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Review

Parasite Infection, Carcinogenesis and Human Malignancy

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ABSTRACT

Cancer may be induced by many environmental and physiological conditions. Infections with viruses, bacteria and parasites have been recognized for years to be associated with human carcinogenicity. Here we review current concepts of carcinogenicity and its associations with parasitic infections. The helminth diseases schistosomiasis, opisthorchiasis, and clonorchiasis are highly carcinogenic while the protozoan *Trypanosoma cruzi*, the causing agent of Chagas disease, has a dual role in the development of cancer, including both carcinogenic and anticancer properties. Although malaria per se does not appear to be causative in carcinogenesis, it is strongly associated with the occurrence of endemic Burkitt lymphoma in areas holoendemic for malaria. The initiation of *Plasmodium falciparum* related endemic Burkitt lymphoma requires additional transforming events induced by the Epstein-Barr virus. Observations suggest that *Strongyloides stercoralis* may be a relevant co-factor in HTLV-1-related T cell lymphomas. This review provides an overview of the mechanisms of parasitic infection-induced carcinogenicity.

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1. Introduction

Cancers are characterized by uncontrolled growth of abnormal and transformed cells, which can invade adjacent tissues. The global burden of cancer in 2012 was estimated to be 14.1 million new cases and 8.2 million related deaths (WHO, 2015). Six types of cancers including lung, liver, stomach, colorectal, breast, and esophagus cancers are the most common causes of cancer death; four of these (liver, stomach, colorectal, and esophagus cancers) are often associated with distinct infectious diseases (WHO, 2015). Multiple factors can significantly contribute to carcinogenesis (WHO, 2015). Meetings of experts from diverse fields of cancer research held at the International Agency for Research on Cancer (IARC) from 2008 to 2009 have reassessed and classified human carcinogens into "discrete" groups including infectious pathogens (Bouvard et al., 2009; IARC, 2012).

Infections with eleven species of pathogens associated with cancers are classified as Group 1 carcinogens, definitely "carcinogenic to humans", by the IARC. These agents include *Helicobacter pylori*, hepatitis B virus (HBV), hepatitis C virus (HCV), *Opisthorchis viverrini*, *Clonorchis sinensis*, *Schistosoma haematobium,* human papillomavirus (HPV), Epstein-Barr virus (EBV), human T-cell lymphotropic virus type 1 (HTLV-1), human herpes virus type 8 (HHV-8) and human immunodeficiency virus type 1 (HIV-1) (Bouvard et al., 2009; IARC, 2012; de Martel et al., 2012). Among parasitic diseases, infections with the two fish-borne liver flukes of the family Opisthorchiidae (trematodes), specifically *Opisthorchis viverrini* and *Clonorchis sinensis,* can induce cholangiocarcinoma, and infection with the blood fluke *Schistosoma haematobium* may cause cancer of the urinary bladder (Bouvard et al., 2009). Although malaria *per se* is not considered carcinogenic to humans by the IARC, the geographical association between the occurrence of malaria and that of Burkitt lymphoma provides a clue that malaria plays as a co-carcinogenic factor, together with EBV infection, for the development of Burkitt lymphoma (Molyneux et al., 2012). Other species of the genera *Opisthorchis* and *Schistosoma* are thought likely to be carcinogenic (Sripa et al., 2007; Pakharukova and Mordvinov, 2016). Intriguingly, *Trypanosoma cruzi*, the etiological agents of Chagas disease, displays apparently paradoxical roles in malignancy in exerting carcinogenic and anticancer properties (Krementsov, 2009; Sacerdote de et al., 1980). Potential causative roles of other parasitic infections have been postulated (Machicado and Marcos, 2016).

Here, we summarize current concepts and facts on associations of parasite infections, namely schistosomiasis, opisthorchiasis, clonorchiasis, strongyloidiasis, malaria, and Chagas disease with human cancers and review mechanisms by which parasites may promote, or impede carcinogenesis (Table 1).

2. Schistosomiasis and Cancer

Schistosomiasis is a neglected disease caused by infection with blood fluke trematodes of the genus *Schistosoma.* Out of 207 million cases of schistosomiasis currently estimated worldwide, 90% occur in sub-Saharan Africa (Steinmann et al., 2006). Schistosomiasis is considered the most important helminth parasite of humans in terms of morbidity and mortality. The five species of *Schistosoma* that infect humans are *Schistosoma haematobium*, *S. mansoni*, *S. japonicum*, *S. intercalatum*, and *S. mekongi*. Most human infections are due to *S. haematobium*, *S. mansoni*, and *S. japonicum*. Of those, *S. haematobium* is the most ubiquitous species in Egypt and in sub-Saharan Africa and causes urogenital schistosomiasis (UGS). The prevalence of schistosomiasis is associated with exposure-related factors, in particular with a favourable environment for the imperative intermediate host snails, sub-optimal sanitation infrastructure, and host genetic factors. Adult worms are usually found in human hosts; their interactions with the host and parasite-derived products including their eggs strongly induce carcinogenesis (Brindley et al., 2015). With regard to schistosomiasis at large, clearly UGS *i.e.* chronic infection with *S. haematobium,* is carcinogenic and thus classified as a Group 1 carcinogen by the IARC (IARC, 2012). Any carcinogenicity of infection with other schistosomes is far less evident. Liver and colorectal cancers and lymphoid tumors may be associated with chronic schistosomiasis. Nonetheless, infection with *S. japonicum* is classified by the IARC as Group 2B, *i.e.* possibly carcinogenic to humans (IARC, 2012; IARC, 1994).

Bladder cancer is a common malignancy of the urinary tract with approximately 400,000 new cases and 150,000 deaths occurring annually (Ferlay et al., 2010). Histological types of bladder cancer include urothelial carcinoma, squamous, adenocarcinoma, micropapillary, small cell and plasmacytoid neoplasms. Urothelial carcinomas account for >90% in the developed world, whereas squamous cell carcinoma is seen predominating in UGS endemic regions (Knowles and Hurst, 2015). Further important risk factors for the induction of bladder cancer are host immune responses and host genetic factors (Fig. 1).

2.1. Schistosoma haematobium and Urinary Bladder Cancer

UGS due to *S. haematobium* has been consistently reported to be associated with bladder cancer. Early epidemiological findings reported from Zambia have indicated that 65% of patients with bladder cancer had concomitant UGS and 75% of them had well-differentiated squamous cell carcinomas (Bhagwandeen, 1976). A study from South Africa analyzing primary malignant bladder tumors found that the cancers were frequently squamous cell carcinomas (61%) (Cooppan et al., 1984). In Tanzania, 72% of bladder cancers were squamous cell carcinomas, and 46% of patients with squamous cell carcinomas were positive for *S. haematobium* eggs in tumor tissues (Kitinya et al., 1986). Another study found that UGS was strongly related to an increased risk of cytological abnormalities in a *S. haematobium* endemic area of Kenya (Hodder et al., 2000). *S. haematobium*-associated lesions were also detected in 69% of patients with squamous cell bladder carcinoma in Sudan (Sharfi and el SS, 1992). Case reports also have suggested a possible association of UGS with other malignant neoplasms such as prostatic adenocarcinoma and squamous cell carcinoma of the cervix (Basilio-de-Oliveira et al., 2002; Helling-Giese et al., 1996).

Several mechanisms may account for the role of infection with *S. haematobium* in urinary bladder cancer, among them epithelium damage, chronic inflammatory processes and oxidative stress (Bouvard et al., 2009; Brindley et al., 2015; Honeycutt et al., 2014) (Fig. 1). The mechanisms, however, need to be investigated further. Fibrosis induced

Table 1
Parasitic pathogens and infection-associated malignancy.

Parasitic pathogens	Disease	Endemic areas	Associated cancer	Proposed mechanism of carcinogenesis
Blood flukes				
Schistosoma haematobium	Schistosomiasis	sub-Saharan Africa	Urinary bladder cancer, adenocarcinoma, squamous cell carcinoma	Inflammation, oxidative stress caused by parasite-derived molecules
Schistosoma japonicum	Schistosomiasis	sub-Saharan Africa	Colorectal cancer, rectal cancer, squamous cell carcinoma, membranous nephropathy, metastatic lung cancer	Inflammation, oxidative stress caused by parasite-derived molecules
Schistosoma mansoni	Schistosomiasis	sub-Saharan Africa	Adenocarcinoma, colorectal cancer, hepatocellular carcinoma	Inflammation, oxidative stress caused by parasite-derived molecules
Liver flukes				
Opisthorchis viverrini	Opisthorchiasis	Southeast Asia	Cholangiocarcinoma	Inflammation, oxidative stress caused by parasite-derived molecules, cell proliferation, *H. pylori* mediated induction
Clonorchis sinensis	Clonorchiasis	China, Korea, northern Vietnam	Cholangiocarcinoma	Inflammation, oxidative stress caused by parasite-derived molecules, cell proliferation
Opisthorchis felineus	Opisthorchiasis	Europe and Russia	Cholangiocarcinoma	Inflammation, oxidative stress caused by parasite-derived molecules, cell proliferation
Plasmodia species				
Plasmodium falciparum *Plasmodium vivax* *Plasmodium ovale* *Plasmodium malariae* *Plasmodium knowlesi*	Malaria	sub-Saharan Africa, Southeast Asia	Burkitt lymphoma (*indirect carcinogenicity*)	Expansion of the EBV-infected B cell population, Suppression of EBV-specific T-cell immunity, Reactivation of EBV, AID-dependent genomic translocation
Strongyloides stercoralis	Strongyloidiasis	sub-Saharan Africa, South and Central America Southeast Asia	HTLV-1 induced lymphomas/leukemias (*indirect carcinogenicity*) Colon adenocarcinoma	Stimulate HTLV-1 replication, Oligoclonal expansion of HTLV-1-infected lymphocytes
Trypanosoma cruzi	Chagas' disease	South and Central America	Gastrointestinal cancer, Uterine leiomyoma	Unknown

by *Schistosoma* eggs may change proliferation, hyperplasia, and metaplasia of host cells that eventually induce carcinogenesis. Nitrosamines and increased levels of urinary b-glucuronidase and cyclooxygenase-2 derived from adult schistosomes are also recognized as bladder carcinogens. A liquid chromatography-mass spectrometry analysis of urine samples from UGS patients revealed numerous estrogen-like metabolites including catechol estrogen quinones (CEQ), CEQ-DNA-adducts and novel metabolites derived from 8-oxo-7, 8-dihydro-2′-deoxyguanosine (8-oxodG) (Gouveia et al., 2015). The detection of 8-oxodG indicates the damage of DNA in UGS *via* oxidative stress as the formation of 8-oxodG is known as a main product of DNA lesion by oxidation. The *S. haematobium*-derived carcinogens may lead to DNA damage and somatic mutations through chronic inflammation and oxidative stress in oncogenes such as *p53*, *RB* (retinoblastoma protein), *EGFR* (epidermal growth factor receptor), and *ERBB2* (erb-b2 receptor tyrosine kinase 2). Of interest is that genomic instability was frequently observed in *p53* and *KRAS* (V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog) genomic regions of patients with schistosomal bladder cancers (Abd El-Aal et al., 2015; Honeycutt et al., 2015; Lim et al., 2006; Santos et al., 2014; Botelho et al., 2013). Chromosomal damage and somatic mutations were frequently observed in these oncogenes in invasive squamous cell carcinomas of the bladder during UGS (Rosin et al., 1994). A recent proteomic analysis of urine samples from UGS patients additionally confirms the involvement of oxidative stress and immune responses in the development of *S. haematobium*-induced bladder cancer (Bernardo et al., 2016).

2.2. Schistosoma japonicum and Colorectal and Hepatocellular Carcinoma

Although evidence is sparse, infection with *S. japonicum* has been implicated in the etiology of colorectal cancer. Epidemiological and clinical studies in China and Japan suggested that *S. japonicum* may act as a carcinogen (Matsuda et al., 1999; Qiu et al., 2005). A Japanese study found that 19% of patients with chronic liver disease and 51% of patients with hepatocellular carcinoma (HCC) were infected with *S. japonicum*. A case-control study has shown that HCC developed in 5.4% of patients with chronic schistosomiasis and in 7.5% of those with chronic liver disease. However, a co-contribution of HCV infection to HCC development could not be reliably excluded (Iida et al., 1999). A matched, case-control study in rural China has indicated that previous infections with *S. japonicum* were independently associated with both HCC and colon cancer (Qiu et al., 2005), membranous nephropathy, and metastatic lung tumors (Matsuda et al., 1999; Chen, 2014; Sekiguchi et al., 1989). An isolated case of cutaneous squamous cell carcinoma associated with sporadic porphyria cutanea tarda due to liver functional disorder after *S. japonicum* infection was reported (Ohtake et al., 1991). Furthermore, a recent case report described a concomitance of *S. japonicum* infection with rectal carcinoid tumor in an asymptomatic patient from the Philippines (Zanger et al., 2010). Soluble egg antigen (SEA) from *S. japonicum,* which has a strong immunogenic activity, may contribute to carcinogenesis through stimulation of chronic inflammation (Ishii et al., 1994). Somatic mutations in the *p53* gene were examined in Chinese patients with both rectal cancer and *S. japonicum* infection, and a higher frequency of arginine missense mutations were observed in schistosomal rectal cancer ostensibly induced by schistosome infection compared to non-schistosomiasis rectal cancers (Zhang et al., 1998). *S. japonicum*-derived products may be involved in induction of host genomic instability (Fig. 1).

2.3. Schistosoma mansoni and Cancer

S. mansoni infection may constitute a risk for the development of HCC during co-infection with HCV. Case reports have described associations of schistosomiasis mansoni with prostatic adenocarcinoma and sigmoid colonic cancer (Basilio-de-Oliveira et al., 2002; HS et al., 2010). A recent case report from Turkey described the etiological relationship between *S. mansoni* and bladder cancer (Kiremit et al., 2015). Cell-mediated responses are depressed during intestinal schistosomiasis and the degree of suppression apparently correlates with the development of hepatosplenomegaly. Anti-idiotype antibodies produced during chronic schistosomiasis may modulate immune responses and *S. mansoni* egg antigens can effectively modify subpopulations of T helper cells (Cheever et al., 2002). Moreover, schistosomal colitis may be associated with earlier onset of multicentric colorectal cancer. Altered

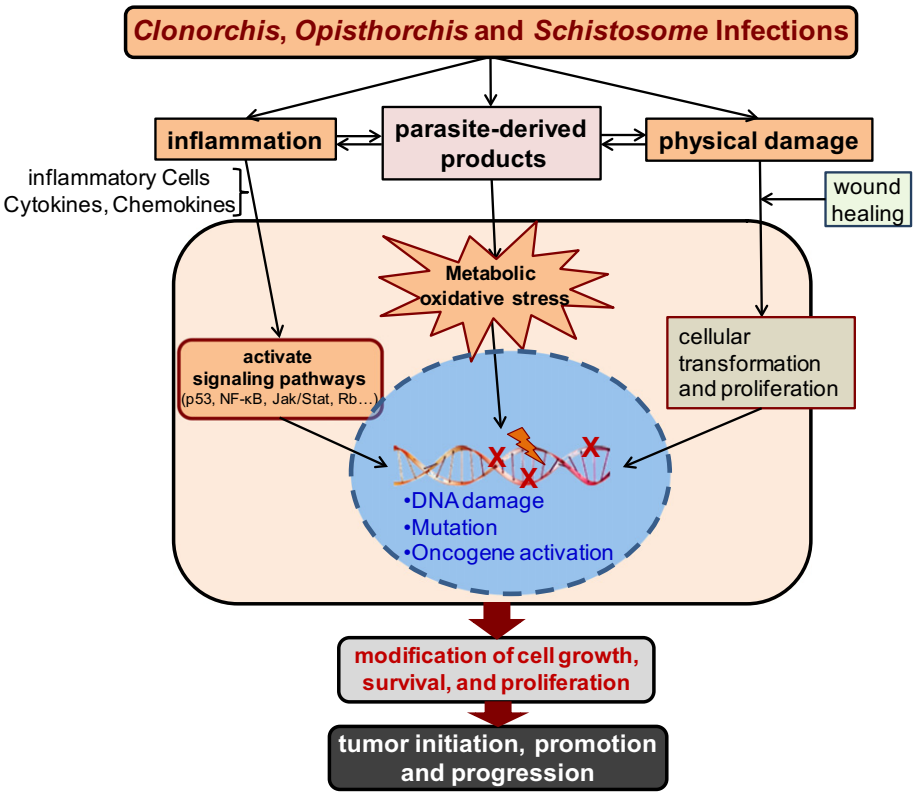

Fig. 1. Proposed mechanisms of carcinogenicity induced by infection with the liver and blood flukes *Clonorchis, Opisthorchis* and *Schistosoma* species. The chronic inflammation during *Clonorchis, Opisthorchis* and *Schistosoma* infections leads to the activation of signaling pathways including p53, NF-κB, Jak/Stat and Rb that could generate somatic mutations and/or activate oncogenes. Fluke-derived products and metabolites secreted to the host microenvironment may induce metabolic processes including oxidative stress that facilitate damage to the chromosomal DNA of proximal epithelial cells, specially cholangiocytes and urothelial cells for the liver and blood flukes, respectively. In addition, physical damage of host tissues during the development of parasites together with the active wound healing process lead to increased cell transformation and proliferation, which also are associated with the DNA damage. Combined parasite-host interaction events (chronic inflammation, parasite-derived products, and physical damage) and their combined effects on the chromosomes and fates of cells lead to the modification of the cell growth, proliferation and survival that in turn initiate and promote malignancy.

expression of the tumor protein 53 (TP53) in patients with *S. mansoni* colitis-related colorectal cancer suggests that schistosome infections may induce carcinogenesis by targeting oncogenes (Madbouly et al., 2007). Other oncogenes such as *Bcl-2* and *C-Myc* also are relevant in the development of colorectal cancer during schistosomiasis (Zalata et al., 2005). Therefore, cancer induction by *S. mansoni* infection could result from somatic mutations in oncogenes and in the regulation of immune responses that can activate several host signaling cancer pathways (Fig. 1).

2.4. Carcinogenicity of Schistosoma intercalatum and Schistosoma mekongi

Two case reports only have pointed to a possible association of infection with *S. intercalatum* and *S. mekongi* with cancer (Cuesta et al., 1992; Muller and van der Werf, 2008). *S. mekongi* infection has been associated with leiomyosarcoma of the small bowel (Cuesta et al., 1992), and intestinal *S. intercalatum* infection was observed in a patient with rectosigmoid carcinoma (Muller and van der Werf, 2008). However, these two case reports lacked evidence indicating that *S. intercalatum* and *S. mekongi* were the causative agents of the observed malignant tumors. To our knowledge, only a single study on an animal model (*Cynomolgus* monkeys) provides evidence of an association of *S. intercalatum* infection with urinary bladder cancer (Cheever et al., 1976). Carcinogenic properties and mechanisms of *S. intercalatum* may possibly be inferred due to the similarity of *S. intercalatum* and *S. haematobium* in both morphology and life cycle of the parasite. However, compelling evidence indicating carcinogenicity of *S. intercalatum* and *S. mekongi* is still tenuous.

3. Liver Fluke Infections and Cholangiocarcinoma

Opisthorchiasis and clonorchiasis are caused by fish-borne liver flukes of the trematode family *Opisthorchiidae*. >45 million people worldwide are infected by these pathogens. Species of opisthorchiid flukes that cause disease in humans are *Opisthorchis felineus*, *Opisthorchis viverrini*, and *Clonorchis sinensis*. The IARC classifies *C. sinensis* as a Group 1 agent (carcinogenic to humans). *O. felineus* is endemic in parts of Europe and Russia; *C. sinensis* in China, the Republic of Korea, and northern Vietnam; while *O. viverrini*-infections occur in Southeast Asia (Petney et al., 2013). *Opisthorchis* and *Clonorchis* are highly endemic in Mekong Basin countries such as Laos (50% to 70% of *O. viverrini* infection), Thailand (16.6% *O. viverrini* infection in the Northeast region and Nakhon Phanom province reported up to 60%), Cambodia (4% to 27% *O. viverrini* infection) and Vietnam (15% to 37% *O. viverrini* infection in southern regions and *C. sinensis* infection 0.2% to 26% in the north) (Sithithaworn et al., 2012). The consumption of raw fish infested with infectious metacercariae and intensifying transmission of the parasites to humans from domestic *O. viverrini* infected animals contributes largely to increased incidences (Forrer et al., 2012; Xayaseng et al., 2013). Pathologic conditions associated with opisthorchiasis are mainly hepatobiliary, specifically caused by bile duct fibrosis, cholangitis and other manifestations such as obstructive jaundice, hepatomegaly, abdominal pain, and nausea (Keiser and Utzinger, 2009). After consumption of raw fish carrying opisthorchiid metacercariae, parasites excyst in the duodenum, migrate to the bile ducts and canaliculi following chemotactic stimuli, and adult worms feed on biliary epithelia and bile ingredients, eventually leading to biliary epithelial hyperplasia and fibrosis (Sripa et al., 2012a).

Cholangiocarcinoma, or bile duct cancer, is a highly aggressive malignancy with poor prognosis. Cholangiocarcinoma accounts for approximately 20% of all hepatobiliary malignancies and it can be classified as intrahepatic and extrahepatic cholangiocarcinoma (Tyson and El-Serag, 2011). Incidences and mortality rates have significantly increased and effective therapies are barely available. Complex factors including genetics, environments, concomitant liver diseases, chronic infectious diseases and the parasitic infections (opisthorchiasis and clonorchiasis) are major risks for cholangiocarcinoma (Palmer and Patel, 2012; Welzel et al., 2007). The association of cholangiocarcinoma with opisthorchiasis and clonorchiasis has been evidenced by experimental, epidemiological and clinical data. Proposed mechanisms of carcinogenesis are biliary epithelium damage by parasites, long lasting immune-mediated pathogenesis, and effects of parasite-derived products on the bile ducts with subsequent modification of host cell proliferation (Brindley et al., 2015; Chaiyadet et al., 2015a; Chaiyadet et al., 2015b) (Fig. 1).

3.1. Carcinogenicity of Opisthorchis viverrini

Opisthorchiasis is inarguably associated with cholangiocarcinoma in Southeast Asia (Khuntikeo et al., 2016; Haswell-Elkins et al., 1994) and is classified as Group 1 carcinogen by the IARC (Bouvard et al., 2009; IARC, 2012; de Martel et al., 2012). Together with *O. viverrini* infection, co-factors such as environmental or exotic microbes in the biliary system that resist host inflammatory responses might also contribute to carcinogenesis (Sripa et al., 2007; Plieskatt et al., 2013; Chng et al., 2016). A mechanism that can explain the association between *O. viverrini* infection and bile duct cancer is that parasite-derived molecules can lead to uncontrolled growth of host cells. An animal model has supported this mechanism by showing that the dimethylnitrosamine derived from *Opisthorchis* can induce cholangiocarcinoma and the levels of precursors of nitroso compounds were elevated in body fluids of *O. viverrini* infected individuals (Haswell-Elkins et al., 1994). The parasite-derived granulin can promote proliferation of biliary cells, and thioredoxin (TRX) and thioredoxin peroxidase (TPX) can prevent apoptosis (Sripa et al., 2012a; Smout et al., 2009; Matchimakul et al., 2015; Smout et al., 2015). In addition, an analysis of *O. viverrini* extract has identified novel oxysterol derivatives in *O. viverrini*, which are potential carcinogenic compounds (Vale al., 2013).

Long-lasting interactions between *O. viverrini* and host responses initiate carcinogenesis. *O. viverrini* extracts could stimulate the production of inflammatory cytokines (Ninlawan et al., 2010) and *O. viverrini* derived products are internalized by cholangiocytes, which consequently induced cell proliferation and IL-6 production (Chaiyadet et al., 2015a). Higher IL-6 levels were observed in infected patients with bile duct cancer compared to those without (Sripa et al., 2009; Sripa et al., 2012b). These data indicate that opisthorchiidae have strong proinflammatory properties, which increase the risk of carcinogenesis (Ogorodova et al., 2015). On the other hand, host immunological factors play also a crucial role in determining the outcome of opisthorchiid infection and in initiation of cholangiocarcinogenesis. In this context, it was shown that *O. viverrini* infection down-regulates RB1 (retinoblastoma 1) and $p16^{INK4}$ (cyclin-dependent kinase inhibitor 2A) expression and up-regulates cyclin D1 and CDK4 (cyclin-dependent kinase 4) expression during cholangiocarcinoma development (Boonmars et al., 2009). These proteins are members of the retinoblastoma protein (RB) pathway, which is strongly involved in cancer development. Moreover, the chronic inflammatory condition caused by *O. viverrini* leads to up-regulation of the PI3K/AKT and Wnt/β-catenin signaling pathways involved in tumorgenesis (Yothaisong et al., 2014). Recently, a proteomic study has indicated that the 14-3-3 eta protein is up-regulated during *O. viverrini* infection and in early stages of *O. viverrini*-induced cholangiocarcinoma (Haonon et al., 2015) and in intrahepatic cholangiocarcinoma of patients void of *O. viverrini* infection (Zhang et al., 2015), indicating that the 14-3-3 eta protein is involved in host responses and contributes to carcinogenesis. This is supported by previous findings on the central role of the 14-3-3 eta protein in different controlling processes of cell cycle and in the regulation of various oncogenes and tumor suppressor genes (Tzivion et al., 2006; Wanzel et al., 2005).

At the genomic level, analysis of the mutation profiles of 108 cases with *O. viverrini*-related cholangiocarcinomas and 101 cases with non-*O. viverrini* infection-related cholangiocarcinomas revealed a significant difference in host genetic mutation patterns (Chan-On et al., 2013). In particular, somatic mutations occur more frequently in the *p53* and *SMAD4* (SMAD family member 4) genes in *O. viverrini* related cholangiocarcinomas compared to non-*O. viverrini* related cholangiocarcinomas. Somatic mutations occurring in the *BAP1* (BRCA1 associated protein-1), *IDH1*, and *IDH2* (isocitrate dehydrogenases 1 and 2) genes are more common in non-*O. viverrini* than in *O. viverrini* related cholangiocarcinomas (Chan-On et al., 2013; Jusakul et al., 2015). Mutations in the tumor suppressor genes *p53* and *SMAD4* directly affect the related cellular signaling pathways p53 and TGF-b, which both are involved in tumorgenesis (Jusakul et al., 2015).

3.2. Carcinogenicity of Clonorchis sinensis

The association between infection with *C. sinensis* and cholangiocarcinoma has been convincingly documented (IARC, 2012; Sripa et al., 2007; Choi et al., 2006), and these helminths have been classified as highly carcinogenic agents (Bouvard et al., 2009; de Martel et al., 2012). Indeed, a case-control study from Korea showed that *C. sinensis* infection was significantly associated with increased risk of cholangiocarcinoma (OR = 7.3, 95%CI = 3.96–13.3) (Choi et al., 2006). An epidemiologic survey performed in 3169 Korean residents also showed that a higher prevalence of *C. sinensis* infection was associated with a higher incidence of cholangiocarcinoma (Lim et al., 2006). The exact mechanisms by which *C. sinensis* contribute to carcinogenesis are not clearly understood, although similar mechanisms to those of *O. viverrini*-induced carcinogenesis (*via* inflammation, parasite-derived products and physical damage) may be anticipated. Pancreatic ducts may harbor *C. sinensis,* which can lead to squamous metaplasia and mucous gland hyperplasia, and a well-differentiated ductal adenocarcinoma of the pancreas (Colquhoun and Visvanathan, 1987). A study has demonstrated that *C. sinensis*-derived excretory-secretory products may promote aggregation and invasion of cholangiocarcinoma cells into the neighboring extracellular matrix (Won et al., 2014). Strong stimulation of Th2-associated inflammation by *C. sinensis* could be a risk factor for the initiation and development of cancer (Kim et al., 2012). During *C. sinensis* infection, peroxiredoxin 6 (Prdx6) expression was inversely correlated with NF-κB activation due to the response to *C. sinensis*-derived excretory-secretory products (ESPs) (Pak et al., 2016). *C. sinensis* induces the expressions of various lipid peroxidation products such as 4-hydroxy-2-nonenal (HNE), cyclooxygenase-2 (COX-2), 5-lipoxygenase (5-LOX) and 8-oxo-7.8-dihydro-2′-deoxyguanosine (8-oxodG) and plasma proinflammatory cytokines (TNF-α, ILβ-1 and IL-6). Among various lipid peroxidation products, 8-oxodG formation (a product of DNA lesion) was initially detected in the nucleus of the inflammatory cells and subsequently in the biliary epithelial cells in a *C. sinensis* mouse model (Maeng et al., 2016). These results indicate that *C. sinensis* demonstrate a strong immunogenic property and robustly induce metabolic oxidative stress.

3.3. Carcinogenicity of Opisthorchis felineus

The association of infection with *O. felineus* with cholangiocarcinoma has been proposed (Sripa et al., 2007; Maksimova et al., 2015). The mechanisms by which *O. felineus* contributes to carcinogenesis are also not clearly understood. Negative correlations between *O. felineus* and responses to allergens suggest that Opisthorchiidae are able to induce regulatory cells (Ogorodova et al., 2007). *O. felineus* infection has been shown to be a relevant modifier of Th1/Th2-regulating genes as

O. felineus antigens were able to modulate expression of specific genes like *SOCS5* (suppressor of cytokine signaling 5) and *IFNG* (interferon gamma) (Saltykova et al., 2014). Moreover, regulatory T cells are associated with faster tumor growth and poor prognosis of cancer (Nomura and Sakaguchi, 2005). A recent report indicates that dysmetabolism of glucose, perhaps in the setting of diabetes (Saengboonmee et al., 2015), and activities of dicarbonyl stress may also be implicated (Saltykova et al., 2016).

4. Malaria and Burkitt lymphoma

4.1. Malaria

Five species of the protozoan parasite *Plasmodium* - *Plasmodium falciparum*, *P. vivax*, *P. ovale*, *P. malariae*, and *P. knowlesi* affect humans. *P. falciparum* is the most virulent and widespread in regions endemic for malaria (Hay et al., 2010). Malaria has caused >200 million clinical episodes worldwide in 2010 (WHO, 2014). There were an estimated 650,000 malaria deaths in 2010, of which 91% (596,000) were reported from Africa. Malaria is almost exclusively transmitted by infective bites of female *Anopheles* mosquitoes. *P. falciparum* exhibits remarkable biological diversity and the ability to rapidly develop resistance to almost all anti-malarial drugs (Hay et al., 2010). Sporozoites released from the mosquitoes invade hepatocytes and multiply into merozoites, which subsequently are released from the hepatocytes and enter the blood stage by infecting erythrocytes. During the blood stage, erythrocytes are damaged as parasites digest haemoglobin to obtain essential amino acids.

4.2. Burkitt Lymphoma

Burkitt lymphoma is a monoclonal B cells cancer and the fastest growing tumor in humans in malaria endemic areas of sub-Saharan Africa (Molyneux et al., 2012). Burkitt lymphoma is classified into the clinical types of endemic, sporadic and immunodeficiency-associated Burkitt lymphoma. The annual incidence is approximately 40–50 per one million children, and in high-risk areas, endemic Burkitt lymphoma accounts for half of all childhood cancers and up to 90% of lymphoma diagnoses (Molyneux et al., 2012; Orem et al., 2007). The chromosome translocation between the *c-Myc* oncogene and immunoglobulin (*Ig*) gene loci that leads to deregulation of c-*M*yc expression together with *p53* gene mutations are known to be most relevant in the pathogenesis of Burkitt lymphoma (Chiarle et al., 2011; Klein et al., 2011; Wilmore et al., 2015; Gutierrez et al., 1997). Burkitt lymphoma is clearly associated with EBV infection, and in non-malaria-endemic areas it is associated with HIV/AIDS (Molyneux et al., 2012; Rochford et al., 2005).

4.3. Malaria as Indirect Risk Factor for Burkitt Lymphoma

Although malaria itself is not classified carcinogenic, endemic Burkitt lymphoma in sub-Saharan Africa is geographically associated with holoendemicity of *P. falciparum* malaria. A plethora of epidemiological, experimental and clinical studies have demonstrated the synergistic effects of host genetic factors and infections such as EBV, *P. falciparum* and HIV on Burkitt lymphoma development (Molyneux et al., 2012). Co-infection with *P. falciparum* malaria and EBV is the main risk factor for endemic Burkitt lymphoma. In a cohort of 711 Kenyan Burkitt lymphoma cases, the rates were higher in regions with chronic and intense malaria transmission compared to regions with no or sporadic malaria transmission (Rainey et al., 2007). A recent study of 303 endemic Burkitt lymphoma and 274 non endemic Burkitt lymphoma-related cancers in Malawi found that patients with endemic Burkitt lymphoma had a higher prevalence and more genetic diversity of *P. falciparum* parasites compared to non-endemic Burkitt lymphoma-related cancers (Johnston et al., 2014). The precise mechanisms of how malaria is related to the increased risk of Burkitt lymphoma and how malaria could induce the pathogenesis of Burkitt lymphoma have remained a mystery for decades. The mechanisms proposed are expansion of the EBV-infected B cell population, suppression of EBV-specific T-cell immunity, reactivation of EBV and activation-induced cytidine deaminase (AID)-dependent genomic translocation (Fig. 2).

4.3.1. Expansion of EBV-Infected B Cells

Interaction of *P. falciparum* and B cells is considered as a key factor. B cell activation and hyper-gammaglobulinemia in malaria have been well described both experimentally and clinically. A study has shown that *P. falciparum*-infected erythrocytes directly adhere to and activate B cells through the CIDR1α domain of *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) (Simone et al., 2011). Binding of PfEMP1 and CIDR1α induces expression of Toll-like receptor (TLR)7 and TLR10 and sensitizes B cells to TLR9 signaling leading to persistent activation of B cells and subsequently to impairment of their functions in chronic malaria (Simone et al., 2011). Interaction of PfEMP1-CIDR1α also induces proliferation of B cells, expression of distinct activation molecules, and differentiation into plasma cells, thereby increasing the secretion of IgM immunoglobulins and cytokines (Donati et al., 2004). Increasing proliferation of polyclonal B cell populations might enhance the risk of expansion and transition of EBV-infected B cells, which could lead to the emergence of a malignant B-cell clone (Rochford et al., 2005). Clinically, *P. falciparum* infection is associated with enhanced proliferation and transformation of EBV-infected cells in both children with acute or asymptomatic malaria (Moormann et al., 2005) (Fig. 2).

4.3.2. Suppression of EBV-Specific T Cell Immunity

The fact that *P. falciparum* can inhibit EBV-specific T cell immunity could explain how EBV and *P. falciparum* infections are associated with the increased risk of Burkitt lymphoma. Failure of EBV-specific T cells to control EBV-infected cells in malaria patients leads to the expansion and abnormal proliferation of EBV-infected B cells (Whittle et al., 1984). In addition, suppression of EBV-specific T cell immunosurveillance and altered differentiation of EBV-specific CD8(+)T cell occur in children resident in malaria regions (Moormann et al., 2007; Chattopadhyay et al., 2013). Furthermore, EBV-specific CD4(+)T cell responses were observed during early infection stages but subsequently decline rapidly (Precopio et al., 2003). Accordingly, dendritic cells could contribute to inhibition of T cell immunity during malaria, as *P. falciparum*-infected erythrocytes are able to adhere to dendritic cells and modulate their functions through a TLR9-dependent pathway (Pichyangkul et al., 2004). These interactions inhibit maturation of dendritic cells (DCs) and their capacity to activate immune responses and alter the IL-12 and IL-10 secretion patterns (Urban et al., 1999; Ocana-Morgner et al., 2003). Support for this mechanism is provided by clinical observations indicating impairment of DC functions, and increased plasma IL-10 levels are associated with high parasite densities and poorer parasite clearance in children during acute malaria (Urban et al., 2001; Hugosson et al., 2004) (Fig. 2).

4.3.3. Reactivation of EBV Viremia Induced by Malaria

The expansion of EBV-infected B cells is associated with higher levels of B cell-carried EBV-DNA and plasma cell-free EBV-DNA (Njie et al., 2009; Rasti et al., 2005). A study has shown that cell-free EBV-DNA levels in plasma of children and pregnant women with malaria were increased compared to those without malaria, showing that EBV can be reactivated during malaria infection (Rasti et al., 2005; Daud et al., 2015). Circulating viral loads were also associated with increased exposure to malaria as well as with severity and the number of disease episodes (Moormann et al., 2005; Rasti et al., 2005; Donati et al., 2006; Yone et al., 2006) indicating that *P. falciparum* infection contributes to reactivate viral replication. Furthermore, elevated plasma EBV viral loads were associated with the development of endemic Burkitt lymphoma (Asito et al., 2010). Providing a deeper insight into

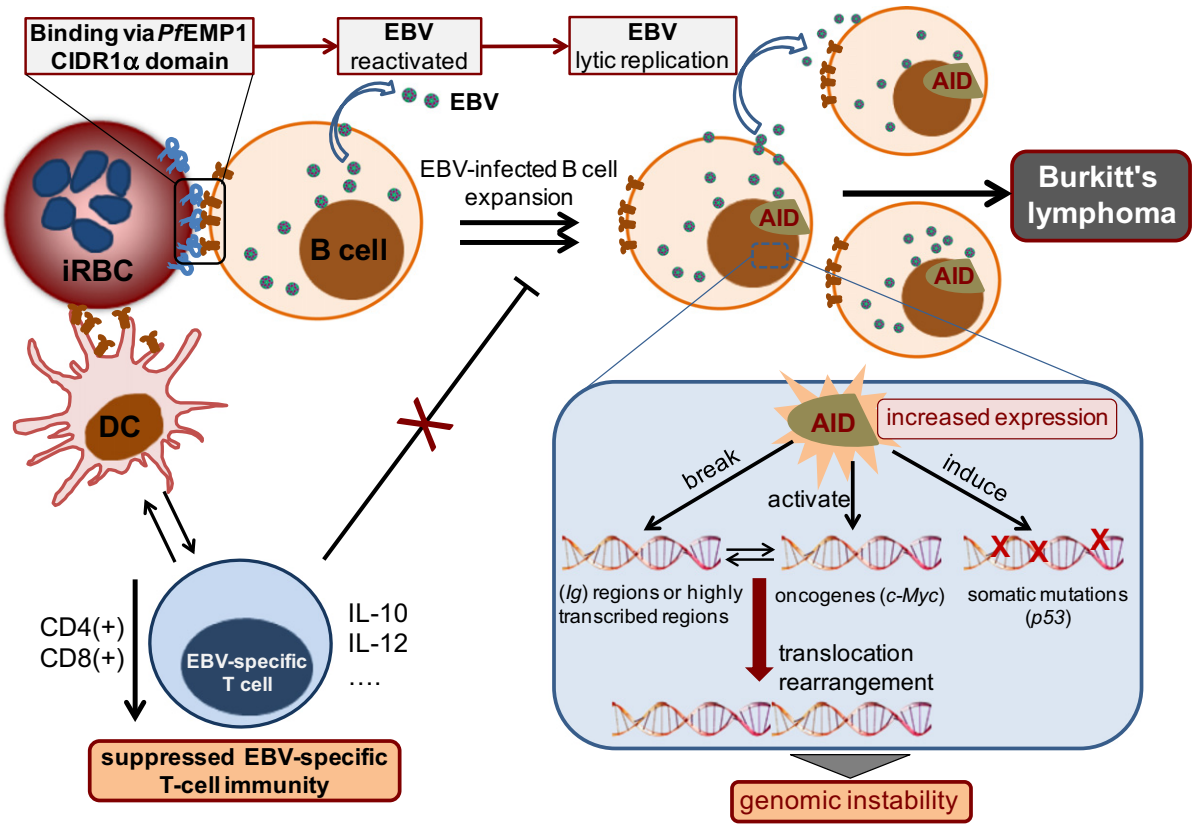

Fig. 2. Proposed mechanisms of induction of Epstein-Barr virus driven Burkitt lymphoma by falciparum malaria. *Plasmodium falciparum* infected red blood cells (iRBC) bind to the Epstein-Barr virus (EBV) latently infected B cells through the CIDR1α domain of *P. falciparum* erythrocyte membrane protein 1 (*Pf*EMP1) that lead to the expansion of the latently infected B cell pool and/or lead to the reactivation of EBV. The interaction between iRBCs and EBV-infected B cells in the germinal center (GC) also results in the increased expression of the Activation-Induced cytidine Deaminase (AID). The AID in turn contributes to break host DNA at the immunoglobulin (*Ig*) or/and highly transcribed regions, to activate oncogenes (*c-Myc*) and to induce somatic mutations. The AID also induces the chromosomal rearrangement especially the translocation between *Ig* regions and *c-Myc* oncogene. All these processes lead to the genomic instability that can drive the proliferation and differentiation of B cells in GC and subsequently lead to the emergence of a malignant B-cell clone. In addition, the binding of iRBC to the dendritic cells (DCs) could lead to a modification of DC functions that contributes to suppress EBV-specific T-cell immunity ($CD8^+$ and $CD4^+$ T cells), therefore resulting in the loss of controlling the expansion of EBV-infected B cells including emergent Burkitt lymphoma clones.

P. falciparum-induced EBV reactivation, a study has uncovered the mechanism that binding between latently EBV-infected B cells and the domain CIDR1α of the PfEMP1 protein directly switches the virus into lytic replication and CIDR1α stimulates EBV production in peripheral blood mononuclear cells (Chene et al., 2007) (Fig. 2).

4.3.4. AID-Dependent Genomic Translocation Induced by Plasmodium falciparum

Molecular mechanisms to explain how *Plasmodium* infection promotes Burkitt lymphomagenesis remain controversial. *P. chabaudi* was used to establish chronic malaria in an animal model; the infection resulted in an increased and prolonged clonal expansion of B cells in germinal centers and primarily induced expression of AID in *Plasmodium*-induced germinal center B cells (Robbiani et al., 2015). AID deficiency was associated with anemia, splenomegaly, extramedullary hematopoiesis, and reduced survival suggesting an essential role of AID in controlling chronic malaria (Robbiani et al., 2015). Similarly, *P. falciparum* extracts were shown to stimulate expression of AID in germinal center B cells *in-vitro* and *in-vivo* (Torgbor et al., 2014). Frequent malaria exposure led to an increased expression of AID, which coincides with decreased IgM^+ memory B cells (Wilmore et al., 2015). Widespread chromosome translocations were also observed in *Plasmodium*-induced germinal center B cells and the rearrangements occurred more frequently in genic regions. In a mouse model of chronic malaria, AID induced genomic instability of germinal center B cells, mostly in immunoglobulin (*Ig*) regions and in highly transcribed genes (Robbiani et al., 2015). Earlier studies have shown that AID contributes to induce somatic mutations and DNA breaks in immunoglobulin genes and in oncogenes (*c-Myc*) that lead to *c-Myc* and *IgH* translocations (Robbiani et al., 2008). AID also causes rearrangement of other genes, which act as translocation partners in mature B cell lymphoma (Klein et al., 2011) by predominantly targeting the super-enhancers and regulatory clusters of B cells, which are the genomic domains with high transcriptional and regulatory activity (Qian et al., 2014; Meng et al., 2014). Therefore, AID is a central player required to control chronic malaria and to promote malaria-induced lymphomagenesis. Taken together, malaria is not a direct trigger of cancer, but *P. falciparum* infection rather modifies the lymphoma phenotype to favor more mature B cell lymphomas by stimulating prolonged AID expression in germinal center B cells (Robbiani et al., 2015) (Fig. 2).

5. *Strongyloides stercoralis* and Cancer

Strongyloides stercoralis, an intestinal nematode, can cause strongyloidiasis and gastrointestinal ulcer. *S. stercoralis* infects approximately 50–100 million people in tropical and subtropical regions (Segarra-Newnham, 2007). Approximately 50% of individuals chronically infected with *S. stercoralis* are asymptomatic while symptomatic forms may lead to severe skin pathology, diarrhea, nausea, and abdominal discomfort. Infection with *S. stercoralis* may be complicated by autoinfection, which results in a hyperinfection syndrome and is associated with sustained infection, high worm burden and high mortality (Segarra-Newnham, 2007). Notably, hyperinfection with *S. stercoralis* has been demonstrated to be in part geographically associated with the

occurrence of HTLV-1 infections. A recent epidemiological study investigated the association of co-infection with *S. stercoralis* and HTLV-1 with cancers in a large cohort of 5209 cancer patients and showed that *S. stercoralis* infection was associated with an increased occurrence of cancers (Tanaka et al., 2016). HTLV-1 causes adult T cell leukaemia/lymphoma by enhancing immortalisation and transformation of T cells and therefore has been classified as a Group 1 carcinogen by the IARC (IARC, 2012; Gabet et al., 2000). The HTLV-1 proteins Tax and HBz are involved in many regulatory processes including induction of growth of infected T cells and transformation, transcription of cellular genes, and genetic instability. HTLV-1 proviral loads were significantly higher in HTLV-1 carriers with strongyloidiasis than in HTLV-1 positive individuals without *S. stercoralis* infection suggesting that *S. stercoralis* may stimulate HTLV-1 replication (Gabet et al., 2000). In addition, the helminth infection has been shown to induce polyclonal expansion of HTLV-1-infected T cells by activation of the IL-2/IL-2R system (Satoh et al., 2002). These findings suggest that *S. stercoralis* is a cofactor for the development of HTLV-1- induced lymphoid cancers (Table 1).

In addition, a case report described a Korean patient presenting with both *S. stercoralis* infection and early gastric adenocarcinoma. Further analysis revealed that the gastric adenocarcinoma and adenoma tissues were positive for *S. stercoralis* suggesting a causative effect of *S. stercoralis* (Seo et al., 2015). An association of colorectal cancer with chronic *S. stercoralis* infection has also been reported in a Columbian patient (Tomaino et al., 2015). These observations suggest that *S. stercoralis* may not only serve as a cofactor for induction of HTLV-1-related lymphoid cancers, but also stimulates induction of colon adenocarcinoma probably by interacting with the host and/or activating the host immune response.

6. Paradoxical Dual Impacts of Chagas Disease in Carcinogenesis

Chagas disease (CD), a parasitic disease caused by the flagellated protozoan *Trypanosoma cruzi*, occurs throughout South and Central America, and affects approximately 15 million people (Coura, 2013). Successful transmission of *T. cruzi* primarily occurs through triatomine insects (kissing bugs). People become infected when feces of the kissing bug containing the trypomastigote stage of *T. cruzi* are deposited on the human skin while the insect feeds on blood; the *T. cruzi* containing insect feces contaminate mucous membranes, conjunctivae, or skin breaks, and initiate human infection (Stevens et al., 2011).

Approximately 40% of persons infected with *T. cruzi* are asymptomatic or present with indeterminate forms. About 2–5% progress annually to symptomatic forms with irreversible cardiac and/or digestive disorders, mostly presenting as megaorgans (Nunes et al., 2013). <1% develop severe acute disease with the clinical manifestations of acute myocarditis, pericardial effusion, and/or meningoencephalitis (Nunes et al., 2013).

6.1. Chronic Infection with Trypanosoma cruzi as a Risk Factor for Carcinogenesis

An association of CD with gastrointestinal cancer has been proposed (Sacerdote de et al., 1980). A case report described a patient with chagasic megaesophagus who had developed esophageal leiomyosarcoma (Adad et al., 1999). A case-control study has shown that 27% of women with uterine leiomyoma were serologically positive for CD compared to 16% of controls with other benign gynecological alterations (Murta et al., 2002). Other case reports have pointed to an association of chagasic megacolon and development of colon cancer (Adad et al., 2002; Oliveira et al., 1997). One documented mechanism is an increase of gastroesophageal reflux into the megaesophagus (de Oliver et al., 2014). A study examined cytogenetic alterations in patients with chagasic megaesophagus and observed aneuploidies of chromosomes 7, 11, and 17 in 60% and the deletion of the oncogene *p53* in 54.5% of 20 study patients; this might increase the risk of tumor development (Manoel-Caetano et al., 2004). While point mutations in exonic regions of *p53*, *FHIT* (fragile histidine triad gene) and *CDKN2A* (cyclin-dependent kinase Inhibitor 2A) genes or genomic imbalances were not frequent in chagasic megaesophagus, a silent mutation in exon7 of the *FHIT* gene and copy numbers of the *CDKN2A* and *CEP9* (C-terminally encoded peptide 9) genes might be involved in esophageal carcinogenesis (SM-C et al., 2009; Bellini et al., 2010). The assumed *T. cruzi*-related carcinogenesis is most likely due to host genetic factors, and the parasite-host interaction resulting in chronic inflammation in particular tissues (Fig. 3).

6.2. Anticancer Activity of Trypanosoma cruzi

Anticancer properties of *T. cruzi* were first reported in 1931 and a product of *T. brucei,* another member of the trypanosome family, has been suggested to exert antitumor properties. A study using a mouse model demonstrated that smaller tumor size was associated with high parasitemia and suggested that surface cellular antigens and an inhibiting or lysing factor of *T. cruzi* contribute to anticancer activities (Kallinikova et al., 2001). Similarly, chronically infected animals have a decreased risk to develop colon tumor compared to non-infected animals after challenge with 1.2-dimethylhydrazine (DMH), a drug inducing colon cancer (Oliveira et al., 2001). Immunization with *T. cruzi* epimastigote lysate strongly inhibited tumor development *in vivo* by inducing the activation of both CD4(+) and CD8(+) T cells as well as by increasing numbers of CD11b/c(+) His48(−) MHC II(+) cells, which correspond to macrophages and/or dendritic cells. Antibodies against *T. cruzi* lysate recognized various rat and human tumor cell types such as colon and human breast cancer cells and thus mediate tumor cell killing through antibody-dependent cellular cytotoxicity (ADCC) (Ubillos et al., 2016). To illustrate this mechanism, studies have identified a parasite chaperone molecule, the *T. cruzi* calreticulin (TcCRT) (Aguillon et al., 2000) and demonstrated its potent antiangiogenic and antitumor effects both *in-vitro* and *in-vivo*. TcCRT is able to directly interact with human endothelial cells through a receptor-dependent mechanism and to inhibit their proliferation, migration and capillary morphogenesis. In an *in vitro* experiment, TcCRT was capable to inhibit growth of murine mammary tumor cells (Lopez et al., 2010; Ramirez et al., 2011a). In addition, TcCRT plays a central role during the host-parasite interplay by interacting with complement proteins such as complement factor (C1), mannose-binding lectin (MBL), and ficolins to inhibit activation of the complement system that leads to increased infectivity of the parasite (Lopez et al., 2010; Ramirez et al., 2011b; Sosoniuk et al., 2014). This indicates that TcCRT does not only act as a virulence factor (Sanchez-Valdez et al., 2014) to persist, sustain and promote infectivity but also inhibits growth and metastasis of tumors. A further study has demonstrated that some *T. cruzi* strains are able to respond to oxidative stress caused by DNA damaging agents (Campos et al., 2011; Grazielle-Silva et al., 2015). The oxidative stress response of *T. cruzi* was mediated *via* the TcMSH2 protein, which is the central component of the mismatch repair (MMR) machinery in *T. cruzi* (Campos et al., 2011; Augusto-Pinto et al., 2001). These findings indicate that the survival ability of *T. cruzi* in the host is most likely granted through protection from oxidative stress by the effective DNA repairing pathway. In addition, MMR deficiency is significantly associated with predisposition to cancer (Bridge et al., 2014). Therefore, the oxidative stress response of *T. cruzi* may also be of importance in protection of host chromosomes during chronic inflammation and, thus, in reduced cancer development.

Further to the anticancer properties, *T. cruzi* is an effective cancer antigen delivery vector (Junqueira et al., 2011). A study utilized the attenuated *T. cruzi* CL-14 clone to express exogenously a cancer testis antigen (NY-ESO-1) and showed that *T. cruzi* parasites expressing NY-ESO-1 were able to induce strong NY-ESO-1 specific immune responses both *in-vitro* and *in-vivo*. Interestingly, immunization with *T. cruzi* parasites expressing NY-ESO-1 would lead to an effective immune response to kill tumor cells and to inhibit tumor development (Junqueira et al.,

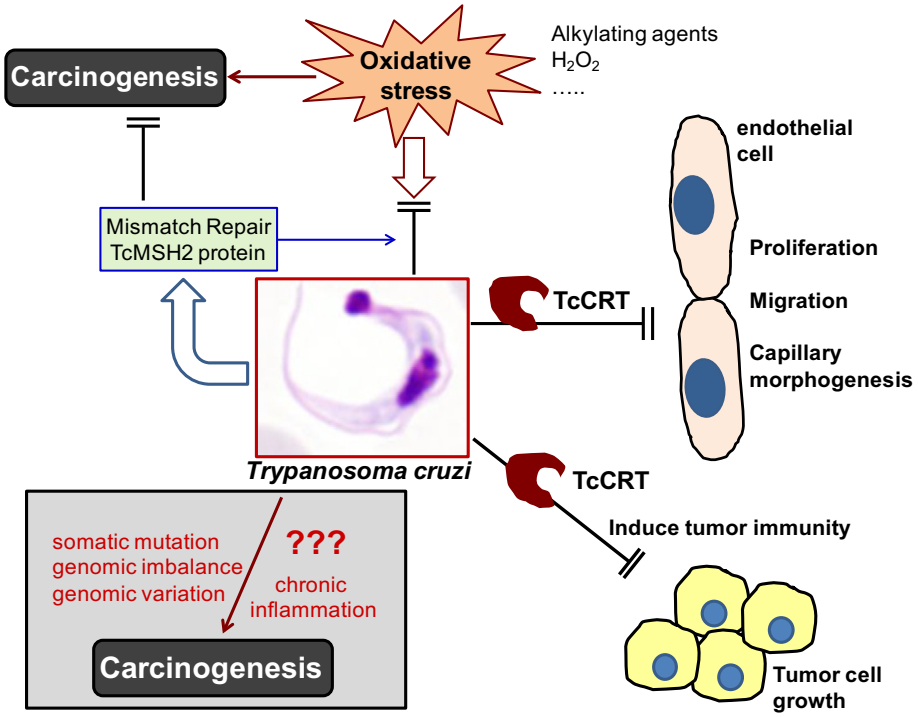

Fig. 3. Paradoxical roles of Chagas disease, infection with *Trypanosoma cruzi*, in carcinogenesis. Infection with *Trypanosoma cruzi* has been proposed in both carcinogenesis and in inhibition of carcinogenesis. *T. cruzi* has antitumor effects by inducing host immunity against tumor. *T. cruzi* expresses a calreticulin (*T. cruzi* calreticulin, TcCRT) that can directly interact with endothelial cells and inhibit their proliferation, migration and capillary morphogenesis as well as inhibit tumor cell growth. The DNA mismatch repair protein (TcMSH2), a central component of the mismatch repair (MMR) machinery in *T. cruzi*, allows *T. cruzi* to respond effectively to the oxidative stress during infection. The oxidative stress mediated by alkylating agents and hydrogen peroxide leads to carcinogenesis by damaging DNA. The TcMSH2 protein of *T. cruzi* may also contribute to protect host chromosomes from oxidative stress during infection, and therefore consequently inhibit tumorigenicity. On the other hand, *T. cruzi* may also cause cancer by inducing somatic mutation and genomic imbalance during chronic inflammation. However, the molecular details of this latter phenomenon are yet not understood.

2011). Taken together, *T. cruzi* may exert both carcinogenic and antitumor effects (Fig. 3).

7. Conclusions and Perspectives

The associations between infections with parasites and human cancers are well-evidenced. *S. haematobium*, *O. viverrini*, and *C. sinensis* are highly carcinogenic while other infectious species of the genera *Opisthorchis* (*O. felineus*) and *Schistosoma* (*S. japonicum* and *S. mansoni*) demonstrate their carcinogenic potential in humans (Table 1). Three main carcinogenic mechanisms have been described for these blood and liver flukes, including chronic inflammation, metabolic oxidative stress induced by parasite-derived products and host tissue damage during parasite development, along with the active wound healing (Fig. 1). However, detailed insights have not yet been obtained into these relationships, and/or into understanding functional consequences of both parasitic and host factors. Studies focusing on the identification of carcinogenic parasite factors and by which mechanisms host signaling pathways or oncogenes contribute to promote tumorgenesis are further warranted.

In malaria-related endemic Burkitt lymphoma, the AID protein appears to be an important factor that contribute to control chronic malaria and to induce human genomic instability (Fig. 2). Future clarification of AID in controlling *Plasmodium* infection and in its interaction with host chromosomes during B cell differentiation needs to be studied. In addition, the mechanisms by which *S. stercoralis* can induce malignancy together with HTLV-1 and/or directly induce carcinogenesis require further studies. While the carcinogenic role and mechanism of *T. cruzi* are not understood, anticancer properties of *T. cruzi* are mediated *via* the TcCRT and probably due to an effective response to oxidative stress (Fig. 3). Functional studies are required to warrant the antiangiogenic and antitumor properties of *T. cruzi* including studies of TcCRT and other molecules, which are potentially involved.

Contributors

HVT conceived this review, did the literature search, data extraction, interpretation of information, prepared the figures, drafted and revised the review. PJB, CGM and VTP provided critical reviews, developed and revised the manuscript. All authors read and approved the final version of the manuscript.

Declaration of Interests

The authors declare that there are no conflicts of interest.

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