reduced levels of ACE2 increased SARS-CoV-induced lung injury by bending the ACE2/Ang-(1-7) regulatory/protective axis towards the pro-inflammatory angiotensin II/AT_1R, and this effect could be attenuated by blocking AT_1 receptor (Kuba et al., 2005). It remains to be tested whether this pathway is defective in the context of COVID-19 and whether the activation of the protective axis by given Ang-(1-7) peptide or inhibiting the pro-inflammatory pathways by blocking AT_1R will constitute a protective approach to control the disease.

Excessive coagulation response, which is also observed in sepsis patients, with enhanced clot formation and suppression/consumption of fibrinolysis is an important characteristic of COVID-19 patients (Moore et al., 2020). In this regard, we have shown that ***plasmin*** a fibrinolytic protein can promote resolution of inflammation (Sugimoto et al., 2017). SARS-CoV-2 induces the macrophage activation syndrome that can be targetted by the cell reprogramming actions of plasminogen/plasmin (Sugimoto et al., 2017; Vago et al., 2019). Indeed, severe COVID-19 patients treated with atomization inhalation of freeze-dried plasminogen presented improved lung lesions and hypoxia (Wu et al., 2020). During physiological coagulation there is upregulation of a cluster of immunoresolvents that enhanced leukocyte antimicrobial responses (Norris, Libreros, Chiang, & Serhan, 2017). Administration of the immunoresolvent RvD4 attenuated the severity of pathological thrombosis (Cherpokova et al., 2019). Therefore, by exploring the properties of pro-resolving based therapies, such as plasmin, we may in the future provide better control of several features of COVID-19, such as hyperinflammatory response, coagulation and tissue damage.

Concluding Remarks

The development of drugs targeting viral replication and entry is the rational therapy for the early stages of disease but may not be as useful at the advanced stages of the illness. Recently, the term resolution pharmacology (Perretti et al., 2015) was proposed to describe therapeutic strategies that explore the activation of endogenous circuits of resolution through novel resolution-based therapeutics. Pharmacological induction of resolution of inflammation, rather than anti-inflammation therapies, do not cause immunosuppression and are a promising tool to treat infectious diseases (Figure 2), at least, as adjunct therapy. As discussed here, several pro-resolving molecules present great capacity to clear viral or bacterial infections and

cellular debris aiding to their anti-inflammatory/pro-resolving abilities. The future in this expanding field deserves great promise and requires further validation to prove the concept that pro-resolving based therapies are a better approach than anti-inflammatory therapies to treat overexuberant inflammation arising from infectious diseases, including COVID-19.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2019/20 (Alexander *et al.*, 2019).

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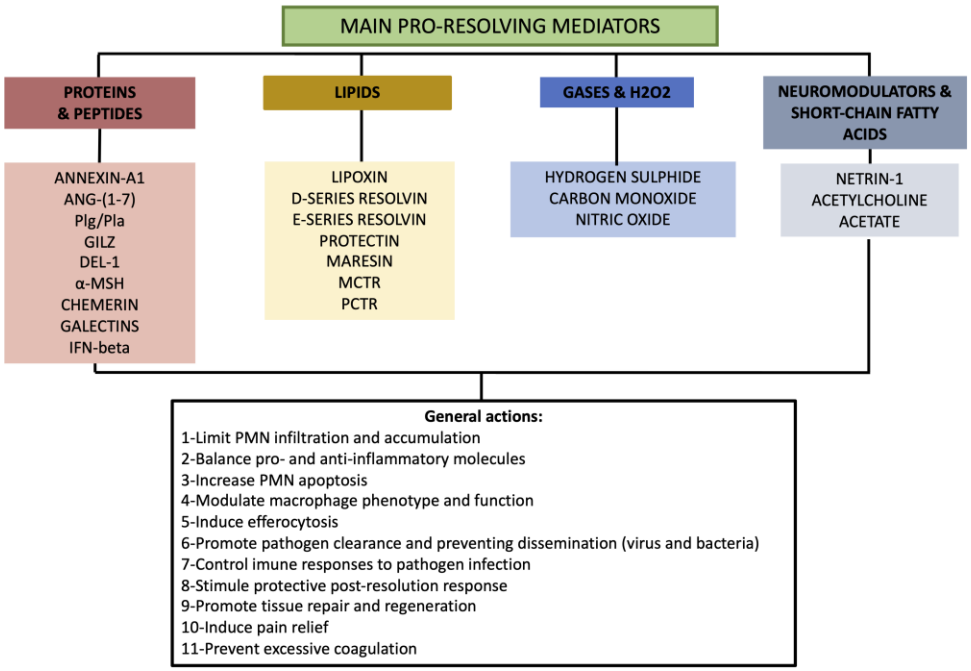

Figure 1 – Schematic representation of the main pro-resolving mediators and their general functions in the context of inflammation.

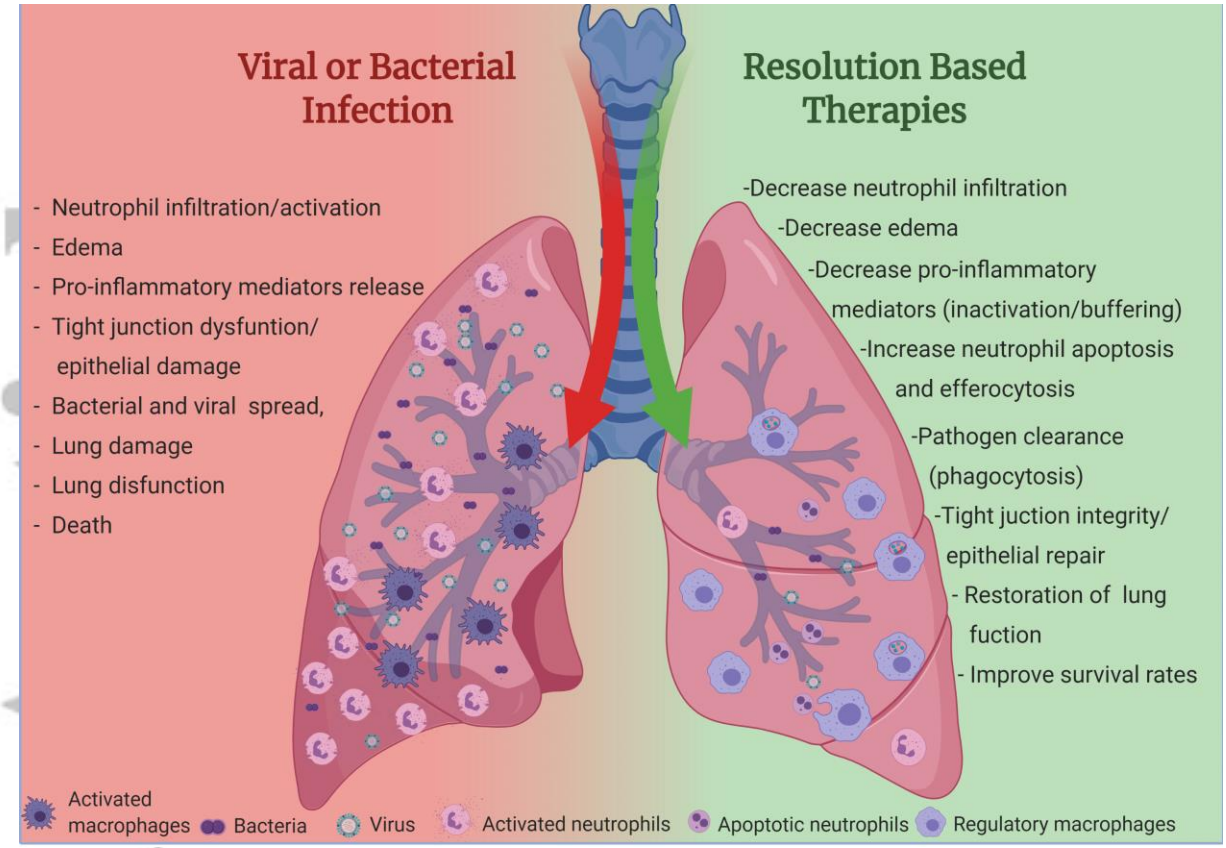

Figure 2- Effects of pro-resolving-based therapies in pulmonary infections. Created with Biorender.com.