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The most prominent modulated Annexins during parasitic infections

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ABSTRACT

Annexins (ANXs) exert different functions in cell biological and pathological processes and are thus known as double or multi-faceted proteins. These sophisticated proteins might express on both parasite structure and secretion and in parasite-infected host cells. In addition to the characterization of these pivotal proteins, describing their mechanism of action can be also fruitful in recognizing their roles in the pathogenesis of parasitic infections. Accordingly, this study presents the most prominent ANXs thus far identified and their relevant functions in parasites and infected host cells during pathogenesis, especially in the most important intracellular protozoan parasitic infections including leishmaniasis, toxoplasmosis, malaria and trypanosomiasis. The data provided in this study demonstrate that the helminth parasites most probably express and secret ANXs to develop pathogenesis while the modulation of the host-ANXs could be employed as a crucial strategy by intracellular protozoan parasites. Moreover, such data highlight that the use of analogs of both parasite and host ANX peptides (which mimic or regulate ANXs physiological functions through various strategies) might suggest novel therapeutic insights into the treatment of parasitic infections. Furthermore, due to the prominent immunoregulatory activities of ANXs during most parasitic infections and the expression levels of these proteins in some parasitic infected tissues, such multifunctional proteins might be also potentially relevant as vaccine and diagnostic biomarkers. We also suggest some prospects and insights that could be useful and applicable to form the basis of future experimental studies.

1. Introduction

Annexins (ANXs) are calcium-dependent phospholipid binding and multi-faceted proteins containing an N-terminal part and four conserved domains at their C-terminal tail. The N-terminus, located on the concave region of the folded protein, harbors a variable sequence, and might be useful to detect conserved regions in different ANXs. This key region exerts a crucial function in the regulation of ANXs-membrane associations. The convex side of this biomolecule contains four conserved repeats. Each repeat is formed by approximately 70 amino acids containing a calcium (Ca^{+})-binding motif (Leow et al., 2019).

ANXs participate in several biological processes which are very relevant to normal functioning but also to infectious and pathologic processes including adaptive immunity, inflammation, phagocytosis, the inhibition of phospholipase A2, cell membrane transport and trafficking, the interaction with cytoskeletal proteins, signal transduction, calcium channel formation as well as the interaction with both coagulant and fibrinolytic factors (Ayón-Núñez et al., 2018; Enrich et al., 2011; Han et al., 2020; Kelly et al., 2022; Lizarbe et al., 2013; Vecchi et al., 2021). These multifunctional proteins may exert opposing or dual functions such as acting as anti-inflammatory and pro-inflammatory agents during inflammation (Mui et al., 2021; Shao et al., 2019; Yuan et al., 2021). Fig. 1 shows several important biological functions of the most prominent ANXs.

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The expression of ANXs in different diseases including sepsis, myocardial infarction, and ischemia reperfusion injury has been also reported. For instance, ANXA1 and ANXA5 promote organ function and reduce mortality rate in sepsis infections, inhibit inflammatory responses, decrease inflammatory mediator secretion, and induce protection against ischemic injury. Furthermore, the effects of ANXA5 on both inflammation and platelet activation could be beneficial in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infections (Mui et al., 2021; You et al., 2021).

Most ANXs regulate different cell processes and responses such as immune responses through the interaction of their motif sites with the downstream signaling. For instance, ANXA1 and ANXA2 have an important role in regulating immune functions and inflammation and specifically, ANXA2 in fibrinolysis and fibrosis in addition to the specific role of ANXA1 in response to DNA damage (Araújo et al., 2021; Croissant et al., 2021; Dallacasagrande and Hajjar, 2020; Han et al., 2020; Lim and Hajjar, 2021; Sousa et al., 2022). ANXA5 is essential for downstream signals leading to T-cell activation as recently demonstrated thus adding knowledge to the role of ANXA1, ANXA2, and ANXA6 in the immunological process (Hu et al., 2020). Therefore, targeting or inhibiting these proteins could offer a number of important outcomes during disorders and infections including parasitic diseases such as controlling infection-induced acute inflammation or promoting host defense (de Araújo et al., 2022; Vago et al., 2021). In addition, the recognition of ANXs-down-stream signaling might be insightful for the in-depth understanding of the complicated mechanisms of such proteins in infections and disorders. Table 1 shows the important correlation of some ANXs with different host-cell signaling and the management of host responses.

2. Parasite ANXs

Different studies that have employed a variety of techniques including genomics, proteomics and *in silico* tools for the identification of ANXs during infections, including parasitic infections (Aziz et al., 2011; Cantacessi et al., 2013; Cava et al., 2020; Cui et al., 2021; Debarba et al., 2020; Einarsson et al., 2016). In helminth parasites, ANX (*Sm*)3 (Smp_077720) has been introduced in Schistosoma mansoni as a biomolecule that holds the plasma membrane and membranocalyx of the parasite together by a calcium-dependent phospholipid binding property (Leow et al., 2019).

Plasminogen (Plg)-binding proteins including ANXs can be recruited by different infectious agents to invade and establish themselves in their infected hosts. During parasite infections (such as protozoan, helminth, and probably taeniid parasites), Plg/plasmin (Plm) might be involved in invasion and migration of the parasites across the infected tissues of the host (Ayón-Núñez et al., 2018; Lin et al., 2012). Evidence has shown that *S. bovis* tegument ANX (ACC78610) has anticoagulant and fibrinolytic features (de la Torre-Escudero et al., 2012). Thus, further research into key molecular interactions involving ANXs will allow the identification of novel mechanisms of invasion, migration and specific parasitic stage activation that could be consequently targeted to control parasitic infections. Table 2 describes the most commonly modulated ANXs during helminth infections.

On the other hand, the ANXs of some protozoan parasites including *Giardia duodenalis* (*α*-giardins form a large class of ANX-like proteins (E-ANXs)). These are located at the outer edges of the ventral disk microribbons and have been found to be correlated with the stabilization of the parasite membrane in the host intestine through microtubule interaction (Steele-Ogus et al., 2022; Weeratunga et al., 2012; Weiland et al., 2005). Moreover, ANXA3, ANXA5 have been described as secretory proteins in interaction with human intestinal epithelial cells during *G. duodenalis* infection, leading to the modulation of host cell responses during pathogenesis, especially inflammatory responses (Ma'ayeh et al., 2017). Parasite *α*-giardins (E-ANXs) and parasite ANXs 1–14 (related to *α*-giardins, E-ANXs) have also been characterized in *G. muris* and *Spironucleus salmonicida*, respectively, located in the parasite structure (parasite cytoskeleton and membrane) and involved in parasite structural functions (Einarsson et al., 2016).

Due to the critical role of ANXs (both parasite and host) mainly in host-parasite interactions and immunoregulation, these proteins have been suggested as potential candidates for the development of new

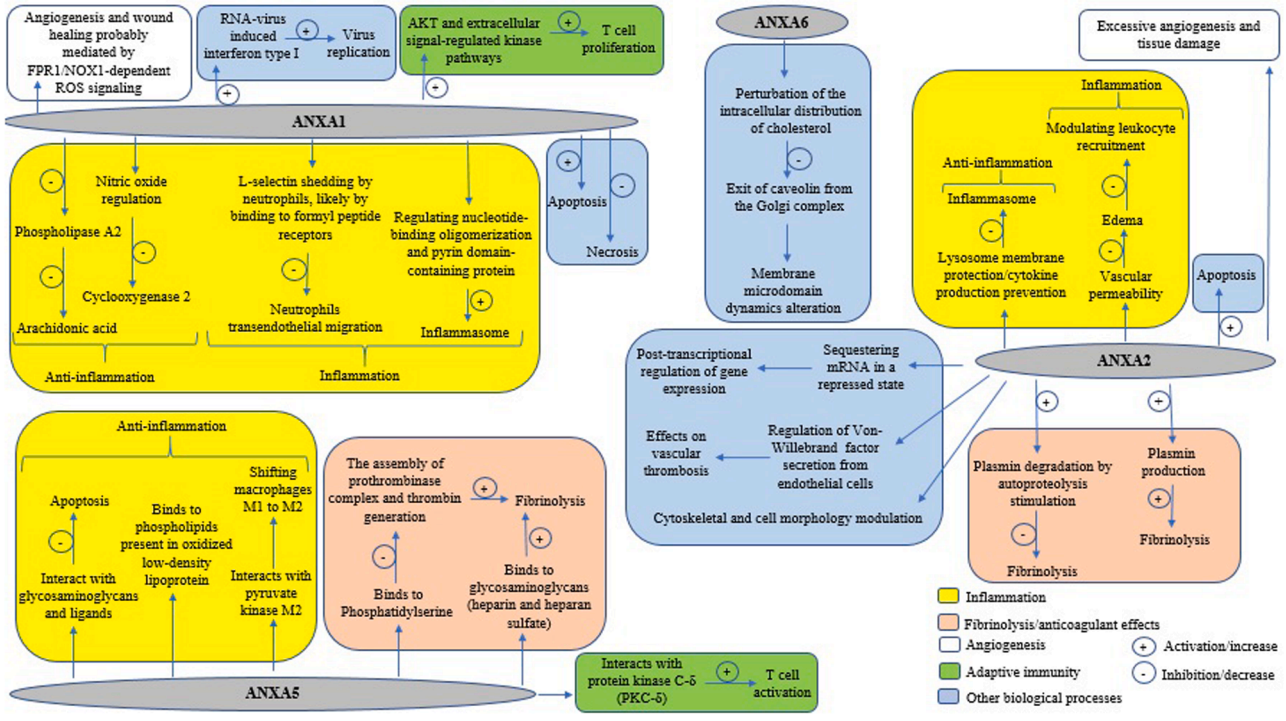

Fig. 1. Several important biological functions of the most prominent ANXs. Formyl peptide receptor 1 (FPR1), nicotinamide adenine dinucleotide phosphate (NADPH) oxidase 1 (NOX1), reactive oxygen species (ROS), the serine/threonine kinase AKT (Protein kinase B).

Table 1
The interaction of host-ANXs with cell signaling to manage cell responses/conditions or pathogenesis during infections/disorders.

Host-Annexins (ANXs)	Infections/disorders	Relevant cell signaling	Effect	References
ANXA1	Cancer	Induction of MAPK/ERK signaling via FPRs	Decrease of neutrophil activity to restrict inflammatory responses	(Shao et al., 2019)
		Activation of ERK/ITGB1BP1 signaling through FPRs and induction of EMT via the NF-κB and TGF-β signaling pathways	Induction of tumorigenesis	(Cheng et al., 2012)
ANXA2	*Trypanosoma cruzi*	*T. cruzi* G strain mucins interact with target cell ANXA2 and activate FAK signaling	Facilitating parasite entry	(Onofre et al., 2022)
	Infection-initiated inflammation	Binding to endosomes and negatively regulating TLR4-triggered inflammatory responses via the TRAM-TRIF pathway	Activation of macrophages and triggering the secretion of anti-inflammatory cytokines	(Zhang et al., 2015)
	Anaplasma phagocytophilum	Loop 2 of sialostatin L2 (an anti-inflammatory protein) bind to ANXA2 and inhibits the formation of the NLRC-4 inflammasome signaling during infection	Inflammasome evasion by pathogens	(Wang et al., 2016)
	Angiostrongylus cantonensis	Parasite Galectin-1 interaction with ANXA2 through activation of the JNK pathway	Impairment of macrophage viability	(Shi et al., 2020)
	Inflammation	Tissue plasminogen activators induce the NF-κB pathway in macrophages through a signaling pathway involving ANXA2/CD11b-mediated integrin linked kinase	Initiation and progression of inflammation	(Lin et al., 2012)
ANXA5	*Leishmania*	Interaction between parasite and host ANXA5 and activation of TGF-β signaling	Silencing of phagocytes and parasite survival	(Aga et al., 2002; van Zandbergen et al., 2004; Walker et al., 2014)
	Cardiac inflammation	Blocking of TLR-4 signaling dendritic cells and cardiomyocytes	Decrease of LPS and inducing the secretion of pro-inflammatory cytokines (IL-1β, IL-6 and TNF-α)	(Arnold et al., 2014; Park et al., 2016; Rand et al., 2012)

Epithelial-mesenchymal transition (EMT), mitogen-activated protein kinase (MAPK)/extracellular signal-regulated kinases (ERK), formyl peptide receptor family (FPRs), integrin beta-1-binding protein 1 (ITGB1BP1), cytosolic NOD-like receptor (NLR) protein 4 (NLRC4), c-Jun N-terminal kinases (JNKs), endothelial growth factor receptor-2 (VEGFR-2), toll-like receptor-4 (TLR4), focal adhesion kinase (FAK), Toll/interleukin-1 (IL-1) receptor (TIR) domain-containing adaptor-inducing IFN-β (TRIF), TRIF-related adaptor molecule (TRAM), transforming growth factor beta (TGF-β), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), tumor necrosis factor alpha (TNF-α).

drugs, vaccines and diagnostic tools in complex helminth infections (Hofmann et al., 2010). The parasite ANXs that have been described as novel potential biomolecules for drug and vaccine development include ANXB1, ANXB2, and ANXB3 isolated from *Taenia solium* cysticercoses and an ANX homolog, *Tp*ANXB1 (showing great similarity with *T. solium* ANXB1 (*Ts*ANXB1)) from the transcriptome of adult *T. pisiformis* (Hofmann et al., 2010; Yang et al., 2014). Recombinant ANXB30 has not provided significant protection against *S. mansoni*, thus, it may not be an appropriate vaccine candidate but it could be a suitable biomarker for immunodiagnostics tools (Leow et al., 2020). Furthermore, the disruption of the apical membrane complex of the schistosome tegument, as a pivotal protective barrier for the parasite, via the inhibition of ANXs function has been also suggested as a plausible therapeutic target for the control of this parasitic infection (Leow et al., 2019).

In contrast to helminth infections, there is no adequate information regarding the employment of ANXs as plausible drugs, vaccines and diagnostic candidates in protozoan parasitic infections. To better study ANXs as effective therapeutic, vaccine and diagnostic targets, we need to fully characterize the molecular biology and the relevant mechanisms of these proteins during parasitic infections and pathogenesis. Accordingly, this study aims to review the most important parasite and host modulated ANXs during intracellular protozoan parasitic infections including leishmaniasis, toxoplasmosis, malaria and trypanosomiasis.

2.1. Leishmaniasis

Leishmaniasis is a group of vector-borne infectious diseases caused by intracellular protozoan parasites belonging to the genus *Leishmania*. These infectious diseases are transmitted to humans by the bite of phlebotomine sand flies. After the entrance of parasites into human skin, different immune cells such as macrophages try to engulf the parasites. However, the parasites can deploy different strategies such as generating parasitophorous vacuoles (PVs) within the macrophage to better adapt to the host cell conditions and remain alive. The most common form of these diseases is cutaneous leishmaniasis (CL), which produces skin sores, whereas the most lethal form is visceral leishmaniasis (VL), which infects several internal organs (Gow et al., 2022; Torres-Guerrero et al., 2017).

In *Leishmania* parasites, a species-specific PV is essential for the differentiation of infective promastigotes into amastigotes (Real et al., 2010). However, the survival and differentiation of some co-infecting parasites including *T. cruzi* occurs in *Leishmania*-containing vacuoles. Thus, the creation of chimeric PVs may be related to the enhancement of the pathogenicity of protozoan parasites (Pessoa et al., 2016). There is evidence for the expression of ANXA1 in PVs containing *Leishmania* parasites and its crucial role in vesicle fusion with endosomes (Collins et al., 1997). Therefore, ANXA1 could be considered as a therapeutic target for the treatment of protozoan intracellular infections.

The high expression of ANXA1 has been reported in apoptotic cells and macrophages in exudative necrotic and exudative necrotic-granulomatous reactions in patients with CL, highlighting the function of this protein in phagocytosis and apoptosis (Pona et al., 2021). Additionally, it has been shown that ANXA1 is differentially expressed in $CD163^{+}$ macrophages and T cells in necrotic lesions in comparison with granulomatous or cellular lesions of *Leishmania*-infected skin (Silva et al., 2015). On the other hand, Leishmania infection can induce alteration in the proteome profile of Extracellular Vesicles (EVs) in infected cells such as macrophages. EVs released from Leishmania infected cells can affect and promote vascularization in leishmaniasis (Gioseffi et al., 2020). Some results have indicated that several ANXs -which are biomarkers of EVs- such as A1, A2, A3 and A5 are secreted in EVs from *Leishmania*-infected cells. Amongst these, ANXA3, as the most prominent enriched protein, plays an important role in the promotion of angiogenesis (Park et al., 2005). Therefore, the recognition of different ANXs expressed in CL and in the proteome of EVs can be employed to gain a more detailed understanding of certain clinical features of this disorder.

ANXA1 induction (up- and down-regulation) in association with

Table 2
The expression of ANXs during helminth parasitic infections.

Echinococcus granulosus Annexins (ANXs)	Location	Property/Function	References
Host-derived ANXA2	Originated from the host granulomatous inflammatory cells	Involvement in the calcification process, associated with an intense local response to the hydatid cyst	(Díaz et al., 2000)
Echinococcus granulosus ANXB33 (Eg-ANXB33)	In parasite secretions, cyst fluid, inflammatory cells and fibroblasts of the host-derived layer	Parasite survival, host-parasite interface	(Aziz et al., 2011; Song et al., 2016; Virginio et al., 2012; Yang et al., 2021)
E. granulosus ANXB3 (*Eg*ANXB3) and *Eg*ANXB38	In all stages of parasite and secretions, in liver tissues both near the cysts or distant from the cysts	In adult parasite growth and development of protoscoleces and protoscolece invasion of the definitive host, regulating the host immune responses or functioning in parasite immune evasion	(Song et al., 2021)

Taenia solium ANXs	Location	Property/Function	References
Parasite (metacestodes) ANXB1	In cyst fluid, sera of hosts and in the host-derived layer surrounding the cysts	Induction of calcium-dependent eosinophil apoptosis and downregulation of the host immune response and enhancing parasite survival by inhibiting the inflammation around parasites	(Gao et al., 2007; Yan et al., 2008; Zhang et al., 2007)
ANXB1 (maybe parasite or host ANX)	Cyst fluid	In the interaction between the cysticerci and the host	(Diaz-Masmela et al., 2013)
ANX (Smp_074150) (maybe parasite or host ANX)			(Cui et al., 2021)

Taenia multiceps ANXs	Location	Property/Function	References
Parasite ANXB2 and ANXB12	High expression level in the larvae (oncosphere) stage	Parasite growth and development	(Guo et al., 2018)
ANXB3	High expression level in the adult stage		(Guo et al., 2018)

Taenia pisiformis ANXs	Location	Property/Function	References
*Tp*ANXB1 (with high similarity with *T. solium* ANXB1(*Ts*ANXB1))	Transcriptome of adult *T. pisiformis*	Immunoreactive protein (with diagnostic property)	(Yang et al., 2014)

Clonorchis sinensis ANXs	Location	Property/Function	References
Parasite ANXB30	Secretory protein	Alteration of the host's autoimmune response, interaction with host plasminogen and maintenance of hemostasis (inhibiting this interaction by lysine)	(Ayón-Núñez et al., 2018; He et al., al.,2014)

Angiostrongylus cantonensis ANXs	Location	Property/Function	References
Host ANXA2	Plasma membrane of host cells (macrophages)	Parasite Galectin-1 and host ANXA2 interaction and decreasing the viability of macrophages (inducing apoptosis) through activation of c-Jun N-terminal kinases (JNKs) pathway	(Donskow-Łysoniewska et al., 2021; Shi et al., 2020)
NEX1 ANX	Down-regulation in adult males and up-regulation in adult females	Probably in parasite survival	(Huang et al., 2013)

Schistosoma bovis ANXs	Location	Property/Function	References
S. bovis ANX (*Sb*ANX)	The expression on the tegument and surface of *S. bovis* schistosomula and adult worms	Fibrinolytic and anticoagulant properties and immunomodulatory function	(de la Torre-Escudero et al., 2012)

Schistosoma mansoni ANXs	Location	Property/Function	References
Parasite ANXA2	In the tegument of schistosomula and adult worms (especially male worms)	Association with the tegument arrangement, mediating the attachment of the membranocalyx to the underlying membrane and a potential target for immune intervention and vaccine candidate	(Braschi et al., 2006; Tararam et al., 2010)
Parasite ANXB2 (Smp_077720)	In the tegument	Parasite biological functions	(Diaz Soria et al., 2020)
Parasite ANXB30, ANXB5a, ANXB7a and ANXB5b	ANXB30 and ANXB7a with high abundance during schistosomulum stage, ANXB5a and ANXB5b with high expression in adult males	Parasite development (playing a role in dynamic membrane-associated tegument maintenance through calcium ion regulation), host-parasite interactions (immunoreactivity property)	(Leow et al., 2019)
Parasite ANXB22	In the tegument	Structural integrity in the tegument, immune evasion function	(Leow et al., 2014)

Ostertagia ostertagi ANXs	Location	Property/Function	References
Parasite ANX-like protein (*Oos*-ANXL-2.1)	Located in the hypodermis in L3 and to the hypodermis in adult worms	Without distinct function (probably immune modulator)	(Sharma et al., 2017)

Brugia malayi ANXs	Location	Property/Function	References
ANX (UniProtKB ID: A0A0K0J0N3_BRUMA)	Parasite extracellular vesicles	Participating in exosome biogenesis and considering as plausible immunomodulators	(Harischandra et al., 2018)

lesion size and parasite burden and also its potential role in the modulation or control of inflammatory responses have been deciphered during *Leishmania braziliensis* infection *in vivo* and *in vitro* (Oliveira et al., 2017). In the absence of ANXA1 expression down-stream proinflammatory signals, apoptotic mechanisms, edema and inflammatory response (increased interferon gamma levels and inducible nitric oxide synthase (iNOS) production) are induced and activated for the efficient control of *Leishmania* parasite replication. Although the absence

of this protein can effectively control parasite multiplication, lesion size and inflammatory infiltrates were increased during leishmaniasis. Therefore, it could be concluded that ANXA1 expression could be crucially involved in the control of tissue inflammation during L. *braziliensis* infection and likely in other leishmaniases. Thus, more investigation into the expression of this protein in *Leishmania* parasites and in infected-host's cells and downstream relevant signaling pathways would provide valuable information about the functions of ANXs in parasite pathogenicity and in the modulation of immune responses. Furthermore, the identification of the expression level of such proteins in infected sera could be evaluated as a diagnostic marker in the prognostic follow-up of leishmaniasis.

The phagocytic S100 proteins are a group of calcium-binding molecules and are pro-inflammatory factors involved in immune responses. S100A10 and S100A11, two relevant members of this family, are up-regulated in *Leishmania* (L. *major*)-infected macrophages and interact with ANXA1 and ANXA2 and form a complex Ca^{2+} sensing system (Guerfali et al., 2008). Due to the pro-inflammatory function of ANXA2 and its down-regulation in *Leishmania*-infected macrophages, the characterization of the exact mechanisms between S100 and ANX proteins and the cell signaling pathways of such proteins may provide novel insights into inflammation, tissue damage and modulation of immune responses during leishmaniasis.

2.2. Toxoplasmosis

Toxoplasma gondii is an obligate intracellular protozoan pathogen belonging to the apicomplexan parasites with a worldwide distribution that has a prominent impact on human health. This parasite can induce different symptoms including encephalitis, necrotic lesions in the central nervous system or retinochoroiditis in immunocompromised patients. In addition, congenital toxoplasmosis (from infected mother to child) correlates with perinatal morbidity and mortality (Buffolano, 2008; de Barros et al., 2022); whereas ocular toxoplasmosis, another clinical manifestation of this disease, appears through congenital or acquired routes (Bosch-Driessen et al., 2002).

ANXA1 has been suggested as a potent regulator of inflammation in ocular toxoplasmosis (*T. gondii* infection by RH strain) (Mimura et al., 2012). Interestingly, the expression levels of this protein changed and increased in neutrophils (*in vivo*) and human retinal pigment epithelial (RPE) cells (ARPE-19) (*in vitro*) after infection. This evidence suggested a potential role for ANXA1 in the neutrophil activation in the ocular toxoplasmosis model. Moreover, the enhanced levels of ANXA1 in ARPE-19 cells probably activate the phagocytosis process of the parasites by cells, suggesting an immune protective function in the tissue (Mimura et al., 2012). The significant modulation of ANXA1 in inflammatory responses during ocular toxoplasmosis may highlight ANXA1 as a therapeutic target. Thus, the expression of other ANXs could be also investigated as interesting candidates.

More information about the differential expression levels of ANXs in pregnancy during toxoplasmosis is needed. The placenta is a potential source of ANXs (Gęca et al., 2022; Sousa et al., 2022), constituting approximately 2% of all placental membrane proteins (Buhl et al., 1991). The expression levels of ANXA1 and ANXA2 are high in trophoblast cells and exert an important function in early embryonic development (through phospholipase A2 inhibition). Proteomics data identified that the expression levels of ANXA1, ANXA2 and ANXA3 were reduced in *Toxoplasma*-infected placentas. The alteration in ANXA1, ANXA2 and ANXA3 expression during *Toxoplasma* infection may lead to aberrant extracellular matrix (ECM) remodeling and trophoblast cell migratory processes and consequently, serve as a mechanism to induce the abnormal pregnancies triggered by this disease (Jiao et al., 2017).

The expression levels of ANXA1 and its receptor (formyl peptide receptors 1 (FPR1)) are decreased in *Toxoplasma*-infected placental explants in third trimester of gestation (compared to first trimester placentas) and the tissue was more sensitive and permissive to the parasite. Interestingly, Ac2–26 (mimetic peptide of ANXA1) treatment enhanced the ANXA1 and FPR1expression levels and reduced intracellular proliferation of *Toxoplasma* parasite in placentas infected with *Toxoplasma*, suggesting a modulatory function of ANXA1 (both anti-parasitic and anti-inflammatory effects) in these tissues (de Oliveira Cardoso et al., 2018). Functions of ANXA1 and its derivative peptide (Ac2–26) are crucially mediated by FPRs (Oliveira et al., 2021; Zharkova et al., 2023), as regulators of innate inflammatory responses. The secretion of ANXA1 is also deeply affected by FPRs (Novizio et al., 2020). Since toxoplasmosis decreased both ANXA1 and FPRs, and due to the immunoregulatory roles of such biomolecules, more investigation might further confirm ANXs as potential therapeutic targets during congenital toxoplasmosis.

T. gondii surface antigen 1 (*Tg*SAG1), an important surface protein of tachyzoites, plays a critical role during *Toxoplasma* infection through different strategies including the regulation of host cell immune responses to favor the parasite. *Tg*SAG1 interact with the host proteins S100A6 and ANXA6 during attachment to infected cells, leading to the progression of pathogenesis (Zhou et al., 2021). *Tg*SAG1 can induce the secretion of TNF-α via the S100A6-Vimentin/PKCq-NF-κB signaling pathway. Accordingly, two scenarios might be imaginable. In one, SAG1 binds to ANXA6 and restricts the plausible function of this protein in regulating the host immune responses. Another hypothesis is that ANXA6 in association with *Tg*SAG1 and through relevant downstream signaling might further facilitate and promote the entrance of parasites into host cells and consequently increase pathogenesis. Thus, further studies are required to better explore the cell biological correlation between *Tg*SAG1 and ANXA6 during *Toxoplasma* invasion.

It is well known that the *Toxoplasma* parasite recruits different host cell proteins to survive and continue its pathogenesis during infection (Portes et al., 2020; Zhang et al., 2019). Therefore, the use of host ANX-proteins by *Toxoplasma*-parasitic proteins could be interesting to better understand host-parasite interactions. Additionally, there are different types of functional ribonucleoprotein (mRNP) granules with varied functions in extracellular *T. gondii* (Lirussi and Matrajt, 2011). Since ANX proteins such as ANXA11 can exert a link action between the mRNP granules and a lysosome or endosome, (transporting the RNP granules) (Broix et al., 2021; Pushpalatha and Besse, 2019; Roscoe et al., 2021), the in-depth investigation of the aforementioned relationship may open up new therapeutic avenues.

2.3. Malaria

Malaria is an acute febrile disease caused by apicomplexan parasites *Plasmodium* spp. with a sophisticated life cycle involving two hosts, the *Anopheles* mosquito (vector) and vertebrate hosts such as humans. The life cycle of the parasite in humans (the asexual stage) includes intra-erythrocytic and exoerythrocytic (liver) stages. The sexual stage occurs in the *Anopheles* mosquito midgut and leads to the formation of ookinete (Su and Wu, 2021; Venugopal et al., 2020).

ANXs expressed in *Plasmodium*-infected cells exert vital functions during infection. For instance, ANXA4 and ANXA11 have been characterized in the Maurer's clefts of infected-red blood cells (RBCs) in *Plasmodium falciparum* infection, playing important roles in RBC membrane remodeling, Maurer's cleft sculpting and vesicle formation or *P. falciparum* erythrocyte membrane protein 1 (*Pf*EMP1) trafficking (McHugh et al., 2020).

ANXA7 has been identified in the EVs of *P. falciparum* (Abou Karam et al., 2022). Since *Plasmodium* parasites use EV subpopulations to target several cellular signaling pathways or host responses (Blow and Buck, 2022), more studies are needed to better characterize the functions of these identified ANXs in the EVs of the parasite.

Surprisingly, evidence has shown that *P. falciparum* (ring stage) infected-RBCs from sickle cell patients induce ANXA7 degradation and phosphatidylserine (PS) exposure on the cell surface and triggered infected-RBC clearance by macrophages. Moreover, in -ANXA7-deficient

mice, PS exposure on the cell surface of infected-erythrocytes accelerated cell clearance (Lang et al., 2009). Thus, the absence of ANXA7 on infected-RBC is most probably related to the decreased pathogenesis and partial protection during malaria infection. Due to the key role of PS in cell responses such as apoptosis and ANXs-PS interaction (Lee et al., 2013; Lizarbe et al., 2013), further experiments might suggest ANXA7 as a prognostic biomarker in *Plasmodium* infections and reveal further details concerning the molecular biology of these biomolecules in the pathogenesis of malaria.

Plasmodium ookinete invasion of the *Anopheles* mosquito midgut is an essential stage of parasite pathogenesis during infection. Nevertheless, the molecular mechanisms of such an event have not been fully investigated especially when dealing with host-parasite protein interaction. ANX-like proteins, aminopeptidase 1 (APN1) and calreticulin have been studied as potential receptors expressed on the luminal surface of the *Anopheles* midgut for ookinete invasion (Dinglasan et al., 2007; Kotsyfakis et al., 2005; Martínez-Barnetche et al., 2007). Ookinete might employ ANXs for protection or to facilitate transition to the midgut (Kotsyfakis et al., 2005). Calreticulin is the only receptor whose attachment to a surface parasitic protein (Pvs25) has been confirmed (Martínez-Barnetche et al., 2007; Sharma and Jaiswal, 2013). This raises the possibility of designing mimotopes of ookinete surface proteins including ANXs for bringing innovation in the field of transmission-blocking vaccines against malaria (Vega-Rodríguez et al., 2014). Moreover, inhibiting ANXs expressed in the midgut by targeting antibodies could be considered as another therapeutic strategy (Kotsyfakis et al., 2005). Therefore, protein-protein docking methods with proteins expressed in the mosquito gut, especially ANXs, will be very insightful in this sense (Sharma and Jaiswal, 2013).

Regarding cellular immune responses during malaria, it has been documented that ANXA1 levels are differentially expressed in T lymphocyte sub-populations ($CD4^+$ and $CD8^+$ T cells and regulatory T cells (Tregs)) and probably influence cell proliferation. Additionally, this immunoregulatory protein most likely induces the secretion of IL-10 in plasma of patients infected with malaria (Borges et al., 2013). Some studies have revealed that the secretion of this cytokine is probably induced via activation of the extracellular signal-regulated kinase (ERK) cascade (da Cunha et al., 2012; Ferlazzo et al., 2003; Parente and Solito, 2004; Weyd et al., 2013). Consequently, IL-10 induction may drive regulatory proinflammatory responses contributing to parasite elimination and participating in pathogenesis (da Cunha et al., 2012; Weyd et al., 2013). Therefore, the joint investigations regarding the correlation between ANX expression in the lymphocyte subpopulations and the release of immunoregulatory cytokines and relevant synergistic signaling may lead to a better understanding of the dynamics of immune responses against *Plasmodium* infections.

2.4. American and African trypanosomiasis

T. cruzi is the causative agent of Chagas disease (American trypanosomiasis), and is transmitted to vertebrate hosts through feces or urine of infected blood-sucking triatomine bugs. Blood trypomastigotes migrate via the bloodstream and infect different visceral organs including the heart, stomach, esophagus of vertebrate hosts (Caputo et al., 2022). The *in vitro* transcriptomic data have clarified that a special strain of *T. cruzi* was able to increase the expression level of ANXA1 in a myoblast cell line during infection (Adesse et al., 2010). However, the effect of this modulated protein on the infected-host cell responses during infection has not been highlighted.

The role of ANXA2 has been defined in actin-based macro-pinocytic rocketing and has been identified as an protein interacting with F-actin and membranes enriched in phosphatidylinositol 4,5,-biphosphate (PIP2) (Hayes et al., 2009; Merrifield et al., 2001). Moreover, this protein is involved in the membrane structures enriched in F-actin during the attachment and entrance of some pathogens to host cells (Grieve et al., 2012). Overall, ANXA2 can bind to or integrate with actin filaments as a monomer or in combination with the S100A10 protein as a hetero-tetrameric complex (Hayes et al., 2004). On the other hand, ADP ribosylation factor 6 (ARF-6) by altering actin cytoskeleton polymerization plays a major role in host cell invasion by intracellular pathogens (Humphreys et al., 2013). Interestingly, it has been suggested that the invasion of host cells by *T. cruzi* amastigotes is a host actin polymerization-dependent phenomenon. The accumulation of ARF-6 on the PV containing *T. cruzi* amastigotes show that both ARF-6 and ANXA2 were critical proteins with a convergent form of host cell invasion (and thus replication) by parasite amastigotes probably through recognizing or disorganizing the actin cytoskeleton during invasion (Teixeira et al., 2015). The elucidation of the exact mechanisms of interaction between ANXs, ARF-6 and actin filaments are required particularly to suggest novel therapeutic approaches against American trypanosomiasis.

Evidence showed that gp35/50 mucins mediate the host cell invasion of *T. cruzi* metacyclic trypomastigote (G strain) and clarified the robust function of ANXA2 as the receptor for gp35/50. Therefore, gp35/50-mediated parasite invasion is induced by interaction with host cell ANXA2 and clathrin-dependent endocytosis. Interestingly, the depletion of ANXA2 and clathrin inhibition decreased host cell susceptibility to metacyclic trypomastigote internalization of this strain, suggesting the plausible therapeutic property of this ANX in American trypanosomiasis (Onofre et al., 2022).

Regarding ANXs and the arthropod protozoan vectors, the salivary gland transcriptome analysis of *T. brucei*-infected *Glossina morsitans* has shown that two ANXs encoding genes, *ANXIX (GMOY009975)* and *ANXX (GMOY009575)* were up-regulated after experimental infection. In line with this, vaccination trials with recombinant mosquito ANXs induce humoral responses that impair *Plasmodium* parasite development in the midgut, suggesting the crucial roles of ANXs during vector midgut invasion by the parasite (Matetovici et al., 2016). Moreover, more data have revealed that ANX expression increased in the posterior midgut of the *T. cruzi*-infected triatomine digestive tract compared to the anterior midgut and interestingly that their homeostasis in the posterior midgut might be correlated with the parasite burden (Gumiel et al., 2020). Thus, the investigation of ANX-proteome and genome of infected-vector tissues by *Leishmania, Trypanosoma* and *Plasmodium* parasites can provide deeper insights into parasite-vector interactions during pathogenesis.

Table 3 summarizes the important functions of host modulated ANXs during the most prominent intracellular protozoan parasitic infections. Furthermore, for a better understanding, Fig. 2 illustrates all the ANXs modulated in parasitic infections reviewed in this study.

3. The relationships between ANX structure and molecular interactions and cell signaling events

Some parasite and host cell ANXs have motif and binding sites in their structures to regulate several cell signals and responses and thus regulate the pathogenesis process. For instance, the Ca^{2+}-binding sites of *E. granulosus* ANX (*Eg*-ANX) in repeats I and IV have Ca^{2+}-dependent phospholipid-binding properties that facilitate a link between Ca^{2+} signaling and different membrane functions including ion flux regulation, maintenance of membrane organization, exocytosis, endocytosis, and vesicle fusion. EGTA, as a kind of calcium chelating agent, is able to inhibit the Ca^{2+}-dependent binding features of *Eg*-ANX. Moreover, the interaction of some parasite ANXs with the actin (actin-binding (IRI) motif in repeat IV of *S. haematobium* (*Sh*-ANX) and *S. mansoni* (*Sm*-ANX), but not in the *Eg*-ANX sequence) can be also considered as another property that could be employed to manage ANX functions (Song et al., 2016). Additionally, some ANXs binding small molecules such as benzo-di/thi-azepine derivatives might attach to a pocket on the concave side of mammalian ANXs (especially ANXA3, ANXA5) and affect their interactions with phospholipid membranes in an allosteric mode. The pocket is composed on one side by the linker peptide between repeats II and III and is restricted by the very N-terminal part on the adjacent side (Hofmann et al., 2010). Thus, the characterization of such

Table 3
The function of host-modulated ANXs during prominent intracellular protozoan parasitic infections.

Annexins (ANXs)	Parasitic infections	Function	References
ANXA1	Leishmaniasis	Regulation of tissue inflammation in CL	(Oliveira et al., 2017)
		Facilitating vesicle fusion with endosomes in PV	(Collins et al., 1997)
		Induction of phagocytosis and apoptosis in apoptotic cells and macrophages	(Pona et al., 2021)
		Differential expression in $CD163^{+}$ macrophages and T cells (affecting CL manifestations)	(Silva et al., 2015)
ANXA1, ANXA2		Interaction with S100A10 and S100A11 in infected macrophages (composing a Ca^{2+} sensing system)	(Guerfali et al., 2008)
ANXA3		Induction of angiogenesis in CL	(Park et al., 2005)
ANXA1	Malaria	Influencing T-lymphocyte proliferation and inducing IL-10 (regulating proinflammatory responses)	(Borges et al., 2013)
ANXA7		Expression on infected-RBCs (increasing pathogenesis)	(Lang et al., 2009)
ANXA4, ANXA11		RBC-membrane and Maurer's cleft organization	(McHugh et al., 2020)
ANX-like proteins		Induction of mosquito infection by parasite	(Dinglasan et al., 2007; Kotsyfakis et al., 2005; Martínez-Barnetche et al., 2007)
ANXA2	American trypanosomiasis	Interaction with ARF-6 (parasite invasion and replication)	(Teixeira et al., 2015)
		Interaction with parasite mucins (mediating parasite invasion)	(Onofre et al., 2022)
ANXA1	Toxoplasmosis	Regulation of inflammation and protective immune responses in ocular toxoplasmosis	(Mimura et al., 2012)
ANXA1, ANXA2, ANXA3		Decreasing expression in infected placentas (triggering abnormal pregnancy)	(Jiao et al., 2017)
ANXA6		Interaction with SAG1 (facilitating parasite invasion and pathogenesis)	(Zhou et al., 2021)

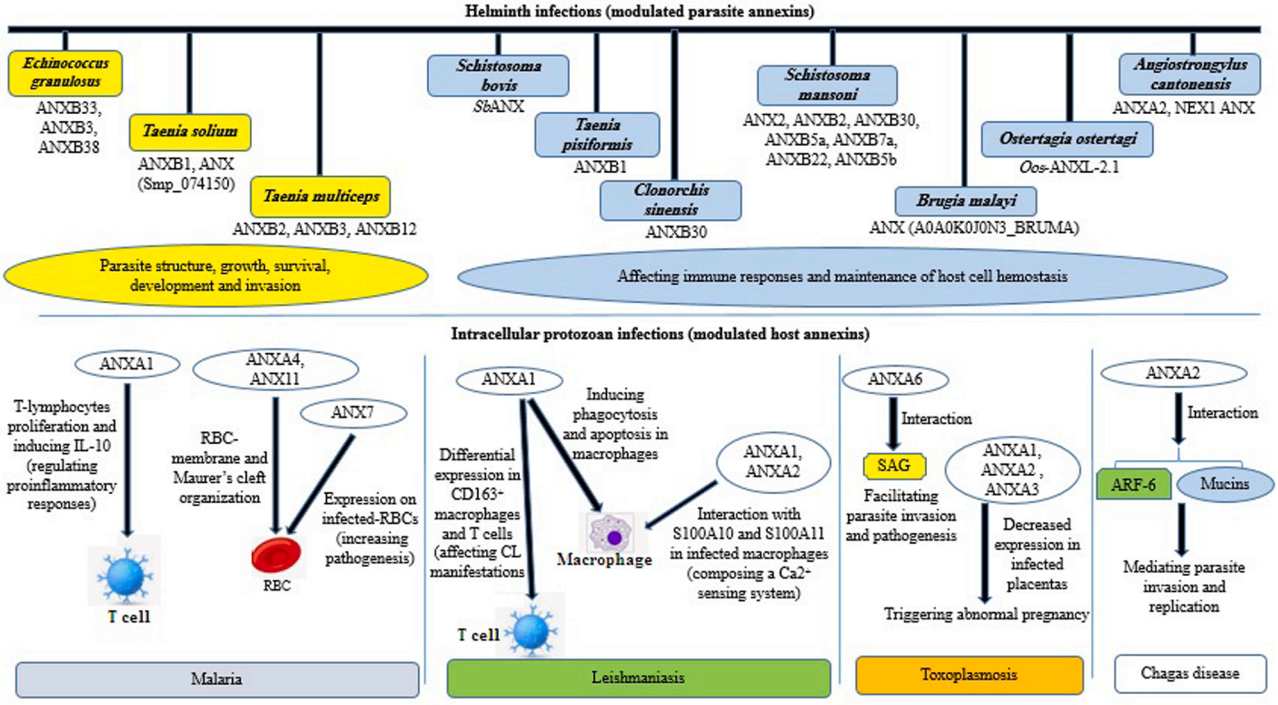

Fig. 2. ANXs modulated in parasitic infections.

motifs can be helpful to manage ANX expression in parasite structure and parasite-infected host cells, suggesting novel and interesting therapeutic strategies. On the other hand, proteomics evidence has revealed a close relationship between S100 proteins and ANXs (Basika et al., 2012). Therefore, in addition to the identification of ANX motif regions as a plausible therapeutic strategy, the characterization of such correlated proteins might also lead to the recognition of other ambiguous biological aspects of ANXs, useful in treatment.

Post-translational modifications (PTMs) are also involved in the ANX functions and their interactions with other proteins and probably downstream cell signaling (Shao et al., 2019). In parasitology, the investigation of PTMs on modulated parasite and infected-host cell ANXs and their effect on the pathobiology of parasitic infections needs to be fostered. However, one phosphorylation site has been identified in the N-terminal zone of each schistosome ANX. The phosphorylated N-terminal zone is variable in this parasite ANX. This motif region is composed of important sites for phosphorylation, proteolysis and interaction with other biomolecules (Leow et al., 2019). Moreover, the absence of a phosphorylation region in *Giardia* ANXs (α-giardins) induced major functional restrictions in such parasitic proteins (Bauer et al., 1999). On the other hand, intracellular protozoan parasites might induce new PTM sites on the host cell ANXs and by this strategy those pathogens alter the host cell condition allowing their survival and the persistence of infection. Consequently, the identification and

management of PTM sites both on parasite and infected-host cells ANXs might recognize the PTM-relevant down-stream cell signaling and offer a novel approach with therapeutic insights into parasitic infections.

As mentioned, ANXs have a close relationship with cell signaling during disease and infection processes. There is an important functional association with regulatory RNAs which is likely relevant during the infectious process (Caserta and Ghezzi, 2021; Monastyrskaya, 2018). Different molecules including microRNAs (miRNAs, miRs) can alter ANX expression levels through direct regulation. Evidence has shown that the taurine-upregulated gene 1 (TUG1)/miR-140–3p/ANXA8 axis exerts an important function in bladder cancer progression and metastasis. TUG1 increases this process via regulating ANXA8 expression by sponging miR-140–3p (Yuan et al., 2021). ANXs expressed in parasites' structure and in infected cells might be also regulated through RNA networks involving mRNAs, miRNAs, and long non-coding RNAs (lncRNAs) during pathogenesis. The characterization of ANXs and miRNAs in parasite secreted exosomes might further reinforce this hypothesis and might constitute the basis for future experimental studies (Nawaz et al., 2019).

4. Conclusion

Preliminary structural information available for parasite ANXs highlights that different parasite clades express ANXs with unique properties. Nevertheless, different pivotal biomolecules expressed on the parasite surface could serve as mimicking or hijacking strategies to evade host immune responses leading to a high sequence similarity between parasites and their host cell proteins (Han et al., 2009; Ludin et al., 2011). The comparison of parasite alignment identity with the host ANXs could be fruitful in this sense, since most host ANXs are correlated with key extracellular and intracellular functions in the host but also those at the host-pathogen interface during immune evasion (Huang et al., 2022; Schloer et al., 2018). The parasite probably mimics and expresses the host ANXs on their structure to adapt to the host cell condition and evade the host immune responses, making these proteins plausible targets for translational research aimed at developing therapeutic or prophylactic solutions mainly against intracellular parasites.

In addition to the direct effect of parasite ANXs on host cell responses, a wide range of other effectible parasitic proteins can also induce sophisticated mechanisms to change host ANX expression and consequently alter the host cell response (Cantacessi et al., 2013). A clear focus on the identification of new ANXs and their relevant cell signaling pathways will provide an in-depth description of their functions, particularly in intracellular protozoan parasites. In this sense, the discovery of relevant protein-protein effector interactions by modern proteomics approaches could allow the identification of important virulence factors of intracellular parasites targeting host ANXs (Knuff--Janzen et al., 2021). Parasites can also recruit potential mechanisms including the secretion of major anticoagulant protein ANXs (through EVs) to manage and restrict host hemostatic responses, facilitating blood feeding (Nawaz et al., 2019). Thus, in addition to the modulated parasite and host ANXs, the identification of ANXs released from parasite EVs and their crucial interactions with host cell proteins might open up a new avenue of research into the processes at play during parasitic infections (Song et al., 2021, 2016; Yang et al., 2021).

Overall, this information supports the idea that the discovery of novel ANXs both in parasites and infected host cells/tissues and relevant proteins and cell signaling might shed some light on the pathogenic processes of parasitic diseases. Consequently, such data indicate that the use of analogous of ANX peptides that mimic their physiological functions or the regulation of different ANXs through various strategies might provide novel therapeutic insights into the treatment of parasitic infections and other diseases (Mui et al., 2021). Furthermore, due to the prominent immunoregulatory actions of ANXs during several parasitic infections and based on the expression levels of these proteins in some parasitic-infected tissues (Song et al., 2021), such promising proteins might be also vaccine and diagnostic biomarker candidates. However, more experimental and trials are required to corroborate and validate the aforementioned hypotheses.

Although ANXs have been detected in genomes and are expressed by parasites, such molecules have been far better characterized in mammals than in parasites. However, their prominent expression levels, functional roles and exposure in many parasite species have led to a number of candidate ANXs and more interestingly, specific epitopes as potential vaccine antigens with variable but moderate protection levels (Hofmann et al., 2010; Leow et al., 2019). Thus, more experimental strategies and approaches are required to confirm the potential of ANX-based vaccines against parasite infections and to understand the molecular mechanisms of these vaccines. The potential for autoimmune responses elicited by cross-reactive antibodies is not very high due to the presence of parasite-specific epitopes or simply the antigen introduction procedure (Carvalho-Queiroz et al., 2004).

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CRediT authorship contribution statement

SR: conceptualized the review and wrote the first draft. **PN and RMR:** supervised, reviewed and improved the paper. **SR, RM, and MAH:** provided the figures and revised the paper. **AM:** critically reviewed the paper. All authors finally approved this final version. All authors contributed to the article and approved the submitted version.

Declaration of Competing Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Data availability

No data was used for the research described in the article.

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