Received: 14 May 2020 | Revised: 29 May 2020 | Accepted: 1 June 2020

DOI: 10.1111/bph.15164

MINI-REVIEWS

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

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Funding information
National Institute of Science and Technology, Grant/Award Number: 465425/2014-3

Inflammation is generally accepted as a component of the host defence system and a protective response in the context of infectious diseases. However, altered inflammatory responses can contribute to disease in infected individuals. Many endogenous mediators that drive the resolution of inflammation are now known. 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-resolution molecules, or strategies that promote their increase, tend to suppress 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 such endogenous mediators of resolution may be useful in the treatment of the late stages of the disease in patients with COVID-19.

1 | GENERAL CONSIDERATIONS

Inflammation is generally accepted as a protective response in the context of infectious diseases (Tavares, Teixeira, & Garcia, 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 adequate inflammatory response, such as elderly individuals and those undergoing cancer treatment, frequently fail to respond to vaccines. However, it is also clear that an altered(decreased, misplaced, excessive, systemic, or modified) inflammatory response can contribute to disease in infected individuals (Tavares et al., 2016). Thus, 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 severely affected patients) inflammatory responses occur. We have argued previously that taming this altered inflammatory response may be beneficial in individuals with severe infections (Costa, Fagundes, Souza, & Teixeira, 2013; Garcia, Guabiraba, Soriani, & Teixeira, 2010). In this review, we will argue for the potential of utilizing the pathways and mediators of resolution of inflammation, as a means of providing 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, Vago, Perretti, & Teixeira, 2019) (see Figure 1). Fundamentally, resolution of inflammation will contribute to the reversal of the

Abbreviations: 5-LOX, 5-lipoxygenase; 17-HDHA, (4Z,7Z,10Z,13Z,15E,19Z)-17-hydroxydocosa-4,7,10,13,15,19-hexaenoic acid; ACE2, Angiotensin-converting enzyme 2; COX-2, cyclooxygenase-2; IAV, influenza A virus; LX, lipoxin; PDE4, phosphodiesterase type 4; RSV, respiratory syncytial virus.

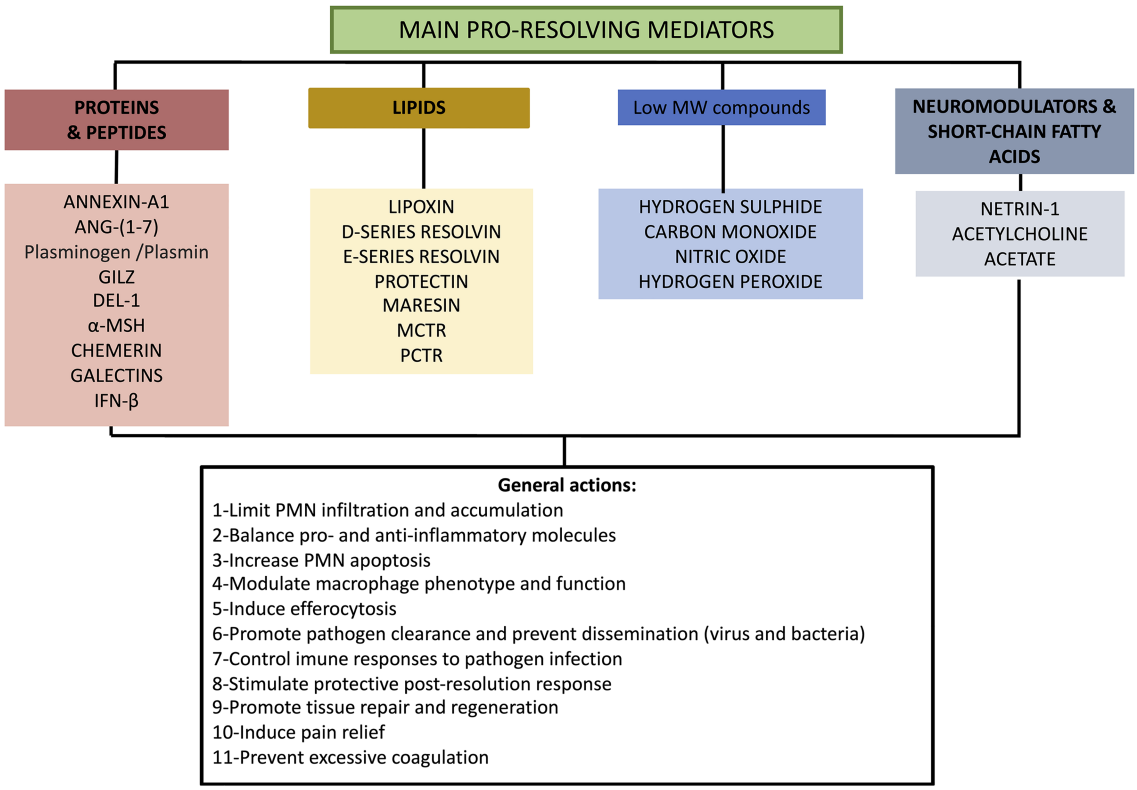

FIGURE 1 The main mediators of the resolution of inflammation and their general functions in the context of inflammation. MCTR: maresin conjugates in tissue regeneration; PCTR: protectin conjugate in tissue regeneration

accumulation of granulocytes in the inflammatory site and reprogramme the cellular and molecular response within the tissue, leading to tissue regeneration and repair. However, tissues tend not to return completely to their pre-inflamed state, in terms of cellular composition and phenotype, as previously thought, but to a state of "adapted homoeostasis," which modifies the severity of subsequent inflammatory responses (Feehan & Gilroy, 2019). Resolution of inflammation is mediated by the endogenous mediators of resolution. These are molecules with very diverse chemical structures that by acting on their corresponding receptors induce a cascade of events (pathways) that lead to the resolution of inflammation and the adapted homoeostasis 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 the treatment of complicated and often chronic, inflammatory diseases, such as rheumatoid arthritis (Perretti, Leroy, Bland, & Montero-Melendez, 2015). There have also 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 the 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-resolution peptide, annexin A1 (**ANXA1**), was actively expressed during infection and its absence was associated with more intense inflammatory responses and delayed ability to resolve the lesion (Oliveira et al., 2017). Similarly, **FPR2/ALX**, the receptor for ANXA1, lipoxin A4 (**LXA_4**), and resolvin D1 (**RvD1**), played 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 the mediators of resolution in the context of experimental models simulating inflammation and infection in the lungs.

1.1 | Effects of pro-resolution-based strategies for treatment of lung infections

Several pro-resolution 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 LXA4 (Levy et al., 2007) all 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 relatively 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 levels of cytokines in the airways, but bacterial burden was not reduced (Tavares et al., 2016). Noteworthy, the combined administration of rolipram and the antibiotic, **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-resolution properties of **cAMP**-elevating agents and cAMP-mimetic drugs (Lima et al., 2017). Interestingly, AnxA1 and Fpr2 KO mice were highly susceptible to pneumococcal 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, the absence of **FFA2 receptor**s (also known as GPR43; a receptor for short-chain fatty acids) led to increased susceptibility to *Klebsiella pneumoniae* infection, which was associated with both uncontrolled proliferation of bacteria and increased inflammatory response. Treatment with another FFA2 receptor ligand, acetate, was protective during bacterial lung infection (Galvão et al., 2018). Early treatment with the aspirin-induced resolvin, **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-resolution molecules or strategies that promote their increase (such as cAMP 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-resolution molecules, their comparative efficacies, and whether there is synergy when more than one agent is used.

A few studies have also evaluated the relevance of pro-resolution molecules and pathways in the context of viral infections of the lung, especially influenza. In an elegant study, Morita et al. (2013) found that another endogenous mediator of resolution, the lipid 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 following 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). The influenza A virus (IAV) H1N1 (strain PR8) enhanced its replication and propagation through the use of the ANXA1/FPR2 axis (Ampomah, Moraes, Lukman, & Lim, 2018; Arora et al., 2016). Indeed, the latter study clearly shows 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 infection, with the same strain of IAV, significantly attenuated pulmonary injury induced by the infection, with significantly improved survival, impaired viral replication in the respiratory tract, and less severe lung damage. These effects were associated with expansion of alveolar macrophages in ANXA1 pretreated animals (Schloer et al., 2019).

At least one study has evaluated the role of pro-resolution molecules in the context of pulmonary viral infections other than influenza. Infection of **5-lipoxygenase (5-LOX)**-deficient mice with respiratory syncytial virus (RSV) resulted in enhanced lung pathology. The 5-LOX pathway, probably through the production of LXA4 and **resolvin E1** (RvE1), appeared to be necessary for the induction of alternatively activated macrophages and induction of bronchiolitis (Shirey et al., 2014). Interestingly, the specialized pro-resolution lipid, 17-HDHA, increased the humoral response and provided greater protective effect against live H1N1 influenza infection in mice, thus demonstrating a biological link between pro-resolution signals and the adaptive immune system (Ramon et al., 2014). Indeed, the lipoxin **LXB_4** 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 resolvin AT-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 IAV infection favoured respiratory bacterial superinfection with S. pneumoniae. In mechanistic terms, reduced production of the predominant short chain fatty acid, **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 defences 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 of inflammation can trigger a prolonged phase of localized immunosuppression which could predispose the host to secondary infections (Newson et al., 2017).

1.2 | COVID-19 and the resolution of inflammation

Since the end of 2019, the world has been swept by the pandemic caused by SARS-CoV-2, a new coronavirus first detected in China. SARS-CoV-2 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 other viral infections of the lung, COVID-19 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 directly is the rational approach during the first stage of COVID-19, regulating the host response during the phase of over-exuberant 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-resolution-based therapies may provide unique new treatment 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 up-regulation of ANXA1 in peripheral blood monocytes (Wen et al., 2020), suggesting a counter-regulation of the inflammatory response in those patients who survived and could be considered as "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, of other pro-resolution 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 – and these are now discussed in greater detail. For the first, expression of the *AnxA1* gene was increased in mice recovering from pneumococcal infection (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.

The cell surface protein, **angiotensin converting emzyme-2 (ACE2)** appears to be the most important receptor for SARS-CoV-2 to enter cells. This enzyme generates angiotensin-(1–7), an endogenous pro-resolution mediator (Barroso et al., 2017; Magalhaes et al., 2018). We have shown that Ang-(1–7) exerted pro-resolving actions during lung inflammation (Magalhaes et al., 2018) and was protective in kidney, heart, and lung diseases (see Simões E Silva, Silveira, Ferreira, & Teixeira, 2013). Indeed, reduced levels of **ACE2**

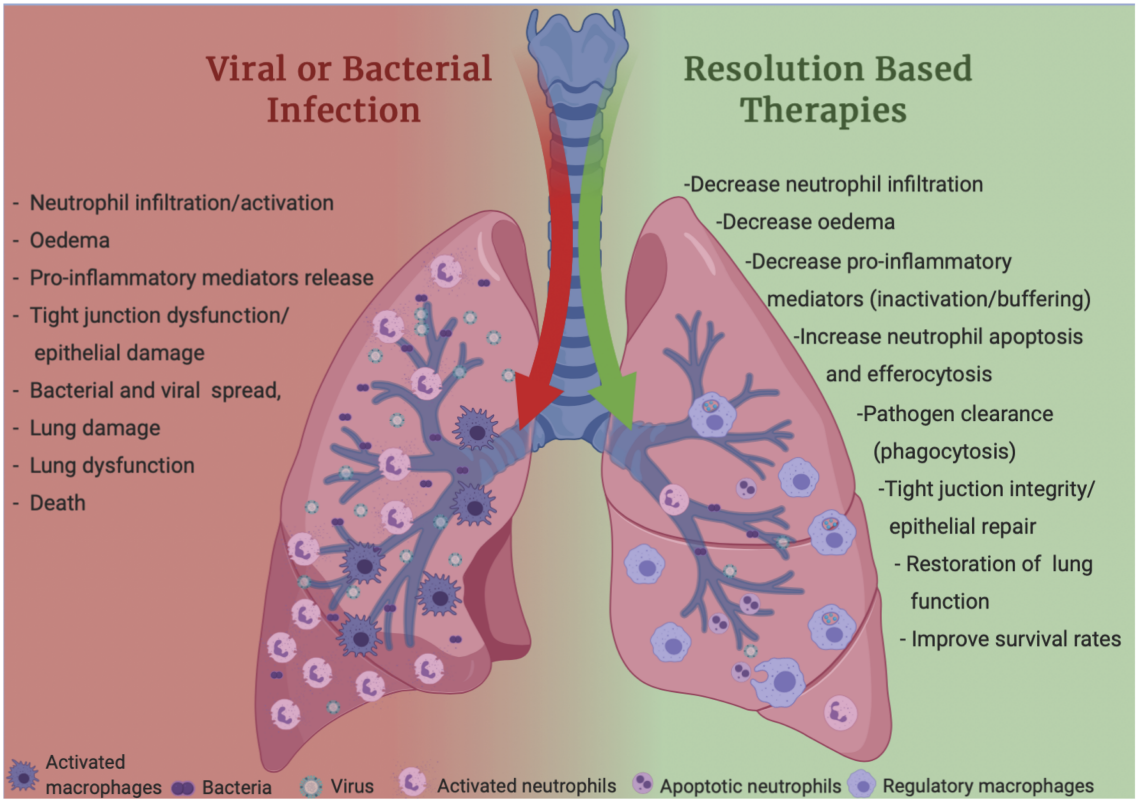

FIGURE 2 Effects of pro-resolution-based therapies in pulmonary infections. Created with Biorender.com

increased SARS-CoV-induced lung injury by re-directing the renin-angiotensin system away from the ACE2/Ang-(1–7) regulatory and protective pathway towards the pro-inflammatory **angiotensin II -AT$_1$** receptor pathway. The effects of this re-direction were attenuated by blocking the AT$_1$ receptors (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 administering the Ang-(1–7) peptide or inhibiting the pro-inflammatory pathways by blocking AT$_1$ receptors will constitute a protective approach to control the effects of COVID-19.

An excessive coagulation response, which is also observed in patients with sepsis, shown by enhanced clot formation and suppression or consumption of fibrinolytic factors 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 targeted by the cell reprogramming actions of **plasminogen**/plasmin (Sugimoto et al., 2017; Vago et al., 2019). Indeed, patients with severe COVID-19, treated with inhalation of atomized, freeze-dried plasminogen demonstrated improved lung lesions and hypoxia (Wu et al., 2020). During physiological coagulation, there is up-regulation of a group of lipid mediators of resolution that enhanced leukocyte antimicrobial responses (Norris, Libreros, Chiang, & Serhan, 2017). Administration of one of these mediators, the resolvin, RvD4, attenuated the severity of pathological thrombosis (Cherpokova et al., 2019). Therefore, by exploring the properties of pro-resolution mediators, such as plasmin, we may in the future provide better control of several crucial features of COVID-19, such as the hyperinflammatory response, coagulation and tissue damage.

2 | CONCLUDING REMARKS

The development of drugs targeting viral replication and entry is the rational therapy for the early stages of COVID-19disease but may not be as useful at the advanced stages of the infection. Recently, the term resolution pharmacology (Perretti et al., 2015) was proposed to describe therapeutic strategies that explore the activation of endogenous pathways of resolution, through novel resolution-based therapeutic agents. Pharmacological induction of resolution of inflammation, rather than anti-inflammation therapies, do not cause immunosuppression and are a promising tool to treat the consequences of infectious diseases (Figure 2), at least, as adjunct therapy. As discussed here, several pro-resolution molecules exhibit a marked capacity to clear viral or bacterial infections and cellular debris, adding to their anti-inflammatory and pro-resolution abilities. The future of this expanding field shows great promise and requires further validation to prove the concept that pro-resolution-based therapies are a more effective approach than anti-inflammatory therapies, to treat over-exuberant inflammation arising from infectious diseases, including COVID-19.

2.1 | 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, Christopoulos et al., 2019; Alexander, Fabbro et al., 2019).

ACKNOWLEDGEMENTS

Work in our laboratories is funded by the National Institute of Science and Technology in Dengue and host-microbial interactions, a programme grant (465425/2014-3) from Fundação do Amparo a Pesquisa do Estado de Minas Gerais (FAPEMIG, Brazil), Coordenação de Apoio ao Ensino de Pessoal de Nivel Superior (CAPES, Brazil), and Conselho Nacional de Ensino e Pesquisa (CNPq, Brazil).

CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

REFERENCES

Abdulnour, R. E., Sham, H. P., Douda, D. N., Colas, R. A., Dalli, J., Bai, Y., … Levy, B. D. (2016). Aspirin-triggered resolvin D1 is produced during self-resolving gram-negative bacterial pneumonia and regulates host immune responses for the resolution of lung inflammation. *Mucosal Immunology*, *9*(5), 1278–1287. https://doi.org/10.1038/mi.2015.129

Alexander, S. P. H., Christopoulos, A., Davenport, A. P., Kelly, E., Mathie, A., Peters, J. A., … CGTP Collaborators. (2019). THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: G protein-coupled receptors. *British Journal of Pharmacology*, *176*, S21–S141. https://doi.org/10.1111/bph.14748

Alexander, S. P. H., Fabbro, D., Kelly, E., Mathie, A., Peters, J. A., Veale, E. L., … CGTP Collaborators. (2019). THE CONCISE GUIDE TO PHARMACOLOGY 2019/20: Enzymes. *British Journal of Pharmacology*, *176*, S297–S396. https://doi.org/10.1111/bph.14752

Ampomah, P. B., Moraes, L. A., Lukman, H. M., & Lim, L. H. K. (2018). Formyl peptide receptor 2 is regulated by RNA mimics and viruses through an IFN-b-STAT3-dependent pathway. *FASEB Journal*, *32*(3), 1468–1478. https://doi.org/10.1096/fj.201700584RR

Arora, S., Lim, W., Bist, P., Perumalsamy, R., Lukman, H. M., Li, F., … Lim, L. H. K. (2016). Influenza A virus enhances its propagation through the modulation of Annexin-A1 dependent endosomal trafficking and apoptosis. *Cell Death and Differentiation*, *23*(7), 1243–1256. https://doi.org/10.1038/cdd.2016.19

Bandeira-Melo, C., Bonavita, A. G. C., Diaz, B. L., Silva, E., e Silva, P. M. R., Carvalho, V. F., … Martins, M. A. (2005). A novel effect for annexin 1-derived peptide Ac2-26: Reduction of allergic inflammation in the rat. *The Journal of Pharmacology and Experimental Therapeutics*, *313*, 1416–1422. https://doi.org/10.1124/jpet.104.080473

Barroso, L. C., Magalhaes, G. S., Galvão, I., Reis, A. C., Souza, D. G., Sousa, L. P., … Teixeira, M. M. (2017). Angiotensin-(1-7) promotes resolution of neutrophilic inflammation in a model of antigen-induced arthritis in mice. *Frontiers in Immunology*, *8*(NOV). https://doi.org/10.3389/fimmu.2017.01596

Cherpokova, D., Jouvene, C. C., Libreros, S., DeRoo, E. P., Chu, L., De La Rosa, X., … Serhan, C. N. (2019). Resolvin D4 attenuates the severity of pathological thrombosis in mice. *Blood*, *134*(17), 1458–1468. https://doi.org/10.1182/blood.2018886317

Cilloniz, C., Pantin-Jackwood, M. J., Ni, C., Goodman, A. G., Peng, X., Proll, S. C., … Katze, M. G. (2010). Lethal dissemination of H5N1

influenza virus is associated with dysregulation of inflammation and lipoxin signaling in a mouse model of infection. *Journal of Virology*, *84* (15), 7613–7624. https://doi.org/10.1128/jvi.00553-10

Costa, V. V., Fagundes, C. T., Souza, D. G., & Teixeira, M. M. (2013). Inflammatory and innate immune responses in dengue infection: Protection versus disease induction. *The American Journal of Pathology*, *182*, 1950–1961. https://doi.org/10.1016/j.ajpath.2013.02.027

Damazo, A. S., Sampaio, A. L. F., Nakata, C. M. A. G., Flower, R. J., Perretti, M., & Oliani, S. M. (2011). Endogenous annexin A1 counter-regulates bleomycin-induced lung fibrosis. *BMC Immunology*, *12*, 59. https://doi.org/10.1186/1471-2172-12-59

Feehan, K. T., & Gilroy, D. W. (2019). Is resolution the end of inflammation? *Trends in Molecular Medicine*, *25*, 198–214. https://doi.org/10.1016/j.molmed.2019.01.006

Galvão, I., Tavares, L. P., Corrêa, R. O., Fachi, J. L., Rocha, V. M., Rungue, M., … Vieira, A. T. (2018). The metabolic sensor GPR43 receptor plays a role in the control of Klebsiella pneumoniae infection in the lung. *Frontiers in Immunology*, *9*(FEB), 1–11. https://doi.org/10.3389/fimmu.2018.00142

Garcia, C. C., Guabiraba, R., Soriani, F. M., & Teixeira, M. M. (2010). The development of anti-inflammatory drugs for infectious diseases. *Discovery Medicine*, *10*(55), 479–488.

Gobbetti, T., Coldewey, S. M., Chen, J., McArthur, S., Le Faouder, P., Cenac, N., … Perretti, M. (2014). Nonredundant protective properties of FPR2/ALX in polymicrobial murine sepsis. *Proceedings of the National Academy of Sciences of the United States of America*, *111*, 18685–18690. https://doi.org/10.1073/pnas.1410938111

Gustinetti, G., & Mikulska, M. (2016). Bloodstream infections in neutropenic cancer patients: A practical update. *Virulence*, *7*, 280–297. https://doi.org/10.1080/21505594.2016.1156821

Harding, S. D., Sharman, J. L., Faccenda, E., Southan, C., Pawson, A. J., Ireland, S., … NC-IUPHAR. (2018). The IUPHAR/BPS Guide to PHARMACOLOGY in 2018: Updates and expansion to encompass the new guide to IMMUNOPHARMACOLOGY. *Nucleic Acids Research*, *46*, D1091–D1106. https://doi.org/10.1093/nar/gkx1121

Kim, N., Lannan, K. L., Thatcher, T. H., Pollock, S. J., Woeller, C. F., & Phipps, R. P. (2018). Lipoxin B4 enhances human memory B cell antibody production via upregulating cyclooxygenase-2 expression. *The Journal of Immunology.*, *201*, 3343–3351. https://doi.org/10.4049/jimmunol.1700503

Kuba, K., Imai, Y., Rao, S., Gao, H., Guo, F., Guan, B., … Penninger, J. M. (2005). A crucial role of angiotensin converting enzyme 2 (ACE2) in SARS coronavirus-induced lung injury. *Nature Medicine*, *11*(8), 875–879. https://doi.org/10.1038/nm1267

Levy, B. D., Lukacs, N. W., Berlin, A. A., Schmidt, B., Guilford, W. J., Serhan, C. N., & Parkinson, J. F. (2007). Lipoxin A_4 stable analogs reduce allergic airway responses via mechanisms distinct from CysLT1 receptor antagonism. *The FASEB Journal.*, *21*, 3877–3884. https://doi.org/10.1096/fj.07-8653com

Lima, K. M., Vago, J. P., Caux, T. R., Negreiros-Lima, G. L., Sugimoto, M. A., Tavares, L. P., … Sousa, L. P. (2017). The resolution of acute inflammation induced by cyclic AMP is dependent on Annexin A1. *The Journal of Biological Chemistry*, *292*, 13758–13773. https://doi.org/10.1074/jbc.m117.800391

Machado, M. G., Pádua, L., Geovanna, T., Souza, V. S., Fernando, C. M. Q., Ascenção, R., … Sousa, L. P. (2020). The Annexin A1/FPR2 pathway controls the inflammatory response and bacterial dissemination in experimental pneumococcal pneumonia. *The FASEB Journal*, *34*(August 2019), 2749–2764. https://doi.org/10.1096/fj.201902172R

Magalhaes, G. S., Barroso, L. C., Reis, A. C., Rodrigues-Machado, M. G., Gregório, J. F., Motta-Santos, D., … Campagnole-Santos, M. J. (2018). Angiotensin-(1-7) promotes resolution of eosinophilic inflammation in an experimental model of asthma. *Frontiers in Immunology*, *9*. https://doi.org/10.3389/fimmu.2018.00058

Moore, H. B., Barrett, C. D., Moore, E. E., McIntyre, R. C., Moore, P. K., Talmor, D. S., … Yaffe, M. B. (2020). Is there a role for tissue plasminogen activator (tPA) as a novel treatment for refractory COVID-19 associated acute respiratory distress syndrome (ARDS)? *The Journal of Trauma and Acute Care Surgery*, *88*(1–8), 713–714. https://doi.org/10.1097/TA.0000000000002694

Morita, M., Kuba, K., Ichikawa, A., Nakayama, M., Katahira, J., Iwamoto, R., … Imai, Y. (2013). The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza. *Cell*, *153*(1), 112–125. https://doi.org/10.1016/j.cell.2013.02.027

Newson, J., Motwani, M. P., Kendall, A. C., Nicolaou, A., Muccioli, G. G., Alhouayek, M., … Gilroy, D. W. (2017). Inflammatory resolution triggers a prolonged phase of immune suppression through COX-1/mPGES-1-derived prostaglandin E2. *Cell Reports*, *20*, 3162–3175. https://doi.org/10.1016/j.celrep.2017.08.098

Norris, P. C., Libreros, S., Chiang, N., & Serhan, C. N. (2017). A cluster of immunoresolvents links coagulation to innate host defense in human blood. *Science Signaling*, *10*(490), eaan1471. https://doi.org/10.1126/scisignal.aan1471

Oliveira, L. G., Souza-Testasicca, M. C., Vago, J. P., Figueiredo, A. B., Canavaci, A. M. C., Perucci, L. O., … Fernandes, A. P. (2017). Annexin A1 is involved in the resolution of inflammatory responses during Leishmania braziliensis infection. *The Journal of Immunology.*, *198*, 3227–3236. https://doi.org/10.4049/jimmunol.1602028

Perretti, M., Leroy, X., Bland, E. J., & Montero-Melendez, T. (2015). Resolution pharmacology: Opportunities for therapeutic innovation in inflammation. *Trends in Pharmacological Sciences*, *36*(11), 737–755. https://doi.org/10.1016/j.tips.2015.07.007

Rago, F., Melo, E. M., Kraemer, L., Galvão, I., Cassali, G. D., Santos, R. A. S., … Teixeira, M. M. (2019). Effect of preventive or therapeutic treatment with angiotensin 1–7 in a model of bleomycin-induced lung fibrosis in mice. *Journal of Leukocyte Biology*, *106*, 677–686. https://doi.org/10.1002/JLB.MA1218-490RR

Ramon, S., Baker, S. F., Sahler, J. M., Kim, N., Feldsott, E. A., Serhan, C. N., … Phipps, R. P. (2014). The specialized proresolving mediator 17-HDHA enhances the antibody-mediated immune response against influenza virus: A new class of adjuvant? *The Journal of Immunology.*, *193*, 6031–6040. https://doi.org/10.4049/jimmunol.1302795

Reis, A. C., Alessandri, A. L., Athayde, R. M., Perez, D. A., Vago, J. P., Ávila, T. V., … Pinho, V. (2015). Induction of eosinophil apoptosis by hydrogen peroxide promotes the resolution of allergic inflammation. *Cell Death & Disease*, *6*(2), e1632. https://doi.org/10.1038/cddis.2014.580

Schloer, S., Hübel, N., Masemann, D., Pajonczyk, D., Brunotte, L., Ehrhardt, C., … Rescher, U. (2019). The annexin A1/FPR2 signaling axis expands alveolar macrophages, limits viral replication, and attenuates pathogenesis in the murine influenza A virus infection model. *FASEB Journal*, *33*(11), 12188–12199. https://doi.org/10.1096/fj.201901265R

Sencio, V., Barthelemy, A., Tavares, L. P., Machado, M. G., Soulard, D., Cuinat, C., … Trottein, F. (2020). Gut dysbiosis during influenza contributes to pulmonary pneumococcal superinfection through altered short-chain fatty acid production. *Cell Reports*, *30*(9), 2934–2947.e6. https://doi.org/10.1016/j.celrep.2020.02.013

Shirey, K. A., Lai, W., Pletneva, L. M., Karp, C. L., Divanovic, S., Blanco, J. C. G., & Vogel, S. N. (2014). Role of the lipoxygenase pathway in RSV-induced alternatively activated macrophages leading to resolution of lung pathology. *Mucosal Immunology*, *7*(3), 549–557. https://doi.org/10.1038/mi.2013.71

Simões E Silva, A. C., Silveira, K. D., Ferreira, A. J., & Teixeira, M. M. (2013). ACE2, angiotensin-(1-7) and Mas receptor axis in inflammation and fibrosis. *British Journal of Pharmacology*, *169*, 477–492. https://doi.org/10.1111/bph.12159

Sugimoto, M. A., Ribeiro, A. L. C., Costa, B. R. C., Vago, J. P., Lima, K. M., Carneiro, F. S., … Sousa, L. P. (2017). Phagocytes, granulocytes, &

myelopoiesis: Plasmin & plasminogen induce macrophage reprogramming & regulate key steps of inflammation resolution via annexin A1. *Blood*, *129*(21), 2896–2907. https://doi.org/10.1182/blood-2016-09-742825

Sugimoto, M. A., Vago, J. P., Perretti, M., & Teixeira, M. M. (2019). Mediators of the resolution of the inflammatory response. *Trends in Immunology*, *40*, 212–227. https://doi.org/10.1016/j.it.2019.01.007

Tavares, L. P., Garcia, C. C., Vago, J. P., Queiroz-Junior, C. M., Galvão, I., David, B. A., … Sousa, L. P. (2016). Inhibition of phosphodiesterase-4 during pneumococcal pneumonia reduces inflammation and lung injury in mice. *American Journal of Respiratory Cell and Molecular Biology*, *55* (1), 24–34. https://doi.org/10.1165/rcmb.2015-0083OC

Tavares, L. P., Teixeira, M. M., & Garcia, C. C. (2017). The inflammatory response triggered by Influenza virus: A two edged sword. *Inflammation Research*, *66*, 283–302. https://doi.org/10.1007/s00011-016-0996-0

Trentin, P. G., Ferreira, T. P. T., Arantes, A. C. S., Ciambarella, B. T., Cordeiro, R. S. B., Flower, R. J., … Silva, P. M. R. (2015). Annexin A1 mimetic peptide controls the inflammatory and fibrotic effects of silica particles in mice. *British Journal of Pharmacology*, *172*, 3058–3071. https://doi.org/10.1111/bph.13109

Vago, J. P., Sugimoto, M. A., Lima, K. M., Negreiros-Lima, G. L., Baik, N., Teixeira, M. M., … Sousa, L. P. (2019). Plasminogen and the plasminogen receptor, PLG-RKT, regulate macrophage phenotypic, and functional changes. *Frontiers in Immunology*, *10*. https://doi.org/10.3389/fimmu.2019.01458

Wang, H., Anthony, D., Yatmaz, S., Wijburg, O., Satzke, C., Levy, B., … Bozinovski, S. (2017). Aspirin-triggered resolvin D1 reduces pneumococcal lung infection and inflammation in a viral and bacterial coinfection pneumonia model. *Clinical Science*, *131*(18), 2347–2362. https://doi.org/10.1042/CS20171006

Wen, W., Su, W., Tang, H., Le, W., Zhang, X., Zheng, Y., … Wang, H. (2020). Immune cell profiling of COVID-19 patients in the recovery stage by single-cell sequencing. *Cell Discovery*, *6*, 31. https://doi.org/10.1038/s41421-020-0168-9

Wu, Y., Wang, T., Guo, C., Zhang, D., Ge, X., Huang, Z., … Li, J. (2020). Plasminogen improves lung lesions and hypoxemia in patients with COVID-19. *SSRN Electronic Journal*, *2*. https://doi.org/10.2139/ssrn.3552628

How to cite this article: Sousa LP, Pinho V, Teixeira MM. Harnessing inflammation resolving-based therapeutic agents to treat pulmonary viral infections: What can the future offer to COVID-19? *Br J Pharmacol*. 2020;177:3898–3904. https://doi.org/10.1111/bph.15164