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REVIEW ARTICLE

The bifacial role of helminths in cancer: Involvement of immune and non-immune mechanisms

Katerina Oikonomopoulou[1], Davor Brinc[2], Andreas Hadjisavvas[3], Georgios Christofi[4], Kyriacos Kyriacou[3], and Eleftherios P. Diamandis[1,2]

[1]Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, Toronto, Ontario, Canada, [2]Department of Clinical Biochemistry, University Health Network, Toronto, Ontario, Canada, [3]Department of Electron Microscopy/Molecular Pathology, The Cyprus Institute of Neurology and Genetics, Nicosia, Cyprus, and [4]Department of Veterinary Services, Ministry of Agriculture, Natural Resources and Environment, Nicosia, Cyprus

Abstract

Infectious agents have been associated with cancer due to activation of pro-carcinogenic inflammatory processes within their host. Several reports, however, indicate that specific pathogens may be able to elicit anti-tumor immune responses that can lead to protection from tumorigenesis or cancer regression. Amongst these ''beneficial'' pathogens are some helminthic parasites that have already been connected with prevention of autoimmune diseases and allergies, immune conditions increasingly associated with cancer. Even though helminths have co-existed with humans and their ancestors for millions of years, investigations of their impact on human (patho)physiology are relatively new and the functions of components that can explain the helminth bi-directional influence on carcinogenesis are not well understood. This review aims to discuss evidence for the helminth-induced immune, genetic, epigenetic, proteomic, hormonal and metabolic changes that may ultimately mediate the potential pro- or anti-carcinogenic role of helminths. This overview may serve future investigations in clarifying the tumorigenic role of the most common helminthic parasites. It may also inspire the development of anti-cancer regimens and vaccines, in parallel to ongoing efforts of using helminth-based components for the prevention and/or treatment of autoimmune diseases and allergies.

Keywords

Cancer, helminths, immunity, infection, inflammation

History

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Abbreviations: AID: activation-induced cytidine deaminase; **APC**: adenomatous polyposis coli; **BCG**: Bacillus Calmette-Guérin; **CXCL8**: CXC ligand 8, also known as interleukin 8 (IL-8); **FDA**: Food and Drug Administration; **GST**: glutathione-S-transferase; **HDAC**: histone deacetylases; **IARC**: International Agency for Research on Cancer; **IBD**: inflammatory bowel disease; **IFNγ**: interferon gamma; **IgG**: immunoglobulin G; **IL-10**: interleukin 10; **Myc**: a regulator gene that encodes for a transcription factor; **NF-κB**: nuclear factor kappa-light-chain-enhancer of activated B cells is a DNA transcription factor; **p53**: tumor protein 53 is a tumour suppressor; **RARβ2**: retinoic acid receptor β2 gene; **KRas**: Kirsten rat sarcoma oncogene; **RET**: oncogene encoding a receptor tyrosine kinase for members of the glial cell line-derived neurotrophic factor family; **RNS**: reactive nitrogen species; **ROS**: reactive oxygen species; **SCFA**: short-chain fatty acids; **STAT3**: signal transducer and activator of transcription 3; **SHE**: Syrian hamster embryo; **T**: Thomsen–Friedenreich mucin-type carbohydrate antigen; **TGFβ**: transforming growth factor beta; **Th cells**: T helper cells; **TLR**: Toll-like receptors; **Tn**: precursor of Thomsen–Friedenreich antigen; **TNFα**: tumor necrosis factor alpha; **Tregs**: regulatory T cells; **TSO**: *Trichuris suis* ova; **VIP**: vasoactive intestinal polypeptide.

Referee: Dr., Morley D. Hollenberg, Department of Physiology and Pharmacology, University of Calgary, Calgary, Alberta, Canada.

Address for correspondence: Dr Eleftherios P. Diamandis, Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, 60 Murray Street, Room L6-201, Toronto, ON M5T 3L9, Canada. Tel: 416 586-8443. Fax: 416 619-5521. E-mail: ediamandis@mtsinai.on.ca
Dr Katerina Oikonomopoulou, Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, 60 Murray Street, Room L6-201, Toronto, ON M5T 3L9, Canada. Tel: 416 586-4800; ext. 8813. Fax: 416 619-5521. E-mail: koikonomopoulou@mtsinai.on.ca

Introduction

Infections and pathogen-induced inflammation have generally been considered to favor carcinogenesis[1,2], taking the blame for an estimated 15.6% of all cancer cases worldwide[3]. Helminths are among the parasites investigated for their adverse carcinogenic effects on their hosts[4,5]. A strong association between *Schistosoma haematobium* and urinary bladder cancer has been historically reported as early as 1911 and confirmed by later reports[6]. The possible relationship

between helminthic infections and cancer also came under the spotlight with the famous observations by Johanes Fibiger on the induction of gastric cancer in rats by the helminth *Spiroptera carcinoma*, that awarded him a Nobel Prize in Physiology or Medicine in 1926[7]. Even though Fibiger's data had been considered highly debatable and contradictory, according to later reports, they clearly inspired thinking about the association of helminth infections with malignancy.

In contrast to promoting cancer, a few reports have also provided evidence that certain types of pathogens can decrease cancer risk or facilitate tumor regression[2]. In this regard, the hygiene hypothesis, which postulates that the rise of allergic and autoimmune pathologies in Western societies is the result of reduced exposure to certain pathogens at a young age[8–13], has also been re-evaluated to explain the increased number of some types of cancer in economically-developed countries[1]. Specifically, helminths have been proposed as playing a central role in the formation of the hygiene hypothesis[14].

Nowadays, the International Agency for Research on Cancer (IARC) recognizes the role of helminths in promoting carcinogenesis[15]. However, reports about their potential anti-carcinogenic role are still sparse. This review promotes the idea that the influence of helminthic infections on their host may occur in a complex and context-dependent fashion that may either promote or inhibit carcinogenesis. Our goal is to overview some of the helminth-induced mechanisms that either directly, or through other pathways, influence cancer genesis or progression. While the balance of the ideas discussed in this review tips in favor of the role of the immune system in the helminth-induced carcinogenic changes, other potential inter-connected or independent mechanisms are also presented and discussed.

Parallel-to-humans helminth evolution and anti-helminth immunity

Several interactions between various microorganisms and the human host have occurred as the human population moved from the hunter–gatherer lifestyle to the domestication of animals and the development of agriculture[14]. Taking advantage of these new settings, some microbes may have evolved to circumvent the host immune response and, therefore, allow progression of their life cycle with minimal harm to the host. In return, some microbes can exert beneficial functions on host physiology (e.g. metabolism)[16]. An example of beneficial microorganisms are the commensals such as lactobacilli and many actinomycetes, including saprophytic mycobacteria, which are relatively harmless microbes that can populate the human body as microflora and affect its (patho)physiology[14].

Helminths have been specifically singled out as organisms that can potentially influence both the host immune system and its metabolism. These worms were inherited by humans from early hominids that existed more than one million years ago and have exerted selection pressure on human populations after the era of animal domestication, which began about 10 000 years ago[14,17,18]. It has been specifically shown that genetic variability of cytokines associated with autoimmunity is correlated with the diversity of an area's parasites, a major portion of which is comprised of helminths[19].

More specifically, the immune response to helminths can involve several innate and adaptive molecular and cellular components[20,21]. Host tissue responds to the parasite at the portal of entry (e.g. gastrointestinal mucosa); innate immune cells (e.g. macrophages, dendritic cells, mast cells), as well as non-immune parenchymal cells respond to parasites by activation of antigen processing/presentation, cell migration and cytokine secretion. Response of local tissue, as well as tissue with specialized immune function (e.g. Payer's patches in gastrointestinal mucosa, draining lymph nodes), leads to engagement of T and B cells[20,21]. The fully developed response to parasites is often characterized as a Th1 or a Th2-type response, presenting as classical or alternative inflammation[20–23]. The overall immune response aims to achieve parasite control and expulsion while, at the same time, regulating host pathology and supporting the pathogen life cycle. This is often achieved by a balanced Th1/Th2 response or by the activation of immune regulatory pathways involving Tregs (e.g. $CD4^+CD25^+Foxp3^+$), as well as immune regulatory cytokines (IL-10, TGFβ)[20–22]. The Th1/Th2 balanced response that is accompanied by an immune regulatory component is often described as a ''modified'' Th1 or Th2 response. The result is an attenuated host inflammatory response, as well as a less effective adaptive immune response.

The actual type of response can vary according to individual species of infectious agents and can also change during the course of an infection. For example, a Th1 response is followed by a Th2 response in *Schistosoma mansoni* and *Echinococcus granulosus* infections; the Th2 response predominates and is essential for worm expulsion in *Heligmosomoides polygyrus*; and a mixed Th1/Th2 response develops in *Trichuris muris* murine infections[21,24]. Disease progression and treatment can also be associated with these changes: for example, in patients undergoing chemotherapy for *E. granulosus*, a Th1 cytokine profile predominates, while in case of a relapse, the profile shifts to a Th2 dominance[25,26]. As discussed below, the host immune response to helminths may be of relevance to cancer, as it may either locally or systemically modify long-term pro-inflammatory or anti-inflammatory conditions, or it may induce or suppress concurrent host anti-tumor immune responses.

Parasite-induced host cancer-related changes

As proposed by the hygiene hypothesis, allergy and autoimmune diseases have been connected to the decreased exposure to microbes and their products in Western societies[8–13]. These allergic and autoimmune pathologies have, in turn, been connected to carcinogenesis[27–32]. For example, autoimmune disease patients have been related to having a higher cancer risk[27,28], while allergic cancer patients are more prone to a favorable disease progression and response to therapy[33]. In support of a more direct linkage between microbe exposure and cancer, and in extension of the original ''immunity-focused'' hygiene hypothesis, recent evidence points to an increased incidence of certain types of cancer in Westernized, economically-developed countries, in higher socio-economic status groups, and in families with decreased daycare attendance or low number of siblings[1,34–37]. It is also

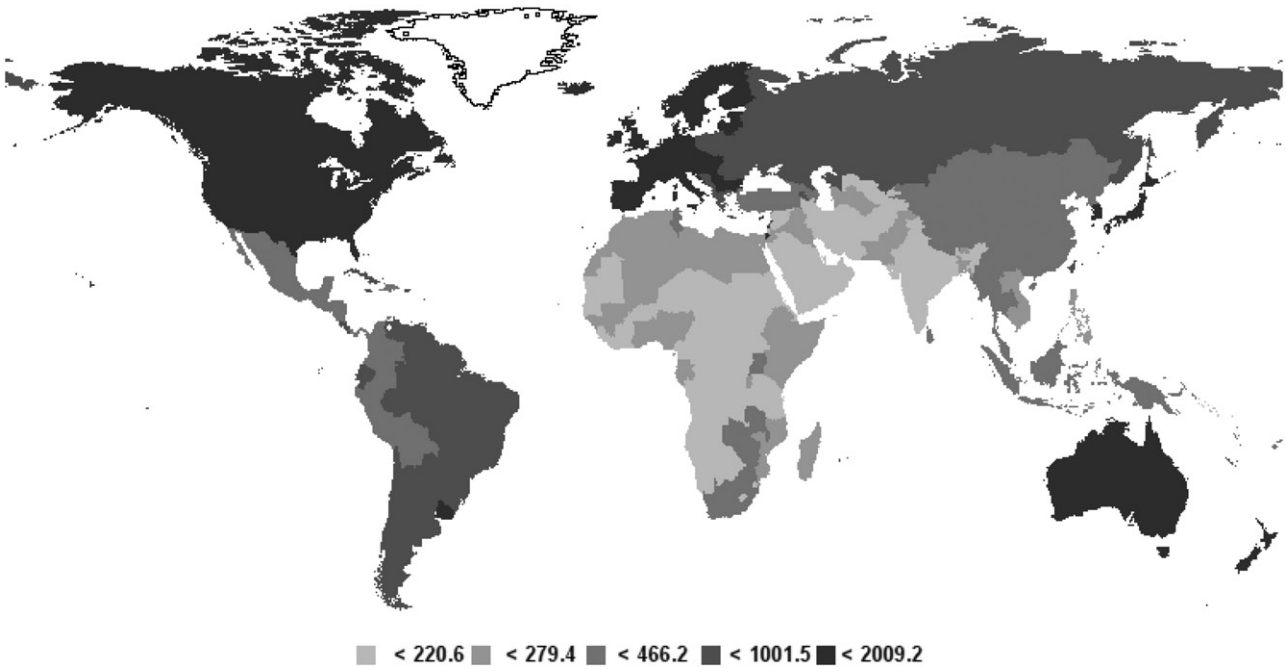

Figure 1. Worldwide cancer prevalence. Estimated 5-year prevalence proportions per 100 000 of all cancers, excluding non-melanoma skin cancer (both sexes, adult population). Source: GLOBOCAN 2008 (IARC) – 7.7.2013[154,155].

noted that some major helminthic infections are reported in areas of the world with decreased prevalence of certain types of cancer such as breast, ovarian or prostate (Figure 1). Although, in the case of a multifactorial disease such as cancer, direct conclusions should not be based merely on such limited observations, it is still an intriguing but overlooked epidemiological phenomenon that merits future investigation.

In principle, the altered immune patterns established during an infection can influence the host ''tolerance'' to cancer genesis, growth and metastasis, changes that can overall translate to an increase or decrease in the number of certain cancer types in pathogen-deprived communities. In this context, a discussion follows on: (a) potential intermediate immune mechanisms that may be involved in the anti- or pro-carcinogenic processes modulated by helminthic infections and (b) other more ''direct'' non-inflammatory pathways through which helminths may modulate carcinogenesis (mechanisms are schematically depicted in Figure 2).

Immune and inflammatory mechanisms

Inflammation

Inflammation can be described as a tissue response to injury, stress or homeostatic disruption, which aims to establish homeostasis but, when left uncontrolled, can lead to a pathology (e.g. autoimmunity, sepsis, fibrosis, metaplasia, cancer[1,38]). Typical helminth-derived tissue lesions suggest inflammatory and, in some cases, already metaplastic changes. For example, fibrosis, muscular hypertrophy, ulcers and urothelium hyperplasia have been observed in *S. haematobium* infections[4]. At the same time, recent studies on carcinogenesis have emphasized several apparent links between inflammation and tumor formation or progression[39]. For instance, an increased risk of colorectal and systemic cancers in inflammatory bowel disease patients and of hepatocellular carcinoma in hepatitis patients, a possible association of obesity-related low-grade inflammation with tumorigenesis, as well as a potential cancer risk reduction during long-term treatment with non-steroidal anti-inflammatory drugs, have been found in epidemiological studies[40–42].

Promotion of anti-tumor immunity

Tumor cell-destructive T cells and antibodies specific for cancer-associated protein and carbohydrate antigens have been described[43–49]. In terms of the type of immune response most effective against tumors, cytotoxic T cells and Th1 T cells have often been associated with anti-tumor effects[50]. There are several possible mechanisms by which helminth infection may promote anti-tumor immunity. Parasites may, for example, have indirect actions by stimulating maturation of antigen-presenting cells, thereby increasing the likelihood of an anti-tumor host response. In a non-helminthic but well-known example, Bacillus Calmette-Guerin (BCG) is successfully used for the treatment of urinary bladder cancer, primarily *via* induction of host Th1-type responses[51,52].

It has also been proposed that cross-reactivity between tumor and helminthic antigens may have an anti-tumorigenic role[53]. In fact, this issue of helminth-tumor antigen cross-reactivity has been documented as a reason for the increased false positive rates of diagnosing infection caused by *E. granulosus*[54], a helminth which has been related to carcinogenesis[55,56]. Notably, antibodies in response to a helminthic infection like *E. granulosus* are known to persist for years after pathogen removal[25,26,57]. One of the most immunogenic helminthic components, the T/Tn antigen (also known as the Thomsen–Friedenreich antigen) is a

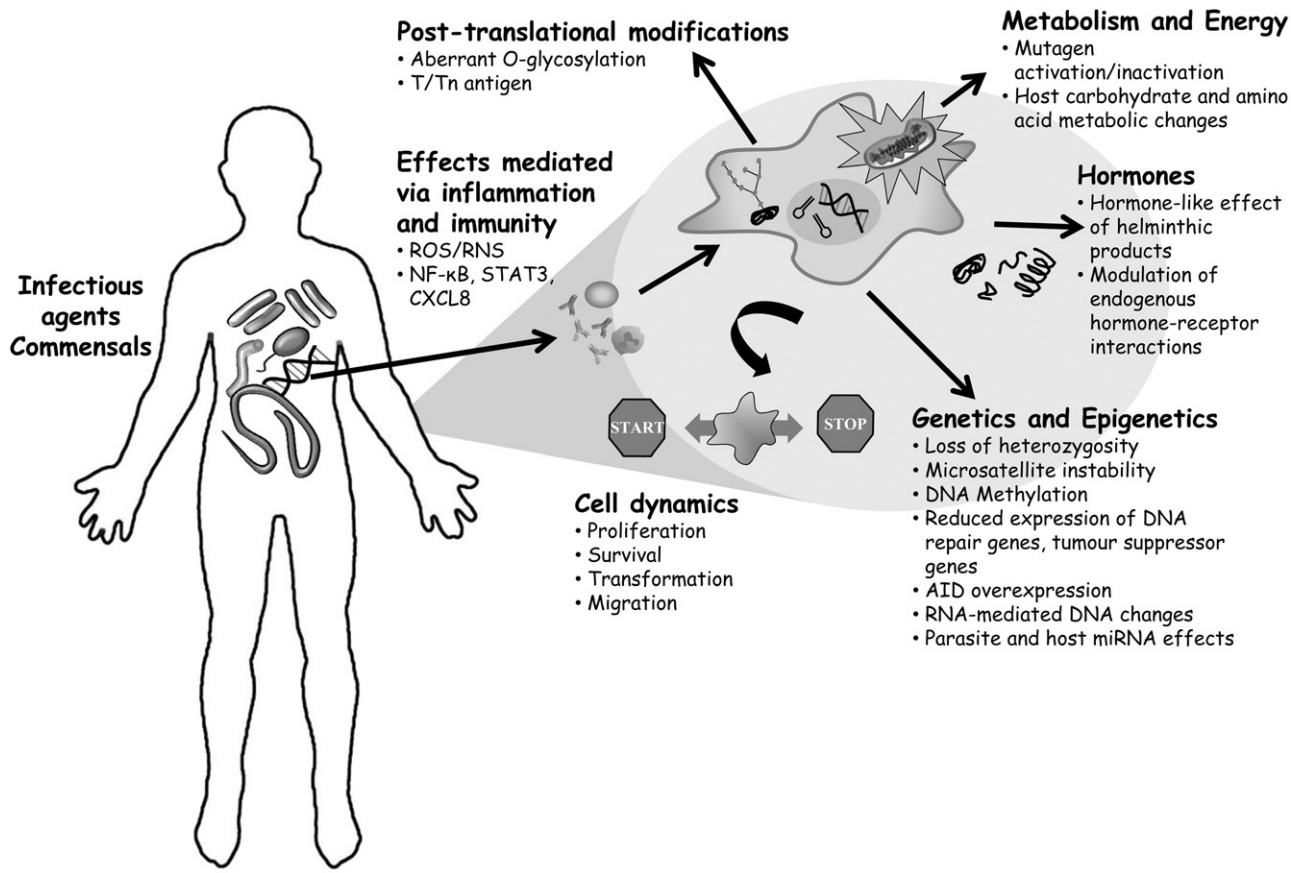

Figure 2. Potential helminth-related processes linked to cancer. A helminthic infection may generate pro- or anti-carcinogenic inflammatory responses and drive immunity in favor of or against a concurrent or subsequent development of a tumor mass. Other alterations at the genetic, epigenetic, proteomic, hormonal and metabolic level may further mediate the beneficial or unfavorable helminthic effects on cancer. AID: Activation-induced cytidine deaminase.

glycoprotein shared by many types of tumors[54,58–60] and expressed more frequently in patients with less extensive malignancy[54]. In support of the potential anti-carcinogenic role of the cross-reactive Tn antigen, experimental vaccination regimens based on T/Tn have been reported successful against breast cancer recurrence[61]. In parallel to the idea of cross-reactivity, the ''concomitant immunity hypothesis'' was suggested to explain the resistance found to the growth of a tumor in animal models previously bearing the same malignant mass[62–64]. Concomitant anti-tumor immunity was considered the result of either immunogenic (e.g. possibly due to the presence of shared antigenic epitopes like the aforementioned T/Tn antigen)[54,58], or non-immunogenic factors (e.g. the presence of putative anti-mitotic components)[62]. The beneficial effect may persist even after removal of the original mass (sinecomitant immunity)[62,64]. However, it should be noted that the presence of an anti-tumor immune response does not by itself prevent or cure tumors, as cancer cells have developed mechanisms to evade the host immunity, such as antigen removal or establishment of an immunosuppressive environment.

Immune suppression

Evidence suggests that a ''functional'' immune system can control spontaneously arising tumors[65–67]. In addition, immune deficiencies are known to increase the predisposition to carcinogenesis[68–70]. Along the same lines, an immunosuppressive environment can be observed in tumor tissues and may be responsible for the limited efficacy of the overall host immune response or of the immune-based anti-cancer therapeutics[71]. Suppression of the immune response is known to be caused by helminths; the effect could be mediated through inflammatory components or directly by specific helminth-derived products[17,20]. For example, helminth cysteine proteinase inhibitors can modify antigen processing and subsequently prevent T and B cell responses, antigen B from *E. granulosus*, diverse lipid and carbohydrate structures can affect T cell differentiation, while cytokine homologues can mimic the effect of host cytokines and reprogram the immune response[20,72,73]. Hypo-responsiveness to unrelated antigens in chronic infections has also been described, probably as a result of activation of immune regulatory pathways[20]. The impact that these immunosuppressive changes may have on carcinogenesis remains an open question, in need of further investigation.

Interactions with concurrent infections

It is known that a persistent helminthic infection can protect the host from a subsequent infection[74]. In principle, during a concurrent helminthic infection, cross-reactive antigens and the overall immune changes may affect the phenotype and survival of other potentially carcinogenic infectious agents in

the human host. Two of the main effects that helminths and the resulting host immune or structural changes may have in terms of carcinogenesis are: (a) to restrict the growth of microbial populations that are potentially carcinogenic and (b) to permit the growth of carcinogen-producing/activating species.

Many helminthic infections can, for example, result in host tissue morphological changes (fibrosis, obstruction, etc.) or offer additional venues for bacterial establishment, all of which may favor the development of local infections or restrict the clearance of endogenous microbial byproducts that can be potentially toxic to the host tissues[4]. In addition, helminths can alleviate the microbially-induced proinflammatory cytokine secretion by secreting IL-10 and TGFβ[75]. They are also known to promote induction of alternatively activated macrophages and subsequent exacerbation of an enteric bacterial infection that results in colitis *in vivo*[76]. Moreover, helminths can make animals more resistant to pathogens sensitive to Th2-like responses and more susceptible to pathogens in which protection depends on a Th1-like response[74]. For example, the Th2-inducing helminth *H. polygyrus* can alter the efficiency of the immune response in removing the Th1-inducing bacterial pathogen *Citrobacter rodentium* in murine models[76]. *Citrobacter rodentium* is known to trigger a transient hyperplastic state that increases susceptibility of the animals to carcinogen-induced tumor formation[77]. Thus, regulation of the host response to certain infections as the result of the helminth-induced immunity can, in principle, have a profound effect on the direction of responses in favor or against carcinogenic stimuli[78].

Changes in microbiome/commensal populations

The human microbiota are known to generate metabolites such as through the digestion of plant polysaccharides, the production of short-chain fatty acids, and vitamin K production, which are beneficial for normal physiology[79–82]. Recent studies have expanded the knowledge about the microbiome effect on the host: for example, microbiome-generated butyrate has been shown to contribute significantly to ATP generation, prevent autophagy, serve as a histone deacetylases' (HDAC) inhibitor, and induce G-protein coupled receptor signaling in mouse colonocytes[83,84]. Any disruption of the microbiota balance can potentially have an impact on the susceptibility of the host to many diseases such as allergies, obesity, diabetes, cancer and other infections[16,85,86]. Specifically, in the case of tumorigenesis, the human microbiome can have a pivotal role in ultimately regulating the pro- or anti-carcinogenic immune response that will decide the fate and establishment of a concurrent cancer cell[87]. Microbes may cause/favor tumors by promoting immune cell transformation (e.g. *Helicobacter pylori* and MALT lymphoma), by causing direct dysplasia/metaplasia of parenchymal tissue, or by triggering inflammation[85]. Altered abundance of individual bacterial species, a condition termed dysbiosis, is known to drive inflammation and inflammation-associated colorectal cancers[88]. Inflammation can, in turn, alter the gastrointestinal environment and cause dysbiosis, i.e. by promoting the presence of tumor-associated microbes (as observed in the mouse model of *Escherichia coli* NC101 and the azoxymethane-treated IL-10-deficient mouse model of colitis-associated cancer[89]). Changes caused in the gut microbiota of mice by obesity have also been shown to increase levels of deoxycholic acid (a bile acid metabolite), which can, upon entering the systemic circulation, reach hepatic stellate cells and induce a senescence-associated secretory phenotype that is characterized by release of inflammatory and tumor-promoting factors in the liver[90]. Moreover, it has recently been shown that bacterial genome integration events into the human somatic cell genome are enriched in certain tumor samples (e.g. acute myeloid leukemia, stomach adenocarcinoma), raising the possibility of a bacterially-mediated genomic influence on host carcinogenic processes[91].

Evidence about the specific effect of helminths on the host microbiota in the case of human infections is still sparse. In principle, helminths, typically a part of the host macrobiome that can also have commensal features, may influence the microbial processes occurring within a host, in a manner similar to what was described about the concurrent infection effect. Preliminary evidence, derived from work on the role of the pig helminth *Trichuris suis*, has reported alterations in the colon microbiota composition and associated metabolism in the precense of the parasitic worm[92]. Major helminth-mediated alterations would be expected at the level of mucosal and systemic immunology that could impact the microflora. Regulating the survival of Th1- or Th2-dependent microorganisms, as mentioned in the previous section, is one example of how helminths may be able to mediate such an effect[74]. Helminths are also suggested to induce the release of inflammatory components (i.e. IL-22) capable of maintaining the mucosal barrier function, therefore, possibly regulating the survival and/or expansion of the mucosal microbiota[93]. In addition, helminths may disrupt host metabolism by modulating the availability of nutrients required by other commensals[94], possibly forcing analogous adaptations to the infectious or host microbiome species (i.e. bacteria thriving in a polysaccharide as opposed to a fatty-diet environment[86]).

A potential helminth-microbiome axis in favor of increasing numbers of beneficial-to-the-host microbial species may also result in tumor prevention (e.g. *H. pylori* has an inverse association with esophageal adenocarcinoma)[85]. Specific microbiota species can also play a key role in production of beneficial food-derived metabolites known to be associated with reduced cancer risk, such as in the case of broccoli[95]. Microbial species can also regulate the metabolic effects of other ''pathogenic'' microorganisms that could otherwise be able to promote carcinogenesis, e.g. by causing an increase in the conversion of pro-carcinogens to carcinogenic molecules *via* secretion of bacterial enzymes like β-glucuronidase[96]. Products of bacterial metabolism may also regulate the host immune system against carcinogenesis. For example, a recent study shows that microbially-induced short-chain fatty acids (SCFA) can stimulate Tregs, an event which may prevent chronic inflammatory conditions in the gut[97]. The relation of helminthic infections with these potentially anti-carcinogenic microbial species should be delineated in the future.

The aforementioned potential helminth-mediated impact on human microbiome/commensals and its subsequent pro- or

anti-carcinogenic complications may take place on sites closely associated with the microbes (e.g. GI tract, oral cavity, liver). A systemic or paracrine effect on other sites, in the case of carcinogenesis, may involve different mechanisms such as control of overall immunity or hormonal levels. These potential distal pro- or anti-carcinogenic effects remain to be proven.

Dependency on microbial load

The impact of microbial infections or commensal species on the carcinogenic alterations in the human host may also depend on the microbial load. The term ''hormesis'' assumes that an agent can have both a beneficial and an unfavorable effect depending on the dose[98], and it has been suggested that the microbially-induced benefits described by the hygiene hypothesis is one example of a hormetic effect on human hosts[99]. In support of this idea, it has been reported that a higher level of infestation by *S. haematobium* can lead to multiplication of the patients' risk for bladder cancer[4]. Further, the spectrum of hyperplasia, metaplasia, dysplasia and squamous cell cancer has been associated with established (late-stage), rather than early, schistosomal infection[100].

Genomic, proteomic, hormonal and cell alterations

Genetic instability and epigenetics

Genetic and epigenetic changes can be observed in helminth-infected tissues[4]. For example, DNA methylation has been described in *S. haematobium*-infected bladder tissues and tumors, and in *S. mansoni*-infected murine liver[4]. Increased incidence of p53 overexpression was found in colorectal cancer samples from *S. mansoni*-infected patients[101]. Oxidative and nitrative DNA damage was associated with *Opisthorchis viverrini* in the case of cholangiocarcinoma, with subsequent double-stranded breaks and genome instability, as well as tumor suppressor gene promoter hypermethylation and histone ubiquitination and acetylation[102]. Methylative damage was detected in patients with bladder cancer and schistosomiasis (O^6-methyldeoxyguanosine) in tumor and normal mucosa, as well as in infection mouse models[103,104]. It should be noted that methylation DNA damage has been suggested to result from anti-schistosomal drug treatment *in vivo* and be affected by the extent of formation of alkylating intermediates[105]. N-nitroso compounds, derived from environmental sources or due to bacterial infection and formation of infiltrating leukocytes, which have been linked to both schistosomiasis and cancer, are known to convert into active alkylating intermediates[106]. Furthermore, promoter hypermethylation of $RAR\beta_2$ and APC genes was detected in schistosomiasis-related bladder cancer patients[107]. In *Taenia solium* infections, that can be associated with brain and hematological malignancies, increased frequency of DNA damage in peripheral blood lymphocytes has been observed[108,109].

The described genetic/epigenetic changes may occur as a result of concurrent helminth-induced inflammation. As an example, ROS/RNS presence and inflammatory cytokine signaling can cause DNA mutations, epigenetic changes and promote cell survival/proliferation, events conducive to tumor cell development[42,110–112]. However, helminths may cause host genome damage *via* other inflammation-unrelated mechanisms. For example, RNA-mediated damage of DNA in *T. solium* infection has been described[4] and *T. solium* cysticerci are known to release an RNA factor that could transform Syrian hamster embryo (SHE) fibroblasts *in vitro*[113].

microRNAs

The functional study of miRNA expression by the different helminth species and their effect on the expression of pro- or anti-carcinogenic host genes and miRNAs is in its infancy. The potential roles of host/parasite miRNAs include pathogen life-cycle progression and host cellular control of pathogens[114–118]. A number of studies, albeit in parasitic protozoa, also show that parasite-mediated changes in host miRNAs may additionally promote inflammation[119].

Altered glycosylation

Post-translational modifications, such as glycosylation, play a role in cell–cell communication and cell adhesion, as well as in modulating the functions of a variety of proteins; altered glycosylation patterns have been described in different pathologies, including cancer[120,121]. The link between specific helminth-induced post-translational modifications, such as the *S. mansoni*-induced aberrantly O-glycosylated apolipoprotein C-III peptides in human urine[122], and their effect on host pathology are not well studied in helminth infections.

Metabolism, enzyme dysregulation and energy

Changes in metabolizing enzymes such as N-nitrosodimethylamine-N-demethylase (NDMA), cytochrome b5 and glutathione-S-transferase (GST) can be observed in helminth infections. Depending on the role that metabolizing enzymes have in activation or inhibition of a mutagen, an increase or decrease in these enzymes may result in the activation of pro-neoplastic compounds or reduced inactivation of active mutagens[4]. In *S. haematobium* infection, enhanced activation of β-glucuronidase can increase the release of carcinogens in a hamster model[4], while *Schistosoma japonicum*-liver-infected mice show decreased metabolism of mutagens[123]. Evidence from animal studies on the increased carcinogenic role of *O. viverrini* with the combined administration of the carcinogen N-nitrosodimethylamine may also indicate a role for this helminth in regulating the metabolic capacity of the host against this carcinogen[4]. Notably, similar experiments in *Fasciola hepatica* infection models pointed to a bidirectional effect of the microorganism on carcinogenesis, namely promoting carcinogenesis during the acute phase of infection (i.e. by inducing immune or genetic changes) and restricting carcinogenesis during the chronic phase, by inhibiting the activation of the carcinogen in the liver (e.g. N-nitrosodimethylamine-initiated malignant transformation)[4].

Furthermore, changes in endogenous host metabolic functions have been observed in infected patients or animal models. For example, *S. mansoni* infection was associated with changes in urine metabolites *in vivo*, suggesting increases in glycolysis and alterations in the metabolism of amino acids like tryptophan and alanine[124]. Abnormal tryptophan metabolites can also be detected in

S. haematobium infection, while *O. viverrini* infection increases nitrosamine and nitrate production, as well as iron accumulation[4].

Hormonal imbalance

The susceptibility of a host to a parasitic infection is often regulated by endocrine factors, either due to modulation of innate immunity or by hormones having several direct effects on the parasites[125]. Parasites themselves can also cause alterations in functions of the host endocrine system during an infection, i.e. by secreting hormones and neuropeptides or by triggering changes in the host's hormonal levels, influencing host immunity and parasite survival[125,126]. Moreover, hormone–host receptor interactions can be affected during a helminthic infection, as in the case of *Spirometra mansonoides* infection where a growth hormone-like function has been attributed to a compound secreted by the parasite[127]. The evolutionary aim of the parasite–host hormonal interactions is for the microbe to achieve favorable establishment, growth and reproduction at the lowest possible cost for the host[126].

A sustained hormonal modulation as a result of a helminth infection may have various secondary effects on host (patho)physiology at several levels, where hormones can be involved (i.e. development, differentiation, cell growth, etc.)[125]. Hormonal changes induced during the infection may potentially lead to uncontrolled cell growth and sustained pro-carcinogenic signals. Not only are hormones able to alter the immune state of the host[125,126] and affect its responsiveness to a new trigger, but they may also induce pathways typically involved in hormone-dependent carcinogenesis (i.e. endocrine-related tumors like prostate, breast, ovarian, etc.). Another hormonal effect that helminths can potentially have is indirectly *via* their action on microbiota: it has been suggested that certain microbes may modulate host estrogen metabolism leading to enhanced absorption and higher level of estrogen exposure, which may in turn promote tumors in women[85]. Another example supporting the hormonal hypothesis is the case of *O. viverrini*, a helminth that causes cholangiocarcinoma, or cancer of the bile ducts. It is now known that the parasite expresses a granulin-like growth factor that can potentially induce cell growth and development of carcinoma[128]. Trematodes are also known to secrete peptides that mimic vasoactive intestinal polypeptide (VIP) leading to villus pathology and hyperplasia[125]. The relationship between parasite-triggered hormonal alterations and cancer is an intriguing field open to future investigations.

Cell proliferation, survival and invasion

Helminth-derived factors can directly promote host cell proliferation. For example, products from *O. viverrini* are able to stimulate murine fibroblast proliferation[129]. Effects on cell proliferation, survival and invasion potential can, in principle, be mediated by the helminth-induced inflammatory responses as well. Recent studies show that oncogene overexpression and activation in epithelial cells (e.g. Kras, Myc, RET) together with secretion of pro-inflammatory cytokines (e.g. IL-6), chemokines (e.g. CXCL8) and growth factors by epithelial cells, stromal cells, and infiltrating immune cells can lead to cell hyperplasia and transformation[42,130–134]. The NF-κB signaling pathway is shown to be of importance for mediating cell invasion of a metastatic ovarian cancer cell line in a mouse xenograft model, as well as facilitating breast cancer metastasis and survival of castrate-resistant prostate cancer[110,111]. NF-κB activation in stromal, immune and tumor cells may be synergistic for tumor promotion. For example, NF-κB activation in myeloid cells leads to IL-6 secretion and subsequent induction of STAT3 signaling in pre-malignant intestinal epithelial cells that, together with cell autonomous NF-κB signaling, lead to proliferation and survival of tumor cells in a mouse model of experimentally-induced colorectal cancer[111]. In some models, however, autonomous NF-kB signaling can promote survival of host cells, which results in preventing compensatory proliferation that would otherwise lead to pro-tumorigenic functions. Finally, some of the receptors and pathways classically involved in inflammation may have inflammation-independent roles in tumorigenesis. For example, TLR2 signaling can promote cell proliferation and tumorigenesis independently of its role in inflammation[135].

Anti-inflammatory helminthic therapy as a paradigm for cancer therapeutics

Given the diverse actions of helminths and their involvement in a variety of diseases ranging from immune pathologies to cancer, the therapeutic manipulation of the ''beneficial'' helminthic species in clinical practice seems an intriguing idea. Several components of parasitic helminths are already under discussion for the treatment of immune and allergic pathologies such as Crohn's disease, ulcerative colitis, allergies, multiple sclerosis, inflammatory bowel disease, and more recently autism[72,136–139]. Of those, attention is drawn to *Trichuris suis*, a pig pathogenic helminth that is not a natural parasite for humans but can still induce immune changes in the human host[139]. Several trials have sought to evaluate the efficacy of *T. suis* parasitic eggs (known as *T. suis* ova or TSO) in the treatment of allergic and autoimmune diseases.

In one of the trials, a randomized controlled protocol was performed in 54 patients with severe ulcerative colitis (by means of index score >4)[140]. One group of 30 patients received 2500 *T. suis* ova orally at 2-week intervals for 12 weeks, while the remaining 24 patients were included in the placebo group. Improvement of the disease activity index score occurred in 43% of patients under the helminth treatment as opposed to 17% of control subjects ($p = 0.04$). The study also reported no significant side effects of the parasitic treatment.

The safety of TSO for use in clinical practice was specifically addressed in other similar trials; overall these studies, referring to the management of multiple sclerosis, allergic rhinitis and food allergy, showed that patients experienced mild-to-moderate gastrointestinal side effects and mild eosinophilia[141–144]. Notably, these effects were not observed in the inflammatory bowel disease (IBD) studies (e.g. ulcerative colitis; see above)[140,145,146], a difference that has been attributed to sample preparation variations, concurrent patient treatments and the characteristics of IBD (i.e. gastrointestinal symptoms)[139].

Many potential mechanisms that may facilitate the beneficial action of *T. suis* have been discussed, including alterations in the commensal populations and regulation of specific immune components (e.g. Tregs or dendritic cells), critical for the helminth-triggered Th2 responses and immune tolerance[139]. Even though the exact processes are largely undiscovered, these trials can serve as an efficient and safe paradigm for developing equivalent cancer therapeutics, under the idea that several of the helminth-induced immunological responses may have the ability to regulate cancer genesis or progression.

As supportive evidence for the potentially favorable therapeutic efficiency of helminths in cancer treatment, studies have pointed to a role for the shared helminth-tumor T/Tn antigen; these antigens are structurally similar to the blood type A glycoprotein and can be expressed in normal tissues, albeit at lower levels compared to malignant cells[147,148]. Despite the non-specific expression of T/Tn antigen, vaccinations based on the T/Tn antigen have been reported to be effective in preventing breast cancer recurrence, an outcome that could be explained as the result of potential anti-tumor immune responses, elicited due to the increase of helper T lymphocytes and the decrease of T suppressor/cytotoxic cells ratio[61]. There has also been an interest in the use of Tn antigen in the management of prostate cancer patients with, however, limited applicability thus far possibly due to the inconsistent expression of this antigen on prostate tumors[149].

The idea of using an infectious agent for the management of cancer patients is not new and resembles the idea behind the BCG vaccine and the William Coley's toxin regimens. The BCG vaccine contains an attenuated form of *Mycobacterium bovis* that is now a formulated FDA-approved vaccine for the first-line intravesical treatment of bladder cancer[51,52]. It has been hypothesized that the anti-cancer effects of the vaccine enhance the host Th1 cytokine production (e.g. IFN-γ, TNFα)[150,151]. Similar preliminary efforts by William Coley took place in the 1900s using an attenuated bacterial mixture (*Streptococcus pyogenes* and *Serratia marcescens*) for the management of cancer patients, an effect that was attributed to the potential action of TNFα[152,153].

Given the tight immune interconnections of helminthic infections with their hosts, as well as the links between cancer and inflammatory conditions that can be treated using helminthic components and the anti-carcinogenic actions of the BCG and Coley's regimens, the role of helminths in the modulation of carcinogenesis (both in favor and against) should witness intense future translational research.

Conclusions and future perspectives

Helminths have been a part of the human evolutionary environment for millions of years. Both the current parasites and the human host may thus have inherited features allowing more ''symbiotic'' rather than parasitic relationships. Even though microorganisms are known to generally have both protective and unfavorable effects in the human host, the specific role of helminths in cancer is only now starting to unravel. Despite the plethora of evidence, discussed in this manuscript, pointing to the carcinogenic impact of parasitic agents like helminths, we aim to draw attention to the often neglected beneficial effects that relatively benign organisms like some helminths can have, as dictated by the supporters of the original hygiene hypothesis. We believe that some helminth-triggered effects and, more specifically, immune-mediated changes, can be beneficial for cancer prevention/regression in the host and should be investigated in more detail in the future.

Clinical trials using helminths in the treatment of allergies and autoimmune pathologies are currently ongoing and cancer therapeutics can also benefit from these novel mechanistic and clinical studies since the findings can potentially provide insights into the role of helminths in modulating the host immune response towards cancer prevention. For example, explorations of the adjuvant and cross-reactive effects of these organisms, as well as their immune functions, have the potential to lead to therapeutic regimens, analogous to the T/Tn vaccination studies discussed in earlier sections, in order to prevent, regress or slow down cancer progression or to improve quality of life for cancer patients. As helminths may be part of the human macrobiome or influence commensal bacterial populations in the human host, it is also important to highlight the possibility of developing personalized treatments for cancer patients, based on their individual spectrum of commensal species in order to maximize the therapeutic benefit in cancer clinical practice.

Acknowledgements

Due to space limitations, we apologize for not citing more reviews and original papers related to this topic.

Declaration of interest

The authors report that no conflicts of interest exist.

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