

Infection and Cancer: Reevaluation of the Hygiene Hypothesis

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Abstract

Several studies have shown that persistent infections and inflammation can favor carcinogenesis. At the same time, certain types of pathogens and antitumor immune responses can decrease the risk of tumorigenesis or lead to cancer regression. Infectious agents and their products can orchestrate a wide range of host immune responses, through which they may positively or negatively modulate cancer development and/or progression. The factors that direct this dichotomous influence of infection-mediated immunity on carcinogenesis are not well understood. Even though not universal, several previous reports have investigated the inverse link of pathogen-induced "benign" inflammation to carcinogenesis and various other pathologies, ranging from autoimmune diseases to allergy and cancer. Several models and ideas are discussed in this review, including the impact of decreased exposure to pathogens, as well as the influence of pathogen load, the timing of infection, and the type of instigated immune response on carcinogenesis. These phenomena should guide future investigations into identifying novel targets within the microbial and host proteome, which will assist in the development of cancer therapeutics and vaccine remedies, analogous to earlier efforts based on helminthic components for the prevention and/or treatment of several pathologies. *Clin Cancer Res*; 19(11); 2834–41. ©2013 AACR.

Introduction

Even though the course of carcinogenesis is undoubtedly multifactorial, major attention has been attracted on the role of infectious diseases and the immune system in cancer development (1–4). Several types of carcinomas are related to infections (2, 5), whereas inflammation is recognized as one of the hallmarks of cancer (1, 6), and inclusion of immunologic assessments in cancer classification and prognosis has been suggested (7, 8). In contrast, immune responses, including those triggered by microorganisms, are known to decrease cancer risk or lead to tumor regression. The relationship between infection and tumorigenesis is not well understood, and both favorable and unfavorable immune-mediated or direct anticarcinogenic microbial effects have been observed. This review aims to provide an update primarily on the inverse association between infections and cancer and provide clues for potential underlying mechanisms. Attention is drawn to the hygiene hypothesis that attempts to explain the increased incidence of pathol-

ogies such as allergies, autoimmune diseases, and cancer in the industrial world. Several historical observations and other theories, such as hormesis (9) and concomitant immunity (10), are revisited to lend more credence to the hygiene hypothesis.

The Cancer Hygiene Hypothesis

Several decades ago, the hygiene hypothesis, referring to the lack of exposure to microbes at childhood, was introduced to explain the higher numbers of allergic and autoimmune diseases in the Western world and urbanized communities (11–14). More recently, the hygiene hypothesis has been restated to account for the association between microorganisms and cancer (13). Following the same pattern observed with some immune pathologies, there is growing evidence of an increased cancer incidence in Westernized economically developed countries (15). Socioeconomic status was also inversely associated with Hodgkin lymphoma (16), and daycare attendance was associated with a lower risk of acute lymphoblastic leukemia (17, 18). The resemblance of the hygiene-immunopathology relationship to the one exhibited by hygiene and cancer is not surprising, given that preliminary observations have associated tumorigenesis with chronic immune-mediated disorders (Table 1); for example, an increased risk of cancer has been observed in patients with autoimmune disease (19, 20), chronic allergic disorders have been connected to pro- and antitumor effects (21–24), and allergic patients with cancer have been suggested to exhibit higher cure rates and more favorable disease progression (25). Some experimental evidence may also support the cancer hygiene hypothesis, that is, the antitumorigenic role of several

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Table 1. Association between different pathologies and cancer, based on epidemiologic and experimental studies

Condition	Association with cancer	References
Infections		
Helminths and protozoa	Negative ^a	(13, 58, 80, 93–95)
	Positive ^b	(43, 96, 97)
Viruses	Negative ^a	(57)
	Positive ^b	(2, 5, 13, 98)
Bacteria	Negative ^a	(13, 26, 28, 47, 54–56)
	Positive ^b	(2, 5, 13, 27, 37, 98)
Allergy	Negative ^a	(21–24)
	Positive ^b	(21, 24)
Autoimmune diseases	Positive ^b	(19, 20)

^aNegative: cancer prevention, cancer regression, decreased cancer risk.

^bPositive: cancer promotion, increased cancer risk.

inflammatory components, the ability of some commensals and benign gastrointestinal parasites like helminths to downregulate inflammation, as well as the ability of pathogens and their products to stimulate anticancer immunity (see sections below). However, the hygiene hypothesis, as it stands, cannot rationalize why specific infectious agents (e.g., *Helicobacter pylori*; refs. 26, 27) or microbial products [e.g., lipopolysaccharide (LPS); refs. 28, 29] can exhibit both pro- and anticarcinogenic functions and, therefore, many questions remain unresolved.

Immune Responses to Infection and Cancer

Host immune response to pathogens generally involves effectors preexisting locally in mucus (e.g., immunoglobulin A, antimicrobial peptides, lysozyme) or plasma (natural immunoglobulin M, complement), followed by activation of more specialized innate (e.g., macrophages, granulocytes, dendritic, mast, natural killer cells) and adaptive (T cells, B cells) immune processes, to facilitate clearance of pathogens or reduction of their impact (30). Innate immune cell activation can trigger phagocytosis, release of antimicrobial compounds and proinflammatory cytokines, as well as lead to immune suppression, fibrosis, angiogenesis, and wound healing (31). T cells, following pathogen recognition and depending on the antigen and local environment, develop into CTL or T-helper cells (T_H), namely T_H1, T_H17, or T_H2 cells, mediating different cytokine expression patterns, known as classical (T_H1, T_H17) or alternative (T_H2) inflammation (32). T_H cells also stimulate production of antibodies from antigen-activated B cells. Another distinct cell subtype, regulatory T cells (Treg), particularly observed in chronic parasitic infections (e.g., helminths), have a role

in preventing immune-mediated damage (33, 34). Notably, the immune response pattern can vary during the infection course; in helminth infections, a T_H1 to T_H2 shift is commonly observed in parallel with infection progression, and may also signal the reduced effectiveness of a drug therapy (35, 36).

The various immune processes induced during infection may also be implicated in cancer. In 1863, it was Rudolf Virchow who showed the presence of leukocytes in neoplastic tissue (reviewed in ref. 37). Paul Ehrlich later suggested that the immune system continuously destroys spontaneously arising tumors (immune surveillance hypothesis), work that was updated by the cancer immunoeediting hypothesis, stating that the immune system has a significant role in shaping the properties of an emerging tumor (38, 39). Both innate and adaptive immune cells are now known to localize at tumor sites, with specific cell subsets, densities, and intratumor locations being associated with cancer risk or survival (8). Antibodies against tumor-associated antigens have also been detected in cancer patients' sera (International SEREX Program, The Ludwig Institute for Cancer Research, Uppsala, Sweden). However, although several studies have considered the role of immunity in cancer survival/progression, the idea that an existing infection may further modulate the pro-/antitumorigenic immune effect has been overlooked.

Infection as a Carcinogenic Factor

Some infectious agents can directly influence carcinogenesis; for instance, human papillomavirus protein E7 can bind the retinoblastoma tumor suppressor and the cyclin-dependent kinase inhibitor p21 in infected cells, promoting DNA replication and cell proliferation (40), whereas Hepatitis B virus can induce hypoxia-inducible factor-1 α , stimulating angiogenesis (41). Pathogens may also promote tumorigenesis indirectly (Table 1; refs. 3, 4), by activating cancer-mediating host inflammatory pathways. The helminth *Schistosoma haematobium* can induce urothelial dysplasia and inflammation upon intravesical administration in mice (42) and has been linked to bladder cancer (43). In another example, *Propionibacterium acnes*, found in prostate cancer and benign hyperplasia samples, when cocultured with prostate epithelial cells results in production of pro-inflammatory cytokines, prostaglandins, and activated matrix metalloproteinases, whereas long-term infection leads to anchorage-independent cancer cell growth (44). Inflammation induced by chronic infections may be able to trigger mutations, epigenetic changes, and protein modifications that may lead to oncogene activation and tumor suppressor inhibition (3). Apart from the typical infectious agents, altered intestinal microbiota may also promote carcinogenesis, DNA damage, and cell proliferation via chronic inflammatory processes (45). Secretion of pathogen-induced cytokines may also have a dual role depending on the settings; for example, TNF α can mediate tumor hemorrhagic necrosis and regression (46, 47), whereas, on the other hand, it can promote carcinogenesis if present in a chronic fashion (48).

In addition to giving rise to the inflammation-mediated detrimental effects, pathogens may also promote tumorigenesis by inhibiting host anticancer immunity, for instance, by stimulating production of immunosuppressive cytokines [e.g., interleukin (IL)-10], causing T-cell apoptosis, promoting T-cell subtypes with attenuated antitumor activity (e.g., T_H2), or triggering recruitment of myeloid suppressor cells and Tregs (49–52). Another potential effect on antitumor immunity triggered by chronic infections, also observed in cancer, is the dysfunction and subsequent elimination of antigen-specific T cells, a phenomenon called T-cell exhaustion (53).

Infection in Cancer Prevention

Several observations, reported as early as the 1700s, support the link between infection-mediated inflammation and cancer prevention or regression (Table 1); most notable are the efforts by William Coley in early 19th century to

vaccinate his patients with cancer with an attenuated bacterial mixture (*Streptococcus pyogenes* and *Serratia marcescens*) that accomplished significant cure and favorable progression rates (47, 54). There is also evidence of the antitumor effect of certain microbial products (e.g., LPS) and attenuated pathogen forms [e.g., Bacillus Calmette-Guérin (BCG) vaccine; refs. 13, 28, 55]; more specifically, BCG, vaccinia, or yellow fever virus vaccinations have been linked to melanoma protection (56, 57). In addition, infectious agents have also been inversely associated with cancer (Table 1), as in the case of *Trypanosoma cruzi*, which can result in lower incidence of experimentally induced rodent colon cancer (58). These observations support the protective action of infections, as proposed by the hygiene hypothesis (11–14). In the subsequent sections, we will expand on this discussion by suggesting potential mechanisms that are often underestimated but may likely explain the favorable association of infection to carcinogenesis (Fig. 1).

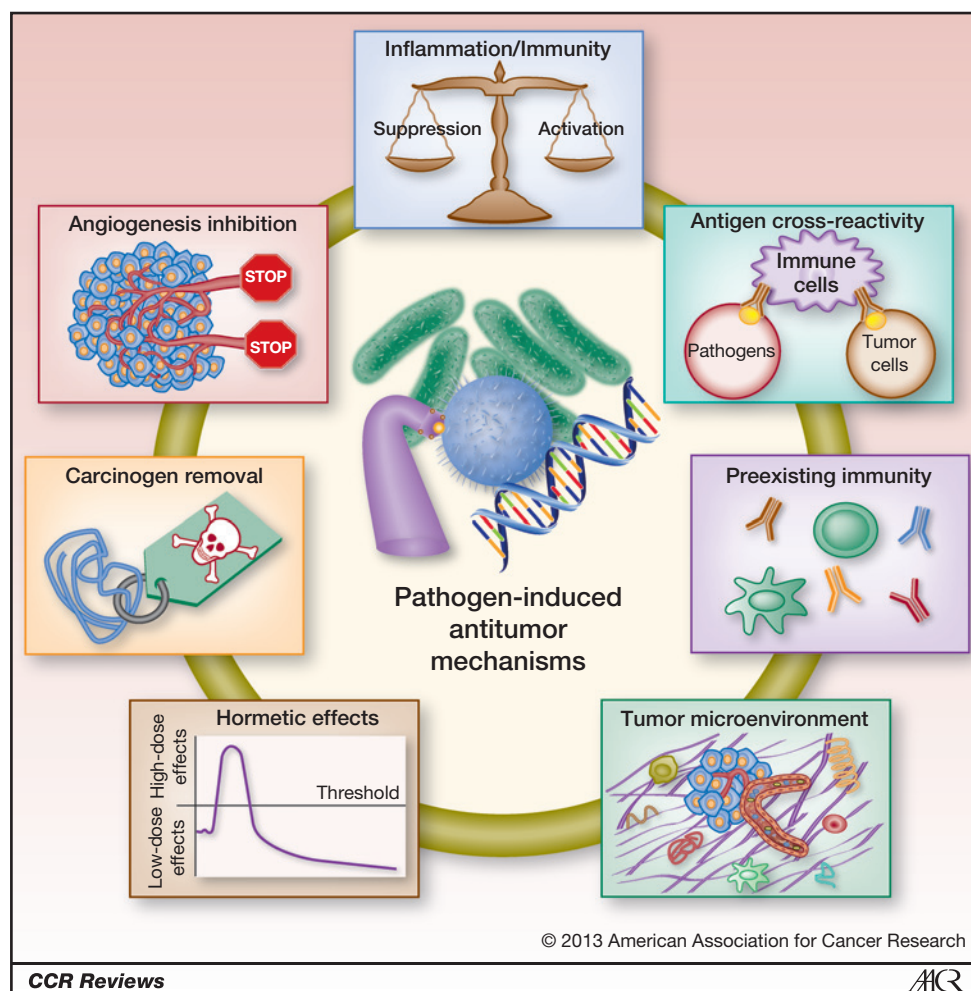


Figure 1. Potential pathogen-mediated antitumor mechanisms. A microorganism may influence the fine balance between immunosuppression and immunity against a concurrent or subsequent tumor by modulating the availability and presentation of cross-reactive antigens, by influencing induction of preexisting immunity, and by shaping the components of the tumor microenvironment. The levels of microbe-triggered stimuli are also decisive factors on the biphasic influence (pro- or anti-inflammatory) that a microorganism can have on immune functions. Several other mechanisms, such as removal of carcinogens and restriction of tumor vascularization may also facilitate the beneficial antitumor effects of microbes on their host.

Suppression of inflammation

Several microbial products (e.g., lysophosphatidylserine) can have anti-inflammatory effects (34, 59); for instance, they can suppress toll-like receptor signaling, inflammatory cytokine and nitric oxide production, as well as inhibit innate immune cell activation and stimulate production of immunosuppressive cytokines and recruitment of Tregs. In this regard, T_H1 or T_H2 responses to some helminth infections rarely result in severe pathology (36) and can, in fact, downregulate allergic or autoimmune pathology (e.g., see ref. 60). However, immunosuppressive cytokines, specifically, have pleiotropic effects on tumorigenesis either by inhibiting inflammation-associated tumorigenesis or by restricting antitumor immunity; for example, IL-10 is known to either inhibit or promote tumor growth, as well as facilitate tumor rejection in mice (61).

Promotion of antitumor immunity

Microorganisms may provide specific triggers (e.g., low-level endotoxin, commonly produced by many pathogens) that increase antigenicity of nascent tumor cells, or keep the immune cells in an "alerted" immunosurveillance state (13). This phenomenon resembles the infection-mediated stimulation of autoimmunity as a result of molecular mimicry, epitope spreading, exposure of cryptic antigens, or bystander activation (62). Epitope spreading has been observed in few cancer vaccine studies, i.e., following injection of dendritic cells in patients with melanoma (63). An infection can also lead to tumor cell destruction, subsequent release of tumor antigens, and activation of antigen-presenting cells. This could potentially trigger T-cell responses with antitumor activities, like the ones that may be responsible for the protective action of BCG (64). Moreover, potential increases in tumor vascular permeability may also facilitate the local recruitment of anticancer T cells (47). Heat shock proteins expressed by stressed cells and found upregulated in virus-infected and several cancer cells can also be immunogenic, thus influencing antitumor responses (65).

Presentation of cross-reactive antigens

Several pathogens contain antigens, mainly glycoproteins, that cross-react with tumor-associated antigens. As an example of such glycoprotein cross-reactivity, the Thomsen–Friedenreich T and Tn parasitic antigens can be detected in more than 80% of patients with cancer and have been under experimental and clinical investigations as markers and therapeutic targets for cancer (66, 67). Furthermore, sera from patients suffering from parasitic infections (e.g., *Echinococcus*) are commonly found to cross-react (contain similar immunogenic epitopes) with sera from patients with cancer (68). Interestingly, it has been observed that such sera are more frequent in patients with less extensive malignancy. Antibodies against these shared parasite/tumor-associated antigens can potentially target tumor cells for destruction or promote antigen presentation to T cells and induce antitumor responses; this antibody-mediated immune enhancement has been observed for nontumor antigens in experimental models (69).

Induction of preimmunity

The "concomitant immunity hypothesis" was originally suggested to explain resistance to secondary tumors or infections, particularly in animal models (10, 70). As an ongoing persistent infection can protect the host from the same infection, similarly, in animal models, immunity to the original tumor can prevent growth of a comparable mass (10, 71). Concomitant immunity was considered the result of either immunogenic factors, for example common antigenic epitopes, or nonimmunogenic factors, such as putative antimitotic components (10). The concomitant effect may be abrogated once the original tumor is removed. It has also been observed that anticancer immunity can be present after the removal of the original malignant mass, a phenomenon termed sinecomitant immunity (10, 71) that can potentially be attributed to the parallel removal of tumor-induced immunosuppression.

Formulation of the tumor microenvironment

In principle, any agent that modulates antigen expression and cell populations in the tumor microenvironment can determine the quality and level of anticancer immunity. For instance, the previously observed effect of Coley's toxin on cancer regression may be the result of $TNF\alpha$ affecting local vascular permeability and enhancing leukocyte recruitment (47, 54). Microorganisms, such as helminthes and commensals, may also contribute to a cancer inhibitory microenvironment by affecting T_H1/T_H2 responses and Tregs recruitment (36, 72). Infection-mediated antitumor immunity can also be restricted by the immunosuppressive microenvironment that is often associated with developed tumors and characterized by T_H2 responses and the presence of myeloid-derived suppressor cells and Tregs (73). Tumor-associated macrophages can also promote angiogenesis, tumor cell invasion, metastasis, and T-cell inhibition. Angiogenesis itself has been related to immune suppression; for example, VEGF may lead to decreased antigen presentation to T cells, due to inhibition of dendritic cells maturation (74). The role of microbial infections in forming the local versus systemic or "secondary" (noninfected site) pro- or anticarcinogenic immune milieu in competition with the immunosuppressive tumor microenvironment remains to be discovered.

Production of low-level "danger" signals

A phenomenon termed hormesis has been coined to describe a biphasic dose-dependent response to an agent characterized by a low-dose beneficial effect and a high-dose inhibitory or toxic effect (9). It can be speculated that microbes, and specifically relatively benign microorganisms and commensals, embody this pleiotropic response by stimulating DNA and tissue repair processes at low infectious agent loads while resulting in extensive inflammatory and genomic changes that can subsequently foster procarcinogenic processes at higher pathogen loads. Interestingly, it has been postulated that the hygiene hypothesis describes this beneficial low-level exposure phenomenon (75). As the hormetic effect would

be highly dependent on spatial and temporal factors, in the case of carcinogenesis, both tumor stage and location at the time of infection may be of paramount importance; the beneficial effects of pathogen-triggered stress repair processes at tumor initiation may, therefore, be replaced by detrimental effects in later stages, when repair may be accompanied by a more immunosuppressive microenvironment.

Removal of carcinogens

The health benefits of bacterially enriched food (probiotics) and certain ingredients that can stimulate growth of indigenous commensal bacteria (prebiotics) have been widely discussed in several settings, including inflammation (76). Although the evidence for the ability of probiotics to reduce risk of colorectal cancer is still controversial, probiotics, particularly containing bifidobacteria and lactobacilli, have been suggested to reduce the production of carcinogens by other gastrointestinal bacteria like clostridia and bacteroides (77).

Inhibition of angiogenesis

It has been suggested that infection can prevent angiogenesis, an effect that may subsequently lead to restriction of tumor growth. For example, despite its potential role in induction of tumor-promoting myeloid suppressor cells (78, 79), *Toxoplasma gondii* infection is also known to suppress vascularization in a mouse melanoma model, an effect that may be attributed in part to secretion of anti-angiogenic cytokines (80).

Cancer Immunotherapy and Pathogen-Based Therapeutics

The concept of using anti-inflammatory agents to regulate not only immune processes but also the tumor load is not new, with the most widely discussed recent example being the benefits of aspirin in carcinogenesis risk reduction (81). The latest approach in immune-related cancer therapy is to promote targeting of specific tumor antigens or stimulate the host immune response to growing tumors using a number of different approaches (82, 83). Several tumor cell antigens, that is, cancer specific, differentiation, viral, and carbohydrate, as well as mutated and overexpressed proteins have been considered as potential vaccine candidates (e.g., see ref. 84). In addition, antibody-based therapeutic agents with reduced immunogenicity have been designed to specifically recognize and destroy tumor cells directly or *via* their specific stromal or immunomodulatory effects (82). T cells have also been investigated in cancer treatment, for example, in patients with leukemia and melanoma (85). In addition, Tregs from mice infected by selected pathogens (e.g., *Helicobacter hepaticus*) have exhibited anticancer activity (86).

In a more microbe-based approach, pathogens and their toxins have been tested as antitumor agents or as carriers for tumor-targeting therapies (87). The concept behind this approach is to use the infectious agent or

its selected components as means to treat/prevent cancer. In this regard, the BCG vaccine, an attenuated form of *Mycobacterium bovis*, is now an U.S. Food and Drug Administration–approved agent for the first-line intravesical treatment of bladder cancer (55). BCG in this context may have a role in stimulating the body's own anticancer immunity via enhancing T_H1 cytokine production (e.g., IFN- γ , TNF α ; refs. 88, 89). Microbial components may also find applicability in preventing cancer, as in the case of the tumor-pathogen T/Tn antigen (90) and the bacterial endotoxin LPS (28). More specifically for the T/Tn antigen, vaccination regimens based on this common microbe–tumor glycoprotein (66, 67) have been previously evaluated in breast cancer prevention (90). Vaccination was accompanied by an increase of helper T lymphocytes and decrease of T-suppressor/cytotoxic cell ratio, possibly leading to regulation of antitumor immune responses and subsequent prevention of breast cancer recurrence.

More recently, the helminth *Trichuris suis* has been under clinical and experimental investigation for its ability to alleviate diseases, such as inflammatory bowel disease (ulcerative colitis, Crohn disease), multiple sclerosis, and allergy (e.g., see ref. 91, 92). Its applicability to cancer pathology, and more specifically to tumors of the gastrointestinal system, is a question open to future investigations.

Conclusion and Future Perspectives

Both protective and detrimental effects of microorganisms have been observed, many of them linked to various immune components. Overall, their effect may depend on the fine orchestration between induction and suppression of cancer-promoting or antitumorigenic immunity as well as on the level of pathogen load and the timing between infection and cancer initiation. In this regard, cancer may be associated with the increased hygiene/decreased exposure to specific microorganisms, similar to what is known for autoimmune diseases and allergies.

That said, it should be noted that not all types of microorganisms are expected to have the same anticarcinogenic effect; for example, viral infections seem to be mainly procarcinogenic, in contrast to bacteria or parasitic worms that have a longer coevolution history with human species and may have, therefore, adapted to exhibit more antitumorigenic effects. Novel clinical studies are therefore needed to delineate the specific role of these relatively benign organisms in modulating the host immune response toward cancer prevention. The adjuvant and cross-reactive effects of parasites and commensals should be investigated in more detail to identify potential novel therapeutic targets. Exploration of the immunogenic epitope availability orchestrated by these agents may also, in the future, assist in the development of personalized treatments and immunization strategies that can be used to prevent, regress, or slow down cancer progression.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: K. Oikonomopoulou, D. Brinc, K. Kyriacou, E.P. Diamandis

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