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Cancer-Promoting Effects of Microbial Dysbiosis

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Abstract

Humans depend upon our commensal bacteria for nutritive, immune-modulating and metabolic contributions to maintenance of health. However, this commensal community exists in careful balance that, if disrupted, enters dysbiosis; which has been shown to contribute to the etiology of colon, gastric, esophageal, pancreatic, laryngeal, breast and gallbladder carcinomas. This etiology is closely tied to host inflammation, which causes and is aggravated by microbial dysbiosis while increasing vulnerability to pathogens. Advances in sequencing technology have increased our ability to catalog microbial species associated with various cancer types across the body. However, defining microbial biomarkers as cancer predictors presents multiple challenges and existing studies identifying cancer-associated bacteria have reported inconsistent outcomes. Combining metabolites and microbiome analyses can help elucidate interactions between gut microbiota, metabolism and the host. Ultimately, understanding how gut dysbiosis impacts host response and inflammation will be critical to creating an accurate picture of the role of the microbiome in cancer.

Keywords

microbiome; cancer; microbial metabolites; dysbiosis; inflammation; genotoxins

Introduction

The relationship between specific pathogenic bacteria and human carcinogenesis has been the subject of extensive investigation. Historically, most of this research has focused on individual pathogens, such as *Helicobacter pylori*, and their potential to initiate and perpetuate disease. Previous research focus was on the disease process rather than beneficial gut-microbe interactions. More recently, extensive research supports commensal bacteria playing a role in protection of host health via nutritive, immune-modulating and metabolic processes [1, 2]. In addition, the more holistic approach of characterizing entire communities

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of gut bacteria and their interactions is now possible through use of high-throughput DNA sequencing technology. Characterization of the gut microbiome as a whole has furthered our understanding of intestinal microbial ecology to include community-level functions and changes. In healthy individuals, the gut microbiome functions as a symbiont that can offer protection from invading pathogens and prevent tumorigenesis [3]. However, this commensal community exists in careful balance that, if disrupted, enters dysbiosis and contributes to host disease processes, including cancer [4-7]. While recent findings still support individual microorganisms influencing carcinogenesis, greater emphasis is on microbial dysbiosis and its larger role in cancer initiation and progression. The focus of this review is on gut microbial community dynamics that shift state from symbiosis to dysbiosis and the subsequent host immune and pathogen response, which drastically alters initiation and progression of multiple types of cancer.

Proposed mechanisms for microbiome involvement in colorectal cancer

Multiple studies report different gut microbiome composition in individuals diagnosed with colorectal cancer (CRC) versus healthy individuals [8-11]. In fact, gut microbiota can play a role in either promotion or prevention of CRC, often through modulation of the inflammatory process due to close contact with host colonic mucosa [5]. For example, chemically induced injury and proliferation induced by azoxymethane (AOM) and dextran sulfate sodium (DSS) was enhanced in germ free mice, which lack protective commensals. In addition, tumor development in the germ-free mice resulted in significantly more and larger tumors compared to specific pathogen free mice [12]. Balance of the gut microbial community, or eubiosis, can be disrupted by an inflammatory environment in the host. For example, host inflammation may influence microbiota composition through generation of specific metabolites such as nitric oxide synthase (NOS2). Nitrate provides a unique energy source for facultative anaerobic bacteria allowing them to outcompete bacteria that cannot utilize nitrates [13], disrupting balance of the gut microbiome and resulting in dysbiosis. Pro-inflammatory responses can also compromise barrier and immune function to allow bacterial translocation through intestinal tight junctions and intensify the inflammatory response [14].

How inflammation interacts with the gut microbiome to influence CRC has been recently synthesized in several hypotheses that summarize our understanding of the interactions to date (Figure 1). The ‘alpha-bug’ hypothesis suggests that a keystone pathogen species, such as Enterotoxigenic *B. fragilis* (ETBF), remodels the colonic microbiota to promote CRC, possibly via IL-17 and T_H17 cell-mediated inflammation. This process could also be initiated by microbial-independent host-mediated inflammation and may be blocked by beneficial commensal microbiota [15]. Similarly, the bacterial driver-passenger model suggests that ‘driver’ bacteria, such as ETBF, cause or aggravate inflammation and produce genotoxins that lead to cell proliferation and mutations. Subsequently, an adenoma forms and is colonized by ‘passenger’ bacteria such as *Fusobacterium spp.* that encourage tumor progression [16]. Following tumor formation, the intestinal barrier is damaged by the continual inflammation and allows bacteria access to tumor tissue. These bacteria and their metabolites stimulate additional inflammatory signals, including IL-17 cytokines, promoting cancer progression [17]. Inflammatory signals may also stimulate macrophages, via

induction to an M1 phenotype, to produce chromosome-breaking factors through a bystander effect, damaging DNA and inducing chromosomal instability in neighboring cells [3]. Likely CRC initiation and progression is engendered by aspects of each of these models.

Once bacteria translocate beyond a damaged intestinal epithelium, the host immune system responds with activation of multiple pattern recognition receptors (PRRs) PRRs important to the CRC process include membrane-bound Toll-like receptors (TLRs) and cytoplasmic NOD-like receptors (NLRs) [6]. Specifically, TLR2 and TLR4 have been shown to be important to tumor formation in murine models and recent associations between human genetic polymorphisms in TLR2 and TLR4 and CRC risk support a role in humans [18]. Furthermore, activation of nuclear factor (NF)-κB plays a role in CRC tumor initiation by enhancing both cytokines [4, 19] and Wnt-signaling, which can convert intestinal epithelial nonstem cells into tumor-initiating cells [20]. The role of NF-κB in CRC is complex and involves additional signaling pathways which have recently been extensively reviewed [21]. Alternatively, in colitis-associated CRC, TLR signaling in tumor-associated fibroblasts initiates an inflammatory cascade independent of NF-κB via epiregulin (EREG). EREG stimulates the extracellular signal-regulated kinase (ERK) pathway, which encourages tumor proliferation [22]. Two NLRs are associated with CRC risk: NOD2, which is activated by the bacterial peptidoglycan, muramyl dipeptide; and NOD-, LRR-, and pyrin domain-containing 6 (NLRP6). With NOD2 deficiency, dysbiosis alone was sufficient for CRC development in mice [23]. However, recent research by Shanahan et al. reveals that NOD2-associated dysbiosis can be overcome by co-housing NOD2 mutants with wild type mice [24]. Future research is necessary to clarify the role of NOD2 and NLRP6 in gut microbial regulation. However, the role of bacterial translocation across intestinal epithelia in activation of TLR and NLR and in promoting inflammation is strongly supported [5, 6, 25, 26].

Also ‘driving’ the cancer initiative process are pathogens that have been shown to promote tumorigenesis via genotoxic effects including: *Escherichia coli*, *Enterococcus faecalis*, and *Bacteroides fragilis*. Pathogenic strains of *E. coli* generally belong to groups B2 and D and produce genotoxic virulence factors, called cyclomodulins. Cyclomodulins can modulate cellular differentiation, apoptosis and proliferation [27] and include colibactin, cytotoxic necrotizing factor (CNF) and cytolethal distending toxin (CDT). Group B2 *E. coli* that produce cyclomodulins are highly prevalent in colonic mucosa of CRC patients [28]. *E. faecalis* indirectly increases genotoxin production in the form of DNA damaging reactive oxygen species (ROS) and reactive nitrogen species (RNS) by inducing an M1 phenotype in host macrophages [3]. ETBF releases fragilysin (also known as BST), a toxic virulence factor that induces DNA damage *in vivo* [29]. All of these organisms have also been shown to play a role in carcinogenesis via induction of inflammatory pathways [7]. In addition, *Fusobacterium* was recently associated with an upregulation of NF-κB–driven inflammatory genes and was identified as being enriched in colonic tumors [30]. While specific organisms exert these genotoxic effects, the effects are made possible and intensified through a prior state of dysbiosis.

Microorganisms associated with tumor occurrence and formation in CRC

A major goal of the Human Microbiome Project has been to define a "core" microbiome that could be useful in identifying deviations from a normal, healthy state. While the identification of a healthy core intestinal microbiome has remained elusive, numerous comparative studies have begun to reveal the relationship of the microbial community to CRC. The importance of the microbiome in tumor initiation and development has been elegantly demonstrated in murine models. Transfer of the microbiota from tumor bearing mice induces tumor formation in healthy animals [11] and mice with a genetic predisposition to develop CRC are spared when treated with antibiotics [31]. Retrospective human cohort studies encompass a range of sample types and populations, addressing questions related to global differences in the microbiome of healthy individuals relative to those afflicted with CRC or adenomatous polyps, and differences in the intestinal microclimates between healthy tissue and tumor tissue of an affected individual. Taken together, these studies are beginning to define a CRC-associated microbiome.

Although no bacteria have consistently been associated with CRC across all studies, the Gram-negative oral commensal *Fusobacterium nucleatum* has been most strongly linked to CRC. Several studies examining the colon tumor microenvironment by comparing tumor tissue to adjacent healthy tissue reported an overabundance of *Fusobacterium* associated with tumors [8, 30, 32]. A Chinese study reported a trend for increased *Fusobacterium* in tumor tissue relative to matched controls, but failed to achieve significance, which may be a result of the small study size (n=8), but could also indicate that *Fusobacterium* association with CRC is not consistent across different ethnicities [33]. Additional studies have confirmed that *Fusobacterium* spp. are enriched in pre-cancerous adenomas, particularly those displaying high grade dysplasia [30, 34]. Kostic et al. also reported higher stool levels of *Fusobacterium* in adenoma and CRC patients compared to healthy controls [30]. They also observed that ApcMin/+ mice infected with *F. nucleatum* had increased tumor multiplicity and selective recruitment of tumor-promoting myeloid cells. Activation of β-catenin signaling, which regulates inflammatory and oncogenic responses via binding of the FadA adhesin produced by *F. nucleatum* to E-cadherin in host membranes provides further evidence for the role of *Fusobacterium* as a driver of CRC initiation and progression [35].

Although it is known that mucosa adherent bacteria differ significantly from those found in the intestinal lumen, the identification of a CRC-associated stool microbiota is appealing for diagnostic and prognostic purposes. Unfortunately, there appears to be little consensus in the existing published literature of specific bacterial associations and even more general measures such as bacterial community diversity do not appear to consistently predict CRC. Sobhani et al. reported no differences in bacterial community diversity between case and control stool samples, but did note enrichment in *Bacteroides/Prevotella* in CRC stool samples, which was corroborated in mucosa samples from tissue biopsies [9]. They also reported depletion of *Bifidobacterium longan*, *Clostridium clostridioforme*, and *Ruminococcus* species. Another study reported higher levels of *Akkermansia muciniphila* and *Citrobacter farmeri* in CRC cases, and decreased butyrate-producing species such as *Ruminococcus* and *Roseburia* relative to controls [10]. *Akkermansia* is a common commensal in the intestines of humans and its depletion was previously associated with

Crohn's disease and IBD [36]; however, it was demonstrated to be important in CRC tumor development in a murine model [11]. In the largest study to date examining stool microbes, a decrease in the microbial diversity of CRC cases was observed, as well as decreased *Clostridium* species [37]. This study also reported higher *Fusobacterium* present in stool samples from CRC cases, suggesting possible utility of stool in reflecting mucosa levels of this tumor-associated bacterium. However, the composition of stool microbial communities appears to be a poor predictor of CRC presence based on current knowledge, and more large cohort studies are needed before effective diagnostic or prognostic tests can be developed using bacterial biomarkers in stool samples.

Microbiome Involvement in Gastric and Esophageal Cancers

Stomach and esophageal linings come in close contact with microbiota and recent evidence supports that the microbiome also influences these cancers. The longest-known and most extensively characterized association between these cancers and a gut microbe is with *H. pylori* infection. Mongolian gerbils, whose gastric system more closely resembles humans than the widely implemented mouse models, showed that 37% of *H. pylori* infected animals developed adenocarcinomas while no tumor development occurred in uninfected controls [38]. More recent work with this animal model suggests that long-term *H. pylori* infection disrupts the gut microbial community. *H. pylori* negative gerbils were observed to have decreased abundance of *Bifidobacterium* spp. , *C. coccoides* group and *C. leptum* subgroup but a higher abundance of *Atopobium* cluster [39]. In addition, three lactobacillus species, *L. reuteri*, *L. johnsonii*, and *L. murinus* inhibit *H. pylori* growth *in vitro*, suggesting that some gut microbes may help prevent *H. pylori* infection [40].

Human studies comparing stomach microbiota in cancer patients and healthy controls indicate that microbes other than *H. pylori* must be present to facilitate mucosal movement toward gastric cancer development [41, 42]. In fact, many people infected with *H. pylori* do not develop gastric cancer [42]. Aviles-Jimenez et al. noted decreases in *Porphyromonas*, *Meisseria*, and *Streptococcus sinesis* and increased *Lactobacillus coleohominis*, *Pseudomonas* and Lachnospiraceae among gastric cancer patients [41]. The noted increase in *L. coleohominis*, a species previously thought to be beneficial, is supported by Dicksved et al., who measured an increase in terminal restriction fragments (TRFs) corresponding to *Lactobacilli* in gastric cancer patients' samples [42]. Further investigation of this phenomenon and of *H. pylori* interactions with the gut microbiome is required to better understand its role in the disease process.

Eradication of *H. pylori* has been shown to correlate with a decrease in incidence of gastric cancer [42]. Shin et al. showed a decrease in the methylation of the LOX tumor suppressor gene with eradication of *Helicobacter felis*, the murine equivalent of *H. pylori* [43]. A study by Cai et al. indicates that eradication therapy is most effective in restoring parietal cells and reducing dysplasia when *H. felis* infection duration is less than 6 months. Infections lasting longer than this time period, when dysplasia and metaplasia are more severe, resulted in only partial reversion of these lesions [44]. Results from human studies of *H. pylori* eradication for prevention of gastric cancers are conflicting and need to be conducted on

larger cohorts with longer follow-ups in order to assess the effectiveness of this strategy for chemoprevention.

Several mechanisms have been proposed by which *H. pylori* induces development of gastric cancer. *Helicobacter pylori* infection increases cell proliferation, leading to the increased turnover of the gastric mucosa which could lead to a higher incidence of mutation and less time for DNA repair [38]. Mice lacking secretory phospholipase A2 (sPLA2), such as C57BL/6 the showed increased levels of apoptosis after oral infection with *H. felis* and expansion of aberrant gastric mucosa cell lineages; indicating that sPLA2 influences the response of gastric mucosa to *H. felis* infection [45]. Raf-kinase inhibitor protein (RKIP) regulates the cell cycle and apoptosis in the gastric mucosa. In infected mucosa, *H. pylori* phosphorylates RKIP, removing apoptotic control and inducing proliferation by removing control of the cell cycle [46]. Another tumor suppressor gene, LOX, was shown by Shin et al. to be methylated in transgenic mice infected by *H. felis* [43]. The down-regulation of these tumor-suppressing proteins allows gastric adenocarcinoma to develop in the presence of *H. pylori* infection.

Helicobacter pylori infection has also been implicated in the development of esophageal cancer, but its role is unclear [47]. Anderson et al. showed an increase in seropositivity for *H. pylori* in junctional tumors, those involving the esophagus and gastric cardia. However, in tumors that do not involve the gastric cardia, *H. pylori* is associated with a lowered risk of tumor development [48]. More is known about the microbiome of reflux esophagitis and Barrett metaplasia, which are precursor states to esophageal cancer. In these conditions, dominance shifts from Gram-positive bacteria to mostly Gram-negative, suggesting that dysbiosis plays a role in the disease process [49]. It's likely that other microbes are also involved in tumor development in the esophagus. Cancerous esophageal tissue shows a higher prevalence of *Treponema denticola*, *Streptococcus mitis*, and *Streptococcus anginosus*, as compared to normal tissue. These pathogens induce inflammation by cytokines, possibly supporting tumor development [50].

Microbiome Involvement in Other Forms of Cancer

The microbiome has also been implicated in the etiology of pancreatic [51], laryngeal [52], and gallbladder [53] carcinoma. Farrell et al. noted significant shifts in oral microbial composition between healthy and pancreatic cancer groups. Among cancer groups, significant decreases were noted in *Neisseria elongata and Streptococcus mitis* (a pathogen also implicated in esophageal cancer [50]). These significant changes in oral microbiota with the development of pancreatic cancer indicate potential for oral *N. elongate* and *S. mitis* to serve as biomarkers for pancreatic cancer occurrence [51].

In gallbladder cancer, *Salmonella* infection is shown to be of particular importance [53] . The gallbladder is a known reservoir of *Salmonella*, leading to increases in secondary bile acid concentrations, which linked to tumor promotion [54]. Sharma et al. showed an association between the typhoid carrier state and gallbladder cancer. In addition, bile culture-positivity is associated with increase in gallbladder carcinogenesis, especially positivity for the Vi antigen (a capsular antigen associated with *Salmonella*) [53]. These

associations indicate the relevance of the microbiome in the etiology of multiple cancer types.

Viruses are also a component of the gut microbiome and can influence cancer risk. For example, DNA from Human Papillomavirus (HPV) is detected in almost all cervical cancers [55]. Extensive study indicates that viral antigens E6 and E7 contribute to the malignancy of HPV-induced cervical cancer [56]. However, estrogen is required for the development of cervical cancer from HPV infection. In mice and rats, 83% of HPV infected animals develop cervical cancer after estrogen treatment [57]. Estrogen treatment leads to increased transcription of viral antigens E6 and E7, contributing to cervical carcinogenesis [56]. In addition, the presence of estrogen receptor α (ERα) is necessary in the development of cervical cancer from HPV infection [58, 59], as ERα knockout mice do not develop cervical cancer when infected with HPV [58]. As intestinal microbes affect circulating estrogen levels [60], these commensal organisms may be involved in the development of cervical cancer from HPV infection; however, further study is needed to support this link.

HPV, in conjunction with *H. pylori*, has also been implicated in laryngeal cancer [52, 61]. Gong et al. associated a total of 15 additional genera with laryngeal carcinoma tissue, with noted increases in *Fusobacterium*, *Prevotella*, and *Gemella*. *Fusobacterium* and *Prevotella* in particular are thought to be associated with the development of biofilms that stimulate an inflammatory response [52], leading to laryngeal cancer development [62]. While HPV and *H. pylori* are both involved in laryngeal cancer development, not much is currently known about how viral and bacterial members of the microbiome interact, an intriguing topic for future research.

Role of microbial metabolites in cancer development and progression

Changes in bacterial metabolism can modulate cancer risk and often accompany dysbiosis of the gut microbiome. Specific bacterial metabolites associated with increased CRC risk include: prostaglandin E2 [63] and multiple secondary bile acids (SBAs) [10]. Conversely, decreased CRC risk is associated with indole [64], anti-oxidants [63] and the anti-proliferative metabolites butyrate [10] and ursodeoxycholic acid [10]. Indole, a bacterial quorum-sensing molecule produced by catabolism of tryptophan, enhances barrier function of colonic epithelial cells *in vitro*. *In vivo* experiments suggest indole is a byproduct of gut microbial metabolism as indole is significantly lower in germ free mice compared to specific pathogen free mice. *In vivo* experiments also suggest that indole enhances function of both tight-junctions and adherens junctions in both germ-free and specific pathogen free mice [64]. Butyrate has known anti-tumorigenic and anti-proliferative effects due to its regulation of genes that inhibit cell proliferation and induce apoptosis via histone deacetylase (HDAC) inhibition [65]. Ursodeoxycholic acid (UDCA), a microbial metabolite of a primary bile acid, has been shown to prevent colorectal tumor development in animal and preclinical models [66]. UDCA has been administered in clinical trials as a chemopreventive agent and a systemic review of UDCA's effect on the incidence or recurrence of CRC is currently underway [67]. However, some evidence also exists to suggest that UDCA may be pro-carcinogenic at higher doses [68].

Secondary bile acids (SBAs) such as deoxycholic (DCA) and lithocholic acid (LCA) are produced as products of microbial metabolism of primary bile acids produced by the host. The promotion of CRC by DCA and LCA and other SBAs has recently been extensively reviewed [69]. Recent evidence points to bacteria in Clostridium cluster IX as a possible source of increased DCA and cancer risk in obese mice [70]. DCA in particular was found to increase rapidly, with 24 hours, on an animal based diet and was linked to overgrowth of inflammation causing microorganisms associated with inflammatory bowel disease [71]. However, DCA also acts as a ligand of the FXR receptor [72], which has been shown to reduce liver and intestinal tumor growth and metastasis [73]. Similarly, LCA may prevent DNA damage, and therefore tumorigenesis, through stimulation of xenobiotic metabolism and excretion [74]. While LCA and DCA are predominantly characterized as promoting CRC, future research in this area may reveal a more complex role for these metabolites in the CRC process.

Extensive study indicates a role of intestinal microbes in the metabolism of dietary estrogens. In patients treated with ampicillin, fecal excretion of estrogen metabolites increases, indicating that re-absorption into the bloodstream is reduced with diminished intestinal microflora [75]. Adding further support to the involvement of intestinal microflora in estrogen metabolism, fecal microbes are shown to carry out oxidation and reduction reactions on estrogens and can shift intestinal concentrations of estrone and estradiol [60]. Although no definite link has been observed between intestinal microflora estrogen metabolism and cancer development, it is reasonable to anticipate the existence of such a mechanism.

Definitive linkage between estrogen levels and breast cancer development has been shown [76]. In rat models, implanted estrogen leads to cyst formation in mammary tissue [77]. In addition, the presence of anti-estrogen antibodies- decreasing estrogen concentrations- delays the onset and growth of mammary tumors in rats and mice [78]. Specifically, 16α hydroxylation of estrogen, a reaction shown to be carried out by the intestinal microflora [60] is associated with an increase in risk for the development of breast cancer [79]. Considering these results and the similarity between the etiology of colorectal cancer and breast cancer, Hill et al. hypothesized a link between breast cancer development and metabolism of estrogen by intestinal microflora [78].

Recent techniques combine analyses of changing metabolites and microorganisms in an effort to understand interactions between gut microbiota, metabolism and the host [10, 80, 81]. Further research in this area will deepen the mechanistic understanding of microbial metabolism in the cancer disease process.

Conclusion

The role of microorganisms in cancer initiation and progression can no longer be simply described as a pathogen-disease relationship. Evidence that our microbiome also functions to promote health and prevent disease by encouraging apoptosis and limiting proliferation and inflammation is growing. A microbiome in a state of balance helps to sustain human health, but as this balance is disrupted via inflammatory processes the community changes

and becomes vulnerable to invasion by pathogenic organisms. If these pathogens successfully establish, then a disrupted state of dysbiosis occurs allowing for further inflammation and production of genotoxins and other carcinogenic microbial metabolites. In addition, dysbiosis was recently hypothesized to contribute to the evolution of pathogens, which could potentially raise cancer risk [82].

However, as we begin to better understand the gradient of eubiosis to dysbiosis (Fig 1), we can develop methods to manipulate the gut microbiome to promote health. As an example, we already know that diet plays a large role in bacterial species of the microbiome, their metabolites and cancer risk. A recent study looked at rural Africans who exhibit significantly lower risk of CRC compared to African Americans. Rural Africans were shown to have increased *Prevotella* spp. and butyrate as compared to African Americans who had higher *Bacteroides* spp. and SBAs [80]. These differences may be a consequence of Rural Africans having higher resistant starch intake and African Americans having higher meat and fat intakes [83]. Dietary choices can affect cancer risk [80, 81, 84] and changing diet to potentially reduce risk is the exciting topic of much current study [85, 86]. Diet represents just one example of how to apply our growing knowledge of gut microbiome dynamics toward health promotion and disease prevention. Other potential therapies to modulate the gut microbiome include fecal transplants [87], probiotics [88, 89], exercise [90] and likely many more that we may have failed to mention. Future studies should focus on these therapies and their mechanisms to improve applications in a clinical setting.

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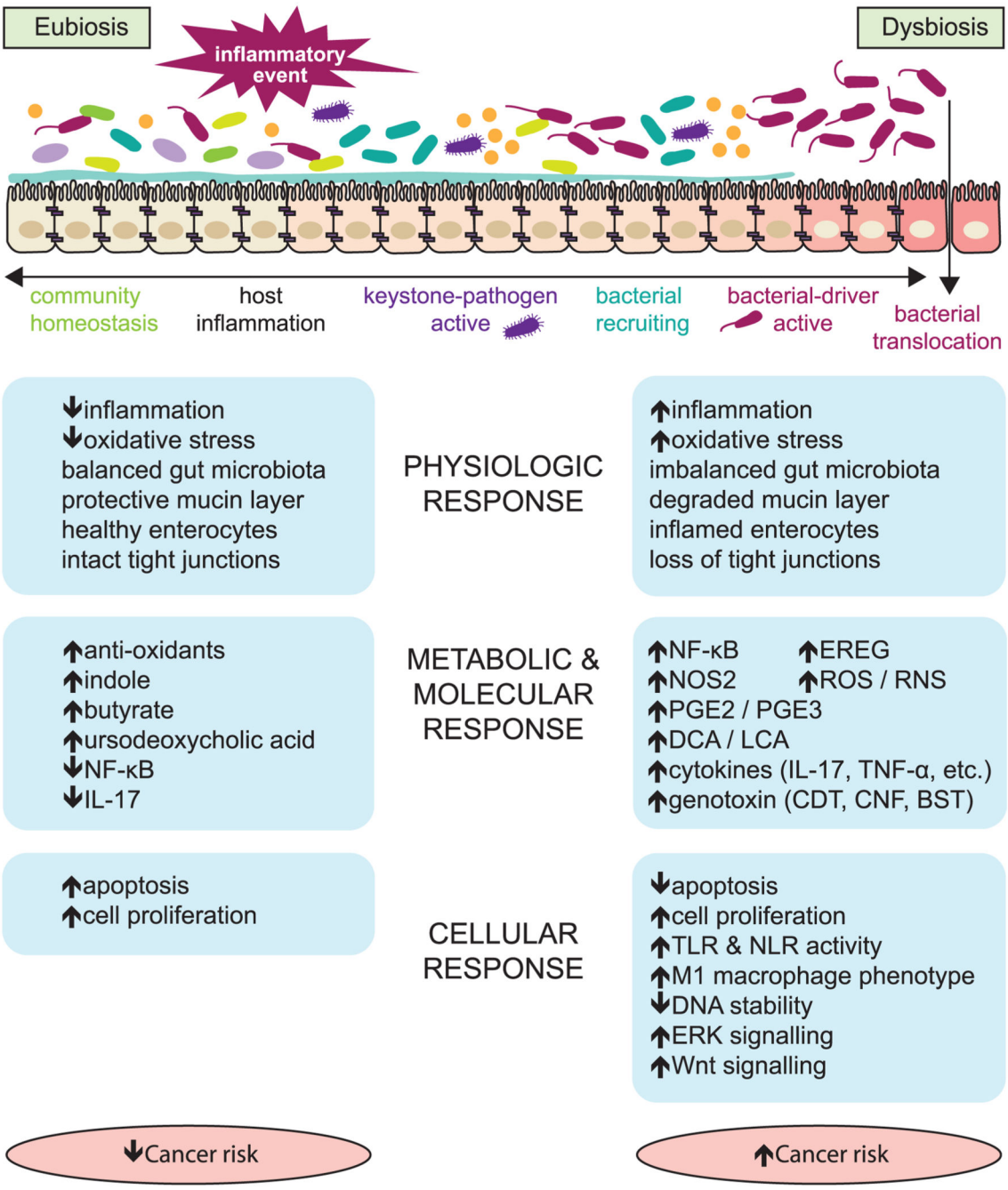

Figure 1.

The progression of the gut microbial community from a state of balance (eubiosis) to imbalance (dysbiosis) is associated with physiologic, metabolic and cellular responses in the host that modulate cancer risk.