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Microbiome and Malignancy

Claudia S. Plottel[1] and **Martin J. Blaser**[1,2,3]

[1]Department of Medicine, New York University Langone Medical Center

[2]Department of Microbiology, New York University Langone Medical Center

[3]Department of Biology, New York University

Abstract

Current knowledge is insufficient to explain why only a proportion of individuals exposed to environmental carcinogens or carrying a genetic predisposition to cancer develop disease. Clearly, other factors must be important and one such element that has recently received attention is the human microbiome, the residential microbes including Bacteria, Archaea, Eukaryotes, and viruses that colonize humans. Here, we review principles and paradigms of microbiome-related malignancy, as illustrated by three specific microbial-host interactions. We review the effects of the microbiota on local and adjacent-neoplasia, present the estrobolome model of distant effects, and discuss the complex interactions with a latent virus leading to malignancy. These are separate facets of a complex biology interfacing all the microbial species we harbor from birth onward toward early reproductive success and eventual senescence.

Introduction

Cancer, which manifests as the uncontrolled proliferation of host cells, is a leading cause of death in human societies worldwide. Disease and death result from local and distant spread of malignant cells, as well as from their metabolic and systemic effects. Although virtually all human tissues containing cells with replicating potential may be affected by cancer, there is host population-specificity in the timing and tissues involved, in histology, and in natural history. While many genetic predispositions to increased cancer risk in general and to the development of specific malignancies have been identified, environmental effects dominate for virtually all of the major human cancers (Lichtenstein et al., 2000).

Significant exposures to environmental carcinogens, including toxic chemicals, ionizing radiation, and microbial pathogens, are extremely varied (Schottenfeld et al., 2006). However, current knowledge is insufficient to explain why only a proportion of heavy smokers develop lung cancer, or who among those with hepatitis B infection will develop hepatomas. Clearly, other environmental factors must be important (Wynder and Gori, 1977) and one such element factor that has received attention more recently is the human microbiome.

Corresponding Author: Claudia S. Plottel, Division of Translational Medicine, Department of Medicine, New York University Langone Medical Center, 550 First Avenue, OBV C/D 640, New York, NY 10016, Phone: 212-263-0862, Fax: 212-263-0596, Claudia.Plottel@nyumc.org.

Since their earliest origins (Ley et al., 2008a), animals have been colonized by residential micro-organisms including bacteria, fungi, protozoa, and viruses, that are collectively described as the microbiome (Lederberg and McCray, 2001). With the development of new scientific tools, there has been increasing interest in the composition, function, stability, and host-specificity of the microbiome, and the aggregate of its genes, the metagenome (Benson et al., 2010; Ley et al., 2006; Li et al., 2008). This review focuses on the relationships of the microbiome to human malignancy. We present general principles and explore three models of microbiome constituents affecting cancer risk and pathogenesis. The three paradigms we describe here illustrate different aspects of the emerging pathogenetic processes involving the microbiome.

General Principles

The Microbiome—Humans are colonized by residential microbes including Bacteria, Archaea, Eukaryotes, and viruses (Turnbaugh et al., 2007). The proportion of bacterial cells represented in the human body is estimated to be ~90%, and of all genes, >99%. Initial colonization occurs at the time of birth and we progressively acquire a population of ~10^{14} bacterial cells at equilibrium, which essentially remain for life and this process is recapitulated in every human lifetime. A human virome consisting of persistent colonizing viruses also exists, but is far less explored. Preliminary examination of the fecal virome has shown numerous bacteriophages, but with no obvious relationship to neoplasia (Reyes et al., 2010).

Each anatomical niche possesses its own mixture of microbial populations. Although generally conserved at higher taxonomic levels and in functional properties (Arumugam et al., 2011) between all humans, interindividual microbiota variation at lower levels (genus, species, and strain) is enormous (Qin et al., 2010). The microbiome composition appears to evolve over the human life span, but the exact magnitude of such changes is unknown. The individual organisms and cells in the microbiome both compete and cooperate with one another (Blaser and Kirschner, 2007), and the metagenome has both functional and genetic plasticity (Arumugam et al., 2011; Muegge et al., 2011).

Interactions with hosts—We do not carry our microbial load passively. There is increasing evidence for a rich, complex, dynamic, and individual-specific microbial interaction with hosts. Interactions involve microbial signaling of host cells that affect metabolic, neurological, inflammatory, immunologic and host-defense functions, among others (Barton et al., 2007; Dethlefsen et al., 2007; Ley et al., 2008b; Muegge et al., 2011). The nature of host responses also shapes microbiome populations and metabolism (Vijay-Kumar et al., 2010). Indeed, a long-term well-choreographed Nash equilibrium may model host-microbial co-evolution (Blaser and Kirschner, 2007). The range of equilibrium arrangements is broad; simplified formulations are shown in Figure 1. Host interactions with the microbiome are both local, e.g. in the gastrointestinal tract lumen, or distant, involving hormonal intermediates, microbial metabolites, and immunologic messengers.

Human cancers must be considered against the background of host-microbiome interactions. In general, cancers are log-linear with host age (Nordling, 1953). Three questions are relevant to this review: How are cancers initiated? Why do some but not all tumors progress? What determines susceptibility to treatment? In summary, there is a theoretical basis for the microbiome to participate in each of these phenomena (Figure 2). For example, microbiome-induced recruitment of lamina propria innate and adaptive immune effectors induces epithelial cell proliferation (Israel et al., 2001) and cell proliferation per se is pro-oncogenic (Ames and Gold, 1990). Microbial adjuvancy or suppression affects immune surveillance (Gaboriau-Routhiau et al., 2009; Ivanov et al., 2009), which limits tumor

progression. Differing drug metabolism affects susceptibility to chemotherapy (Wallace et al., 2010).

We are living at a time of great ecological change; global warming at the macro-level and "disappearing microbiota" at the micro-level (Blaser and Falkow, 2009). Thus, long-established human-microbial ecological relationships, and their contribution to cancer risk, are changing. For example, in developed countries, the incidence of gastric cancer is falling, whereas esophageal adenocarcinoma is rising (see below). Nevertheless, several different types of cancer development can be considered (Figure 3) at the crossroads of our ancient and our "post-modern" microbiota. Of the microbe-induced human malignancies, Class A is defined as involving immunologic tissues, Class B requires direct microbial interactions with parenchymal cells, and Class C involves distant effects from local interactions. Several examples (Table 1) may provide a model for not-yet recognized relationships between microbiome and particular cancers (Blaser, 2008). We illustrate general types of relationships between different constituents of the human microbiome and several human cancers through the following paradigms.

Paradigm 1. Active inflammation promoting cancer in a lumenal organ (*H. pylori*)

H. pylori are microaerophilic, highly motile, curved gram negative bacilli that colonize the human stomach (Atherton and Blaser, 2009). Considerable evidence reveals that *H. pylori* is ancestral in humans, colonizing our ancestors before the major out-of-Africa migration 58,000 years ago (Linz et al., 2007). Acquired in early childhood and carried for nearly all of the life span, *H. pylori* was ubiquitous in all human populations in which it was studied (Bardhan, 1997). Also, examination of gastric 16S rRNA genes indicates that *H. pylori* dominates the gastric microbiota (Andersson et al., 2008; Bik et al., 2006). Thus, *H. pylori* has been the ancient, dominant, and highly interactive member of the human gastric microbiota. Nevertheless, *H. pylori* prevalence has steadily decreased over the course of the 20th century (Chen and Blaser, 2008; Roosendaal et al., 1997); this is both a major and surprising shift in human microecology.

As such, we can now measure the consequences of carrying *H. pylori* or not. As discussed below, the presence or absence of the organism can lead to very different gastric physiologies and each of the 3 classes of microbe-induced malignancies outlined in Figure 3 can be attributed to the presence or absence of *H. pylori*. Substantial epidemiologic, histologic, and experimental animal studies implicate *H. pylori* in the causation of gastric adenocarcinoma (Peek and Blaser, 2002), the second leading cause of cancer death worldwide (Class B relationship). In addition, *H. pylori* is strongly associated with gastric MALT-lymphomas (Parsonnet et al., 1994) (Class A relationship). Conversely, *H. pylori* has an inverse association with esophageal (gastro-esophageal junction) adenocarcinoma, consistent with a protective effect (Islami and Kamangar, 2008) (Class C relationship).

Gastric cancer

Via secreted substances, physical attachment, as well as the injection, by a type IV secretion system (TFSS), of its own constituents, *H. pylori* are highly interactive with host cells (Odenbreit et al., 2000), consistent with the Class B model (Figure 3). A major injected constituent is the ~128 KDa CagA protein, which contains several tyrosine phosphorylation (EPIYA) domains that are recognized by host cell kinases, that convert CagA into p-CagA (Backert and Selbach, 2008). As an indication of *H. pylori* complexity, the EPIYA-rich encoding region contains many DNA repeats, permitting the expansion or diminution of EPIYA site number. Strains with C or D type EPIYAs signal host epithelial cells via the Src/Shp-2/MAPK pathway whereas EPIYA lacking proteins signal through gp130/JAK/STAT3 (Lee et al., 2010). Since these are cross-inhibitory pathways, the population biology of *H.*

pylori within a particular locale determines, with very fine tuning, the nature of host responses, enabling persistence, but also leading to tissue responses and injury. Individuals carrying *H. pylori* strains that possess CagA are at increased risk for the development of precursor lesions for gastric cancer (i.e. atrophic gastritis and intestinal metaplasia) and therefore the cancer itself. Multiple signaling pathways may be involved since particular alleles of *H. pylori* genes are associated with increased risk of cancer development (Batista et al., 2011). Particular host polymorphisms that relate to innate immunity (e.g. affecting IL-1, IL-1RA, and TNF-α expression) enhance the risk of gastric cancer associated with *H. pylori* positivity (El-Omar et al., 2001; El-Omar et al., 2003; Figueiredo et al., 2002). *H. pylori*-induced gastric inflammation recruits stem cells from the bone marrow, which may also participate in tumorigenesis (Houghton et al., 2004). The traditional model of gastric carcinogenesis focuses on host, strain, or interaction differences in explaining *H. pylori*-induced gastric adenocarcinoma (Peek and Blaser, 2002). An alternative model is shown in Figure 4 in which the *H. pylori*-host interaction causes progressive degradation of the gastric niche over decades, *H. pylori* is essentially lost (Karnes et al., 1992) and the changes lead to the success of new competing microbiome populations that are cancer-promoting.

Gastric lymphoma

The presence of *H. pylori* is strongly associated with primary gastric lymphoma (Parsonnet et al., 1994; Wotherspoon et al., 1993). The presence of *H. pylori* is important in the proliferation of the tumors, since when *H. pylori* is eliminated, they often regress (Yamamoto et al., 2008; Zullo et al., 2010). The tumors are clonal, but a spectrum encompassing benign polyclonal lymphoid expansion, emergence of a dominant clone, and malignant transformation of the clone can be observed (Thiede et al., 1999). This scenario is consistent with the Class A model for microbiome-mediated hematopoietic and lymphoid malignancies consistent as outlined in Figure 3.

Esophageal adenocarcinoma (EAC)

The incidence of GE junction adenocarcinomas (namely EAC and gastric cardia adenocarcinoma) is rapidly rising in Western countries (Devesa et al., 1998) just as *H. pylori* is disappearing (Chen and Blaser, 2008; Roosendaal et al., 1997). The development of these cancers (and those on the gastric cardia side of the GE junction) follows gastro-esophageal reflux disease (GERD), and its metaplastic sequela (Barrett's esophagus). The presence of *H. pylori,* especially *cagA+* strains, is inversely associated with all three lesions (Peek and Blaser, 2002). These findings have been confirmed (Islami and Kamangar, 2008), and are consistent with the hypothesis that a change in the gastric microbiome resulting from the absence of *H. pylori* is contributing to this epidemic of GE junction adenocarcinomas. This is biologically plausible based on emerging trends, and on the knowledge that loss of these highly interactive (especially *cagA*+) organisms change gastric physiology, affecting acid secretion (Moss & Calam, 1992), hormone interactions (Francois et al., 2008; Francois et al., 2011), and T-cell populations (Robinson et al., 2008). Further, the loss of *H. pylori* is associated with changes in the composition of the gastric microbiome involving many other microbial taxa (Maldonado-Contreras et al., 2011). That change in the microbiome in one location (gastric) may affect cancer risk in an adjacent, but separate, compartment (distal esophagus) suggests an important paradigm for other cancers: the causal agents need not be residents of the affected tissues (Figure 3, **Class C**). Nevertheless, there is an esophageal microbiota (Pei et al., 2004), that it is clearly perturbed in pre-malignant lesions of the esophagus (Yang et al., 2009). Whether this is cause or effect is uncertain at present, but is a promising area for exploration.

Paradigm 2. Metabolic effects of residential organisms leading to distant malignancies (Estrobolome)

The human estrobolome—We postulate that an important contribution of the human gut microbiota to host physiology is a functional **estrobolome**, the aggregate of enteric bacterial genes whose products are capable of metabolizing estrogens. Especially important are bacterial species possessing β-glucuronidases and β-glucuronides, enzymes involved in estrogen de-conjugation and conjugation (Cole et al., 1985; Dabek et al., 2008; Gadelle et al., 1985; Gloux et al., 2011; McBain and Macfarlane, 1998). The estrobolome is predicted to impact endogenous estrogen metabolism by modulating the enterohepatic circulation of estrogens, thus affecting circulating and excreted estrogen levels (Figure 5). A woman's lifetime burden of estrogen exposure may reflect in part the metabolic functioning of her estrobolome. An estrobolome enriched in gene products promoting estrogen metabolite deconjugation reactions may result in greater reabsorption of free estrogens. Estrobolome variation in levels of functional deconjugative ability may thus influence development of estrogen-driven neoplasia (Figure 3, **Class C**).

Estrogens and estrogen-driven cancer—Estrogens, steroid hormones derived from the progressive reduction of C21 cholesterol, may act locally (intracrine function), or circulate to exert effects on target organs (endocrine function). The three major forms of endogenous estrogen, estradiol (E_2, dominant during reproductive years), estrone (E_1, dominant after menopause), and estriol (E_3, dominant during pregnancy) are 4-ring C18 molecules. Estrogens appear in circulation as free or protein-bound entities, and in both conjugated and unconjugated states. Estrogen exposure begins prenatally and is lifelong. The multiple beneficial effects (cardiovascular, metabolic, bone, fertility, cognition), contrast with roles in estrogen-driven cancers. Women with the highest circulating estrogen levels are at increased risk for developing postmenopausal endometrial (Lukanova et al., 2004) and breast cancers (Hankinson et al., 1998; Kaaks et al., 2005; Key et al., 2002; Lukanova et al., 2004; Toniolo et al., 1995; Woolcott et al., 2010). Estrogen metabolism varies between women with the full physiologic repertoire of its metabolites being unknown. Estrogens and estrogen-like molecules classically exert their cellular effects by binding to and activating estrogen receptors, although other receptor-independent mechanisms do exist.

Healthy and cancerous cells express receptors for estrogen—The two recognized estrogen receptors (ERα, ERβ) are homologous ligand-modulated transcription factors. Both are present in many healthy tissues (including breast, ovary, testis, prostate, bone, brain, vascular system) and in certain cancers of the breast, endometrium, prostate, bone, and lung (Kuiper et al., 1996). Ligands other than E_2, E_1 and E_3 can bind with varying affinities to both ERα and ERβ (Kuiper et al., 1998) with activation increasing or repressing host cell transcription with consequent biologic activity (Jeyakumar et al., 2011). The centrality of estrogen to malignancy is reflected in therapeutic interventions that target estrogen receptor signaling, including the selective estrogen receptor antagonists (SERMs), widely used to treat ER(α)-receptor-expressing breast cancer.

Hepatic estrogen metabolism and the enterohepatic circulation of estrogens —Both E_1 and E_2 undergo Phase I oxidative hepatic metabolism leading to the formation of catechol estrogens, (e.g. 2-OH, 4-OH, and 16-OH estrogens) (Yager et al., 2009) that then are conjugated or transformed to semiquinones, which have been implicated in oncogenesis (Cavalieri et al., 2006). The ratio of circulating and urinary 2-OH to 16-OH estrogen pathway metabolites may be a marker of breast and endometrial cancer risk (Bradlow et al., 1995; Gupta et al., 1998; Kabat et al., 1997; Meilahn et al., 1998; Muti et al., 2000). Phase II hepatic conjugation reactions include methylation, via catechol-*O*-methyltransferase; glucuronidation via uridine 5′-diphospho-glucuronosyltransferase; or sulfonation, via

sulphotransferase (Raftogianis et al., 2000). Some methylated estrogens, such as 2-methoxyestradiol, exhibit proapototic, antiangiogenic, and antiproliferative activities (Lakhani et al., 2003) and are currently being studied as anticancer agents. Conjugated estrogens are not important ligands for the estrogen receptors (Raftogianis et al., 2000) and are subject to biliary excretion (Adlercreutz and Martin, 1980; Sandberg and Slaunwhite, 1957). Most importantly, there is an enterohepatic circulation of estrogens (Figure 5) with repeated re-circulation circuits (Adlercreutz, 1962; Sandberg and Slaunwhite, 1957). Recent refinements in analytic methodologies now permit accurate measurements of conjugated and unconjugated estrogens and estrogen metabolites in serum and urine (Zeigler et al, 2010), and should stimulate investigations of estrogen metabolism in malignancies.

Estrogen metabolism requires a functional estrobolome—Gut microbial functions driving estrogen metabolism and contributing to the proportions of recirculated and excreted estrogens and estrogen metabolites has long been considered (Adlercreutz and Jarvenpaa, 1982; Eriksson, 1970). Reduction in populations of specific gut bacteria in humans, as occurs with exposure to antibiotics, causes increased fecal excretion of conjugated estrogens and decreases in urinary estrogens (Martin et al., 1975), highlighting the modulatory role of the gut microbiome's deconjugating machinery (Adlercreutz and Jarvenpaa, 1982; Adlercreutz et al., 1979; Adlercreutz et al., 1978; Martin et al., 1975). Human fecal extracts metabolize estrogens ex vivo, as would be expected of the estrabolome. The reactions include reduction and oxidation, the generation E_2 from E_1 as well as from estradiol 3-glucuronide; E_1 from E_2 and from estrone 3-sulfate; and E_3 from 16α-hydroxyesterone (Lombardi et al., 1978). Similarly, in-vitro incubation of E_1, E_2, and 16α-hydroxyestrone with human feces leads to the interconversion of E_1 and E_2, the reduction of 16α-hydroxyestrone to E_3, 16-oxoestradiol to 16-epiestriol, and 15α-hydroxyestrone to 15α-hydroxyestradiol (Järvenpää et al., 1980). Finally, germ-free mice provide additional evidence for the centrality of host-microbe interactions in estrogen metabolism (Shimizu et al., 1998).

Interventions that target the estrobolome affect estrogens—Bacterial composition of the human estrobolome likely reflects host factors, such as delivery mode at birth as well as lifetime environmental influences, including antibiotic use and dietary composition. Vegetarians have increased fecal excretion of conjugated estrogens (Goldin et al., 1982; Gorbach and Goldin, 1987) and dietary manipulations affect overall gut microbiome composition and function (Turnbaugh et al., 2009; Faith et al., 2011; Muegge et al., 2011). Such pressures exerted over time on the bacterial communities that constitute the estrobolome may lead to emergence of functionally distinct patterns, analogous to the broader categorization of the gut phylogenetic enterotypes (Arumugam et al., 2011). The confluence of both genetic and environmental modulators may shape estrobolome functionality that affects cancer risk (Figure 5); as such, estrobolome analysis could be harnessed to reduce emergence of estrogen-driven malignancies, such as Type I (endometrioid) endometrial cancer, estrogen receptor-positive breast cancer, and some ovarian cancers. Interventions that modify the bacterial constituents of the estrobolome also could modulate functional activity. Manipulations that specifically target species with β-glucuronidase and β-glucuronide activities could aid in reducing estrogen-related cancer risk. Changing bacterial populations to diminish hydroxylation and reductive functions can be accomplished with of antimicrobial agents, pre-biotics, or probiotics. If such interventions proved successful, estrobolome status might inform future risk of malignancy and measures could target restoration and maintenance of a "healthy" estrobolome for that host.

Paradigm 3. Abrogation of clinical latency leading to malignant outcomes

Epstein-Barr virus (EBV)—EBV is an ancient (Lacoste et al., 2010; McGeoch et al., 1995), ubiquitous, and persistent virus that obligately infects humans, leading to life-long latency. By adulthood, nearly all humans have acquired EBV (Henle et al., 1969). As such, EBV should be considered part of the human virome and it is with this premise that we discuss EBV and associated malignancies in this review.

EBV is a 172 kb, double-stranded DNA virus of the γ-herpesvirus subfamily of *Lymphocryptovirus*, present as a characteristic (Penkert et al., 2011) circular episome within the human memory B-lymphocyte nucleus (Niederman et al., 1970). EBV is associated with relatively low short-term cost and even possible benefit to the host (Barton et al., 2007), but harbors long-term malignant potential. The emergence of an EBV-associated cancer, often decades after EBV acquisition, reflects complex interactions between the virus and its host that culminate in the loss of latency and highlights how a nearly universal member of our commensal microbiota contributes to malignancy. In hosts who develop Burkitt's lymphoma (BL), post-transplantation lymphoproliferative disorders (PTLD), or nasopharygeal carcinoma (NC), EBV has a bi-phasic life cycle. However, most EBV positive individuals do not develop EBV-associated cancers, but instead just harbor latent virus. EBV's presence is thus necessary, but not sufficient for the emergence of an EBV-associated malignancy.

Interactions of Epstein-Barr Virus with its human host—EBV is transmitted between humans through saliva. Children become susceptible to EBV transmission after maternal antibody protection wanes; infection is either asymptomatic or may lead to non-specific symptoms. EBV acquisition in adolescence or in young adulthood, as seen in Western societies, results in illness termed infectious mononucleosis (IM) in about half of the infected individuals. The intensity of the host's T-cell responses to primary EBV is responsible for this acute illness (Callan et al., 1996).

After the initial replicative lytic phase, EBV undergoes a shift to one of a series of tightly regulated latency states, each characterized by transcriptional repression to evade immune surveillance (Figure 6). Differential regulation of promoter utilization underlies EBV latency gene expression, possibly involving chromatin insulator protein (Tempera et al., 2011). Compared to the >80 genes expressed in the lytic cycle, in a Latency III program EBV principally expresses 6 nuclear antigens (EBNAs) and all 3 integral latent membrane proteins (LMPs) whereas in Latency II, only EBNA 1, and LMP 1 & 2 are expressed, and in Latency I, only EBNA1 is expressed (Figure 6). EBNA1 is crucial for EBV episome replication and maintenance, and Latency I represents the most restrictive form of latency in dividing cells. A state of "Latency 0" in which there is no viral antigen expression is postulated to occur in vivo, consistent with the life-long persistence of the EBV genome in memory B-cells in healthy hosts (Babcock et al., 1998; Miyashita et al., 1995). Even in latency, EBV is capable of regulating B-cell protein expression and proliferation and the viral genome can replicate as an episome, in tandem with host cell division.

EBV manipulates host innate immune signaling pathways—EBV exploits fundamental host innate signaling pathways including NF-κB, TNF-alpha, and Notch receptor pathways, throughout its life cycle. It does so to its advantage, beginning when viral envelope glycoprotein (gp350) binds to host B-cell surface CD21 and TLR 2, leading to persistent NF-κB classical pathway activation (Gaudreault et al., 2007). Later, EBV achieves immortalization via activation of both the alternative and classical NF-κB pathways (Kung and Raab-Traub, 2010; Mosialos et al., 1995; Song and Kang, 2010). EBV is able to convert host B lymphocytes into lymphoblastoid cell lines by expressing EBV nuclear and membrane proteins, EBNAs, and LMPs (in Latency III) that regulate

transcription through the Notch and TNF-alpha receptor pathways (Cahir-McFarland et al., 2004). EBV is able to reroute the TNF receptor family signaling pathway (Izumi and Kieff, 1997; Le Clorennec et al., 2008; Liebowitz, 1998; Mosialos et al., 1995). Such interactions favor EBV persistence, yet EBV latency may also provide mutualistic benefit to its hosts as an immune adjuvant (White et al., 2010), protecting against lethal *Listeria monocytogenes* and *Yersinia pestis* infections (Barton et al., 2007). Over a host's lifetime, incompletely characterized stimuli occasionally induce EBV to emerge from latency and initiate a lytic state via sequential expression of genes responsible for replication and whole virion assembly. This (generally clinically silent) replication results in viral shedding and potential spread to other EBV-naïve hosts.

EBV-associated cancer as a consequence of persistence—EBV plays a part in neoplastic transformation when latency is breeched.. EBV LMP 1 and LMP2A can activate the mTOR, AKT, and PI3K pathways regulating functions relevant to tumorigenesis, including cellular proliferation, growth, survival, and mobility (Fukuda and Longnecker, 2007; Moody et al., 2005; Swart et al., 2000), whereas LMP1 miRNA inhibits the tumor suppressor p53 (Fukuda and Longnecker, 2007; Liu et al., 2005; Moody et al., 2005; Swart et al., 2000). Signaling of tumor suppression pathways that initiate cell cycle arrest and priming of apoptotic pathways occur when latency is lost. EBV-associated neoplasms show three distinct patterns of latency-associated gene expression (Rowe et al., 1992). Burkitt's lymphoma (BL) exemplifies the Latency I program in which the Qp promoter-induced EBNA1 is expressed with small EBV-encoded RNAs (EBERs) and BamHI-A rightward transcript (BART). Latency II, characteristic of nasopharyngeal carcinoma (NPC), EBV-positive Hodgkin's lymphoma, EBV-positive gastric carcinoma, and T and NK-cell lymphomas, involves expression of EBERs, BART, and Qp promoter-induced EBNA, with added LMP 1, 2A, and/or 2B expression (Brooks et al., 1992). Post-transplantation lymphoproliferative diseases (PTLD) are associated with the Latency III program in which all EBV latent gene products are expressed. EBV Latency III-regulated gene products mediate cell migration, antigen presentation, MAP kinase pathway, and interferon (IFN) signaling (Cahir-McFarland et al., 2004).

Latency I program: EBV-associated Burkitt's lymphoma, exogenous cofactors, and *c-Myc*—Burkitt's lymphoma (BL), a high grade B-cell malignancy, has distinct clinical-epidemiological variants: endemic Burkitt's lymphoma (eBL), sporadic (sBL) and HIV-associated (HIVBL). Each of these tumors have reciprocal chromosomal translocations involving immunoglobulin loci on chromosomes 14, 22, or 2, and *c-myc* (*MYC*) on chromosome 8 (Manolov and Manolov, 1972; Dalla-Favera et al., 1982), but only eBL tumors incorporate EBV DNA. Typical of Latency I, only EBNA-1 is expressed in eBL, which is the most common pediatric tumor in Sub-Saharan Africa where EBV acquisition occurs very early in life. Its distribution in regions of Africa and Papua New Guinea where malaria is holo-endemic has implicated *P. falciparum* as co-factor, promoting lymphoma through immunosuppressive effects on EBV-specific T-cell immunity (Njie et al., 2009; Whittle et al., 1984) and B-cell proliferation involving *P. falciparum* erythrocyte membrane protein 1 (PfEMP1) interactions with host memory B-cells harboring latent EBV (Chene et al., 2007). An alternative mechanism implicates malaria and initial EBV-induced B-cell proliferation, with consequent activation-induced deaminase (AID) dysregulation leading to the characteristic *c-myc* translocation and lymphoma (Thorley-Lawson and Duca, 2007). In that schema, emergence of sBL reflects spontaneous (non-microbe driven) *c-myc* translocation whereas, in eBL, an EBV-driven series of events, abetted by *P. falciparum,* culminates in the characteristic oncogenic *c-myc.*

Latency II program: Host HLA types and EBV-associated nasopharyngeal carcinoma—EBV is present in epithelial nasopharyngeal carcinoma (NPC) cells where it establishes a latency pattern with EBNA 1 and either LMP 1 or LMP 2 protein expression (Latency II) (Brooks et al., 1992). The highest incidence of NPC is in Southeast China, particularly in Guangxi Province, where it occurs in association with specific host HLA haplotypes (Tang et al., 2010). The underlying pathogenesis of EBV-induced nasopharyngeal carcinoma remains obscure.

Latency III program: Host immune suppression and EBV-associated PTLD—Post-transplantation lymphoproliferative disorders (PTLD) represent heterogeneous diseases that vary from reactive polyclonal B-cell hyperplasia, to monoclonal tumors, to fatal, aggressive non-Hodgkin's lymphomas (Penn et al., 1969). PTLD may occur after hematopoietic stem cell or solid organ transplantation. Most cases of PTLD are of B-cell origin and EBV-associated (Young et al., 1989). Intensive immunosuppressive regimens to avoid graft rejection affect risk for PTLD development. The highest incidence of PTLD after small bowel transplantation compared to other organs, (e.g. kidney) may relate to the quantity of transplanted lymphoid tissue, with more EBV+ B-cell populations. (Cohen, 2000). EBV latency becomes disrupted in PTLD, diseases related to the intersection of 20th Century medical technologies with an ancient virome constituent. PTLD lesions express EBV Latency III genes, the encoded proteins involved in signal transduction, transcription, protein catabolism, and cell motility, shape, and adhesion characteristics (Carter et al., 2002; Delecluse et al., 1995; McKnight et al., 1994; Rea et al., 1994). Impaired α-EBV T-cell function permits EBV-driven B-cell proliferation resulting in PTLD.

Future therapies

Hanahan and Weinberg outline 10 therapeutic approaches to target the central functional and enabling pathways involved in cancer (Hanahan and Weinberg, 2011). We envision that microbes can be harnessed (Blaser, 1997, 2010) to perform many of these therapeutic functions. For example, colonization of specific niches in the gut lumen (stomach, distal esophagus, rectum) with probiotic bacterial strains capable of modulating local inflammation and immunity, could help control luminal gastro-intestinal tract neoplasia. Similarly, establishment and maintenance of an estrobolome (with diminished deconjugation activity) that favors estrogen excretion pathways may reduce risk of developing estrogen-driven malignancy. Knowledge of the microbiome can be applied to targeting both specific anatomic sites and functional capabilities. Members of the human microbiota can suppress aspects of cellular immunity (e.g.: *B. fragilis* (Mazmanian et al., 2008; Round et al., 2011) whereas others (e.g. *cagA*$^{+}$ *H pylori*) induce pro-inflammatory cytokines (Backert and Selbach, 2008). In the future, we can either beneficially target particular effector microbes to the desired location or engineer the desired genes into microbes that naturally colonize those sites.

Conclusions

The examples provided are not comprehensive, but rather indicate several conserved and paradigmatic mechanisms; microbiome constituents likely will have roles in other human cancers (Garrett et al., 2009; Wu et al., 2009). As recently discussed (Dominguez-Bello et al., 2011), nature must remove senescent individuals to liberate resources for younger members of the same species. A role for our ancient, interactive residential microbes in clock-like functions (Blaser, 1997) is intuitive. In that manner, our residents may be true symbionts, improving host fitness early in life through metabolic and pathogen-defense functions, and leading to demise through neoplasia in the post-reproductive period. If the hypothesis that malignancy is part of mammalian selection is correct, then other human

cancers whose rates are log-linear with age will predictably be found to reflect microbiome-induced pathogenesis.

Finally, the microbiome affects the metabolism of xenobiotics (Figure 2), such as pharmaceutical agents (Clayton et al., 2009), including those used to treat cancer. Responses to particular chemotherapeutic agents have been linked to specific gut microbiome metabolic activities (Wallace et al., 2010). Better knowledge of microbiome composition and metabolic activities will ultimately improve therapeutic choices, with new agents, dosing regimens, and monitoring strategies. Using such knowledge should improve therapeutic/toxic ratios, and represents another exciting frontier in cancer research.

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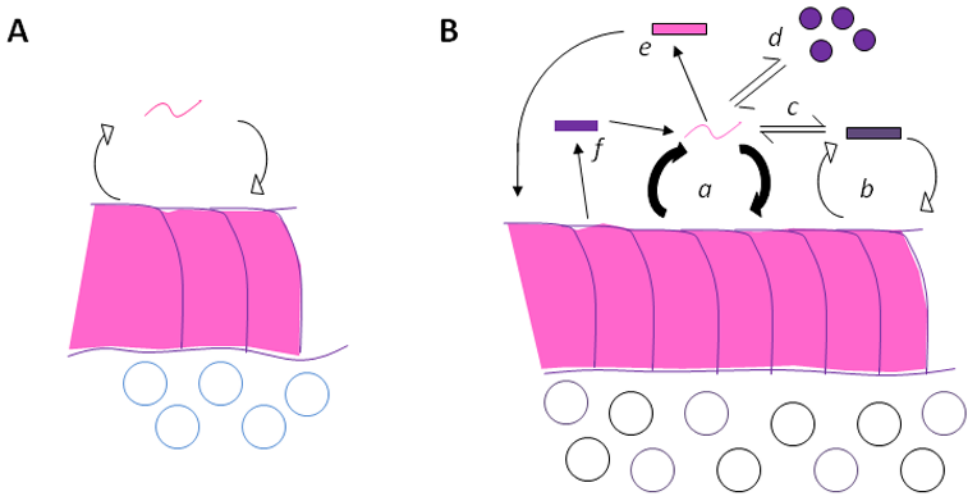


[Ed: colored circles reflect the different inflammatory and immune cells of the lamina propria; to be drawn by artist].

Figure 1. Equilibrium between co-evolved microbes and host cells. Panel A: Single organism equilibrium

In this model, there is a counter-regulatory (negative feedback) interaction involving metabolic and physical signals between microbe and host. **Panel B: Multiple organisms in equilibrium.** In this much more complex system, organisms may have individual equilibrium relationships (e.g. *a* and *b*) with host cells as in Panel A. However, the interaction between these two microbes (*c*) will affect their individual interactions. Similarly, another microbe (*d*) might interact exclusively with an organism (*a*), but not with the host, with the extent of the interaction affecting the equilibrium relationships. An alternative is that an interactive microbe (*a*) can interact with a second microbe (*e*) that directly signals the host, but does not receive direct host signals back. Finally, the host might have a specific interaction with another microbe (shown as *f*), which can have a unidirectional interaction with microbes (e.g. with organism *a*) but not directly with the host.

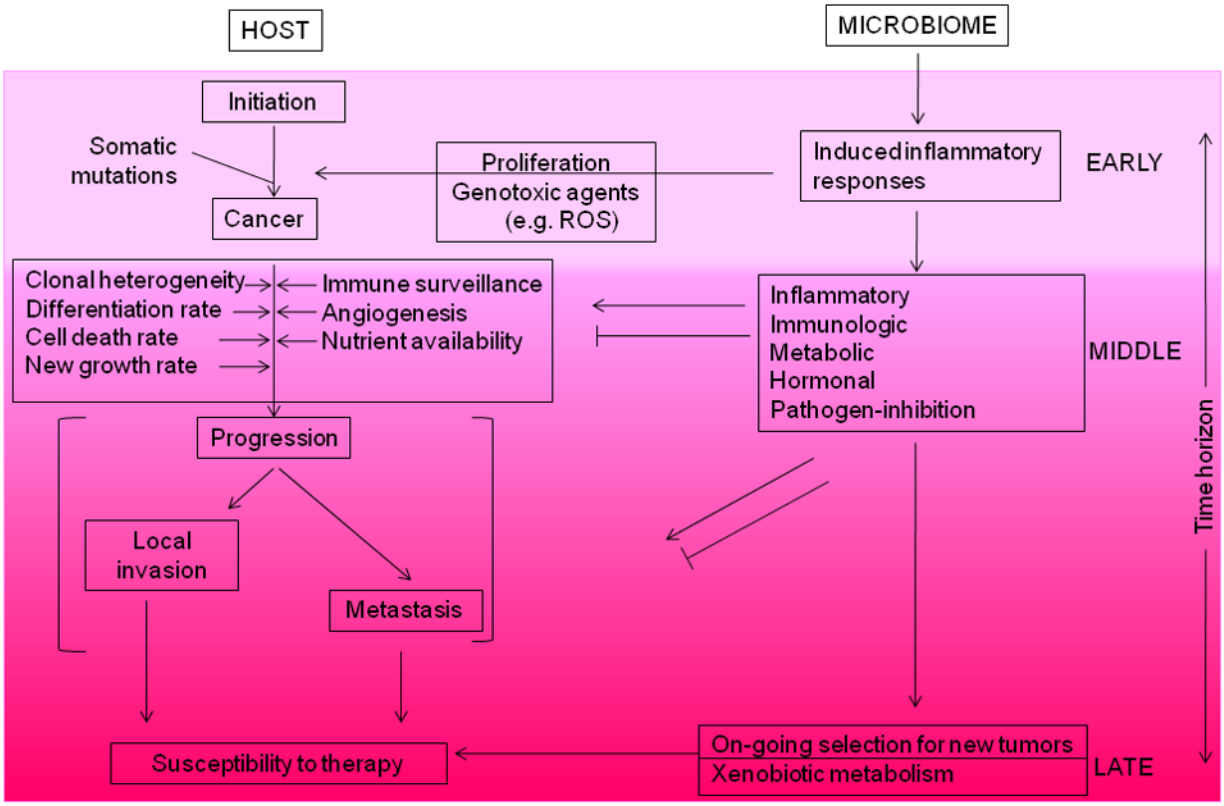


Figure 2. Mechanisms by which the microbiome can enhance malignant transformation and cancer spread

Cancer involves the transformation of physiologically responsive cells into autonomously replicating tumors that have the capacity to invade local tissues or spread widely. Multiple host processes (indicated on the left) govern the success of neoplastic cells to cause cancer. However, the interaction of the microbiome with the host (right) yields effects that can enhance or suppress tumorigenesis. Microbiome-induced inflammation affects the initiation ('EARLY') of cancers. Medium-term interactions affect multiple facets that influence whether or not tumors progress, and if so, in which ways. Finally, 'LATE' interactions affect the susceptibility of the tumor to therapies.

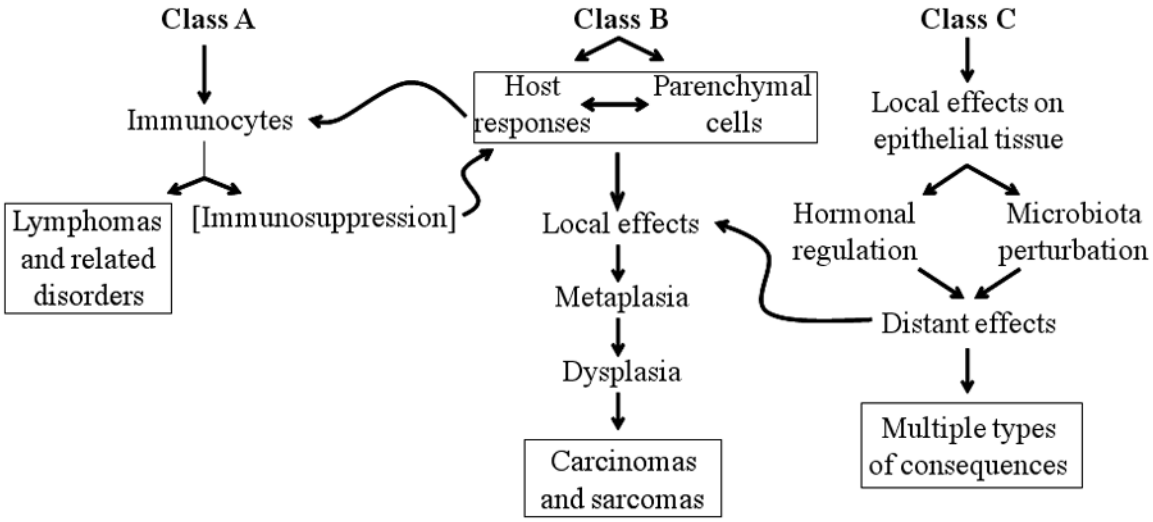
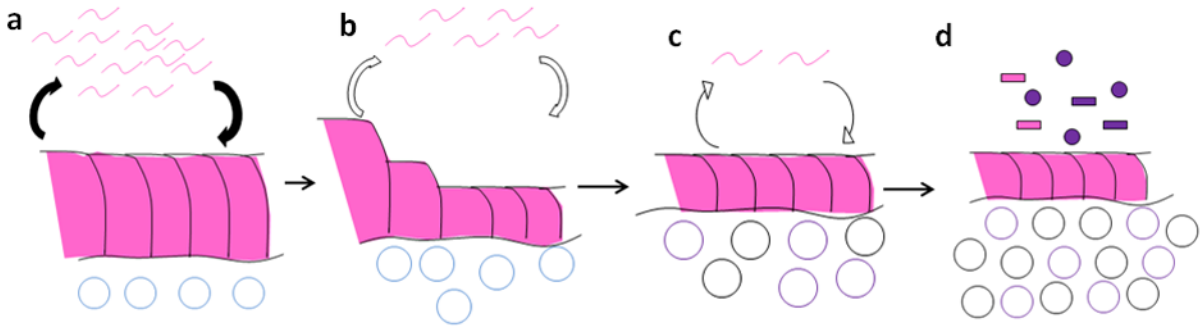


Figure 3. Classification of microbiome-associated human malignancies

Three types of relationships can be envisaged between the microbiome and mechanisms that give rise of cancers. In Class A, the primary interactions involve immunocytes; in Class B, involve local parenchymal cells, and in Class C, the local interactions produce distant effects. Specific examples of all three classes are indicated in Table 1. Adapted from MJ Blaser (2008), with permission.



[Ed: lamina propria cells, as in Figure 1; different colors represent different cell populations].

Figure 4. Multi-decade development of gastric adenocarcinoma initiated by *H. pylori*: ecologic model

The equilibrium relationship of *H. pylori* and its host involves recruitment of a population of immune and inflammatory cells in the gastric lamina propria (**Panel a**). Over time (decades), the conjunction of the organism and its host response results in continued injury to the epithelium with progressive loss of normal architecture and function (**Panel b**). This leads to the development of atrophic gastritis (**Panel c**), with permanently altered architecture, and a reduction in acid secretory function. With hypo-chlorhydria, the gastric niche now is dominated by competing microbiome members that have pathogenic properties leading to further inflammation and tissue injury (**Panel d**). Over this decades-long (essentially life-long) progression, *H. pylori* bacterial populations gradually decline. In the final stage, the *H. pylori*-induced atrophic gastritis lowers gastric acidity which then is a reduced barrier to the intrusion of adventitious pathogenic oro-pharyngeal and intestinal bacteria.

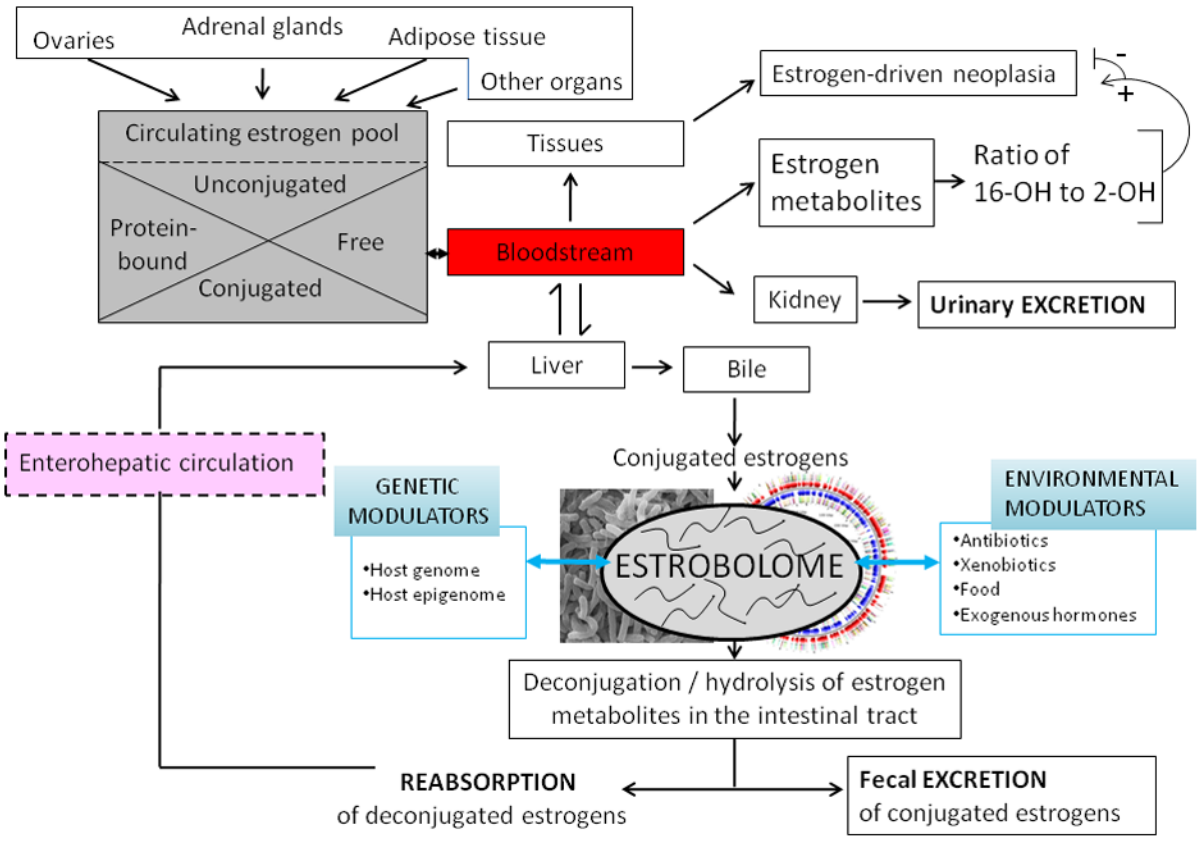


Figure 5. The estrobolome and its switch

Estrogens are steroids hormones derived from the step-wise reduction of C21 cholesterol. The ovaries are the only organs capable of full C21 (cholesterol) → C18 (estrogen) synthesis; at all other sites of estrogen synthesis (e.g. adrenals, adipose tissue), the availability of C19 androgens as substrates and aromatase are limiting factors. Estrogens circulate in the bloodstream free or protein-bound, and are conjugated or unconjugated molecules that may enter target tissues or be eliminated by the kidneys. Circulating estrogens undergo Phase I hepatic metabolism. In the liver, estrogens and their resultant estrogen metabolites (EMs) then may be conjugated, through methylation, glucuronidation, or sulfonation reactions. Conjugated estrogens are subject to biliary excretion. The estrobolome, the aggregate of enteric bacterial genes whose products are capable of metabolizing estrogens, acts on conjugated estrogens and estrogen metabolites, with downstream physiologic effects. An estrobolome enriched in genes encoding enzymes favoring deconjugation promotes reabsorption of free estrogens that contribute to the host's total estrogen burden. Suppression of deconjugation, that may follow antibiotic exposure, leads to increased estrogen excretion (Martin et al., 1975). Estrobolomes varying in functional activity lead to different host-estrogen equilibria, via enterohepatic circulation of varied proportions of conjugated to unconjugated estrogens. The composition of the estrobolome can be modulated by host-specific and/or environmental drivers (e.g. antibiotics) exerting selective pressure on its parental bacterial populations. Shown here for illustration is the ratio of 2-OH/16-OH hydroxylated EMs, that may serve as urinary or serum markers of risk for certain estrogen related cancers (Bradlow et al., 1995; Gupta et al., 1998; Kabat et al., 1997; Meilahn et al., 1998; Muti et al., 2000)

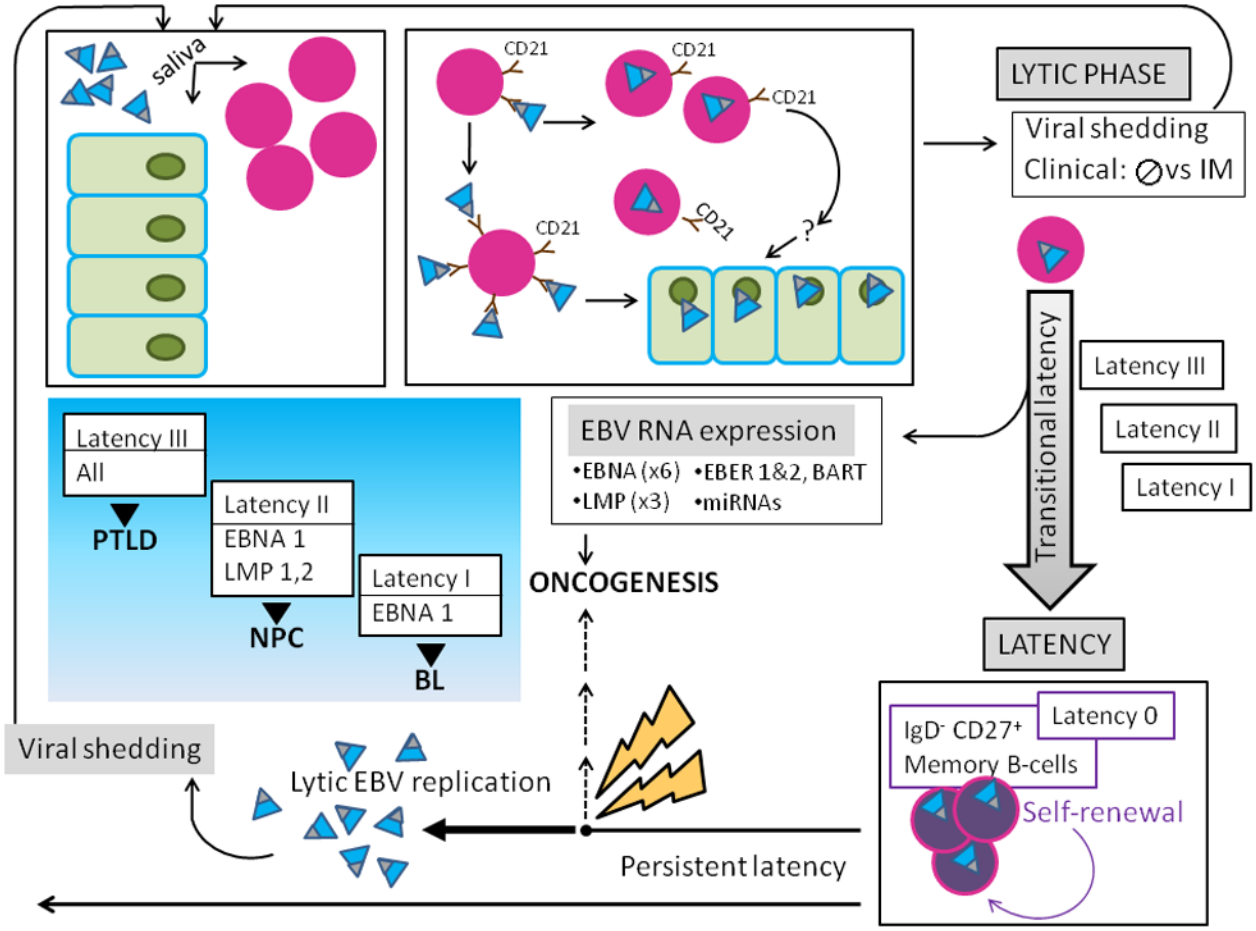


Figure 6. Schematic of EBV-host interactions

A) EBV (teal virions with black tip) is acquired orally, and targets B-cells (lavender nucleated circles) and permissive epithelial cells of the oral pharynx (green). The major EBV envelope glycoproteins gp350 and gp220 (black tip) interact with complement receptor CD 21 (brown) on the surface of naïve resting B-lymphocytes, leading to viral binding. Additional EBV B-cell interactions involving fusion proteins and HLA class II molecules (not shown) lead to virus-cell fusion and EBV internalization. EBV bound to the B-cell surface likely allows for its transfer to orophangeal epithelial cells. The initial lytic viral reproductive phase may be asymptomatic (usually) or may manifest clinical symptoms and is termed infectious mononucleosis (IM). During the lytic phase, virus is shed via the saliva and can infect naïve hosts.

B) After the initial lytic phase, EBV evades host immunosurveillance to achieve persistence though “translational latency”, the tightly regulated selective expression of viral latent proteins and of non-coding RNAs. The former include six Epstein-Barr virus Nuclear Antigens (EBNAs) (1, 2, 3A, 3B, 3C, and LP) and three integral Latent Membrane Proteins (LMPs) (1, 2A, and 2B). The latter include EBERs (1 and 2), small non-coding RNAs abundantly expressed in latently infected EBV cells and multiple microRNAs, encoded by two transcripts (in the BART and BHRF1 loci), that contribute to EBV-associated cellular transformation. Three distinct “transitional” EBV latency programs (Latency I, II, and III) are characterized by specific gene expression profiles that allow for establishing latency and enhancing cell survival and proliferation. After the initial lytic phase, EBV replicates as an episome, in tandem with the host cell genome. EBV employs host cell-driven DNA genomic

methylation and modulation of NF-κβ activity, and Notch signaling pathway manipulations (not shown) to establish true latency (Latency 0) in resting memory B-cells (purple circles), with highly restricted EBV gene expression. Non-pathogenic and invisible to the host immune system, Latency 0 EBV persistently populates memory B-lymphocytes. In the course of the latently infected hosts' life, episodic disruptions of latency occur (depicted as 'STRESS' and yellow bolt), resulting in EBV replication and viral shedding with potential spread to other hosts. Latent EBV also can contribute to several cancers (dashed line), including lymphomas such as Burkitt's Lymphoma (BL), and Nasopharyngeal Carcinoma (NPC). Exogenous immunosuppression may result in Post-Transplantation Lymphoproliferative Disorders (PTLD). The emergence of malignancy appears to require interactions of co-factors, for example *P. falciparum* in BL, and individual host characteristics, including HLA type in NPC.

Table 1

Examples of microbe-induced human malignancies, by class

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

*Represents microbes that are constituents of the ancestral human microbiome.

**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 usual microbial constituents, changes (Δ) in the microbiome also may be involved in inducing some cancers.