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Cancer and *Trypanosoma cruzi*: Tumor induction or protection?

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ABSTRACT

Trypanosoma cruzi causes Chagas disease, a neglected disease that can be divided, overall, into acute and chronic phases. Understanding the mechanisms underlying its progression is based on the parasite–host interactions occurring during the infection. Although the pathophysiology of the main symptomatic forms of Chagas disease has been the subject of several studies, little is known about their relationship with the development of different types of cancer. Therefore, knowledge regarding the molecular aspects of infection in the host, as well as the influence of the immune response in the parasite and the host, can help to understand the association between Chagas disease and tumor development. This review aims to summarize the main molecular mechanisms related to *T. cruzi*-dependent carcinogenic development and the mechanisms associated with tumor protection mediated by different parasite components.

Contents

1. Introduction

Despite scientific and technological advances over the decades, clinically important parasitic diseases, including American or African trypanosomiasis, toxoplasmosis, malaria, schistosomiasis, and leishmaniasis, continue to represent an enormous challenge to public health, with high morbidity and mortality rates worldwide

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[1–3]. Studies addressing the control and elimination of parasitic diseases, especially Chagas disease (CD) caused by *Trypanosoma cruzi*, are mostly based on understanding the mechanisms underlying biological development and parasite–host interactions during infection and parasite adaptation [4–10]. However, little is known about the connection between trypanosomiasis and the development of different neoplasms. Therefore, understanding the molecular aspects of parasite–host interactions during parasite infection, adaptation, and host immune responses during infection is critical for investigating the pathogenesis of the disease and its possible connection to neoplasm development.

Previous studies on the molecular basis of infectious and parasitic diseases have shown that carcinogenesis involves the production of free radicals and nitric oxide, which can both breakdown and modify nucleic acids, causing genomic instability and the development of neoplastic processes [11]. In addition, the inflammatory response can damage DNA during the strand repair process, thereby facilitating mutations, evasion of human host defense mechanisms, and cell invasion and metastasis [11]. The correlation between CD and neoplasms emerged from data that revealed that *T. cruzi* infection usually occurs in childhood and promotes cellular destruction and proliferation underlying the inflammation caused by the protozoan, possibly favoring a neoplastic appearance [12].

Cancer is a global public health problem that can be induced by various external agents, including viral, bacterial, and parasitic infections. Cancer onset is associated with inducing agents such as chemical and physical carcinogens, including heavy metals and radiation. In addition, an increasing number of studies have shown the participation of parasites as carcinogens in different tumor types, including those that consider the relationship between CD and different types of cancer (Fig. 1).

The general mechanisms of pathogen–associated carcinogenesis include persistent infection with consequent inflammation, DNA damage, expression of oncogenes, and host immunosuppression [13]. The acquisition of different characteristics by neoplastic cells favors tumor growth. Cancer hallmarks can be affected by different parasites, leading to modifications in the immune response [14,15]. Modulating the immune response, promoting tumor inflammation and resistance to cell death, and inducing angiogenesis are tumor processes that can be influenced by parasitic infections [15]. Thus, further studies are needed to better establish how these markers are altered in *T. cruzi* infection and to protect against the disease. In addition to the hallmarks mentioned before, epigenetic alterations, such as DNA/histone methylation or acetylation changes, were also focused on cancer and the relationship with other pathogen infections. While this relationship was described in *Leishmania donovani* [16], *Schistosoma hematobium, and Clonorchis sinensis* infection [17,18], there is no study that suggests that epigenetic changes in *T. cruzi* infection can promote carcinogenesis.

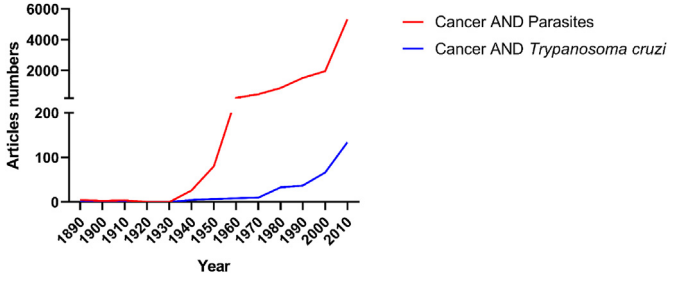

Fig. 1. Interest in cancer and parasites (red) and cancer and *Trypanosoma cruzi* (blue) in the scientific community in recent decades. The y-axis represents the number of publications, and the x-axis represents time. The data were obtained by searching PubMed for 'cancer AND parasites' and 'cancer AND *Trypanosoma cruzi*'. Data for 2022 were not used in the graph.

CD is a chronic zoonotic disease known worldwide; however, it is still considered a neglected tropical disease. CD, caused by the protozoan *Trypanosoma cruzi*, affects approximately 6–7 million people worldwide [19]. The disease is transmitted mainly during blood repass by triatomine (barber) insects infected with trypomastigotes [20]. After infection, approximately 70% of patients are asymptomatic or present with indeterminate forms of the disease, of which approximately 30% evolve to symptomatic forms presenting with cardiac and/or digestive disorders, mainly represented by megaorgans [21].

Previous reports have proposed an association between CD and gastrointestinal cancer [12], esophageal carcinoma [22,23], colon cancer [24], and gynecological neoplasms (Table 1). However, the mechanisms by which *T. cruzi* favors the emergence and progression of different types of cancers are still unclear. Tong et al. (2017) suggested that the complex mechanisms of *T. cruzi*-dependent carcinogenesis are related to host genetic factors and the intrinsic parasite–host relationship, which results in a chronic inflammatory process in specific tissues (Fig. 2) [25]. Thus, the CD–cancer relationship will be discussed in the following sections, and the main carcinogenic mechanisms possibly associated with tumor onset and progression, along with the mechanisms associated with *T. cruzi*-dependent tumor protection, will be presented.

2. *T. cruzi* and gastrointestinal tract cancers: a role for *TP53* and *PI3KCA* in tumor progression

Chronic gastrointestinal manifestations of CD have been described in different organs, including the salivary glands, esophagus, stomach, small intestine, colon, and gall bladder [26]. Chagas-associated megaesophagus is one of the leading late complications of CD and increases the risk of esophageal carcinoma by up to 33 times compared with the normal population [27,28]. Esophageal cancer is the seventh most frequent neoplasm in the world and the sixth leading cause of death in 2020 [29]. A recent study by Martins et al. (2019) showed that approximately 4–10% of patients with CD-induced megaesophagus developed esophageal carcinoma. In this study, the main risk factor for cancer development was achalasia. Achalasia, a disorder of esophageal motility, is mainly characterized by peristalsis of the esophageal body and failure to relax the lower esophageal sphincter, which favors the onset of megaesophagus and progressive dysphagia in patients with Chagas disease [30]. In addition, food stasis and prolonged mucosal contact with dietary carcinogens could lead to chronic esophagitis, consequently favoring the development of esophageal neoplasia [23], in addition to other risk factors, such as destruction of intramural myenteric neurons by the parasite, hyperkeratosis, and leukoplakia [31].

The molecular mechanisms underlying the development of esophageal carcinoma in patients with Chagas-associated megaesophagus have rarely been explored. A pioneering study by Lacerda et al. (2017) demonstrated that 40.6% of patients with Chagas-associated megaesophagus and esophageal carcinoma had mutations in *TP53*, suggesting a central role for this molecule in regulating this neoplasm in patients with Chagas disease [32]. The results showed mutations in codons 151 and 275 of *TP53* [32]. Mutations in codon 151 promote gain-of-function, leading to resistance to cell death by anoikis and tumor progression [33], and mutations in codon 275 are reported to be somatically deleterious and inactivate p53 [34]. The group also demonstrated the presence of microsatellite instability in patients with esophageal carcinoma and Chagas-associated megaesophagus [35]. The p53 signaling pathway is described as a tumor suppressor activated by a range of

Table 1
Association between *Trypanosoma cruzi* and different tumor types.

Cancer type	Chagas disease phase	Chagas disease form	Chagas disease total cases number evaluated	Cancer cases number	Reference
Esophageal cancer	Chronic	Megaesophagus	107	5	Rocha et al., 1983 [95]
Esophageal cancer	Chronic	Megaesophagus	90	7	Camara-Lopes, 1961 [28]
Ulcerative gastric adenocarcinoma	Chronic	Megacolon	1	1	Carneiro et al., 2011 [96]
Acute lymphoblastic leukemia	Acute	–	2	2	Rivero et al., 1974 [58]
Gynecologic neoplasias	Chronic	Chagas cardiopathy/Megaesophagus/ Megacolon	284	30	Dominical et al., 2010 [56]
Colorectal cancer	Chronic	Megacolon	894	0	Garcia et al., 2003 [46]
Colorectal cancer	Chronic	Megacolon	120	0	Rocha et al., 1981 [97]
Colorectal cancer	Chronic	Megacolon	327	1	Meneses et al., 1989 [98]
Colorectal cancer	Chronic	Megaesophagus	140	13	Brandalise et al., 1985 [99]

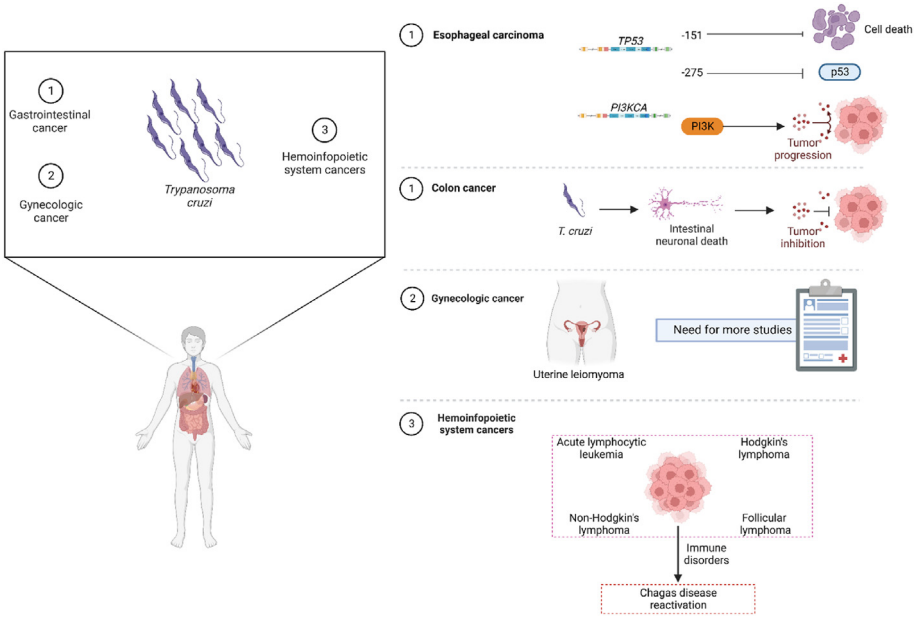

Fig. 2. Carcinogenic-dependent mechanisms of the CD-cancer relationship. (1) The molecular mechanisms of carcinogenesis in esophageal neoplasms associated with *T. cruzi* infection include genetic mutations in tumor suppressor genes, such as *TP53* and *PI3KCA*, which favor resistance to cell death and tumor progression. In contrast, *T. cruzi*-dependent myenteric neuronal ablation inhibits tumor progression in individuals with Chagas-associated megacolon. (2) The relationship between gynecologic neoplasms and *T. cruzi* needs further elucidation. (3) Neoplasms of the hemolymphopoietic system are related to cases of CD reactivation dependent on immune imbalance arising from the neoplasm. Created with BioRender.com.

stress signals and is related to the transcriptional activity of genes associated with different cellular processes [36]. Mutations in p53 are common in different human cancers, with a large majority of the missense mutations producing mutant p53 with added amino acids and loss-of-suppressor-function (mu*TP53*). In addition, mutant p53 proteins can acquire new oncogenic functions through gain-of-function, favoring tumor progression [37].

Mutations in *PI3KCA* have also been reported in individuals with esophageal carcinoma and Chagas-associated megaesophagus [38]. Approximately 22% of the patients analyzed had mutations in different exons of *PI3KCA*, suggesting its participation in esophageal carcinogenesis in patients with Chagas-associated megaesophagus [38]. *PI3KCA* encodes phosphatidylinositol 3-kinase (PI3K), which participates in various cellular processes, such as cell growth and proliferation, apoptosis, motility, and cell survival. Moreover, it is involved in the development of different types of cancers [39,40]. In esophageal cancer, this pathway is associated with increased survival of esophageal carcinoma cells *in vitro* and the induction of metastasis *in vivo* [41–43].

Chagas-associated megacolons are another common manifestation of CD. *T. cruzi* infection induces colorectal myenteric neuronal destruction and consequent megacolon formation [44]. Reports indicate a negative association between Chagas-associated megacolon and colon cancer [24,45]. Contrary to what has been observed in esophageal carcinoma, patients with megacolon do not have a higher incidence of colon cancer. Garcia et al. (2003) observed in a retrospective study that among 894 cases of megacolon, no cases of preneoplastic lesions and/or colon cancer were observed. These findings contradict essential findings regarding the risk factors for colon cancer because patients with Chagas-associated megacolon have chronic constipation, hyperplasia, mucosal ulcers, and inflammation [46]. In addition, previous studies from the same group showed that mice infected with *T. cruzi* developed fewer colon tumors than the control groups [47].

Neurons and glial cells modulate not only peristalsis and mechanical stimulation of the intestines but also participate in epithelial proliferation and subepithelial angiogenesis and may participate in cancer proliferation and facilitate tumor invasion [48]. Indeed, experimental myenteric neuronal ablation has been shown to protect against colon cancer development, with decreased expression of neoplastic markers, such as β-catenin [49,50]. Kannen et al. (2015) observed that myenteric neurons are key elements in the initiation of colon carcinogenesis from its early stages in humans and mice. They found intense myenteric neuronal denervation in patients with Chagas-associated megacolon and infected mice and fewer preneoplastic colon lesions. In addition, analysis of argyrophilic nucleolar organizer regions in the crypt fundus revealed a reduced risk of colon cancer in patients with Chagas-associated megacolon [51]. Enteric glial cells are essential for maintaining intestinal homeostasis and function, and their loss promotes the collapse of the intestinal epithelium [52]. In the tumor microenvironment, they can release tumorigenic factors, such as prostaglandin E2 (PGE2), which favors colon carcinogenesis. Indeed, glial cells and neurons can be activated by tumor cells and contribute to tumorigenesis through the activation of downstream proliferative pathways, such as the MAPK and PI3K/Akt pathways [53,54].

Although the complex mechanisms of this neuronal dependence and tumor proliferation in CD have not been fully elucidated, it is suggested that a specialized microenvironment containing neurotrophins, neurotransmitters, adhesion molecules, matrix metalloproteinases, and other neuron- and glial cell-dependent mediators is altered during CD pathogenesis [5], which may protect against the onset of colon cancer.

3. *T. cruzi* and gynecological cancer

Gynecological cancers pose a notable threat to women's health worldwide, with a high incidence of cervical, ovarian, and endometrial cancers [55]. The correlation with *T. cruzi* has been studied since women with CD present gynecological neoplasms, such as cervical cancer. A study by Domingos et al. (2010) revealed no correlation between the occurrence of CD and gynecological neoplasms (uterine leiomyoma and cervical carcinoma), concluding that CD was neither a risk nor a protective factor for the development of gynecological neoplasms in the 671 cases analyzed [56]. In contrast, in a study on CD frequency among women with uterine leiomyoma, Murta et al. (2002) observed a positive association between CD and leiomyoma, wherein 27.1% of women were serologically positive for CD and were diagnosed with leiomyoma [57].

The scarcity of studies makes it evident that the relationship between CD and gynecological cancers needs further elucidation, with research focused on identifying possible molecular mechanisms that prove the parasite's participation in the emergence and development of these types of neoplasms or even as a protective agent.

4. *T. cruzi* and cancers of the hemolymphopoietic system

Unlike the other tumor types described here and their close relationship with CD target organ carcinogenesis, hemolymphopoietic cancers seem to favor CD reactivation. Thus, CD reactivation has been observed in patients with hematologic malignancies (acute lymphoblastic leukemia [58], acute lymphocytic leukemia [59], Hodgkin's lymphoma [60], non-Hodgkin's lymphoma [61], and follicular lymphoma [62]) undergoing antineoplastic or non-antineoplastic chemotherapy/corticotherapy. In addition to the tumor characteristics and the impact on the organism, antitumor treatments can also induce immunosuppression by affecting the balance of the cellular immune response and, consequently, delinking mechanisms that control *T. cruzi* infection [58,63]. This relationship between CD and hematologic cancer chemotherapy has been demonstrated in patients with chronic Chagas-associated myocarditis or even undiagnosed CD who underwent chemotherapy for Hodgkin's [60] and non-Hodgkin's [61,64] lymphoma. In these cases, amastigote nests were observed in the heart, larynx, esophagus, and gastric mucosa after treatment for neoplasms, characteristic of the acute phase of CD [61]. Although the parasite was found in these studies, none of them evaluated its immune response. Thus, it is necessary to extend such evaluations to strengthen the relationship between hematologic malignancies and CD reactivation.

5. *T. cruzi* against carcinogenesis: main characters involved

5.1. The infection and the role of epimastigote extract

The molecular mechanisms underlying *T. cruzi*-dependent carcinogenic induction have been poorly explored in the literature. However, protective and anticancer properties of the parasite have been reported (Fig. 3). In the 1940s, researchers from the former Soviet Union postulated the antitumor activity of *T. cruzi* based on the toxic effects of infection and parasite extracts on different tumors in humans and experimental models [65]. They described the components of the extract as toxins, which reduced pain, tumor growth, bleeding, and local inflammation caused by the tumor [65]. Years later, a French laboratory marketed a formulation known as Cruzin Antibiotic, but soon after, it was discontinued owing to a lack of knowledge of its mechanisms of action [66,67]. A later study showed a preference for parasite infection by tumor cells over normal host cells, suggesting antagonism between *T. cruzi* infection and tumor progression [68]. In this way, the relationship between *T. cruzi* and cancer has begun to be established, primarily focusing on the antitumor potential of the protozoan components.

Indeed, epimastigote lysate extracts have been reported to exhibit antitumor potential [69,70]. In an experimental model infected with *T. cruzi* and subjected to colon cancer induction by chemical carcinogens, such as 1,2-dimethylhydrazine (DMH), chronic infection was demonstrated to increase resistance against tumor growth [47]. In addition to the infection itself, an extract of lysed epimastigotes was able to inhibit tumor growth in a mouse model of colon and breast cancer [71]. This extract was shown to induce innate immune cells in the spleen of the animals, with increased macrophages, dendritic cells, and NADPH oxidase activity, regardless of the cancer subtype. Immunization also stimulated components of acquired immunity by inducing the proliferation rate of splenocytes and activating $CD4^+$ and $CD8^+$ T cells when the spleens of the animals were isolated and stimulated with parasite antigens *in vitro*. Furthermore, splenocytes from mice immunized with the extract demonstrated greater *in vitro* cytotoxicity toward NMU (adenocarcinoma) cells than those not immunized. Moreover, immunization led to the production of *T. cruzi*-specific antibodies that induce cytotoxicity in tumor cells *in vitro* and recognize breast and colon cancer cells in experimental models and the respective tumor types in humans [71].

5.2. Influence of calreticulin

In addition to the role of infection and the extract of epimastigotes from different strains of *T. cruzi*, recent studies have demonstrated the participation of the protozoan calreticulin in tumor inhibition. Calreticulin (TcCRT) is a chaperone present in the endoplasmic reticulum of the parasite and, when externalized, interacts with the C1 component of the complement, causing its

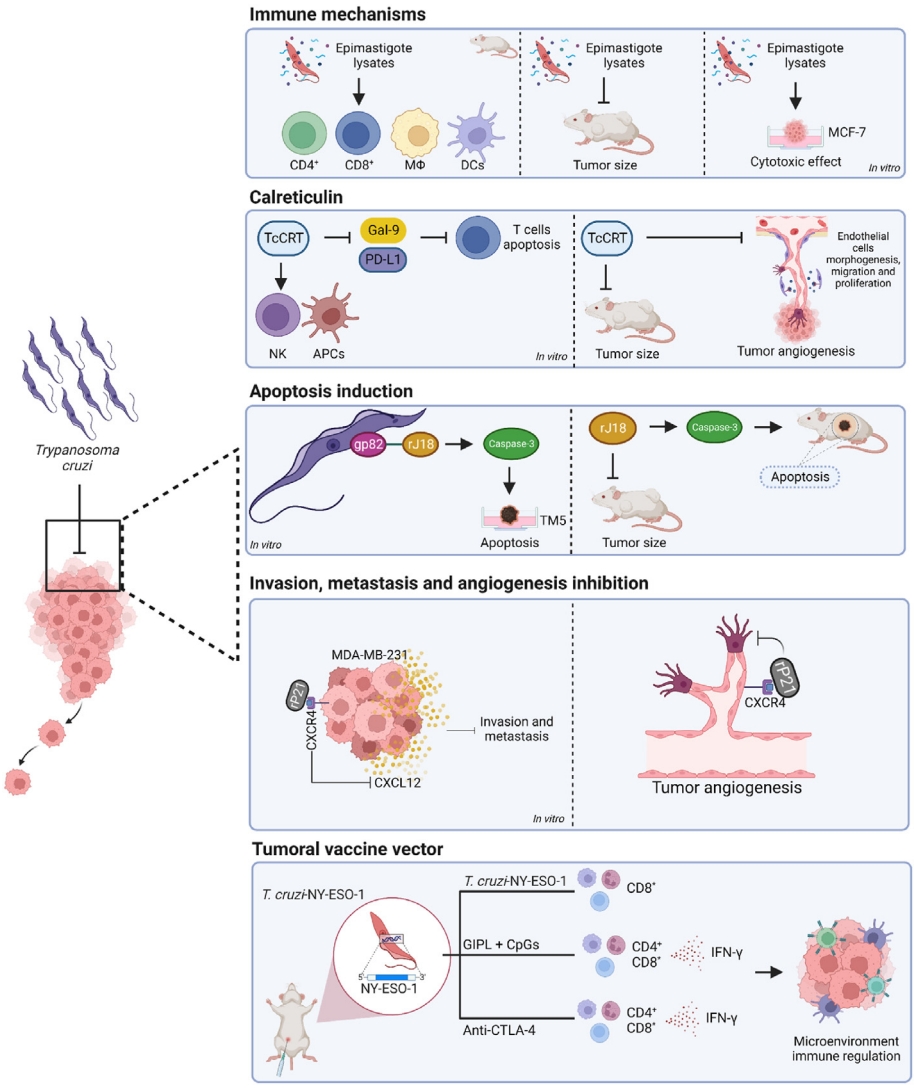

Fig. 3. *T. cruzi*-dependent tumor protection mechanisms. The *T. cruzi*-dependent tumor protection mechanisms are varied and related to immune mechanisms, the action of proteins such as calreticulin, the induction of apoptosis, the inhibition of invasion, metastasis, and angiogenesis, and cancer vaccine vectors. Lysates of epimastigotes could promote increased stimulation of $CD8^+$ and $CD4^+$ lymphocytes, along with increased macrophages and dendritic cells. In addition, epimastigotes also reduced tumor size *in vivo* and promoted cytotoxic effects *in vitro*. Calreticulin, a *T. cruzi*-derived protein, could promote antitumor effects, as evidenced by stimulation of NK cells and APCs, and inhibit T lymphocyte apoptosis *in vitro*. The *in vivo* effects were similar, with reduced tumor size in murine models and further inhibition of tumor angiogenesis. Recombinant *T. cruzi* proteins also induced apoptosis. Recombinant J18 promoted apoptosis by increasing caspase-3 in a melanoma cell line *in vitro* and *in vivo*. The aggressive phenotype of neoplastic cells (MDA-MB-231), represented by increased invasion, metastasis, and angiogenesis, was also altered by *T. cruzi*-derived molecules. rP21 can bind to chemokine receptors (CXCR4) on tumor and endothelial cells and promote decreased chemotaxis of CXCL12, thereby inhibiting metastasis and angiogenesis in experimental breast cancer models. In addition, *T. cruzi* has also been reported as an effective agent for tumor antigen delivery in clinical cancer vaccines. Experimental models were used for testing vaccines containing *T. cruzi* and the tumor antigen NY-ESO-1, as well as adjuvant delivery and CTLA-4 immune checkpoint blockade. The data show an increase in immune cells, such as $CD4^+$ and $CD8^+$, and an increase in INF-γ, associated with increased lymphocyte infiltration in the tumor immune microenvironment in the face of the vaccine. Created with BioRender.com.

inhibition and increasing parasite infectivity [72].

An *in vitro* breast adenocarcinoma cell line (TA3) treated with TcCRT showed enhanced phagocytosis and immunogenicity. The antitumor effects were mediated by the inhibition of T-cell apoptosis via galectin-9 and PD-L1, activation of natural killer (NK) cells, and inhibition of regulatory cytokines in the tumor microenvironment, such as those produced by regulatory T lymphocytes [73].

In vivo antiangiogenic effects were observed, with interference in the morphogenesis, migration, and proliferation of endothelial cells [74–76]. When inoculated into the peritumoral area, TcCRT reduced tumor growth in mouse mammary adenocarcinoma [74] and a murine melanoma model [77]. From a molecular point of view, TcCRT may promote an enhanced antitumor immune response since the parasite can translocate tumor cell-bound TcCRT. This mechanism can activate antigen-presenting cells, with subsequent activation of cytotoxic $CD8^+$ T lymphocytes and induction of cell death [78].

5.3. The importance of recombinant T. cruzi proteins

The induction of apoptosis by recombinant proteins from the protozoan demonstrated the antitumor effects of *T. cruzi*-specific compounds. The recombinant J18 protein based on gp82, a *T. cruzi* surface molecule, induced apoptosis in a melanoma cell line (Tm5) and reduced NF-κB translocation, culminating in reduced cell growth [79]. The *in vivo* effects were similar, with decreased tumor growth in J18-treated animals and increased levels of apoptotic

markers, such as caspase-3 [79].

Cell invasion and metastasis activation are fundamental characteristics for acquiring aggressive phenotypes by neoplastic cells [14]. P21, a *T. cruzi* protein involved in parasite cell invasion and host residence, has also been evaluated for its antitumor action. Its recombinant form (rP21) has biological activity, including binding to CXCR4 receptors in macrophages, production of chemokines, such as CXCL12, and, consequently, chemotaxis of immune cells [80,81]. Borges et al. (2020) demonstrated that rP21 binds to CXCR4 receptors on breast cancer cells and interferes with their migratory and invasive phenotypes. Furthermore, rP21 also binds to CXCR4 on endothelial cells, inhibits blood vessel formation, and promotes an increase in the number of cells in the S phase of the cell cycle, leading to their arrest in this phase [82]. The negative regulation of CXCR4 caused by rP21 may inhibit metastasis since chemotaxis of CXCL12, a chemokine associated with cell proliferation and invasion, is inhibited [83,84].

The TcMSH2 protein may also represent a component participating in the *T. cruzi*-tumor protection relationship [25]. This protein is part of the group of molecules involved in the DNA repair machinery, commonly called mismatch repair machineries (MMR). Basically, this machinery acts to remove base substitutions and mismatches in the DNA structure that are beyond the reach of DNA polymerase, which consequently increases the quality/fidelity of the replication of the genetic material [85]. Thus, TcMSH2 present in the protozoan is an important ally against DNA damage, especially oxidative stress-induced damage [86,87]. In fact, oxidative stress has a direct influence on tumor development, mainly because it is related to DNA damage in normal cells [88]. Although protocols for the recombinant expression of TcMSH2 already exist [86,87], there are still no studies describing the importance of TcMSH2 from *T. cruzi* in tumor protection, which makes this protein an important target.

5.4. *T. cruzi* as a vaccine vector

In addition to the anticancer properties described here, *T. cruzi* has been used as a vaccine vector [89]. Currently, the discovery of viable cancer vaccines aimed at inducing protective and long-lasting immunity is one of the main challenges in scientific research [90]. The main justification for using *T. cruzi* is its ability to induce a complex immune response, primarily mediated by T cells, a major requirement in cancer vaccines [91]. Junqueira et al. (2011) used a recombinant nonpathogenic *T. cruzi* clone as a vaccine vector for the delivery of an antigen member of the testicular cancer antigen family (NY-ESO-1) to induce T-cell-mediated immunity. *T. cruzi*-induced NY-ESO-1-specific immune responses both *in vitro* and *in vivo*. There was an increase in the number of $CD8^+$ T cells, which was dependent on the IL-12 and MyD88 pathways, and a reduction and delay in tumor development in experimental models [89].

Subsequently, glycosyl inositol phospholipid (GIPL) adjuvants and *T. cruzi*-derived CpG oligodeoxynucleotides (CpG ODNs) induce an immune response through the activation of Toll-like 4 (TLR4) and 9 receptors. In a melanoma model, increased $CD4^+$ and $CD8^+$ T-cell responses were observed, characterized by increased IFN-γ levels [92]. Furthermore, the use of attenuated *T. cruzi* expressing NY-ESO-1 as a vaccine vector, associated with the blockade of cytotoxic T lymphocyte antigen 4 (CTLA-4), increased the number of $CD8^+$ T cells, promoted increased IFN-γ production, and increased lymphocyte migration into the tumor microenvironment [93].

These results highlight the importance of *T. cruzi* as an efficient tumor antigen delivery agent in the clinical vaccines under development. Multiple molecules and mechanisms of the parasite are most likely involved in the tumor resistance mediated by *T. cruzi* infection [94]. Identifying these target molecules, developing intervention tools, and understanding the molecular aspects of the host immune response could provide crucial insights into the molecular basis of parasitic diseases and their relationship with the development of new, more effective cancer therapies and vaccines.

6. Perspectives and future directions

In this review, we highlight the main carcinogenic mechanisms of the protozoan Trypanosoma cruzi in different tumor types. *T. cruzi*-dependent carcinogenesis is associated with the potential to generate a chronic inflammatory environment, oxidative stress, and tissue damage caused by the permanence of the parasite in specific tissues. Thus, the molecular mechanisms underlying this intrinsic relationship may be related to various mutations in tumor suppressor genes and oncogenes. However, further studies are needed to understand the precise relationship between these factors and tumor development. Since antitumor protective mechanisms have also been described, identifying which parasite and host factors contribute to this process is urgently needed.

However, there are still challenges in using parasites in the field of cancer theranostics because of the complicated interactions between cancer cells and parasitic factors. First, the wide diversity of *T. cruzi* strains with varying biological behaviors, particularly in parasite-host interactions, exerts distinct impacts that may contribute to carcinogenesis in a tumor-type-dependent manner. Second, cancer cells secrete growth factors and molecules that influence parasite survival and function, in addition to the complexity of the tumor microenvironment. Third, the variability of the antitumor response depends on factors, such as the cancer subtype and stage of transformation. Finally, a deeper understanding of the potential antitumor activity of *T. cruzi* is essential to better understand how the parasite or its molecules can be applied in antitumor therapy as well as to elucidate the mechanisms by which the parasite may favor tumor progression.

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Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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