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# *Toxoplasma* and Cancer: Friends or Faux? Uncorking the Paradox

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## ABSTRACT

Cancer is a life-threatening disease that occurs because of the uncontrolled proliferation of cells in any organ or tissue of the body. An obligate intracellular protozoan, *Toxoplasma gondii* (*T. gondii*), reproduces only after invading host cells. Some studies elucidated that there is a high seroprevalence of *T. gondii* in various cancers. *T. gondii* was linked to several types of malignancies such as leukaemia, lymphoma, myeloma, glioma, meningioma, neuroblastoma, breast and ovarian tumours, and lung cancer. On the contrary, other studies reported low titres of anti-*Toxoplasma* antibodies with a state of resistance to cancer. The current research focuses on the use of the auxotrophic mutant of *T. gondii* in the treatment of the most aggressive malignancies like melanomas, cancer pancreas, lung carcinoma, and ovarian cancer. This manuscript reviews how *T. gondii* can promote cancer, the anti-cancer effects of *T. gondii* and the possible mechanisms of these effects.

**Keywords:** Anti-cancer; Cancer; immunotherapy; *Toxoplasma gondii*

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## Introduction

In accordance with GLOBOCAN 2020, there are currently an estimated 19.3 million new cases of cancer worldwide [(1)]. Globally, the burden of cancer mortality is escalating, and as a result, 11 million deaths are anticipated to be attributable to cancer by 2030 [(2)].

Cancer development is a sophisticated multi-factorial process called carcinogenesis, where genetic predisposition, microenvironment, and lifestyle all seem to have a big impact. Infectious diseases also can influence the development of cancer. Moreover, infectious diseases can modulate cancer development [(3)].

### Hallmarks of cancer

The hallmarks of cancer are indeed a combination of eight biological properties attained during the multi-step genesis of human tumours [(4)].

The eight cornerstones of cancer entail (Fig.1) “the acquired capabilities for sustaining proliferative signalling, evading growth suppressors, resisting cell death, enabling replicative immortality, inducing/ accessing vasculature, activating invasion and metastasis, reprogramming cellular metabolism, and avoiding immune destruction. In the most recent elaboration of this concept, deregulating cellular metabolism and avoiding immune destruction were segregated as "emerging hallmarks"” [(5)].

Complex multifactorial pathways, such as the establishment of a sustained inflammatory processes that ignites pro-oncogene and culminates in oncogenic mutation, release and build-up of toxic ammonia and genetic products during infection, are supposed to stimulate pathogen-based tumorigenesis. In addition, some microorganisms can disrupt T-cell activation, which consequently ends with increased inflammation [(6)].

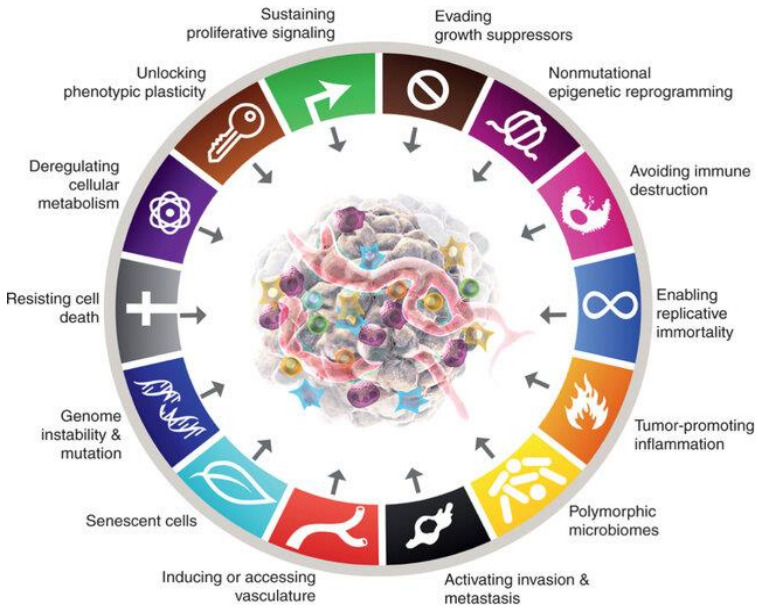


**Figure 1**. "The hallmarks of cancer. Figure adapted from Hallmarks of Cancer: New Dimensions" [(7)].

## Oncogenic parasites

Globally, 15% of cancers are a result of infection with oncogenic pathogens which comprise certain viruses, bacteria, fungi, and parasites. Moreover, in some cases, co-infection with multiple microbial agents is proposed to greatly enhance carcinogenesis [(8)].

Currently, certain species of trematodes are accused of specific types of malignant tumours in humans. For instance, cholangiocarcinoma is caused by the liver trematodes "*Clonorchis sinensis* and *Opisthorchis viverrini*". Also, various cancers are initiated by blood flukes which include "*Schistosoma haematobium*" (urinary bladder carcinoma), "*Schistosoma japonicum*" and "*Schistosoma mansoni*" (colorectal and hepatocellular carcinoma). The first three aforementioned species have been designated as Group 1 carcinogens by the International Agency for Research on Cancer (IARC) [(9)].

## Parasites as cancer-negative regulators

Regardless the breakthrough in cancer detection and therapy, cancer has remained a serious health issue and one of the world's leading causes of death. Successful treatment of cancer is a big enigma, owing to the distinct pathophysiology and the predictable emergence of resistance. Conventional treatment modalities including chemotherapy, radiotherapy and immunotherapy all have their own demerits [(10)].

Cancer is a great challenge of the 21st century. Therefore, it is crucial to find novel, more potent therapies. Immunotherapy, which uses specific types of microorganisms, is one of the most promising research areas. The immune system is anticipated to be stimulated by this form of treatment to target and selectively eliminate cancerous cells [(11)].

Although inflammation induced by pathogens can contribute to cancer, science has the power to change the situation and incorporate microbes as part of the treatment plan. The capability of infections to inhibit neoplasia has long been well evidenced and was first observed by Dr William Coley in the 1890s when he noticed that patients had remission of their tumours when they contracted bacterial infections [(6)].

There are certain antigens that both parasites and cancers share. There is a lot of scientific evidence to show that the parasites have an important anti-cancer effect in animal models and in vitro studies. In recent decades, cancer immunotherapy research has focused on "*Echinococcus granulosus* (*E. granulosus*), *Toxoplasma gondii* (*T. gondii*), *Trypanosoma cruzi (T. cruzi)*, *Plasmodium* spp., and *Trichinella spiralis (T. spiralis)*" [(11)].

The anti-cancer properties of "*T. cruzi*" has been postulated to be via inhibiting angiogenesis, reviving the immune response, and inducing apoptosis in some cancer cell types. By contrast, "*E. granulosus* and *T. spiralis*" possess different mechanisms to combat cancer, for example by activating the innate immunity and

immunosuppressive impact on transformed cells or by regulating invasion and metastasis as well as conveying antiproliferative signals [3].

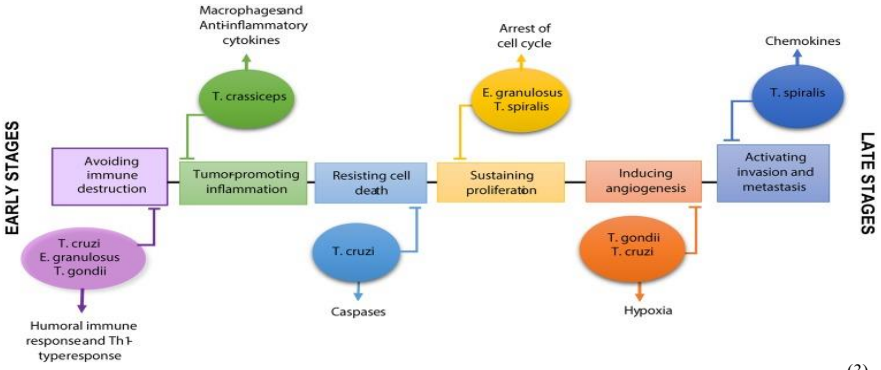


**Figure 2.** Parasites with therapeutics targeting the hallmarks of cancer. [3]

## *Toxoplasma gondii* as a cancer promotor

Evidence of exposure to *T. gondii* is found in nearly 30% of the human population worldwide. (13) *T. gondii* prevalence, estimated by serology, varies widely across the world: for example, there can be a high prevalence level of nearly 90 % in very endemic areas like parts of Africa; but it is 60 % in some European populations [12].

*T. gondii* was linked to myriad types of malignancies including leukaemia, lymphoma, myeloma, glioma, meningioma, neuroblastoma, breast and ovarian tumours, and lung cancer [13].

To assess the global seroprevalence of *T. gondii* among cancer victims, a meta-analysis was performed. It revealed that the pooled seroprevalence of *T. gondii* infection among patients with cancers worldwide was 30.8% (95% CI=26.3–35.6). Based on the type of cancer, the pooled prevalence was as follows: Breast cancer 81% (95% CI: 72–89), lymphoma 49% (95% CI: 27–70), leukaemia 35% (95% CI: 22–49), and hepatocellular carcinoma 24% (95% CI: 21–28) [2]

A meta-analysis conducted in 2016 revealed potential evidence of a link between *T. gondii* infection increased risk of leukaemia acquisition [14].

It is not clear how *T. gondii* initiates neoplasia. *T. gondii* latent infection can boost the host's inflammatory responses. This enhances mutations which can be a factor in cancer development [15].

Furthermore, *T. gondii*, as an intracellular parasite, could inhibit apoptosis. The common framework needed for the evolution of neoplasia might be established by these phenomena together with dysregulating cell proliferation. In addition, by exporting *T. gondii* miRNAs into the host cell, which may lead to the development of cancer, the regulation of host gene expression can be altered [16].

In two human cases with primary intraocular B Lymphocyte lymphoma, The DNA of *T. gondii* has been found in tumour cells by performing PCR. The authors assumed that by promoting inflammation, *T. gondii* can induce cancer [17].

## Can non-replicating *Toxoplasma* be used for cancer therapy?

A significant proportion of cancer patients have benefited from a major advance in immunotherapies over the next few years because of an emerging era of immuno-oncology [18].

It is well established that toxoplasmosis elicits a potent protective T helper 1 ($Th^1$) immune response, which in turn triggers T-lymphocytes to produce interferon-γ (IFN-γ), interleukin-12 (IL-12), tumour necrosis factor-α (TNF-α). This cell-mediated immune response shields the host against pathological lesions and prevents tachyzoite multiplication, while the humoral immune response prevents reinfection with the parasite [14].

The administration of an avirulent strain of *T. gondii* intratumorally in a melanoma murine model induced an immunogenic effect that could trigger the antitumor immune response, facilitated by CD8+ T cells and NK cells, as well as upregulation of MHC-I and MHC-II molecules on antigen-presenting cells (APCs) [19].

*T. gondii* is nearly a 6-µm long eukaryotic microbe in the form of a bottle with unique secretory

organelles called micronemes, rhoptries, and dense granules [20].

Researchers have been deciphering the precise *Toxoplasma* effectors involved in the activation of the host anti-tumour immunity. Previous studies have shown a high tumour-targeting activity in mice and rat when vaccinated with *T. gondii* lysate antigen (TLA). TLA can also intramuscularly injected to suppress the growth of the chemically induced (20-methylcholanthrene-induced) tumour cells [21].

Being an obligate intracellular microbe, *T. gondii* reproduces only after successfully invading a host cell. Via blocking the de novo pathway of pyrimidine synthesis, the synthesis of uridine 50-monophosphate (UMP) could be halted. It is required for the synthesis of RNA and DNA. *Toxoplasma* is now a uracil auxotroph. Although they do not multiply, auxotrophs enter host cells to create parasitophorous vacuoles [22].

Dendritic cells and monocytes/ macrophages are two innate myeloid cell types that *Toxoplasma* preferentially invades in living hosts. Following immunization with Non-replicating *Toxoplasma* uracil autotrophs (NRTUAs), the selective targeting of myeloid cells for invasion is also seen [10].

The current research focuses on utilization of the uracil auxotrophic carbamoyl phosphate synthase mutant *T. gondii* (CPS) in the treatment of some of the most aggressive malignancies. Following administration, a significant rise in the level of IL-12 which plays a bid role in suppressing angiogenesis, resulting in hypoxia and diminished cancer growth [23].

## Concluding remarks

As stated above, the debate is still ongoing. Theoretically speaking, *T. gondii* is assumed to induce carcinogenesis via a sustained state of inflammation, hence oncogenic mutations are compiling. On the contrary, cancer resistance was linked to low doses of asymptomatic infections. On the other hand, anti-*Toxoplasma* antibodies could interact with murine breast cancer cell lines indicating the existence of shared epitopes thus enhancing the putative antineoplastic activity of *T. gondii*. Questions remain to be answered in more and more future studies regarding the molecular mechanisms of both carcinogenicity and antitumor therapeutic potential by *T. gondii*.

## Authors' contributions

All authors have contributed to the conception and design of the review article and have been involved in writing the review article and/or revising its content.

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## Declaration of interest

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