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Review

Exploiting the pro-resolving actions of glucocorticoid-induced proteins Annexin A1 and GILZ in infectious diseases

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ABSTRACT

For decades, glucocorticoids (GC) have been used to treat several inflammatory conditions, including chronic and autoimmune diseases, due to their potent anti-inflammatory properties. In the context of infectious diseases, the use of GCs may be effective as adjuvant to antibiotic therapy by controlling excessive inflammatory responses resulting in better outcome in some cases. However, the use of GCs has been associated with a vast number of side effects, including increased probability of immunosuppression and consequent risk of opportunistic infection. Glucocorticoid-induced leucine zipper (GILZ) and Annexin A1 (AnxA1) are GC-induced proteins intrinsically involved with the anti-inflammatory functions of GCs without the associated adverse metabolic effects. Recent studies have shown that these GC-proteins exhibit pro-resolving effects. An essential characteristic of pro-resolving molecules is their ability to coordinate the resolution of inflammation and promote host defense in most experimental models of infection. Although the role of GILZ and AnxA1 in the context of infectious diseases remain to be better explored, herein we provide an overview of the emerging functions of these GC-proteins obtained from pre-clinical models of infectious diseases.

1. Introduction

Inflammation is a vital host defense response triggered by invading pathogens or foreign substances. The activation of an inflammatory response is considered a physiological process and its major purpose appears to be the maintenance of tissue homeostasis [1,2]. In the context of infection, the early inflammatory response can be self-limited, protect the host and evolve to appropriate resolution [3]. At the site of inflammation, the activation of resident macrophages and endothelial cells lead to the production of cytokines and chemokines and consequent neutrophil and macrophage recruitment, which play an important role in the control of pathogen spread [2,4]. However, failure to eliminate the inciting stimuli and excessive leukocyte recruitment/activation can progress to a non-resolving inflammatory response causing damage to the host [4–6]. In the context of infectious diseases, the proinflammatory milieu is essential to kill microorganisms and control pathogen dissemination [7], while uncontrolled inflammatory response may contribute to bacteria spread and organ failure, instead of regulating the infection [3]. In this regard, the activation of the resolution program appears therefore to be a critical event to guarantee a self-limited inflammatory response and restoration of normal tissue function.

The resolution of inflammation is an orchestrated and active process, involving mediators and cellular events with the purpose of restoring tissue homeostasis [8]. Proper resolution of inflammation involves catabolism of proinflammatory molecules and shift to pro-resolutive mediators. The clearance of microorganisms with further cessation of polymorphonuclear (PMN) cell recruitment and induction of PMN apoptosis is also an important step to prevent the release of PMN toxic contents that to leads to tissue damage. Non-phlogistic monocyte influx and differentiation to macrophages helps with removal of apoptotic PMN (efferocytosis). Macrophage switch from a pro- to an anti-inflammatory /pro-resolving phenotype is also important to facilitate further production of pro-resolving mediators and tissue repair [6, 8–10]. Thus, the resolution of the inflammatory response is

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accompanied by a series of crucial events that balance and control inflammation, in order to restore tissue homeostasis.

Glucocorticoids (GCs) have been used for decades for their capacity to inhibit the production of pro-inflammatory mediators and dampen inflammation. This class of anti-inflammatory drugs is widely used and represents the first successful exploitation of an endogenous molecule (cortisol) that has been used effectively for therapeutic purposes [11]. The mechanisms of GCs actions are complex, including transactivation – the induction of anti-inflammatory proteins (IL-10, GILZ, Annexin A1), as well as transrepression – the inhibition of transcription factors, NF-κB and AP-1 [11,12]. It has generally been believed that the adverse side effects of GC therapy are related to the transactivation pathway [11]. During transactivation, in addition to the increased expression of anti-inflammatory proteins, several enzymes involved in glucose and lipid metabolism are also activated. In this regard, selective glucocorticoid receptor agonists (SEGRAs) that favor transrepression were developed. However, recent studies indicate that transactivation is indispensable for the anti-inflammatory properties of GCs [11]. In this context, the GC-induced proteins (GILZ, Annexin A1) may be important candidates for the development of new therapeutic strategies that mimic the immunomodulatory functions of GCs and limit metabolic side-effects.

While anti-inflammatory molecules act mainly by inhibiting events which contribute to the onset of inflammation, pro-resolving molecules on the other hand, act by favoring events that limit inflammation but also which enhances its resolution [13]. In the context of infectious diseases, the role of pro-resolving mediators is an emerging field. There is evidence indicating that pro-resolving molecules may contribute to resolution by enhancing host defenses and accelerating the return of homeostasis after infection [3,14,15]. The GC-induced proteins GILZ and Annexin A1 (AnxA1) has also been described as pro-resolving molecules and few studies have explored their role in infection diseases. Given that the pathophysiology of infectious diseases is implicated to an excessive inflammatory response and that pro-resolving molecules may boost host defenses, the purpose of this review is to determine what is currently known about the role of the GC-induced proteins GILZ and AnxA1 in the context of infectious diseases.

2. Pro-resolving actions of GILZ and Annexin A1

Glucocorticoid-induced leucine zipper (GILZ) was identified in 1997 during a study designed to characterize genes transcriptionally induced by dexamethasone, a synthetic GC. Since then, GILZ has been described to mediate multiple anti-inflammatory effects of GCs [16,17]. The control of inflammation mediated by GILZ has been associated with its capacity to interact and inhibit key pro-inflammatory transcription factors, such as NF-κB and AP-1 as well as other signaling molecules including Raf-1, Ras and ERK1/2 [18]. More recently, the pro-resolving effects of GILZ have also been described. It has been shown that GILZ induces neutrophil apoptosis [19,20] and shortened resolution intervals in a model of acute inflammation [19]. Interestingly, GILZ expression is enhanced during the resolution phase of inflammation [19] and GILZ has been reported to be pivotal for macrophage polarization and efferocytosis of apoptotic neutrophils [21].

Although the pro-resolving actions of GILZ have recently been described, AnxA1 has been considered a well-established pro-resolving mediator [8]. AnxA1 was originally described in 1979, as an anti-inflammatory protein acting mainly by inhibition of phospholipase A2 [22]. Later, it was demonstrated that AnxA1 has many anti-inflammatory and pro-resolving actions. AnxA1 inhibits neutrophil trafficking [23,24] and induces neutrophil apoptosis at inflammatory sites [25,26]. AnxA1 also exerts a pivotal role in resolution of inflammation by promoting non-phlogistic monocyte recruitment, inducing macrophage polarization and efferocytosis of apoptotic cells [25]. Previous studies have also suggested the involvement of GILZ as a critical mediator of AnxA1 anti-inflammatory/pro-resolving activities [19,27,

Table 1
Summary of beneficial effects of GILZ and AnxA1 in infectious diseases.

GILZ

Model/infection	Strategy	Findings	Ref.
Mouse – LPS (from E. coli) - endotoxemia	TAT-GILZ	Improvement of survival rates	[50]
Mouse - Polymicrobial sepsis (CLP)	GILZ-overexpressing transgenic mice	Improvement of survival rates, increased bacterial clearance	[52]
Mouse - Polymicrobial sepsis (CLP)	Monocytes/ macrophages GILZ-overexpressing transgenic mice	Increased bacterial clearance, limitation of systemic inflammation, improvement of survival rates	[53]

AnxA1

Model/infection	Strategy	Findings	Ref.
Mouse – LPS (from E. coli) - endotoxemia	AnxA1-null mice	Increased organ injury and lethality	[58]
Mouse – LPS (from E. coli) - endotoxemia	Recombinant human AnxA1	Decreased lethality	[58]
Mouse - Polymicrobial sepsis (CLP)	FPR2/3-KO mice	Exacerbation of disease severity, decreased phagocytosis	[60]
Mouse - Polymicrobial sepsis (CLP)	CR-Ac2–50	Protection against myocardial dysfunction	[60]
Mouse – Mycobacterium tuberculosis	AnxA1-KO mice	Increased mortality, decreased efferocytosis and cross-presentation	[45]
Mouse – Mycobacterium tuberculosis	AnxA1-KO mice	Increased pulmonary bacterial burden, exacerbated and disorganized granulomatous inflammation	[44]
Mouse - Streptococcus pneumoniae	AnxA1 and FPR2/3-KO mice	Increased mortality, bacterial dissemination and pulmonary dysfunction	[46]
Mouse - Streptococcus pneumoniae	AnxA1 mimetic peptide Ac2−26	Decreased lung damage and bacterial burden, increased phagocytosis	[46]
In vitro - Hepatitis C virus	Human hepatoma cell line overexpressing full-length AnxA1	Inhibition of viral replication	[61]
Mouse – Influenza A virus	Human recombinant AnxA1	Limits viral burden/ replication, reduced lung damage and improvement of survival rates	[64]
Mouse - Leishmania (Viannia) braziliensis	AnxA1-KO mice	Delayed ability to resolve lesion size; pronounced inflammatory infiltrate;	[69]

(*continued on next page*)

Table 1 (*continued*)

AnxA1			
Model/infection	Strategy	Findings	Ref.
		increased TNF-α, IFN-g, IL-4, IL-10, phospho-ERK-1/2, NF-kB and inducible NO synthase levels	
Human placental explants - Toxoplasma gondii	AnxA1 mimetic peptide Ac2−26	Ac2−26 treatment increases endogenous AnxA1 and decreases parasitism rate	[73]

Ac2−26 = short active N-terminal mimetic peptide of AnxA1; CR-Ac2–50 = active N-terminal mimetic peptide of AnxA1 cleavage resistant; CLP = cecal ligation and puncture; TAT-GILZ = cell permeable GILZ fusion protein.

28].

Although the pro-resolving activities of GILZ and AnxA1 have been described in several models of non-infectious inflammation, there is also an effort to understand their roles in infectious diseases. Some of these studies are discussed in the following sections, where we describe the roles of GILZ and AnxA1 in bacterial, viral and parasitic diseases. A summary of the major findings is provided in Table 1.

3. Bacterial infection

The most primitive role of the immune system is to fight infections [29]. The fascinating interactions between pathogens and hosts were the bases for the evolution of host defenses barriers and pathogen evasion mechanisms. The recognition and defense against a potential invader are survival requirements for every living organism [30]. In mammals, the inflammatory responses are an important first line of defense against bacterial infections.

Inflammation is a pathophysiological response of vascularized tissues to noxious stimuli, including infections [1]. Ideally, the inflammatory responses triggered by an invader are self-limited and efficient, leading to pathogen clearance and promoting restoration of tissue homeostasis [2,31]. Bacterial pathogens can be sensed by innate immune receptors (pattern recognition receptors -PRRs) including Toll-like receptors (TLRs), NOD (nucleotide-binding oligomerization-domain protein)-like receptors (NLRs) and RIG (retinoic acid-inducible gene-I)-like receptors, (RLRs). Pathogen or damage-associated molecular patterns (PAMPS and DAMPs, respectively) activate PRRs triggering expression of pro-inflammatory genes that lead to production of cytokines and other mediators, activation and recruitment of leukocytes and expression of surface adhesion molecules [32]. Neutrophils are one of the first leukocytes recruited to the site of bacterial infections [7]. The production of proteases, reactive oxygen species (ROS), neutrophil extracellular traps (NETs) and other antimicrobial molecules help the phagocytic and killing function of neutrophils [7]. Importantly, macrophages and other innate immune cells such as natural killers are also important players limiting bacterial spread and enhancing the defense against invaders.

Besides the obvious protective role of inflammation during infections, uncontrolled responses are often correlated with the severity of disease [33]. Overactivation of inflammatory responses can cause increased tissue damage, organ dysfunction and may contribute to pathogen dissemination [34]. Therefore, counter-regulative processes, such as the induction of resolution of inflammation are necessary to ensure a proper termination of infectious inflammation [3]. Excessive inflammation or failure of resolutive responses are the mechanisms behind pathological inflammation during bacterial infections [14,35,36]. Understanding the dynamics of inflammation onset and resolution during bacterial infections may be useful to develop novel therapies focused on the regulation of these responses [14,36].

The lungs are vital organs continuously susceptible to infections given their enormous mucosal surface [37]. Indeed, lower respiratory tract infections are a leading cause of death worldwide [38]. Infections in the lungs must be rapidly contained by limited inflammatory responses avoiding damage to the delicate respiratory surface [39]. The thin epithelial layer in the respiratory alveoli ensures proper gas exchange to support the organism metabolic needs. Uncontrolled inflammation in the lungs leads to increased edema, recruitment and activation of neutrophils and pulmonary epithelial damage. The resulting fibrous exudate that fills up the alveoli and loss of respiratory surface impairs diffusion of gases potentially causing respiratory failure and death [40]. Indeed, novel treatment strategies for bacterial pneumonia has focused in both, preventing pathogen replication/spread and balancing inflammatory responses [41]. In this regard, anti-inflammatory adjunctive therapies have been suggested to treat pneumonia [41,42]. However, one must see this possibility with caution. Anti-inflammatory drugs may cause immunosuppression potentiating bacteria replication in the lungs [43]. Therefore, pro-resolving therapeutics, rather than anti-inflammatory, may be of interest [3].

As mentioned before, GC-induced proteins such as GILZ and AnxA1 are endowed with pro-resolving features that hold interest for pneumonia management. The protective role of AnxA1 was evidenced in pre-clinical models of tuberculosis and pneumococcal pneumonia [44–46]. The absence of AnxA1 increased mortality and proliferation of bacteria in mice infected with *Mycobacterium tuberculosis,* the cause of tuberculosis [45]. In addition, lack of AnxA1 potentiated the granulomatous inflammation in the lungs of mice infected leading to enhanced lung damage [44]. By controlling efferocytosis [45] and expression of costimulatory molecules in dendritic cells [44], AnxA1 was shown to coordinate antigen presentation and effective anti-tuberculosis responses in the lungs. Therefore, the pro-resolving and immunoregulatory actions of AnxA1 were shown to be crucial for an effective but controlled immune response during chronic *M. tuberculosis* infection.

The role of AnxA1 in acute pulmonary bacterial infections was recently observed by our group [46]. In line with the *M. tuberculosis* studies, we have shown that AnxA1-deficient mice are more susceptible to *Streptococcus pneumoniae* infection in the lungs. The absence of AnxA1 promoted uncontrolled neutrophilic inflammation in the lungs, cytokine production and increased lung damage and dysfunction [46]. Besides the increased infiltration of leukocytes, AnxA1-deficient mice presented unrestrained proliferation and dissemination of bacteria to the bloodstream. Mechanistically, AnxA1 was shown to promote expression of tight junction genes and enhance macrophage phagocytosis of bacteria. Of importance, Ac2-26, an AnxA1 active peptide, reduced severity of infection and inflammation in a murine model o pneumococcal pneumonia by acting through the ALX/FPR2 receptor [46]. Indeed, in this pre-clinical model of pneumonia the lung protective effects of the phosphodiesterase 4 inhibitor rolipram was associated to the increased local levels of AnxA1 [47], suggesting that therapeutic strategies aimed to increase AnxA1 levels or the engagement of FPR2 by receptor agonists may be beneficial to treat lung infection. Altogether, we have shown that the pro-resolving (phagocytosis and lung barrier stability) and anti-inflammatory (reduction in production of pro-inflammatory cytokines and neutrophil number and activation) actions of AnxA1 were crucial to balance inflammation promoting clearance of bacteria while preventing bystander lung damage.

Although the shared role of AnxA1 and GILZ in induction of resolution, GILZ triggered responses were not yet explored in pulmonary infections. However, TAT-GILZ peptide, a cell permeable GILZ fusion protein which increases the intracellular levels of GILZ, induces resolution of pleurisy, a condition often caused by pneumonia [19]. Interestingly, while absence of GILZ may cause a compensatory increase in AnxA1 expression [19], further studies to address the role of GILZ in the

resolution of pulmonary infectious diseases will clarify the network between these pro-resolving molecules.

The GC-induced proteins GILZ and AnxA1 also exhibit protective effects in the control of sepsis. Sepsis is a complex infection disease responsible for the major cause of death among critically ill patients [48]. This condition results from an intense host response to infection causing systemic inflammation and tissue damage. Despite recent advance in sepsis therapy, its mortality is still alarmingly high [49]. Thus, novel therapeutic strategies for sepsis management that will favor the outcome of septic patients is crucial. A few studies have described the beneficial effect of GILZ and AnxA1 in the control of the infection and increased survival rates in experimental models of sepsis. The first evidence that GILZ could exhibit a beneficial effect in sepsis was described in a model of endotoxemia induced by LPS by using SPRET/Ei mice [50]. These mice exhibit a remarkable resistance to LPS (and to Gram-negative infections) which make this strain useful for identifying new molecular targets for the treatment of sepsis. Pinheiro et al., showed that increased expression of GILZ was associated with resistance of SPRET/Ei mice in a model of endotoxemia. Also, administration of TAT-GILZ enhanced the survival rates of lethal endotoxemia induced by LPS [50]. Consistently, GILZ mRNA was increased in LPS-tolerant human alveolar macrophages, whereas cytokine induction and MAPK activation were rescued in endotoxin-tolerized GILZ-KO murine macrophages [51]. *In vivo*, tolerized WT mice displayed reduced *Tnf* and *Il1b* mRNA levels expression in serum and tissues upon high-dose of LPS while cytokine induction was preserved in tolerized GILZ KO mice [51]. In addition, in a model of cecal ligation and puncture (CLP), considered the gold standard model for polymicrobial sepsis, it has been described that transgenic mice overexpressing GILZ exhibited improvement of survival rates and increased bacterial clearance [52]. In the latter study, GILZ mRNA expression was downregulated in blood leukocytes from septic patients and also in blood leukocytes from mice after CLP sepsis induction [52]. Another study using the same model of polymicrobial sepsis showed that macrophages overexpressing GILZ was essential to limit systemic inflammation that occurs in sepsis, associated with increased bacterial clearance and improvement of survival rates [53]. Despite the findings in the context of lack of GILZ showing increased phagocytosis and killing activity in *Candida albicans* and *Salmonella* infections [54,55], these studies in sepsis suggest that overexpression of GILZ could be a valuable strategy to improve the outcome of this disease. Interestingly, we have shown that GILZ overexpression in a model of LPS-induced pleurisy increased efferocytosis while reduces the numbers of M1 macrophages, a phenotype associated to better microorganism control by phagocytosis [21]. One could argue that increased GILZ expression, would compromise the ability of the host to deal with infections. However, the results from pre-clinical models of sepsis using whole-body GILZ-TG-mice [52] or specifically in macrophages [53] show that they were protected from CLP-induced peritonitis by reducing blood bacterial counts and improving bacterial phagocytosis and clearance *in vivo* [52,53]. Indeed, efferocytosis by macrophages was shown to contribute to bacteria clearance in different models of pneumonia [56,57]. Thus, GILZ might favor intracellular pathways involved in both efferocytosis [21] and phagocytosis [52,53] acting in the promotion of antimicrobial cellular responses. From a therapeutic point of view, further studies giving TAT-GILZ peptide or other system to delivery GILZ *in vivo* will support these results from transgenic mice.

Similar findings have also been reported for AnxA1. For instance, in a model of endotoxemia induced by LPS, AnxA1-null mice exhibited increased pro-inflammatory cytokine levels such as IL-6 and TNF-α, associated with increased organ injury and lethality [58]. Interestingly, AnxA1-null mice were rescued from LPS-induced lethality by receiving human recombinant AnxA1 [58]. AnxA1 exerts its pro-resolving functions in part through the activation of the formyl peptide receptor ALX/FPR2 [59]. Consistently, in a model of polymicrobial sepsis FPR2/3-deficient mice exhibited exacerbation of disease severity involving increased hypothermia, cardiac dysfunction and higher levels of chemokines CXCL1 and CCL2, and the cytokine TNF-α [60]. Decreased phagocytosis and bacteremia were also reported in FPR2/3-deficient mice [60]. Importantly, administration of CR-Ac2–50, a AnxA1 peptide cleavage resistant, protected WT mice against myocardial dysfunction induced by CLP, an effect not seen in FPR2/3-deficient mice [60]. Despite the findings from the pre-clinical model of endotoxemia and polymicrobial sepsis in the context of AnxA1 and FPR2 deficiency respectively, there is no report of the impact of AnxA1 absence in a model of microbial sepsis. Considering the studies published so far, GILZ and AnxA1 seem to have a protective role in sepsis, mainly by dampening exacerbated inflammatory response and inducing phagocytosis of bacteria.

4. Viral infection

A few studies have evaluated the importance of GILZ and AnxA1 in the control of viral infections. Hiramoto et al. reported *in vitro* that AnxA1 can exhibit beneficial effect against hepatitis C virus infection [61]. Hepatitis C virus infection frequently causes chronic hepatitis and can progress to liver cirrhosis and hepatocellular carcinoma. Full length AnxA1 overexpression prevented hepatitis C virus replication in human hepatoma cells by regulating viral RNA replication rather than viral entry in human hepatocytes [61], suggesting that AnxA1 could also display antiviral activities. In the context of lung disease, although AnxA1/FPR2 axis has been described as important for the replication and propagation of influenza A virus (IAV) [62,63], administration of human recombinant AnxA1 decreased viral loads and lung damage of mice, with consequently increasing survival rates in a model of IAV infection [64]. Is important to mention that the elevated mortality related to IAV infection has been associated with secondary bacterial pneumoniae infection normally mediated by *S. pneumoniae*. As previously mentioned, AnxA1 has demonstrated a beneficial effect during pulmonary infections induced by *M. tuberculosis* and *S. pneumoniae* [44–47]. Lastly, AnxA1 downregulation has been associated with arboviral infections. Molás et al. recently reported that placentas from women infected by Zika virus presented decreased expression of AnxA1 when compared to control groups [65]. Likewise, serum levels of AnxA1were lower in patients infected by chikungunya virus [66].

Although studies that evaluate the role of GILZ during viral infections are still incipient, Xia et al. demonstrated that respiratory syncytial virus infection of BEAS-2B bronchial epithelial cell line is associated with downregulation of GILZ expression, which dampens the anti-inflammatory activity of GCs [67]. In addition, GILZ was shown to regulate anti-viral and inflammatory responses to infectious bursal disease virus (IBDV) *in vitro*. In this context, GILZ was shown to interact with a viral protein leading to reduction of type I interferon levels. Therefore, this study suggest that some virus might have evolved strategies to use the immunomodulatory actions of GILZ to overcome the host innate responses [68]. Together, these preclinical studies reinforce that AnxA1 plays an important role in the control the immune responses to infectious diseases of the lung. More specifically, AnxA1 mimetics may represent an important pharmacological strategy for the resolution of viral and bacterial infections in the respiratory tract. The role of GILZ as a target for viral diseases, is yet to be better explored.

5. Parasitic infections

In line with the role of AnxA1 in the context of bacterial and viral infections, a growing amount of evidence suggest that it may also be beneficial in parasitic diseases. It has been reported that AnxA1-deficient mice exhibited a more pronounced inflammatory response and delayed ability to resolve leishmaniasis lesions induced by *Leishmania (Viannia) braziliensis* [69]. Leishmaniases are infectious diseases caused by protozoa of the genus Leishmania, transmitted by the bite of a female infected sand fly [70]. In the context of *L. braziliensis*localized cutaneous or mucosal leishmaniasis can be developed. While the

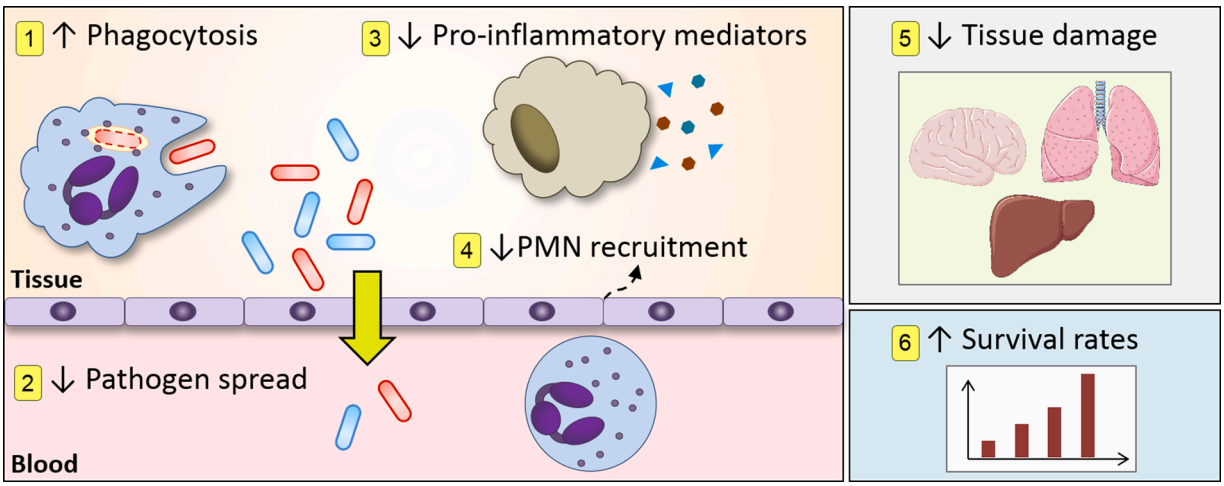

Fig. 1. Overall contribution of GILZ and AnxAl on resolution of infectious diseases. Studies published so far in the context of infection show that GILZ and AnxAl have been associated with increased phagocytosis of bacteria (1). AnxA1 also decreased parasitism after Toxoplasma gondii infection, limited Leishmania braziliensis- induced inflammation, reduced replication of hepatitis C virus in vitro and Influenza A in vivo (associated to expansion of alveolar macrophages). GILZ and AnxAl decreased the dissemination and translocation of the pathogen to blood (2) and reduced production of pro-inflammatory mediators, including chemokines and leukocyte (3). Consequently, leukocyte recruitment, especially polymorphonuclears (PMN), arc diminished (4). Together, these effects mediated by GILZ and AnxAl reduce tissue damage (5), and increase survival rates (6).

cutaneous manifestation heals spontaneously, the mucosal form is characterized by chronic and intense inflammation and scanty parasitism [71]. In a study published by Oliveira et al., AnxA1 deficiency led to pronounced inflammatory infiltrate and increased lesion skin size after *L. braziliensis* infection. Bone marrow-derived macrophages (BMDMs) from AnxA1-deficient mice displayed lower parasite intake but no difference in parasite burden when compared to WT BMDMs, associated with an early increase of TNF-α and later of IL-10 cytokine levels post-infection. *L. braziliensis* infection was also associated with increased levels of IFN-γ, IL-4 and IL-10 in lymph nodes from AnxA1-deficient mice. In addition, increased phospho-ERK-1/2 was detected in the infected tissue as well as increased activation NF-κB and inducible NO synthase levels [69]. In this same study the authors also evaluated the systemic levels of AnxA1 in patients with cutaneous and mucosal leishmaniasis manifestations. Interestingly, increased levels of AnxA1 were found in sera from mucosal leishmaniasis patients, which are known to display chronic exacerbated inflammatory responses.

Another study showing beneficial effect of AnxA1 in parasitic infection was conducted in human placental explants infected with *Toxoplasma gondii*. Toxoplasmosis is a globally zoonosis caused by the protozoan Toxoplasma gondii, a parasite that infects humans by congenital transmission and either by the ingestion of cysts in undercooked meat or oocysts in the environment (reviewed by [72]). Usually, T. gondii is asymptomatic and causes a life-long latent infection in healthy individuals. However, in immunocompromised hosts (such as AIDS patients) and in fetus or newborns, T. gondii infection may result in severe and life-threatening consequences (reviewed by [72]). In a study published by de Oliveira Cardoso et al., AnxA1 mimetic peptide Ac2-26 increased endogenous levels of AnxA1 and decreased parasitism rate in human placental explants infected with T. gondii [73]. Despite the beneficial effect of AnxA1 in controlling parasitic diseases, few studies have explored its potential as anti-parasitic strategy. Importantly, to the best of our knowledge, the role of GILZ in controlling parasitic diseases is still not explored.

6. Concluding remarks

The current guidelines for the treatment of infectious diseases are based on the inhibition of microbial growth using antibiotics and using drugs that treat symptoms, such as fever and pain. More recently, especially after COVID-19, there has been interest in the development of drugs that block the pathogen-triggered overwhelming inflammatory response as adjuvant therapy for infectious diseases. However, the latter pharmacological approach can lead to immunosuppression, as is the case for GC therapy. An important effect of pro-resolving molecules is their ability to coordinate the resolution of inflammation while favoring the ability of the host to deal with certain infections. Indeed, recent findings demonstrated that adjuvant administration of pro-resolving mediators successfully improved bacterial clearance and viral replication, and reduced the required antibiotic [74] and antiviral [75] doses to terminate an ongoing infection. As discussed here, recent studies have successfully explored the pro-resolving potential of the GC-induced proteins, GILZ and AnxA1 in the context of infectious diseases. Although there remains much to be studied, this review compiles evidence to suggest that both GILZ and AnxA1 may be useful pharmacological adjunctive therapies to antibiotics in the context of infectious diseases. We suggest that therapies that mimic GILZ or AnxA1 could be an alternative therapy to control excessive inflammation and improve the immune response against infections. The potential mechanisms triggered by GILZ and AnxA1 that might favor the control of infections include the 1) increase of phagocytosis and killing of bacteria, 2) enhancement of innate antiviral responses, 3) prevention of inflammation-related tissue damage and 4) promotion of tissue repair responses, as listed in Fig. 1.

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Declaration of Competing Interest

The authors declared no conflict of interests.

References

[1] R. Medzhitov, Origin and physiological roles of inflammation, Nature 454 (7203) (2008) 428–435.

[2] R. Medzhitov, Inflammation 2010: new adventures of an old flame, Cell 140 (6) (2010) 771–776.
[3] M.C. Basil, B.D. Levy, Specialized pro-resolving mediators: endogenous regulators of infection and inflammation, Nat. Rev. Immunol. 16 (1) (2016) 51–67.
[4] C. Nathan, Points of control in inflammation, Nature 420 (6917) (2002) 846–852.
[5] C. Nathan, A. Ding, Nonresolving inflammation, Cell 140 (6) (2010) 871–882.
[6] C.N. Serhan, S.D. Brain, C.D. Buckley, D.W. Gilroy, C. Haslett, L.A. O'Neill, M. Perretti, A.G. Rossi, J.L. Wallace, Resolution of inflammation: state of the art, definitions and terms, FASEB J. 21 (2) (2007) 325–332.
[7] W.M. Nauseef, N. Borregaard, Neutrophils at work, Nat. Immunol. 15 (7) (2014) 602–611.
[8] M.A. Sugimoto, J.P. Vago, M. Perretti, M.M. Teixeira, Mediators of the resolution of the inflammatory response, Trends Immunol. 40 (3) (2019) 212–227.
[9] C.N. Serhan, J. Savill, Resolution of inflammation: the beginning programs the end, Nat. Immunol. 6 (12) (2005) 1191–1197.
[10] M.A. Sugimoto, L.P. Sousa, V. Pinho, M. Perretti, M.M. Teixeira, Resolution of Inflammation: What Controls Its Onset? Front. Immunol. 7 (2016) 160.
[11] S. Vandevyver, L. Dejager, J. Tuckermann, C. Libert, New insights into the anti-inflammatory mechanisms of glucocorticoids: an emerging role for glucocorticoid-receptor-mediated transactivation, Endocrinology 154 (3) (2013) 993–1007.
[12] Q. Cheng, E. Morand, Y.H. Yang, Development of novel treatment strategies for inflammatory diseases-similarities and divergence between glucocorticoids and GILZ, Front. Pharmacol. 5 (2014) 169.
[13] M. Perretti, X. Leroy, E.J. Bland, T. Montero-Melendez, Resolution Pharmacology: Opportunities for Therapeutic Innovation in Inflammation, Trends Pharmacol. Sci. 36 (11) (2015) 737–755.
[14] C.N. Serhan, Treating inflammation and infection in the 21st century: new hints from decoding resolution mediators and mechanisms, FASEB J. 31 (4) (2017) 1273–1288.
[15] J. Dalli, Does promoting resolution instead of inhibiting inflammation represent the new paradigm in treating infections? Mol. Aspects Med. 58 (2017) 12–20.
[16] E. Ayroldi, C. Riccardi, Glucocorticoid-induced leucine zipper (GILZ): a new important mediator of glucocorticoid action, FASEB J. 23 (11) (2009) 3649–3658.
[17] E. Beaulieu, E.F. Morand, Role of GILZ in immune regulation, glucocorticoid actions and rheumatoid arthritis, Nat. Rev. Rheumatol. 7 (6) (2011) 340–348.
[18] O. Bereshchenko, G. Migliorati, S. Bruscoli, C. Riccardi, Glucocorticoid-induced leucine zipper: a novel anti-inflammatory molecule, Front. Pharmacol. 10 (2019) 308.
[19] J.P. Vago, L.P. Tavares, C.C. Garcia, K.M. Lima, L.O. Perucci, E.L. Vieira, C. R. Nogueira, F.M. Soriani, J.O. Martins, P.M. Silva, K.B. Gomes, V. Pinho, S. Bruscoli, C. Riccardi, E. Beaulieu, E.F. Morand, M.M. Teixeira, L.P. Sousa, The role and effects of glucocorticoid-induced leucine zipper in the context of inflammation resolution, J. Immunol. 194 (10) (2015) 4940–4950.
[20] M.A. Espinasse, A. Pepin, P. Virault-Rocroy, N. Szely, S. Chollet-Martin, M. Pallardy, A. Biola-Vidamment, Glucocorticoid-induced leucine zipper is expressed in human neutrophils and promotes apoptosis through Mcl-1 down-regulation, J. Innate Immun. 8 (1) (2016) 81–96.
[21] J.P. Vago, I. Galvao, G.L. Negreiros-Lima, L.C.R. Teixeira, K.M. Lima, M. A. Sugimoto, I.Z. Moreira, S.A. Jones, T. Lang, C. Riccardi, M.M. Teixeira, J. Harris, E.F. Morand, L.P. Sousa, Glucocorticoid-induced leucine zipper modulates macrophage polarization and apoptotic cell clearance, Pharmacol. Res. 158 (2020), 104842.
[22] R.J. Flower, G.J. Blackwell, Anti-inflammatory steroids induce biosynthesis of a phospholipase A2 inhibitor which prevents prostaglandin generation, Nature 278 (5703) (1979) 456–459.
[23] F.N. Gavins, S. Yona, A.M. Kamal, R.J. Flower, M. Perretti, Leukocyte antiadhesive actions of annexin 1: ALXR- and FPR-related anti-inflammatory mechanisms, Blood 101 (10) (2003) 4140–4147.
[24] L.H. Lim, E. Solito, F. Russo-Marie, R.J. Flower, M. Perretti, Promoting detachment of neutrophils adherent to murine postcapillary venules to control inflammation: effect of lipocortin 1, Proc. Natl. Acad. Sci. U. S. A. 95 (24) (1998) 14535–14539.
[25] M.A. Sugimoto, J.P. Vago, M.M. Teixeira, L.P. Sousa, Annexin A1 and the resolution of inflammation: modulation of neutrophil recruitment, apoptosis, and clearance, J. Immunol. Res. 2016 (2016), 8239258.
[26] J.P. Vago, C.R. Nogueira, L.P. Tavares, F.M. Soriani, F. Lopes, R.C. Russo, V. Pinho, M.M. Teixeira, L.P. Sousa, Annexin A1 modulates natural and glucocorticoid-induced resolution of inflammation by enhancing neutrophil apoptosis, J. Leukoc. Biol. 92 (2) (2012) 249–258.
[27] Y.H. Yang, D. Aeberli, A. Dacumos, J.R. Xue, E.F. Morand, Annexin-1 regulates macrophage IL-6 and TNF via glucocorticoid-induced leucine zipper, J. Immunol. 183 (2) (2009) 1435–1445.
[28] E. Ricci, S. Ronchetti, E. Pericolini, E. Gabrielli, L. Cari, M. Gentili, E. Roselletti, G. Migliorati, A. Vecchiarelli, C. Riccardi, Role of the glucocorticoid-induced leucine zipper gene in dexamethasone-induced inhibition of mouse neutrophil migration via control of annexin A1 expression, FASEB J. 31 (7) (2017) 3054–3065.
[29] B. Rinkevich, Primitive immune systems: are your ways my ways? Immunol. Rev. 198 (2004) 25–35.
[30] K. Asehnoune, J. Villadangos, R.S. Hotchkiss, Understanding host-pathogen interaction, Intensive Care Med. 42 (12) (2016) 2084–2086.
[31] C.N. Serhan, Resolution phase of inflammation: novel endogenous anti-inflammatory and proresolving lipid mediators and pathways, Annu. Rev. Immunol. 25 (2007) 101–137.
[32] T. Kawai, S. Akira, The role of pattern-recognition receptors in innate immunity: update on Toll-like receptors, Nat. Immunol. 11 (5) (2010) 373–384.
[33] P. Hunter, The inflammation theory of disease. The growing realization that chronic inflammation is crucial in many diseases opens new avenues for treatment, EMBO Rep. 13 (11) (2012) 968–970.
[34] L.P. Tavares, M.M. Teixeira, C.C. Garcia, The inflammatory response triggered by Influenza virus: a two edged sword, Inflamm. Res. 66 (4) (2017) 283–302.
[35] T. van der Poll, F.L. van de Veerdonk, B.P. Scicluna, M.G. Netea, The immunopathology of sepsis and potential therapeutic targets, Nat. Rev. Immunol. 17 (7) (2017) 407–420.
[36] M. Cazzola, M.G. Matera, G. Pezzuto, Inflammation–a new therapeutic target in pneumonia, Respiration 72 (2) (2005) 117–126.
[37] J.R. Glasser, R.K. Mallampalli, Surfactant and its role in the pathobiology of pulmonary infection, Microbes Infect. 14 (1) (2012) 17–25.
[38] G.B.D.L.R.I. Collaborators, Estimates of the global, regional, and national morbidity, mortality, and aetiologies of lower respiratory infections in 195 countries, 1990-2016: a systematic analysis for the Global Burden of Disease Study 2016, Lancet Infect. Dis. 18 (11) (2018) 1191–1210.
[39] L.J. Quinton, A.J. Walkey, J.P. Mizgerd, Integrative physiology of pneumonia, Physiol. Rev. 98 (3) (2018) 1417–1464.
[40] M.A. Matthay, R.L. Zemans, The acute respiratory distress syndrome: pathogenesis and treatment, Annu. Rev. Pathol. 6 (2011) 147–163.
[41] V.F. Corrales-Medina, D.M. Musher, Immunomodulatory agents in the treatment of community-acquired pneumonia: a systematic review, J. Infect. 63 (3) (2011) 187–199.
[42] M. Confalonieri, R. Urbino, A. Potena, M. Piattella, P. Parigi, G. Puccio, R. Della Porta, C. Giorgio, F. Blasi, R. Umberger, G.U. Meduri, Hydrocortisone infusion for severe community-acquired pneumonia: a preliminary randomized study, Am. J. Respir. Crit. Care Med. 171 (3) (2005) 242–248.
[43] D. Basille, R.W. Thomsen, M. Madsen, P. Duhaut, C. Andrejak, V. Jounieaux, H. T. Sorensen, Nonsteroidal antiinflammatory drug use and clinical outcomes of community-acquired pneumonia, Am. J. Respir. Crit. Care Med. 198 (1) (2018) 128–131.
[44] K.H. Vanessa, M.G. Julia, L. Wenwei, A.L. Michelle, Z.R. Zarina, L.H. Lina, A. Sylvie, Absence of Annexin A1 impairs host adaptive immunity against Mycobacterium tuberculosis in vivo, Immunobiology 220 (5) (2015) 614–623.
[45] F. Tzelepis, M. Verway, J. Daoud, J. Gillard, K. Hassani-Ardakani, J. Dunn, J. Downey, M.E. Gentile, J. Jaworska, A.M. Sanchez, Y. Nedelec, H. Vali, M. Tabrizian, A.S. Kristof, I.L. King, L.B. Barreiro, M. Divangahi, Annexin1 regulates DC efferocytosis and cross-presentation during Mycobacterium tuberculosis infection, J. Clin. Invest. 125 (2) (2015) 752–768.
[46] M.G. Machado, L.P. Tavares, G.V.S. Souza, C.M. Queiroz-Junior, F.R. Ascencao, M. E. Lopes, C.C. Garcia, G.B. Menezes, M. Perretti, R.C. Russo, M.M. Teixeira, L. P. Sousa, The Annexin A1/FPR2 pathway controls the inflammatory response and bacterial dissemination in experimental pneumococcal pneumonia, FASEB J. 34 (2) (2020) 2749–2764.
[47] L.P. Tavares, C.C. Garcia, J.P. Vago, C.M. Queiroz-Junior, I. Galvao, B.A. David, M. A. Rachid, P.M. Silva, R.C. Russo, M.M. Teixeira, L.P. Sousa, Inhibition of Phosphodiesterase-4 during pneumococcal pneumonia reduces inflammation and lung injury in mice, Am. J. Respir. Cell Mol. Biol. 55 (1) (2016) 24–34.
[48] D.C. Angus, T. Van der Poll, Severe sepsis and septic shock, N. Engl. J. Med. 369 (21) (2013) 2063.
[49] B.D. Winters, M. Eberlein, J. Leung, D.M. Needham, P.J. Pronovost, J.E. Sevransky, Long-term mortality and quality of life in sepsis: a systematic review, Crit. Care Med. 38 (5) (2010) 1276–1283.
[50] I. Pinheiro, L. Dejager, I. Petta, S. Vandevyver, L. Puimege, T. Mahieu, M. Ballegeer, F. Van Hauwermeiren, C. Riccardi, M. Vuylsteke, C. Libert, LPS resistance of SPRET/Ei mice is mediated by Gilz, encoded by the Tsc22d3 gene on the X chromosome, EMBO Mol. Med. 5 (3) (2013) 456–470.
[51] J. Hoppstadter, S.M. Kessler, S. Bruscoli, H. Huwer, C. Riccardi, A.K. Kiemer, Glucocorticoid-induced leucine zipper: a critical factor in macrophage endotoxin tolerance, J. Immunol. 194 (12) (2015) 6057–6067.
[52] M. Ballegeer, J. Vandewalle, M. Eggermont, G. Van Isterdael, L. Dejager, L. De Bus, J. Decruyenaere, R.E. Vandenbroucke, C. Libert, Overexpression of gilz protects mice against lethal septic peritonitis, Shock 52 (2) (2019) 208–214.
[53] M. Ellouze, L. Vigouroux, C. Tcherakian, P.L. Woerther, A. Guguin, O. Robert, M. Surenaud, T. Tran, J. Calmette, T. Barbin, G. Perlemuter, A.M. Cassard, P. Launay, V. Maxime, D. Annane, Y. Levy, V. Godot, Overexpression of GILZ in macrophages limits systemic inflammation while increasing bacterial clearance in sepsis in mice, Eur. J. Immunol. 50 (4) (2020) 589–602.
[54] J. Hoppstadter, B. Diesel, R. Linnenberger, N. Hachenthal, S. Flamini, M. Minet, P. Leidinger, C. Backes, F. Grasser, E. Meese, S. Bruscoli, C. Riccardi, H. Huwer, A. K. Kiemer, Amplified host defense by toll-like receptor-mediated downregulation of the glucocorticoid-induced leucine zipper (GILZ) in macrophages, Front. Immunol. 9 (2018) 3111.
[55] E. Ricci, S. Ronchetti, E. Gabrielli, E. Pericolini, M. Gentili, E. Roselletti, A. Vecchiarelli, C. Riccardi, GILZ restrains neutrophil activation by inhibiting the MAPK pathway, J. Leukoc. Biol. 105 (1) (2019) 187–194.
[56] D.H. Dockrell, H.M. Marriott, L.R. Prince, V.C. Ridger, P.G. Ince, P.G. Hellewell, M. K. Whyte, Alveolar macrophage apoptosis contributes to pneumococcal clearance in a resolving model of pulmonary infection, J. Immunol. 171 (10) (2003) 5380–5388.
[57] M. Sekheri, D. El Kebir, N. Edner, J.G. Filep, 15-Epi-LXA4 and 17-epi-RvD1 restore TLR9-mediated impaired neutrophil phagocytosis and accelerate resolution of lung inflammation, Proc. Natl. Acad. Sci. U. S. A. 117 (14) (2020) 7971–7980.
[58] A.S. Damazo, S. Yona, F. D'Acquisto, R.J. Flower, S.M. Oliani, M. Perretti, Critical protective role for annexin 1 gene expression in the endotoxemic murine microcirculation, Am. J. Pathol. 166 (6) (2005) 1607–1617.

[59] M. Perretti, N. Chiang, M. La, I.M. Fierro, S. Marullo, S.J. Getting, E. Solito, C. N. Serhan, Endogenous lipid- and peptide-derived anti-inflammatory pathways generated with glucocorticoid and aspirin treatment activate the lipoxin A4 receptor, Nat. Med. 8 (11) (2002) 1296–1302.
[60] T. Gobbetti, S.M. Coldewey, J. Chen, S. McArthur, P. le Faouder, N. Cenac, R. J. Flower, C. Thiemermann, M. Perretti, Nonredundant protective properties of FPR2/ALX in polymicrobial murine sepsis, Proc. Natl. Acad. Sci. U. S. A. 111 (52) (2014) 18685–18690.
[61] H. Hiramoto, H. Dansako, M. Takeda, S. Satoh, T. Wakita, M. Ikeda, N. Kato, Annexin A1 negatively regulates viral RNA replication of hepatitis C virus, Acta Med. Okayama 69 (2) (2015) 71–78.
[62] P.B. Ampomah, L.A. Moraes, H.M. Lukman, L.H.K. Lim, Formyl peptide receptor 2 is regulated by RNA mimics and viruses through an IFN-beta-STAT3-dependent pathway, FASEB J. 32 (3) (2018) 1468–1478.
[63] S. Arora, W. Lim, P. Bist, R. Perumalsamy, H.M. Lukman, F. Li, L.B. Welker, B. Yan, G. Sethi, P.A. Tambyah, A.M. Fairhurst, S. Alonso, L.H. Lim, Influenza A virus enhances its propagation through the modulation of Annexin-A1 dependent endosomal trafficking and apoptosis, Cell Death Differ. 23 (7) (2016) 1243–1256.
[64] S. Schloer, N. Hubel, D. Masemann, D. Pajonczyk, L. Brunotte, C. Ehrhardt, L. O. Brandenburg, S. Ludwig, V. Gerke, U. Rescher, The annexin A1/FPR2 signaling axis expands alveolar macrophages, limits viral replication, and attenuates pathogenesis in the murine influenza A virus infection model, FASEB J. 33 (11) (2019) 12188–12199.
[65] R.B. Molas, M.R. Ribeiro, M.J.C. Ramalho Dos Santos, A.U. Borbely, D.V. Oliani, A. H. Oliani, S. Nadkarni, M.L. Nogueira, J.B. Moreli, S.M. Oliani, The involvement of annexin A1 in human placental response to maternal Zika virus infection, Antiviral Res. 179 (2020), 104809.
[66] V.N. Puttamallesh, S.K. Sreenivasamurthy, P.K. Singh, H.C. Harsha, A. Ganjiwale, S. Broor, A. Pandey, J. Narayana, T.S.K. Prasad, Proteomic profiling of serum samples from chikungunya-infected patients provides insights into host response, Clin. Proteomics 10 (1) (2013) 14.
[67] Y.C. Xia, A. Radwan, C.R. Keenan, S.Y. Langenbach, M. Li, D. Radojicic, S. L. Londrigan, R.C. Gualano, A.G. Stewart, Glucocorticoid insensitivity in virally infected airway epithelial cells is dependent on transforming growth factor-beta activity, PLoS Pathog. 13 (1) (2017), e1006138.
[68] Z. Li, Y. Wang, X. Li, X. Li, H. Cao, S.J. Zheng, Critical roles of glucocorticoid-induced leucine zipper in infectious bursal disease virus (IBDV)-induced suppression of type I Interferon expression and enhancement of IBDV growth in host cells via interaction with VP4, J. Virol. 87 (2) (2013) 1221–1231.
[69] L.G. Oliveira, M.C. Souza-Testasicca, J.P. Vago, A.B. Figueiredo, A.M. Canavaci, L. O. Perucci, T.P. Ferreira, E.A. Coelho, D.U. Goncalves, M.O. Rocha, E.S. PM, C. N. Ferreira, C. Queiroz-Junior, L.P. Sousa, A.P. Fernandes, Annexin A1 is involved in the resolution of inflammatory responses during leishmania braziliensis infection, J. Immunol. 198 (8) (2017) 3227–3236.
[70] E. Torres-Guerrero, M.R. Quintanilla-Cedillo, J. Ruiz-Esmenjaud, R. Arenas, Leishmaniasis: a review, F1000Res 6 (2017) 750.
[71] C.I. de Oliveira, C.I. Brodskyn, The immunobiology of Leishmania braziliensis infection, Front. Immunol. 3 (2012) 145.
[72] C. Yan, L.J. Liang, K.Y. Zheng, X.Q. Zhu, Impact of environmental factors on the emergence, transmission and distribution of Toxoplasma gondii, Parasit. Vectors 9 (2016) 137.
[73] M.F. de Oliveira Cardoso, J.B. Moreli, A.O. Gomes, C. de Freitas Zanon, A.E. Silva, L.R. Paulesu, F. Ietta, J.R. Mineo, E.A. Ferro, S.M. Oliani, Annexin A1 peptide is able to induce an anti-parasitic effect in human placental explants infected by Toxoplasma gondii, Microb. Pathog. 123 (2018) 153–161.
[74] N. Chiang, G. Fredman, F. Backhed, S.F. Oh, T. Vickery, B.A. Schmidt, C.N. Serhan, Infection regulates pro-resolving mediators that lower antibiotic requirements, Nature 484 (7395) (2012) 524–528.
[75] M. Morita, K. Kuba, A. Ichikawa, M. Nakayama, J. Katahira, R. Iwamoto, T. Watanebe, S. Sakabe, T. Daidoji, S. Nakamura, A. Kadowaki, T. Ohto, H. Nakanishi, R. Taguchi, T. Nakaya, M. Murakami, Y. Yoneda, H. Arai, Y. Kawaoka, J.M. Penninger, M. Arita, Y. Imai, The lipid mediator protectin D1 inhibits influenza virus replication and improves severe influenza, Cell 153 (1) (2013) 112–125.