

Commentary

Understanding Microbe-Induced Cancers

Martin J. Blaser

Abstract Microbes are important causes of human cancers, and our estimation of their significance continues to grow as cancer biology is better dissected. A classification system is proposed that highlights common and proposed microbe-induced pathways toward oncogenesis, with an emphasis on types of targeted cells and host-microbial interactions. The central principles that underlie oncogenesis induced by the many diverse microbes and the major mechanisms involved are outlined. The phenomenon of microbe-induced cancers raises a number of important biological questions, the solving of which may inform other fields, including aging and degenerative disorders. Finally, our challenge for the future is to better understand the steps in microbe-induced cancers to optimize both prevention and therapy.

Microbes induce an estimated 20% of all fatal cancers in humans (1), suggesting the tremendous potential of controlling microbe-related processes for cancer prevention. Pathogenic microbes can be indigenous or exogenous (foreign), although distinctions between these two categories may not always be obvious. Many infectious agents induce cancer (2–7), but the following three types of agents account for most known microbe-related cancer cases in humans: human papilloma viruses (HPV; causing anogenital cancers), *Helicobacter pylori* (gastric cancers), and hepatitis B and C viruses (hepatic cancers; refs. 8–10). The HPVs and hepatitis viruses have provided notable successes of infectious disease control for cancer prevention. A vaccine against infection with HPV-6, HPV-11, HPV-16, and HPV-18 received U.S. Food and Drug Administration approval for preventing cervical cancer (8). In Taiwan, vaccinating children against hepatitis B dramatically reduced hepatic cancer and has been standard preventive care for over 20 years (11). These are the only two established effective interventions in this field to date, however, and work with *H. pylori* has illustrated the highly complex nature of particular microbial interactions that have thus far limited the ability of interventions to prevent the cancers they cause.

Although microbes, especially viruses, had long been known to induce cancers in animals (12), our understanding of the extent of this problem in humans began only in recent decades and continues to expand. I predict that microbes will be found to play a much larger role in malignancies than we understand today, involving as yet undiscovered mechanisms

and malignancies not yet suspected of any relationship with infection.

For example, many people exposed to the major risk factor for lung cancer, heavy smoking, never develop the disease. Investigations of what determines which heavy smokers do or do not develop lung cancer (and differential risk issues in other cancer settings) have focused on genetic differences among exposed individuals. It is becoming clear, however, that our indigenous microbes, the *human microbiome*, which consist of mutualistic or pathogenic, transient, or residential microbes (preponderantly bacteria) that normally inhabit the surfaces of human tissues (e.g., the lumen of the gastrointestinal tract), also may play a role in cancer risk because they are part of our metabolism and our very make-up (13–16). Differences in the genes of the microbes we carry, encoding the microbial constituents expressed, and in the microbial products that interact with us (17) may affect differential susceptibility to disease (e.g., affecting hormone homeostasis and downstream cancers; refs. 18, 19). In a parallel fashion, varying exposures to microbial agents could modulate lung cancer risk among hosts of similar smoking status. Therefore, the “microbial” genotype of a host may be as relevant to disease risk as is the host’s own “human” genotype (13–16). Underscoring this issue, investigators have just discovered a previously unknown agent called the Merkel cell polyomavirus and evidence of its potential etiologic link with Merkel cell carcinoma, one of the most aggressive forms of skin cancer (20).

In addition to inducing cancer, microbes also may influence the course of an established cancer (or may both induce and influence a particular cancer). Although there may be a fine line between these microbial actions, exploring this distinction may help in developing interventions for treating as well as preventing microbe-associated cancers.

Despite important advances of the past decades, we are still at the early stages of understanding the processes of infection-linked carcinogenesis, and the goal of this report is to highlight some of the major concepts that govern the field. The cancer prevention successes of the hepatitis B and HPV vaccines highlight the importance of translating discoveries on

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the specific biology, immunology, and epidemiology of an oncogenic microbe into new preventive initiatives.

Classification of Oncogenic Microbes

Many microbes, including viruses, bacteria, and helminths, have been implicated in the causation of cancers, and many more surely will be discovered. Rather than reviewing each of the known agents, this article will develop a schema for classifying oncogenic interactions, both known and those that may be found in the future, with the goal of providing a conceptual framework to better understand and thus facilitate research of microbe-induced cancers. The proposed system includes three major classes of relationships (Fig. 1).

Class A microbes target cells that are central to host immunity and thus can promote lymphomas and related disorders and/or immunosuppression that can facilitate other microbe-induced cancers (as well as infections). Examples of class A agents include human T-cell lymphotropic virus type 1, which promotes adult T-cell leukemia/lymphoma (refs. 5, 6; Table 1), and HIV, which strongly promotes lymphoma development and, through immunosuppression, other microbe-induced malignancies including human herpesvirus 8-induced Kaposi's sarcoma and HPV-induced anogenital cancers (7).

Class B agents promote malignancies through their direct relationships with the parenchyma, whether epithelial, endothelial, or mesenchymal. These interactions typically generate host responses, and the combined effects of these microbial-host interactions lead to metaplasia and dysplasia that can promote malignancies. The numerous examples of class B processes include carcinomas due to the hepatitis viruses, *H. pylori*, and helminths (such as *Clonorchis sinensis* and schistosomes; refs. 4, 21). Host responses to these organisms also can promote the emergence and development of malignant lymphoid clones (22), as occurs with the mucosa-associated lymphoid tissue lymphomas that can be induced by *H. pylori* (ref. 23; Fig. 1).

I postulate the existence of a third group, or class C agents, with local effects that can lead to either distant or other local effects. For example, *H. pylori*-induced development of atrophic gastritis could lead to repopulation with microbiota that are toxic to gastric tissue and directly oncogenic, or microbiome-induced disturbances in hormonal regulation could lead to cancers distant from the locus of the change. Although no well-established models for class C phenomena have yet been proved, the metabolic activities of the indigenous colonic microbiota potentially could provide a relevant example. Estrogens undergo an enterohepatic circulation, and the estrogen conjugates are substrates for the colonic microbiota (18, 19, 24, 25). For example, perturbations in the complex ongoing metabolism of estrogens could promote the risk of cancers in hormonally responsive tissues such as of the breast, ovary, and endometrium (26–30). Either the blooming or suppression of a particular indigenous organism possessing a critical metabolic activity could change the substrates entering host metabolic pathways. Parallel phenomena involving androgens could promote testicular cancers, which are increasing in incidence (31, 32). The documented relationships between body size, height, and testicular cancer (33, 34) could be mediated by changes in the indigenous microbiota (35). Another potential example of proposed class C-associated phenomena is the markedly increased risk in postmodern societies of esophageal adenocarcinoma (36), which has a clear environmental etiology. Alterations of the acidity or microbiome of the esophagus (37) due to changes in the gastric microbiome (38) could be potential mechanisms for the increased cancer risk (9). As a final note, local changes may influence inflammation at a distant site, with malignant and nonmalignant (“degenerative”) consequences.

All of the recognized microbial agents certainly do not fit neatly into this system of class A, B, and C agents. As noted above, some microbes promote the development of more than one type of cancer (e.g., hepatitis C virus, *H. pylori*, and HIV;

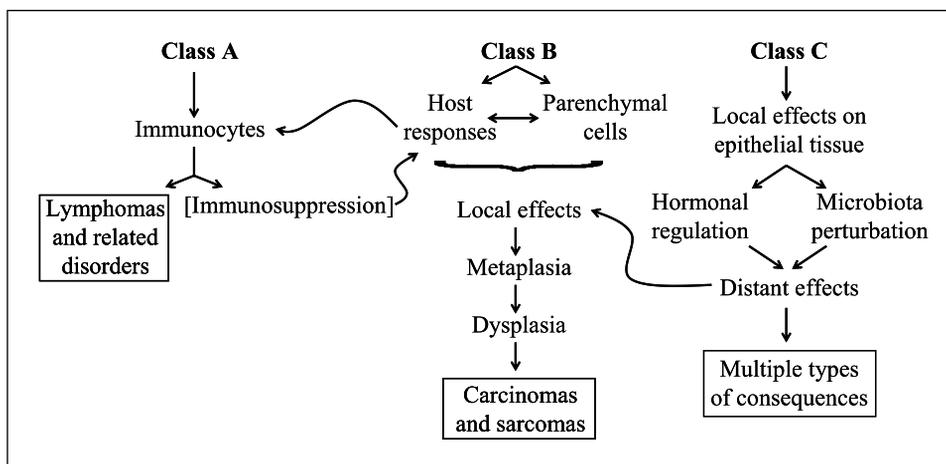


Fig. 1. Three classes of microbes that induce cancers. Class A microbes induce cancers including lymphomas by targeting immunocytes leading to immunosuppression. This immunosuppression also contributes to the cancer-inducing effects of class B microbes, which include local effects on parenchymal cells and induction of host responses. At present, class B microbes induce the most commonly recognized microbe-associated cancers. Class C microbes are a postulated class in which a microbe produces local effects on epithelial tissues that change the regulation of a systemic operator (e.g., a hormone) that promotes cancer at a distant site. Alternatively and/or in addition, some effect on local indigenous microbiota can cause them to react in a way that affects less local microbiota or tissue operators. A class C process might include deranged enterohepatic estrogen circulation due to altered luminal metabolic activities, with consequent effects on tissues. In addition to inducing cancers, class C microbes could induce degenerative processes in distant tissues (e.g., atherosclerosis and neurodegeneration).

Table 1. Classification of microbe-induced human malignancies

Microbe(s)	Examples of malignancies by class		
	A	B	C
EBV	Lymphoma		
HTLV-1	ATL		
HHV-8		Kaposi's sarcoma	
HIV	Lymphoma	Kaposi's sarcoma	
Hepatitis B		Hepatocellular carcinoma	
Hepatitis C	Lymphoma	Hepatocellular carcinoma	
<i>H. pylori</i>	MALT gastric lymphoma	Gastric adenocarcinoma	[Esophageal adenocarcinoma]*
HPV		Anogenital carcinomas, oropharyngeal carcinoma	
Schistosomal species		Bladder cancer	
Liver flukes		Cholangiocarcinoma	
Hypothesized scenarios: microbiome			[Breast, endometrial carcinomas]
ΔMicrobiome [†]			[Testicular adenocarcinoma]
Microbiome		Colon adenocarcinoma	

Abbreviations: ATL, adult T-cell leukemia/lymphoma; HHV-8, human herpesvirus 8; HTLV-1, human T-cell lymphotropic virus type 1; MALT, mucosa-associated lymphoid tissue.

*Brackets indicate that the presence of a specific microbe (e.g., *H. pylori*) or as yet unidentified member(s) of the microbiome may either inhibit or promote the development of the bracketed malignancy.

[†]In addition to metabolic activities of normal members, changes (Δ) in the microbiome also may account for some cancers.

Table 1). The discovery of new agents and mechanisms also may expand this system. However, this classification system provides an initial framework for understanding the types of interactions that do and can occur. Heretofore, the field has tended to approach oncogenic microbial interactions on a case-by-case basis. Thinking about them more systematically not only may advance our understanding but also could facilitate the development of effective interventions against microbe-induced cancers.

Principles of Microbial Oncogenesis

Although the microbial agents and tumors they promote are quite varied, several principles are conserved and can be used to guide future considerations. First, oncogenic microbes generally persist in their hosts for long periods (years or longer). Acute infections may be resolved but also may leave scars that promote neoplasia. This process seems to be exceptional, however. Much more common are persisting microbes that the host cannot eliminate and which engage the host in an ongoing battle that damages tissues (14) and promotes malignancy. For example, squamous cell carcinomas follow the long-term inflammatory consequences of chronic osteomyelitis with sinus tract formation. A group of colonizing organisms rather than a single pathogen has been recognized as provoking this chronic inflammation. Second, variation in oncogenic potential exists within a microbial species. This variation has been well established for HPV, certain types of which cause most cancers, and for the hepatitis viruses and *H. pylori*, in which particular genotypes are most virulent (39–42). Third, microbial load often matters, as illustrated by the hepatitis viruses (41, 42) and schistosomes. Fourth, the interactions between microbial genotype and load may be synergistic, leading to markedly enhanced disease risks (43, 44). Fifth, host

genotypes and phenotypes (e.g., host age and age on acquiring an organism) are part of the microbial genotype-load interaction and modulate risk (40, 45–47). Sixth, because microbes are communicable agents, their prevalence in individuals in a prior generation influences their prevalence in the next. Therefore, secular trends toward intergenerational amplification (of prevalence or virulence) can develop in a population without any known increase in exposure, in contrast to chemical carcinogenesis, for example.

Oncogenic Mechanisms

The array of mechanisms under which microbes become oncogenic can be categorized within four general processes: direct effects on signal transduction pathways in host cells, chronic inflammation, changes in host physiology, and effects on other microbes. These processes are not exclusive because many important microbial agents are known to have several mechanisms belonging to more than one process. An example of the first process (signal transduction pathways) is microbes that invade cells that ultimately are sloughed, which often have a selective advantage if they can delay turnover of the host cell. Microbial promotion of cell longevity could involve inhibition of apoptosis via effects on p53 (2, 3), up-regulation of cell cyclins (48), or effects on stroma (49). The second process, chronic inflammation, promotes neoplasia per se through many mechanisms (50) including increased host cell turnover that increase the probability of mutagenic events and genotoxic effects of reactive oxygen and nitrogen species stemming from inflammation (2, 3, 17). The third process, changes in host physiology due to microbes and the host responses they promote, can occur at a tissue, organ, or cellular level (18, 28, 51). Phenomena such as immunosuppression, hormonal perturbation, and effects on motility in organs where flow is

critical are examples of these physiologic changes. The fourth process, microbes affecting other microbes, can involve any and all of the previously described processes and mechanisms. For example, as cited above, multidecade gastric *H. pylori* colonization often leads to atrophic gastritis, which (besides possibly directly promoting oncogenesis) permits new microbial populations to enter the stomach and play critical roles in the oncogenic process initiated by *H. pylori*. In other words, *H. pylori* may be allowing other genotoxic microbes to invade by facilitating long-term pathophysiologic changes in gastric epithelial biology.

Biological Considerations

Context is all-important in biology in general and with respect to host-microbial relationships in particular. Rather than being fixed, these relationships may exist within a probability envelope. The important context for microbial oncogenesis is provided by other environmental factors (e.g., aflatoxin exposure); the host's age, experiences (e.g., parity), and genotype; and, as we now are beginning to consider, the microbiome genotype. The most consistent and universal factor in this group is host age. Cancer is generally a disease of aging in which rate increases are log linear with each decade of life (52). In this sense, cancer is part of the biological clock that limits human life span, but it ticks differently for men and women.

If microbes are an important part of human cancers, then they also must be a cog in this biological clock. For example, gastric cancer, for which the fraction attributable to *H. pylori* is ~80%, has a strong male predominance (53). The curve of age-specific rate increases for women parallels that for men, but is shifted 15 to 20 years later (53, 54). Paralleling the pattern in atherosclerotic cardiovascular disease, women also have a number of extra years of protection from gastric cancer. Therefore, *H. pylori*-induced progressive aging of the stomach leading to oncogenesis is gender-specific. As life span increases for women and men, cancer rates predictably also will increase, and a proportion of the increased cancers will be due to microbes. A better understanding of host-microbial relationships with regard to selection, symbiosis, and parasitism (14) will facilitate improved microbe-induced cancer prevention and treatment.

That certain cancers run in families usually is ascribed to host genes but also could involve the intra-familial transmission of microbes with particular genotypes. Transmission within families occurs for many indigenous organisms (14) and can resemble inheritance patterns (55). Furthermore, whether a microbe is acquired from a family member (and so is preadapted to the next host) or from a genetically unrelated stranger could modify the risk of a disease that may present clinically decades later (46).

Challenges Facing Cancer Preventive Interventions

Cancer prevention is generally highly complex, and there is no guarantee that a strong knowledge base can make it any simpler. For an exogenous agent such as HPV, a vaccination program provides considerable benefit with essentially no known biological cost (8). For organisms within the human microbiome such as *H. pylori* (13), however, the situation is much more complex. An *H. pylori* vaccine would seem to be

beneficial, but *H. pylori* is deeply interconnected with human physiology (17), and increasing evidence indicates that persons without this microbe have new disease costs including childhood asthma (56) and diseases of the esophagus and gastroesophageal junction, which can lead to adenocarcinoma (9, 57).

If preventing infection is not optimal, then what about eradicating the microbe after infection? Numerous opportunities exist for eradicating *H. pylori* (e.g., with a relatively short course of antibiotics) during the several-decade-long pathogenesis of *H. pylori*-induced gastric cancer. Eradication on a mass basis, too early, and without good biomarkers, however, may have a high cost [e.g., increased risks of childhood asthma (56) and diseases of the esophagus and gastroesophageal junction (9, 57)] in relation to the cancer prevention benefits that are realized decades later (58). The nonspecific effects of antibiotics also highlight the advantage of specificity that vaccines (such as the HPV and hepatitis B vaccines) can have. If eradication is done too late, the point of no return for cancer risk may have passed in many individuals (59). Stratifying populations (60) and developing biomarkers that accurately predict risk (39, 61) are critical to resolving this dilemma.

A third intervention approach is palliation with antioxidants (for example) to lessen the host-microbe interaction. The track record of this approach in diminishing *H. pylori*-induced gastric cancer is mixed (62–64), however, and its specificity is low. In conclusion, it is clear that we must improve our knowledge base to develop creative and ultimately specific, personalized approaches for preventing microbe-induced cancers.

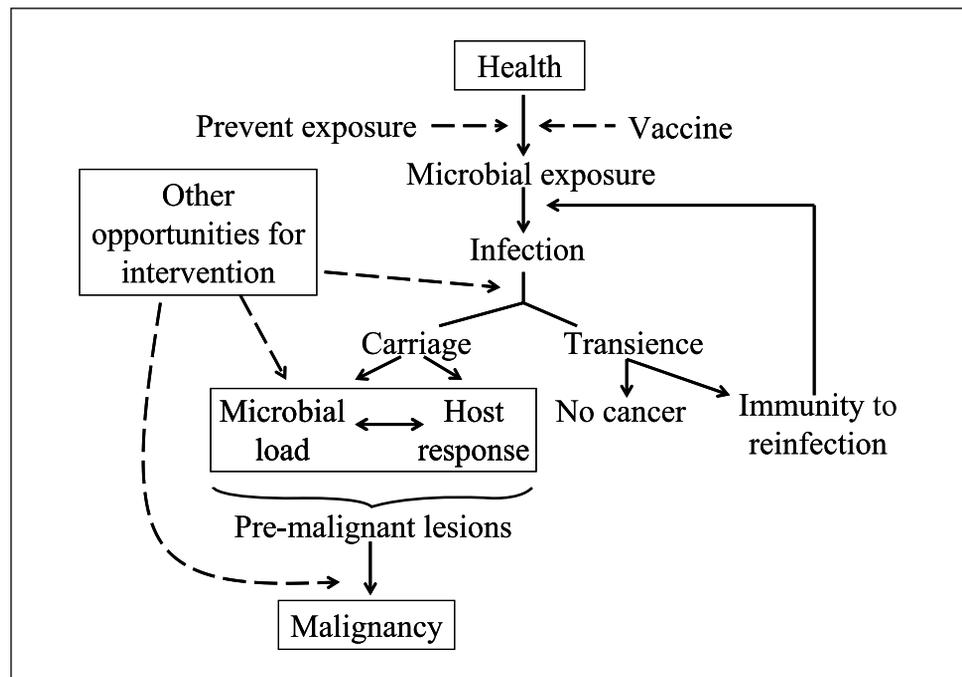
The Future

The multistep nature of microbial oncogenesis (Fig. 2) provides ample opportunities for interventions to mitigate the process and prevent cancer. The best strategy is to prevent infection by preventing exposure to oncogenic agents. Important elements of this strategy include recognizing new agents of potential concern and then preventing exposures to them, either natural or the sometimes very important iatrogenic exposures due to injections and the use of blood and tissue products. Infection also can be prevented by developing vaccines against oncogenic microbes and deploying them to persons at risk before exposure. The HPV and hepatitis B vaccines are examples of specific immune enhancements for cancer prevention.

Important frontiers for intervention after exposure and infection involve ways of influencing the course of an infection toward transience rather than permanence (65). If this approach is not successful, then diminishing microbial load and/or directing host responses down less oncogenic pathways would be desirable. Lowering the velocity of the transition from microbe-related premalignancy to malignancy also could save or substantially extend life.

Accomplishing these goals will require a much better understanding of microbial oncogenesis. Progress in the field will require better clinical diagnostics to identify specific agents, specific microbial genotypes, specific host genotypes, and other critical factors of the host-microbe interaction (61, 66, 67). To eliminate the tendency for certain persistent microbes to push toward malignancies, we will

Fig. 2. Pathogenesis of microbe-induced malignancies and opportunities for intervention. Microbial exposure may lead to infection, which then can lead to long-term, frequently asymptomatic carriage of the microbe with subsequent host responses, progression to premalignant lesions, and finally to cancer. Numerous points in this sequence offer opportunities for interventions (dashed lines) designed to lessen exposure, infection, or the consequences of infection.



need new pharmacologic approaches based on a better understanding of host-microbe interactions. Certain indigenous organisms are symbionts during early life and may be pathogenic in older age, when eliminating these organisms could improve human health. An example of this phenomenon may be *H. pylori* (9, 56, 57), which also could be germane to other commensal bacteria and viruses. Probiotics (“good microbes”) or prebiotics (dietary supplements as substrates to promote the growth of probiotic microbes) could be used pharmacologically to help prevent or ameliorate infections by pathogenic organisms. Improving the understanding of our microbiome should lead to developing better barriers against generally circulating pathogens and to eliminating host-specific pathogens.

The dynamic nature of microbe-induced cancer biology is reflected, in part, by the now frequent discovery of new putative agents (20). Many of the issues outlined in this report are global challenges confronting the prevention of all types of cancers, regardless of etiology. It is certain, however, that following the biology of microbe-induced cancers to understand the microbial actors and their cellular and tissue targets will lead to developing new clinical tools for preventing and treating these cancers. It is hoped that the concepts presented here will enhance our ability to follow this biology.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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