Spotlights on helminth pathogens' innovative pathways of tumorigenesis

Review Article

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ABSTRACT

Chronic infections with microbes, such as viruses, bacteria and parasites contribute to a considerable proportion of the worldwide burden of cancer cases. Helminthic infections cause a relatively small proportion of the infection-related cancers, but the higher exposure to the worldwide helminth infections presents an importance of health problem. Notably, these infections are a preventable cause of cancer that highlights the prevention and control as well as health education in endemic areas to reduce infection levels and consequently reduce the risk of development of infection-related cancers. This review intends to spotlight the association of certain helminth infections with human malignancy and to focus on their innovative pathways of causing neoplasia.

Keywords: blood flukes; cancer; helminth; liver flukes; neurocysticecosis; *Schistosoma* spp.; *S. stercoralis*.

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INTRODUCTION

Cancer is a worldwide disease where around 18.1 million new cases with 9.6 million deaths were estimated in 2018[1]; and is predicted to increase by at least 60% over the next 20 years[2]. Chronic infections with some viruses, bacteria and parasites were linked to human carcinogenesis. Four types of cancers including hepatic, stomach, colorectal, and oesophageal malignancies are often linked with various infections[3]. Microbial infections are incriminated in 17.8% of the global burden of cancer worldwide, and in more than 20% of cancers in the developing world[4]. Infections with pathogens linked to cancers are categorised as group 1 carcinogens, and others with possible carcinogenic effects to humans are categorised as group 2 carcinogens, by the International Agency for Research on Cancer (IARC)[5]. All forms of infectious pathogens can induce an inflammatory immune response which eventually can provoke cancer cells to grow. Over the last few decades, scientists searched for links between parasites and cancers especially in tropical regions. Among protozoal diseases, El-Gayar and Mahmoud reviewed various epidemiological correlations between *Cryptosporidium* spp. and *Blastocystis* spp. in digestive carcinogenesis, *T. vaginalis* and *T. gondii* in cervical and central nervous system neoplasia, respectively. In addition, they highlighted the geographical association between malaria infection and Burkitt lymphoma as a clue to parasitic-induced cancers[6].

Accordingly, the present review is confined to highlighting current concepts and facts associated with selected helminthic parasitic infections that may cause human neoplasms and reviewing their novel pathways to promote carcinogenesis.

Mechanisms of carcinogenesis/cancer development

The frequency of multiplication and differentiation of human and/or animal cell types is genetically controlled by complex signaling pathway networks[7,8]. Without accurate control of these differentiation processes, cells change their behaviors and may proliferate in a disorderly manner with subsequent cancer development. The latter is a complex process that eventually passes through three stages: initiation, promotion, and progression. Initiation is triggered by a genotoxic cancer-causing agent by which irreversible mitochondrial or nuclear DNA genomes alterations may follow[9,10]. Exposure to a secondary stimulus such as chronic irritation and inflammation[11] will consequently increase the expression of oncogenes or decrease the expression of tumor-suppressor genes[12]. Consequent action involves clonal expansion of pre-neoplastic cells with subsequent malignant uncontrolled growth[13]. Finally, host immunopathological responses mediate progression *via* the critical production of oxidizing free radicals and nitrogen particles causing genetic instabilities and neoplastic changes[14]. The deposition of parasites' excretory/secretory (ES) by-products[8,15,16] is a key feature in inducing cancers that are generally found close to the site of the surrounding chronic inflammation[9,10,15,17].

Tumor cells can use various strategies to evade anti-tumor immune responses[18-21]. These include down-regulation of major histocompatibility MHC1 molecules[22], stimulation of cytokines secretion, such as

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transforming growth factor beta (TGF-β) and interleukin (IL)-10[23], down regulation of immune response[21] and alteration in the T-helper lymphocyte cells, Th1–Th2. Balance towards a Th2 response consequently, inhibits the cell-mediated immune response involved in tumor rejection[19,20,23]. In the same context, most helminth infections induce Th2 immune responses, with production of Th2-related cytokines IL-4, -5, -9, -10, and -13. Thus, long-lived helminths may affect host immune response by altering the Th1–Th2, balance causing downregulation of the Th1 immune response[23,24] and inhibition of tumor rejection, therefore causing clonal expansion of malignant transformed cells[19].

Helminth infection-induced cancers

Trematodes

Flatworms infect millions of individuals worldwide, and several flukes are known to be involved in human cancer. According to IARC, blood flukes including *S. haematobium*, and liver flukes including *C. sinensis* and *O. viverrine* are classified as group 1 carcinogens, whereas *S. japonicum* and *S. mansoni* are classified as group 2B carcinogens (potentially carcinogenic to humans)[5,25].

Schistosoma spp.

In terms of morbidity and mortality, schistosomiasis is considered the most important parasitic helminth infection in humans. Most human infections are caused by *S. haematobium*, *S. mansoni*, and *S. japonicum*. Schistosomiasis prevalence is linked to favorable environments for their intermediate host snails, environmental sanitation, and host genetic factors. Adult worms and parasite-derived products including their eggs, interact with the host inducing carcinogenesis[26].

Urogenital schistosomiasis: Cancer bladder is one of the common malignancies of the urinary tract with nearly 549,000 new cases, and deaths that approximate 200,000 cases/year[1]. Forms of cancer bladder exceed 6 different histological types, of which urothelial carcinoma accounts for approximately 90% of cases[27]. However, in regions endemic for urogenital schistosomiasis, squamous cell carcinoma is more abundant than urothelial carcinoma and may be the cancer of highest incidence[28,29]. Urogenital *S. haematobium* infection is linked with cancer of the urinary bladder. Moreover, urogenital schistosomiasis may be associated with other malignancies as squamous cell carcinoma of the cervix and adenocarcinoma of the prostate[30,31]. In fact, schistosomiasis *haematobium* was associated with a five-fold rise in the risk of bladder squamous cell carcinoma[25].

Various factors that may be involved in cancer bladder with urogenital schistosomiasis include epithelium damage, chronic inflammation, and oxidizing free radicals[26,32]. In addition, a proteomic analysis of urine samples from patients with *S. haematobium*-induced bladder cancer proved the contribution of oxidative stress and immune responses as a significant factor for the development of bladder cancer[33]. In an earlier report[34], fibrosis induced by *Schistosoma* eggs was implicated in triggering carcinogenesis by intensifying proliferation, hyperplasia, and metaplasia of host cells. Furthermore, increased levels of urinary bladder carcinogens; nitrosamines and parasite-derived b-glucuronidase and cyclooxygenase-2 were observed. Additionally, abundant estrogen-like metabolites were found in urine samples from patients with urogenital schistosomiasis. This was achieved by using liquid chromatography-mass spectrometry such as catechol oestrogen quinones, and novel metabolites derived from 8-oxo-7, 8-dihydro-2′-deoxyguanosine. The latter was identified as the major product of oxidative DNA damage.

Carcinogenic metabolites derived from parasites can cause chromosomal damage in patients with invasive bladder squamous cell carcinomas as a complication of urogenital schistosomiasis[35]. These carcinogens also cause genomic DNA damage and mutations through altering the oncogenes, e.g., *p53*, retinoblastoma protein, epidermal growth factor receptor, and erb-b2 receptor tyrosine kinase 2. Interestingly, frequent genomic instability was detected in bladder cancers with *S. haematobium* patients. This was recorded in regions of V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog and in regions of *p53*[36-39].

Intestinal schistosomiasis: Schistosomiasis *mansoni* is consistently associated with liver cirrhosis as a result of the accumulation of parasitic eggs and formation of granulomas[40]. The relation between *S. mansoni* and hepatocellular carcinoma (HCC) showed an indirect association. Recent evidence points to the high risk of early development of cirrhosis and rapid progression towards end-stage liver affection in patients suffering from schistosomiasis *mansoni* and additional hepatitis B (HBV) and/or hepatitis C (HCV) viruses' co-infection[41,42]. Moreover, immunosuppression due to depression of the cell mediated immune response and enhanced expression of lymphocyte activation markers in chronic HCV and *S. mansoni* induced liver disease, increased with the progression of the disease and was apparently linked with the progress of hepatosplenomegaly[43,44]. Prolonged carrier state of HBV and HCV may occur as an effect of schistosomiasis on the immune system, which carries a higher risk of developing complications including HCC[45,46]. Two hypothesises were proposed for the effects of schistosomiasis on host immune response. First is the suppression effect of anti-idiotype antibodies produced in patients with chronic schistosomiasis on the specific and non-specific immune responses[47]. Second, *S. mansoni* egg antigens may modify Th2 cells activity with stimulation of the cytokines involved, eosinophilia, IgE secretion, and with downregulation of Th1 cells activity and CD8 cytotoxic T cells[48]. Furthermore,

colitis attributable to schistosomiasis was linked to earlier onset of multi-centric colorectal cancer. Schistosomiasis *mansoni* was observed to induce carcinogenesis by targeting oncogenes[49] as evidenced by altered expression of the tumor protein 53 and other oncogenes such as Bcl-2 and C-Myc[50] in patients with *S. mansoni* colitis-related colorectal cancer. Consequently, schistosomiasis *mansoni*-induced cancer may result from somatic mutations in oncogenes and regulation of immune responses that can activate multiple neoplastic signaling paths. Patients suffering from schistosomiasis *mansoni* showed reduced hepatic cytochrome p450, cytochrome b-5 and NADPH cytochrome C reductase enzymes. Alteration of these enzymes increased aflatoxin metabolites by 300% *in vitro*. This indicates a probable role of schistosomiasis *mansoni* in enhancing the effect of environmental cancer-causing agent and consequently elevating the possibility of inducing malignancy[51].

Despite the inadequate link between *S. japonicum*, and cancer, schistosomiasis *japonicum* is involved in the pathogenesis of colorectal cancer. Several studies revealed an association between schistosomiasis *japonicum*, liver and colon cancer, and proposed that *S. japonicum* is a potential carcinogenic parasite[52,53]. An early case-control study in Japan indicated that *S. japonicum* infection was found in 51% of HCC patients and showed that HCC developed in 7.5% of those with chronic liver disease, especially with co-contribution of HCV infection and in 5.4% of patients with chronic schistosomiasis[54]. Furthermore, a case report in the Philippines described an association of rectal carcinoid tumor with *S. japonicum* infection in an asymptomatic patient[55].

The strong immunogenic activity of *S. japonicum* soluble egg antigen (SEA) is involved in stimulation of chronic inflammation that may contribute to carcinogenesis[56]. In Chinese patients with schistosomiasis *japonicum* and rectal malignancy, genetic mutations in the *p53* tumor-suppressor gene, and increased frequency of arginine missense mutations were observed, in comparison to rectal cancer patients without *S. japonicum* infection. Antigens derived from *S. japonicum* can be involved in initiation of instability of the host genome[57].

An increase in the frequency of hepatic cancer was observed in *S. japonicum*-infected mice exposed to the carcinogen 2-acetylaminofluorene[56]. Other experimental results showed that mice infected with *S. japonicum* had decreased ability of metabolizing mutagens[58,59], reduced aflatoxin B1-binding and increased retention of mutagens[60]. In contrast to the categorization of *S. haematobium* as definitely carcinogenic to humans (group 1), IARC decided that the carcinogenic evidence of *S. japonicum* infection in humans is limited (group 2B)[5,32,61].

Liver flukes (*C. sinensis, O. viverrine* and *O. felineus*)

These fish-borne liver flukes are closely related zoonotic trematodes that pose a major community health problem in Eastern Asia and Eastern Europe with 601.0 and 79.8 million people at risk for infection with *C. sinensis*, and *Opisthorchis* spp., respectively[62]. Pathologic conditions caused by opisthorchiasis and clonorchiasis are mainly hepatobiliary[63]. The adult worms feed on biliary epithelial cells and bile constituents causing bile duct fibrosis, cholangitis and eventually lead to biliary epithelial hyperplasia and fibrosis. The IARC classified *C. sinensis* and *O. viverrine* as a group 1 carcinogenic agent to humans[5]. Association of these infections with cholangiocarcinoma (bile duct cancer) in humans was evidenced by experimental, epidemiological, and clinical data[64].

Cholangiocarcinoma is a highly aggressive malignancy with poor prognosis and increased incidences and death rates and is often diagnosed only at advanced stages when the primary tumor is no longer amenable to radical surgery[65]. They are slow-growing adenocarcinomas that metastasize to distant sites due to their proximity to lymphatic vessels. It forms about 20% of all hepatobiliary carcinomas and it may be categorized as intrahepatic and extrahepatic tumors[66]. Genetic elements, environmental factors, associated liver diseases, chronic infectious diseases including parasitic infections (opisthorchiasis and clonorchiasis) are main risks factors for development of bile duct carcinoma[67,68].

Possible mechanisms contributing to uncontrolled growth of bile ducts cells with subsequent modification of host cell proliferation and initiation of neoplastic changes are likely multifactorial, attributed to either the damage of biliary epithelium by parasites, or to long-lasting interactions between the parasite and the host immune responses. These stimulate Th2-associated inflammatory cytokines[69], and consequently induce cell proliferation and production of IL-6, platelet-derived growth factor, tumor necrosis factor-alpha (TNF-α) and transforming growth factor-beta (TGF-β). These have strong pro-inflammatory properties and are associated with noticeable rise in risk of periductal fibrosis and proliferation of cholangiocytes. Autonomous proliferation and evasion of apoptosis increase the risk of cancer development[64,70-72].

Furthermore, the effects of parasite-derived mitogens and other mediator molecules, such as dimethyl nitrosamine, a precursor of nitroso compounds, can induce cholangiocarcinoma in animal models. Oxysterol derivatives are potential carcinogenic compounds that initiate the oxidation of cholangiocyte chromosomal DNA[26,64,73], parasite-derived granulin, thioredoxin, thioredoxin peroxidase, and hence promote biliary cells proliferation[64,74–76]. Induction of expression of various products of lipid

peroxidation and proinflammatory cytokines can induce potent immunogenicity and metabolic oxidative stress[77].

Moreover, *O. viverrini* infection was found to upregulate expression of cyclin D1 and cyclin-dependent kinase 4 and downregulate expression retinoblastoma 1 and cyclin-dependent kinase inhibitor 2A[78]. These proteins are members of the retinoblastoma protein (RB) pathway, which is strongly tangled in tumorigenesis. Besides, the chronic inflammatory condition upregulates the PI3K/AKT and Wnt/β-catenin signaling pathways involved in carcinogenesis[79]. Interestingly, pancreatic ducts can harbor *C. sinensis*, which may lead to metaplasia and mucous gland hyperplasia, as well as well-differentiated pancreatic duct adenocarcinoma[80]. Excretory secretory products of *C. sinensis* can induce cancer cell aggregation and invasion into the adjacent extracellular matrix[81]. Regulatory T cells were found to be associated with rapid malignant growth and poor prognosis[82]. In this context it was found that O. felineus infection modifies Th1/Th2-regulating genes and the parasite's antigens were also able to regulate the expression of specific genes such as suppression of cytokine signaling-5 and interferon gamma[83].

Fasciola hepatica

The relation between *F. hepatica* and cancer has so far remained unconfirmed, and the infection is rarely complicated by neoplastic development[84]. Two opposing effects, neoplastic growth stimulation and inhibition, are found in experimental studies. In the acute phase of infection, stimulation of tumor growth and hepatocyte proliferation was observed when immature stages of the parasite migrate through the liver parenchyma releasing antigens and excretory products promoting an intense inflammatory response. Formerly, components of the inflammatory process were shown to induce proliferation of worm-adjacent cells and accumulation of inflammatory cells that can induce reactive oxygen species-mediated DNA damage during fascioliasis-induced oxidative stress[85-87]. Acute infection may elevate the liver metabolizing enzymes and consequently activate the exogenous carcinogens[87].

On the other hand, in the chronic phase of infection, there was an observed inhibition of tumor growth and reduction of the hepatic metabolic activity[86]. Therefore, the observed suppression of N-nitroso-dimethyldiamine-induced cancer development in chronic *F. hepatica* infected experimental animals may be a consequence of inhibition of hepatic carcinogen biotransformation in chronic conditions[85].

Cestodes

There are limited reports on the role of tapeworms in inducing carcinogenesis. Soluble factors from *T. solium* have been shown to exert immunosuppressive effects[88] and induce lymphocyte DNA damage[89] *in vitro*. Neurocysticercosis caused by cysticercous cellulosae, the larval stage of *T. solium*, was linked to local malignant neoplasms particularly glioblastoma and some tumors outside the CNS e.g., haematological malignancies. However, the latter systemic effects are not easily understood. Localized neoplasms, such as glioblastoma, could be explained by the induction of DNA damage in the cells neighbouring the cysticerci and chronic exposure to the host's inflammatory response that may predispose to cancer development. This may be due to: a) chronic inflammation leading to release of potential carcinogens in the brain tissue e.g., nitric oxide; b) the cysticerci modulate the host immune response leading to loss of regulatory mechanisms implicated in tumor suppressor mechanisms; c) DNA damage due to transfer of the parasite genetic material into the host, and potential mutations in the tumor suppressor genes of proliferating astrocytes surrounding cysticerci lesions[90]. Moreover, chromosomal aberrations induced in peripheral lymphocytes during neurocysticercosis, and increased translocation frequency of chromosomes 7, 11 and 14 suggest that persistent antigenic stimulation can cause instability in lymphocytes chromosomes and that helminthic parasites may pose an important factor in inducing malignancy[19,91].

Nematodes

There is no clearly documented evidence for a link between nematode infection and neoplastic development in humans. It was reported that asymptomatic carriers of human T-cell lymphotropic virus type 1 (HTLV-1) infection may develop clinical leukaemia more rapidly when co-infected with *S. stercoralis*. This was attributed to the possible stimulation of the oligoclonal proliferation of cells infected with HTLV-1. However, the mechanism by which *S. stercoralis* contributes to initiation and/or progression of neoplasia is uncertain. It is also uncertain whether it shows direct carcinogenic potential. It is assumed that stimulation of the oligoclonal proliferation of HTLV-1 infected cells by the parasite causes adult T cell leukemia/lymphoma[92]. Additionally, helminth infection was shown to activate the IL-2/IL-2R system thus stimulating polyclonal expansion of HTLV-1-infected T cells[93]. Subsequently these data suggested that, *S. stercoralis*, is a cofactor for the growth of HTLV-1-induced lymphocytic carcinoma[94]. The link between *S. stercoralis* and HTLV-1 was supported by data showing that the prevalence of *S. stercoralis* above two-folds, increased in HTLV-1 patients as compared to HTLV-1 free individuals[95].

Moreover, infection with *S. stercoralis* can last a lifetime, and patients may be prone to chronic inflammation of the bowel and colon. Lasting for decades, it leads to the chronic colitis seen in inflammatory bowel disease (IBD)[96]. The two are frequently confused. Since chronic colitis due to IBD is

associated with an increased risk of colorectal cancer, it is conceivable that chronic colitis due to *S. stercoralis* infection may carry a similar risk. Epidemiological data reporting an association between *S. stercoralis* infection and gastrointestinal cancers is restricted to few reports of case-control studies and few case reports[97-103]. A case report of associated *S. stercoralis* infection and early gastric carcinoma was described in a Korean patient, revealing gastric adenocarcinoma and adenomatous tissue positive for *S. stercoralis*; implicating the causative effect of *S. stercoralis*[98]. In addition, a case of colorectal cancer associated with *S. stercoralis* colitis was reported from Colombia, where colon biopsies revealed invasive low-grade adenocarcinoma; a duodenal biopsy revealed parasites morphologically compatible with *S. stercoralis*; and pertinent stool analysis identified larvae of *S. stercoralis*[99,101].

In addition, a case-control study between 1991 and 2005 in Japan investigated the association between infection with *S. stercoralis* and the incidence of hepato-pancreato-biliary cancer. It indicated that the prevalence of biliary tract cancer seems to be significant and almost three-folds higher amongst patients with a *S. stercoralis* infection than that in control patients, and proposed that *S. stercoralis* infection is a risk factor for cholangiocarcinoma[97]. *S. stercoralis* not only functions as a cofactor for induction of HTLV-1-associated lymphocytic carcinoma, but also, the chronic inflammation and metabolic oxidative stress induced by *S. stercoralis*-derived excretory-secretory products during parasitism may act as cofactors for host tissue injury and may interact with the host and/or activate the host immune response inducing carcinogenesis.

CONCLUDING REMARKS

1. Chronic infection and chronic inflammation contribute to approximately a quarter of all cancer cases worldwide. Cancer development associated with helminthic infections is a multifaceted process that includes numerous mechanisms, but chronic inflammation is a crucial feature that creates a favorable microenvironment for the initiation, promotion, and progression of tumorigenesis and development of neoplasms.
2. Though only a relatively small proportion of the infection-related cancers can be attributed to helminth infections, some helminth infections are very strongly linked with cancers and are significant prompting factors for certain malignancies; and other helminth parasites may have a probable role in growth of some malignancies.
3. Species of blood flukes (*Schistosoma*) and hepatobiliary flukes (*Opisthorchis* and *Clonorchis*) are involved in human neoplastic development and have potential contributions in the process of carcinogenesis. *Fasciola* spp. are rarely associated with neoplastic development.
4. There is limited evidence linking between cestodes and nematodes and cancer. However, this doesn't rule out their possible potential as cofactors of inducing carcinogenesis.
5. Prompt diagnosis, proper handling and preventive measures for those infections can assist significantly to decrease the prevalence of such malignancies.

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