1 | Introduction: The Barrier Theory of Cancer and the Symbiosis Continuum

The barrier theory of oncogenesis integrates cellular protections against oncogenesis with infectious and environmental factors that abrogate these protections (Ewald & Swain Ewald, 2013). It organizes the vast array of information on oncogenesis within a causal framework that distinguishes the small number of barriers to oncogenesis from the many restraints on oncogenesis. Barriers are defined as processes that block the process of oncogenesis and that therefore must be broken or inactive in a particular cell for oncogenesis to occur. The five noted barriers to oncogenesis are cell cycle arrest, apoptosis, regulation of telomerase, cell adhesion, and asymmetric cell division. Abrogations of these barriers are considered essential causes of oncogenesis, which are distinguished from exacerbating causes. The latter contributes to oncogenesis by relaxing restraints on oncogenesis, which are defined as defenses against cancer that suppress but do not block oncogenesis. The barrier theory is diagrammed in Figure 1. From a practical perspective, the barrier theory draws attention to interventions that preserve barriers and therefore can most directly prevent or cure cancer.

Abrogation of barriers could arise by mutation, epigenetic modification, and direct interference from pathogens. The most powerful contributions of pathogens to oncogenesis arise from mechanisms that evolved to promote productive pathogen persistence within hosts because barriers to cancer are often barriers to this persistence (Ewald & Swain Ewald, 2012). Pathogens that evolve increased persistence by compromising these barriers thus contribute directly to the process of oncogenesis. Less direct effects of pathogens on oncogenesis arise from haphazard effects of pathogens, such as stimulation of inflammatory responses that may increase the probability of mutations or enhance cellular proliferation (Garrett, 2015).

The barrier theory is evolutionary because it integrates the evolution of protective mechanisms against cancer as well as the...
evolution of symbiotic characteristics that compromise or enhance these protective adaptations. It draws on several conceptual frameworks for understanding cancer, including the clonal evolution theory (Nowell, 1976), the stem cell theory (Clarke et al., 2006), the Hallmarks of Cancer (Hanahan & Weinberg, 2000, 2011), and the concept of tumor virology (Moore & Chang, 2010). The barrier theory, however, is distinct from each of these frameworks because it integrates the known processes of oncogenesis into a causal evolutionary framework based on first principles. It differs, for example from the clonal theory by integrating mechanisms beyond mutation through which oncogenic viruses contribute to oncogenesis. It differs from the stem cell theory by building from principles of somatic evolutionary selection on cells rather than the metaphor of organogenesis and thus proposes how tumor cells may have stem-cell-like characteristics without suggesting that oncogenesis reflects the process of organogenesis. The Hallmarks of Cancer was formulated to emphasize the major features of cancer rather than to serve as a theory of cancer causation. The barrier theory embeds the concept

![Diagram](image)

**FIGURE 1** Diagrammatic representation of the barrier theory. Lines ending in bars indicate suppressive influences. Lines ending in arrows indicate enhancing influences. (a) Barriers block cancer when they are active in a cell by blocking cellular reproduction, survival or metastasis. (b) Restraints inhibit but do not block oncogenesis. Illustrative examples of restraints are provided.
of tumor virology in a broader framework of oncogenesis that can
classify pathogens other than viruses and differentiates oncogen-
ic characteristics of pathogens that are adaptations from side
effects of infection.

Although the barrier theory incorporates insights from these
other conceptual frameworks, its value derives from its differences
from them. Some of the Hallmarks of Cancer, for example, involve
processes that block cancer; others do not. Enhancement of angio-
genesis and immune evasion are hallmarks of cancer but may not
be necessary for oncogenesis to proceed. According to the barrier
theory, these effects involve relaxation of restraints and thus play
an exacerbating rather than an essential role in oncogenesis. Also,
in contrast with these other frameworks, the barrier theory builds
on the foundation of evolutionary selection—differential survival
and reproduction—to characterize barriers and restraints (Figure 1).
But the barrier theory applies this foundation to a subcategory of
somatic selection, termed oncogenic selection, to identify the bar-
riers that must be inactive or inactivated for oncogenesis to occur
(Figure 1; Ewald & Swain Ewald, 2013).

The goal of this paper is to broaden the scope of the barrier
theory to include protection against oncogenesis arising from
the microbiome. We consider direct protective effects of microbiota
well as the interplay between protective microbiota and parasites
that contribute directly or indirectly to oncogenesis. This analysis
complements recent papers that have considered the joint contribu-
tions of parasitic organisms to oncogenesis (Dheilly, Ewald, Brindley,
Fichorova, & Thomas, 2019; Ewald & Swain Ewald, 2014) and pro-	ection against oncogenesis that arises from immune responses to
pathogens that are not oncogenic (Cramer & Finn, 2011; Iheagwara
et al., 2014; Jacqueline & Finn, 2020; Oh et al., 2019).

2 Illustrative Overview Of Microbiome
Composition and Protection Against Cancer

Mutualistic microbiota can function as a symbiotic complement to
the immune system, shaped by (a) the environment of the host, (b)
the environment of the symbionts within the host, and (c) genes of
the hosts and symbionts. Like host genes, the microbiome may have
significant effects on host fitness.

In this context, microbiome composition has been associated
with risk of cancer. In the gastrointestinal tract, for example, some
symbionts contribute to cancer by processes such as inflammation
and damage to the intestinal lining whereas others protect against
cancer through a variety of mechanisms, such as production of
short-chain fatty acids, which can reduce inflammation, suppress
cellular proliferation, and facilitate apoptosis (Dejea et al., 2018;
dosReis, da Conceicao, & Peluzio, 2019; Garrett, 2015; Louis, Hold,
& Flint, 2014). Microbiota may also enhance immunosurveillance
and immune cell infiltration of tumors (Kroemer, Senovilla, Galluzzi,
Andre, & Zitvogel, 2015).

Accumulating evidence indicates that a shifted microbiome con-
tributes to oncogenesis of colorectal cancer, which is associated
with reduced representation of gut mutualists (reviewed in Wong &
Yu, 2019). Low dietary fiber and large quantities of red meat, which
characterize the typical Western diet, are associated with changes
in microbiome composition and increased rates of colorectal can-
cer (Wu et al., 2018). Short-chain fatty acids produced by specific
gut microbiota may be protective via effects on regulatory T cells
and inflammation through interactions with cell surface receptors
and epigenetic changes (Louis et al., 2014). The short-chain fatty
acid butyrate is a metabolite of many gut bacteria that ferment fiber
and may play a direct role in decreasing the risk of colorectal cancer.
Lumenal butyrate taken up by colonocytes and immune cells results
in increased acetylation of genes. These epigenetic modifications
promote regulatory T cell differentiation and reduced inflammation
in the gut (Furusawa et al., 2013; Louis et al., 2014). When trans-
ported into colonocytes butyrate can stimulate increased produc-
tion of tight junction proteins and mucins, thereby protecting the
physical connection between intestinal epithelial cells and assisting
in the stabilization of the mucous layer, both processes being criti-
cal for gut integrity (Jung, Park, Jeon, & Han, 2015; Yan & Ajuwon,
2017). A breakdown of the gut barrier can lead to damaging inflam-
mation which may be pro-oncogenic.

Experiments using colon cancer cell lines indicate numerous can-
cer-preventive or suppressing effects of biologically relevant levels
of butyrate exposure (Wu et al., 2018). A downstream effect of bu-
tyrate modulation of p53 and its subsequent reinforcement of the cell cycle
arrest barrier to cancer. Additionally, butyrate can stimulate the bar-
ier of apoptosis both through and independently of p53 (Mahyar-
Roemer & Roemer, 2001)—this effect is especially significant given
that p53 is often mutated in cancer cells. Butyrate also appears to
be able to suppress angiogenesis which is an important restraint on
oncogenesis. Studies have shown that this microbial metabolite can
attenuate cancer risk and development through both epigenetic (via
histone deacetylase inhibition) and nonepigenetic mechanisms.

Relationships between microbiome composition and cancer de-
velopment can be bidirectional—the microbiota can influence and be
influenced by oncogenesis. In a mouse model, induction of lung can-
cer resulted in a microbiome with a lower species diversity relative to
cancer-free controls (Jin et al., 2019). Transfer of the cancer-associ-
ated microbiota to germ-free mice exacerbated cancer in these mice;
moreover, transfer of microbiota from mice with late stage cancer to
mice at the early stages, exacerbated the development of cancer in
these recipients relative to mice that did not receive the transfer (Jin
et al., 2019). Overall, these results indicate that lung cancer favored
the development of microbiota that further contributed to cancer
development.

Similarly, a mouse model of colitis-associated colorectal cancer,
using a carcinogen plus an inflammatory agent, revealed that the pro-
cess of tumorigenesis shifted the microbiome (Zackular et al., 2013).
Over the course of tumor development, step-wise alterations from
the baseline microbiome resulted in less overall microbial diversity and
major changes in microbial composition. When this altered microbiome
was established in germ-free mice prior to initiating tumorigenesis,
more and larger tumors developed relative to germ-free mice preestablished with a healthy microbiota. Importantly, repeated exposure to the inflammatory agent alone had an initial and sustained impact on the microbiome but did not reduce overall diversity.

3 | Effects of Symbionts on Immune Checkpoints

Symbionts may help destroy cancer cells by fostering the responsiveness of immune checkpoints (see Box 1), which integrate signals that are relevant to the activation and suppression of different immune functions. T cells that destroy infected or cancerous cells can be suppressed through the interaction of cytotoxic T lymphocyte antigen-4 (CTLA-4) and its ligand on antigen-presenting cells. Similarly, the tendency of cells to be destroyed by cytotoxic lymphocytes can be checked by signaling through the programmed cell death protein (PD-1) and its ligand PD-L1 (Walker, 2017; Wei, Duffy, & Allison, 2018). The control of T-cell attack and cell killing that results from this communication represent two of many immune checkpoints that can restrict friendly fire damage to normal cells but increase vulnerability to problematic cells (e.g., cancerous or infected cells). At a mechanistic level, the balance maintained by these checkpoints is influenced by microbiome components. At an evolutionary level these interactions must surely be molded by natural selection because a rogue immunological response would lower the organism’s fitness by destroying valuable cells, but over suppression of these processes would make organisms vulnerable to infection and cancer.

The current spectrum of cancer treatments includes inhibition of these checkpoints, which is often associated with improved control of the cancer (Routy, Gopalakrishnan, et al., 2018). Current evidence indicates that symbionts help maintain this responsiveness.

One line of evidence has been generated from antibiotic treatment of cancer patients. Administration of broad-spectrum antibiotics was associated with decreased effectiveness of checkpoint inhibition through the PD-1 mechanism in lung, renal, and bladder cancer (Routy, Le Chatelier, et al., 2018). This finding implicates microbes in a process that permits escalated immunological destruction of cancer cells.

A complementary line of evidence involves effects of microbial supplementation on checkpoint inhibition. In particular, experimental transfers of bacteria have been associated with responsiveness to checkpoint inhibition. Transfer of stool samples from patients who responded to immune checkpoint inhibition (“responders”) enhanced the ability of mice to respond to this inhibition and better control of cancer (Routy, Gopalakrishnan, et al., 2018). This favorable response did not occur in mice receiving stool samples from nonresponder patients, but could be generated subsequently in these mice by selective introduction of bacterial species from responders (Routy, Le Chatelier, et al., 2018; Sivan et al., 2015; Vetizou et al., 2015; Vlaud et al., 2013).

The bacterium Akkermansia muciniphila was isolated more frequently from feces of cancer patients who responded strongly to checkpoint inhibition of PD-1 than from patients who showed a weaker checkpoint blockade response (Matson et al., 2018; Routy, Le Chatelier, et al., 2018). A. muciniphila restored the response to checkpoint inhibition in mice that had been treated with broad-spectrum antibiotics or had received fecal transplants from nonresponders.

The mechanism by which A. muciniphila improves response to checkpoint inhibition may involve effects on T-cell function. Interferon associated memory T cell responses were stronger in responders than in nonresponders when the T cells were cultured in

Box 1 Terminology

**Immune checkpoint**: a biochemical mechanism by which the immune system restricts its destruction of potentially dangerous cells to reduce peripheral damage to normal cells; immune checkpoint inhibition refers to the relaxation of checkpoints, which thus reduces constraints on immune action.

**Cell cycle arrest**: the halting of cell division by biochemical inhibition of progress through the cell cycle; it is sometimes referred to as a cellular checkpoint or a cell cycle checkpoint but is conceptually distinct from immune checkpoint.

**Symbiosis**: any intimate interspecific association; the spectrum of symbioses encompasses parasitism, commensalism, and mutualism.

**Parasitism**: a symbiosis in which an individual (the parasite) lives in or on another individual (the host) and causes harm to the host.

**Mutualism**: an interspecific association that provides fitness benefits to both interacting individuals.

**Symbiosis continuum**: the spectrum of symbiotic associations extending from obligate mutualisms on one end to lethal parasitisms on the other; synonymous with the parasitism-mutualism continuum.1,2

**Commensalism**: a symbiosis in which the symbiont neither helps nor harms the host. It best considered a dividing line between parasitism and mutualism on the symbiosis continuum.1 Use of the term commensalism reflects an inability to discern whether the symbiont has a net positive or a net negative effect on the host.

**Ambisymbionts**: symbionts that traverse the commensalism dividing line between parasitisms and mutualisms depending on circumstances.2

**Pathogen**: a parasite with organization at or below the level of the individual cell; this category includes protozoal, bacterial, and viral parasites.

**Oncogenic**: pertaining to the development of cancer; oncogenic pathogens to refer to pathogens that contribute to the process of oncogenesis.2

1Ewald (1987) 2Swain Ewald and Ewald (2018)
the presence of monocytes that had been cultured with *A. muciniphila* (Routy, Le Chatelier, et al., 2018).

The effects of *A. muciniphila* in mice depended on interleukin-12, which favors the development of cell-killing functions of T cells, and were correlated with reductions in regulatory T cells, which enforce cellular checkpoints (Routy, Le Chatelier, et al., 2018). In sterile mice, *A. muciniphila* led to the presence in mesenteric lesions of a helper T cell subset that is associated with regression of the lesions (Routy, Le Chatelier, et al., 2018).

Associations of cancer with different abundances of gut microbiome species and outcomes of bacterial supplementation suggest the important role of mutualist bacteria in cancer prevention as well as treatment efficacy and tolerability (Routy, Gopalakrishnan, et al., 2018; Wang, Yin, Chen, & Davis, 2018). Using *Bifidobacterium* species as an example, studies have found an association between lower levels of these bacteria in colorectal cancer patients relative to healthy controls, higher levels in patients that responded to immune checkpoint inhibition therapy, and slower progression to this cancer in a mouse model according to the relative presence of *Bifidobacterium*. Supplementation with *Bifidobacterium* species was associated with a better response to immune checkpoint inhibition therapy and a reduction in therapy-associated colitis in mice, as well as better recovery after colon cancer surgery in humans (Routy, Gopalakrishnan, et al., 2018; Wang et al., 2018).

In a rat model, *B. animalis* subsp. lactis protected against the development of colorectal cancer (Le, Hu, Brown, Woodman, & Young, 2010). Other bifidobacterial species have been shown to activate cytotoxic T cells and antitumor effects of anti-PD-L1 checkpoint inhibition (Sivan et al., 2015).

Increased abundance of *Faecalibacterium* species was associated with longer disease-free survival of melanoma patients, with increased cytotoxic T cell infiltration of tumors, and lower immune suppressive T cell populations (Gopalakrishnan et al., 2018). Accordingly, germ-free mice that received fecal material from responders had slower tumor growth and better responses to anti-PD-L1 immunotherapy than those receiving stool from nonresponders. In mice that received fecal samples from responders, enrichment of *Faecalibacterium* was associated with dense CD8+ T cell infiltrate in the tumor microenvironment (Gopalakrishnan et al., 2018). In melanoma patients undergoing combination therapy with anti-CTLA-4 and anti-PD-1 antibodies, the abundance of *Faecalibacterium prausnitzii* was elevated in baseline stool samples from responders relative to nonresponders (Frankel et al., 2017).

The responders also had a higher incidence of immune-related colitis, which is a common side effect of checkpoint inhibition therapy (Garrett, 2015) and probably reflects a tradeoff associated with immune checkpoints, namely that relaxation of the constraints on immunological attacks increases the risk of friendly fire from the immune system. The association between mutualistic symbionts and checkpoint responsiveness suggests that the actions of both mutualists and parasites must be integrated into our understanding of the physiological and evolutionary maintenance of checkpoints. The tradeoff between the positive and negative effects of checkpoint inhibition also raises the possibility that the symbionts that increase immune checkpoint responsiveness could be ambisymbionts that have an overall negative effect on host survival if the negative effects of checkpoint relaxation (e.g., due to autoimmunity damage) outweigh the positive effects of escalated destruction of dangerous cells.

## Interactions Among Parasites and Mutualists

In the last few years, cancer research has increasingly recognized the need to understand the joint contribution of parasites to oncogenesis. Knowledge in this area has been integrated with the barrier theory with many illustrative examples (Ewald and Swain Ewald, 2014, Dheilly et al., 2019). A major challenge will be to broaden this understanding to determine the ways in which mutualists interact with parasites to inhibit oncogenesis. These interactions include protective effects of mutualists against oncogenic pathogens. *Bifidobacterium adolescentis*, for example, induces a protein with activity against hepatitis B virus and is associated with a decline in viral titer (Lee, Kang, Shin, Park, & Ha, 2013). This effect may protect against hepatobiliary cancers caused by hepatitis B virus.

Interactions between mutualists and parasites may involve chains of effects. Mutualistic microbes may, for example, inhibit pathogens that indirectly exacerbate cancers for which other pathogens play a more direct oncogenic role. Using malaria as an example, recent research suggests that specific groups of gut microbiota may be protective against *Plasmodium* infection (Ippolito, Denny, Langelier, Sears, & Schmidt, 2018). This appears to be true for multiple *Plasmodium* species that are found across separate as well as overlapping geographic regions (Ippolito et al., 2018). By helping to control plasmodia, these gut microbiota may help curb the development of Burkitt’s lymphoma, which is caused by the Epstein Barr virus infection acting through the abrogation of barriers to cancer but exacerbated by *Plasmodium falciparum* (Ewald & Swain Ewald, 2012, 2014).

Interactions between mutualists and parasites may sometimes involve exacerbation of oncogenic infections by organisms that are generally beneficial. If such interactions cause a symbiont that is normally mutualistic to have a net negative effect on the host in the presence of an oncogenic pathogen, the symbiont would be best considered an ambisymbiont (see Box 1) rather than a mutualist. In a mouse model of colorectal cancer, for example, *A. muciniphila* contributed to tumorigenesis, but suppressed it in the presence of *Helicobacter typhlonius* (Dingemanse et al., 2015). Similarly, *A. muciniphila* can worsen *Salmonella enterica* infection (Routy, Gopalakrishnan, et al., 2018), which in turn has been associated with hepatobiliary carcinomas (Samaras, Rafailidis, Mourtzoukou, Peppas, & Falagas, 2010). *A. muciniphila*, therefore may act mutualistically in the presence of *H. typhlonius* but parasitically in the absence of *H. typhlonius* and presence of *S. enterica* in the mouse model of colorectal cancer. *A. muciniphila* is therefore an ambisymbiont with effects that need to be assessed across the spectrum of environmental conditions to determine whether it is sometimes exacerbating oncogenesis.
through effects on pathogens, even though it appears to be mutu-
ality in most circumstances. A practical benefit of understanding
this spectrum of interactions would be to identify circumstances in
which probiotic exposure to A. muciniphila would have net beneficial
or detrimental effects on oncogenesis. Complicating the picture is
evidence that opisthorchis trematodes, and hepatitis B and C viruses
also contribute to hepatobiliary carcinomas (Ewald & Swain Ewald,
2014; Song et al., 2019).

5 Conclusion: Integration of Symbiont Effects with the Barrier Theory

This paper considers how oncogenesis may be influenced by sym-
bionts that have positive effects on their hosts and are therefore
mutualistic. Current evidence indicates that protective effects of
symbionts against cancer tend to involve enhancement of restraints
rather than direct activation of barriers (Figure 1). The likely evolu-
tionary reason is that natural selection has favored sophisticated,
flexible defenses against cancer that require complex orchestration
of different cells and chemicals of the immune system. This orches-
tration is made possible by natural selection acting on the survival
and reproduction of the multicellular organism. Tumor viruses tweak
the system by interfering directly with key biochemistries of barri-
ers such as p53 and retinoblastoma proteins, apparently because
the resulting proliferation fosters survival and reproduction of the
tumor viruses. Mutualistic microbiota, however, tend to be not only
extracellular but external to the epithelium. They are part of the en-
vironment of the multicellular organism and therefore coevolve to
enhance the function of organ systems, as with tuning of the im-
une system.

In spite of this tendency for mutualists to act through restraints
on oncogenesis, the protective mechanisms of these restraints may
depend on the presence of barriers. Symbiont-enhanced checkpoint
responsiveness, for example, allows the immune system to shift to-
ward a more aggressive T-cell attack on cancerous or precancerous
cells. If p53 control of the apoptosis barrier is no longer functional,
the relaxation of immune checkpoints might allow a mechanism of
cell killing that is independent of apoptosis (Martinez-Lostao,
Anel, & Pardo, 2015), thereby invoking a restraint on oncogenesis.
Alternatively, cytotoxic T cells and natural killer cells that are re-
leased from immune checkpoints may trigger apoptosis by stimu-
lating the part of the pathway that is not damaged (Martinez-Lostao
et al., 2015). If, for example, intracellular control of apoptosis was
blocked by a p53 mutation or a tumor virus, cytotoxic lymphocytes
might still stimulate the caspase cascade of apoptosis that would
have been activated by a functional p53 protein. By indirectly mo-
bilizing barriers, these protections could contribute to prevention,
control or cures of cancer.

Aside from the direct contribution of oncogenic pathogens to
cancer, explorations of the possible role of the microbiota in the
etiology, progression, inhibition, and prevention of cancer are in
early stages. The human microbiome and host have been shaped by
coevolutionary forces. In this dynamic setting, species outcompete
others, provide resources for other microbiota and the host, impact
metabolism, exploit and or damage the host, and interact with the im-
mune system. When considering cancer, it may be necessary to look
both at the level of function (e.g., provisioning of short-chain fatty
acids, competitive colonization of pathogen binding sites) as well as
the interactions among symbionts across the symbiosis continuum.
Symbionts are influenced by their immediate environment and the
environments of their hosts, including aspects such as host diets and
transmission between hosts (Swain Ewald and Ewald, 2018). Their
capabilities for causing or protecting against cancer depend on their
evolutionary adaptations to abrogate barriers or enhance host pro-
tective systems. A thoroughly integrated barrier theory of cancer
will need to incorporate these environmental influences along with
an understanding of evolutionary adaptations of host and microbe
that result in vulnerability to or protection from oncogenesis.

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DATA AVAILABILITY STATEMENT

All information used for this study are available in the cited
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