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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.

Contents

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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

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