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Review

Gut bacteria and cancer

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ABSTRACT

Microbiota on the mucosal surfaces of the gastrointestinal (GI) tract greatly outnumbers the cells in the human body. Effects of antibiotics indicate that GI tract bacteria may be determining the fate of distal cancers. Recent data implicate dysregulated host responses to enteric bacteria leading to cancers in extra-intestinal sites. Together these findings point to novel anti-cancer strategies aimed at promoting GI tract homeostasis.

Contents

1. Introduction

Breast cancer is the most frequently diagnosed cancer in women [1–3]. It has been known for some time that antibiotics and anti-inflammatory drug therapy, such as aspirin, alter relative risks for breast cancer in women [4–6]. However, the etiopathogenic factors leading to breast malignancy are not well understood [5,7,8]. During studies of gastrointestinal (GI) tract inflammation, it was discovered that certain gut commensal bacteria trigger not only colonic tumors but also mammary and prostate gland tumors in susceptible mouse models [9,10]. More recently, human milk-borne microbes were found to inhibit mammary neoplasms in predisposed mice [11], with effects transcending several generations [12]. This raises the intriguing possibility that our microbial passengers may unveil novel targets for cancer prevention and therapy.

1.1. Cancer development is a multi-factorial process

Cancers of tissues including the colon and breast are attributable to complex interactions between cells surviving genetic damage and their micro- and macro-environments [13–16]. This continuous interplay eventually leads to the formation of indestructible cancer cell clones through a natural selection process [14]. Immune and stromal cells, cytokines, proteases and hormones are now acknowledged as major environmental contributors in the natural history of cellular malignant transformations [13,14]. Consequently, the immune system status [17], the metabolic profile [18] and the psychological condition of the host [19], which influence each other at the whole organism level,

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could be viewed as external determinants of the perturbed ecosystem of abnormal cells with neoplastic potential.

Studies in animal models of cancer increased the understanding of the multistep evolution of dysplasia and pre-neoplasia to cancer [11,20–22]. Several of these studies have also highlighted the fact that early neoplastic lesions are less autonomous in their growth than previously thought [11, 22–26]. Instead, their thriving and evolution depends on their micro- and macro-environment [13–15,17,27,28]. This finding raises interesting possibilities for cancer prevention. Indeed, accidental gene mutations occurring during the lifetime of a human being are countless [15,29]. Therefore, most people develop focal dysplastic and pre-neoplastic lesions during their lifetimes. These lesions rarely develop into cancer. However, co-existing local or systemic smoldering inflammatory disturbances of homeostasis have a trophic effect on them, promote their development, and greatly increase the chances of carcinogenesis [15,17,23].

Taken together these recent conceptual advances in tumor biology suggest that immune system elements, hormones and psychosomatic factors may determine the fate of pre-neoplastic lesions towards progression to cancer through interrelated mechanisms. This raises an important question whether effective modalities that could contribute towards shaping an overall systemic homeostatic, non-tumor promoting status may exist.

Recent findings using mouse models suggest this may be possible. It appears that supplementation with certain gastrointestinal bacteria initiates multifaceted systemic events that overlap with basic pro-carcinogenic signaling [12,27,28,30–34]. In this case, bacteria apparently suppress the evolution of early neoplastic lesions to cancer in epithelia locating distally from the gut, such as those of mammary gland, by down-regulating the systemic inflammatory index in the form of pro-inflammatory cytokine levels and inflammatory cells [11]. Beneficial Firmicutes bacteria including *Lactobacillus* spp. are likewise able in mice to interrupt metabolic disorders such as obesity and induce a reproductive fitness-matching hormonal milieu with youthful testosterone, free thyroxin (T4), and oxytocin levels [35–37]. Interestingly, these same hormones have been connected with healthful mentality and anxiolytic effects [38–40]. As pivotal elements of the gut microbiota-brain axis, certain gastrointestinal tract bacteria are being introduced as psychobiotics due to their potential to counteract depression and promote a sense of well-being [41].

2. Our gut reactions: a balancing act that shapes systemic immune tone

The GI tract encompasses the largest surface of the human body where microbial products interact with the immune system. It has become clear that balance of systemic health is routinely enforced by activities of CD4 + T regulatory (T_{REG}) cells along mucosal surfaces. These lymphocytes have evolved to play a sophisticated balancing act of allowing host protective immune responses during acute inflammatory responses, while later regaining suppressive roles that limit deleterious pathological sequelae of chronic smoldering inflammation [42–44]. Recent evidence highlights the important developmental and functional associations of intestinal microbiota with T_{REG} cells [45–48]. Both in vitro data and lymphocyte titration experiments in preclinical models have revealed that homeostatic potency of T_{REG} [ie., ability of T_{REG} to restore homeostasis after environmental insults] is modulated by prior intestinal bacterial challenges [9,23,49–55]. These studies on T_{REG} cells complement other data showing an array of different effects of gut bacteria on systemic innate and adaptive immunity [56] thus solidifying a pivotal role for gut microbiota in shaping systemic immune tone and responses [Fig. 1].

Disruptive events in the GI tract also increase risk for microbial translocations [57] together with systemic immune cell trafficking. Microbial translocation from gut to mammary tissue has been postulated in breast cancer etiopathogenesis [74]. The subsequent increase of the systemic inflammatory index would be expected to increase likelihood of cancer in distal tissues. However, the bacterial translocation due to the compromised intestinal integrity caused by cancer treatment therapies has been shown to augment anti-tumor immunity networks of activated myeloid cells and T-lymphocytes. This beneficial effect was lost in germ-free mice or animals treated with antibiotics. Therefore, in this setting, bacterial translocation worked synergistically to certain cancer therapeutic regimens [32,33,56,58]. This discrepancy is not surprising. The divergent effects of translocating bacteria-induced systemic immune responses on neoplastic disease outcomes reflect the multifaceted relationship of inflammation with cancer.

Taken together, there is abundant evidence that bacteria modulate cancer development and growth. Finding that bowel bacteria or their products promote a competent, healthy immune system provides an explanation for perplexing increases in cancers arising from epithelia in colon, breast and other sites in countries with more stringent hygiene practices [23,59]. Along similar lines, chronic antibiotic therapy may disrupt constructive bacterial processes, ultimately leading to higher rates of breast cancer in women [4]. Systemic NSAID therapy has been linked with significant decreases in several types of cancer [60–63]. Thus, ways in which gut microbiota stimulate inherent host homeostatic properties are an attractive target for systemic good health approaches using probiotic bacteria or microbial product vaccines.

3. Cancer and inflammation: interleukin-6 and neutrophils

In the context of cancer, inflammation is widely believed to represent the body's fight against tumor cells [64,65]. Other data, however, suggests just the opposite; chronic smoldering inflammation may be a cause of cancer and is a powerful stimulus for tumor growth and invasion [66–68]. These opposing observations are not easily reconciled, and are most easily comprehended in the context of immune balance, with cancer arising during dysregulated attempts by the host animal to restore homeostasis after an insult.

Several lines of evidence support that pathogenic GI tract microbiota stimulate certain innate immune cells to enhance tumor formation throughout the body [9,22,69–74]. In order to identify the key immune cell players, prior studies have built upon reciprocal systemic relationships existing between neutrophils, mast cells and macrophages with cells of adaptive immunity [70,75–81]. During homeostasis, these immune networks are persistently down-regulated by anti-inflammatory activities of CD4 + T_{REG} that bestow intestinal homeostasis [9,52,69]. In this context, a weakened T_{REG}-mediated inhibitory loop imparts carcinogenic consequences of elevated IL-6 and possibly IL-17, leading to more frequent inflammation-associated distal cancers [82]. In this context, neutrophils have been identified in animal models as an important factor in cancer initiation and development [24–26,70,83–88]. A distant neoplastic effect of a commensal gut microbe was recently shown in FVB-Tg(C3-1-TAg)cJeg/JegJ mammary tissue by a neutrophil-mediated mechanism [75]. Importantly, systemic interplay between microbes, IL-6, and neutrophils was recently shown in human patients with breast cancer [77].

To the same extent that pathogenic gut bacteria can lead to carcinogenic events in distant tissues, it appears that beneficial bacteria may inhibit or even suppress carcinogenesis. A prototype beneficial microbe *Lactobacillus reuteri* was recently shown to rescue mice from age-associated obesity and the deleterious IL-6 and IL-17-rich smoldering systemic inflammatory obese status [10]. Obesity has been linked with postmenopausal mammary cancer [89–91]; thus, it was subsequently examined and shown that beneficial *Lactobacillus* sp. microbes inhibit obesity-associated mammary carcinogenesis in mice [75]. Interestingly, the same anti-neoplastic effect occurred in the Her-2/Neu mouse, a genetically engineered mouse model of mammary cancer, in which the association between immunity and mammary carcinogenesis is less obvious. This animal model is transgenic for ErbB2 Epidermal Growth Factor [EGF] receptor and over-produces the protein HER-2; a condition that occurs in up to 30% of breast cancer patients and carries a poor prognosis [20].