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Commensal bacteria modulate the tumor microenvironment

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Abstract

It has been recently shown that gut microbes modulate whole host immune and hormonal factors impacting the fate of distant preneoplastic lesions toward malignancy or regression. This raises the possibility that the tumor microenvironment interacts with broader systemic microbial-immune networks. These accumulated findings suggest novel therapeutic opportunities for holobiont engineering in emerging tumor microenvironments.

Keywords

tumor microenvironment; tumor macroenvironment; commensal microbes; carcinogenesis

Introduction

Accumulated cancer research has revealed that the tumor microenvironment contributes to neoplastic disease progression, invasion, and metastasis [1–3]. Recent findings in mice, however, take this notion further by showing that many tumors are less autonomous than previously thought. Intriguing data reveal that immune cells and other factors in the whole host environment determine the fate of dysplastic and preneoplastic lesions toward carcinogenesis or regression [4–11]. This systemic modulation of neoplastic disease may be described as the “tumor-macroenvironment.” [5]. In this context, the host microbiome is emerging as an important modulator of the tumor microenvironment even in extra-intestinal sites.

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The Whole Host Shapes the Tumor Microenvironment

Using Paget's "seed and soil" paradigm, where "seed" is a cancerous cell and "soil" is the tissue environment, the "soil" may either promote or hinder the carcinogenic process. Neoplastic outcomes appear to depend upon coinciding systemic immune-related events [1–4], perhaps explaining why people commonly exhibit pre-neoplastic lesions throughout their body though they don't develop cancer [12]. Recognizing that human genes could be mutated up to 10^{10} times during an individual's lifetime, it follows that 'seeds' are inevitable and 'soil' is a tractable target to modulate cancer growth.

Among elements of "soil" the immune system is composed of cellular elements and secreted factors that convey powerful signals to preserve homeostasis in epithelia throughout the body [4]. When functioning optimally, a balanced immune system conveys potent immune-stimulatory responses to external challenges with rapid restoration of homeostasis and minimal collateral tissue damage. More specifically, clinically silent gastrointestinal (GI) tract immune networks including neutrophils and regulatory T cells are integrated with commensal microbiota in whole host balance directing cancer development and growth [4, 6–11, 13–15]. Following this reasoning, harnessing the natural power of microbe-immune synergy may serve to suppress carcinogenic processes throughout the body.

At the whole organism level, the interactions of gut bacteria with the immune system is only one aspect of the complex, mechanistically inter-related systemic effects of gut microbiota. Accumulating evidence suggests that gut bacteria and products of their metabolic activities such as short-chain fatty acids, choline and bile salts, influence important metabolic pathways of the host relating to food intake, adiposity and lipid and energy homeostasis [11, 13, 15–23]. Gut bacteria and their products have also been shown to affect the hypothalamic-pituitary-adrenal axis and the production of neuroactive substances and various hormones including oxytocin, testosterone and thyroxin [17, 19, 20, 22, 24]. On this basis, the association of gut bacterial dysbiosis with a wide range of disease syndromes is not surprising. Changes in gut microbiota were originally linked mainly with inflammatory disorders such as autoimmune diseases and allergy. Recent data, however, expand the array of gut bacteria-associated diseases to include metabolic (obesity, type 2 diabetes and fatty liver), psychiatric (autism, depression and chronic fatigue syndrome) and senility-related disorders (hypogonadism, sarcopenia) [17, 18, 20, 22, 24, 25].

Commensal Microbes Help Define the Tumor Environment

It follows that the immune system, the metabolic profile, and the psychological condition of the host are all influenced by the microbiome. These factors, which also affect each other at the whole organism level, are important determinants in carcinogenesis and tumor progression. In accordance with the 'holobiont' concept, it was recently introduced that the gut microbiome shapes whole host biology or 'tumor macroenvironment' impacting tumor growth [5, 6]. Although there is substantial evidence that carcinogenic effects of gut bacteria are transplantable in mice when using purified immune cells alone [7, 8, 11, 26–29], there may be other direct effects of microbiota. According to recent data gut bacteria metabolites and inflammatory molecules such as bacterial lipopolysaccharide(LPS) may enter blood

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circulation and affect neoplasia in tissues locating distally from the GI tract [21, 30]. Ohtani's group has recently described that the obesity-related intestinal microbiota increases the circulating deoxycholic acid, which, by inducing a senescence-associated secretory phenotype in hepatic stellate cells promotes liver carcinogenesis [21, 23].

These modulatory effects of microbiota upon cancer are testable in animal model systems using targeted infections or transplantable immune cell populations to survey interplay between bacteria and systemic processes (Fig. 1) [8, 13]. Clinically silent gastrointestinal (GI) tract immune networks are integrated with commensal microbiota for good health, or alternatively to stimulate distant smoldering carcinogenic processes in distant mammary and prostate glands [4, 8, 10, 13, 14, 28, 31]. In these studies, consuming certain microbes or their sterile products imparts downstream health benefit via systemic homeostasis, a microbe-based strategy that may ultimately overcome therapeutic limitations in preventing or treating cancer [7, 10, 32]. These promising findings put cancer into a new broader context of the "holobiont" comprised of the mammalian host plus resident microbes.

The Hygiene Hypothesis and Cancer

The biological significance of bacterial exposures much earlier in mammalian life is now becoming more fully appreciated [15, 33, 34]. Indeed, the "hygiene hypothesis" concept links bacteria with good health [10, 35, 36]. Conversely, pathologies arise later in life after too few perinatal and infant microbe exposures [4, 33–35, 37]. Studies in mouse models show that early-life exposures to bacteria [10, 11] and sterile [lysis-killed] microbes are sufficient for later-life anti-cancer effects [7]. It remains to be determined whether data from mouse models linking early- life microbe exposures with later cancer risks will translate to novel therapies for human patients. While many formative processes occur in utero or during infancy, recent data suggest that commensal bacteria-host crosstalk is also continuous and reciprocal throughout life. In this way, microbe-immune interactions constitute a vast gut-immune-endocrine-brain signaling axis that continuously modulates interferon (IFN)-γ and CD25 expression and host inflammatory tone [8, 13, 33, 34]. For example, dissecting temporal dynamics of wound healing as a proxy for cancer revealed that oral microbe [L reuteri] supplementation serves to enhance host inflammatory response (i.e. microbes were immune-stimulatory), with expedited healing, minimal collateral tissue damage, and return to homeostasis afterwards [20]. In those studies, expedited skin wound repair was attributable to microbe-induced hormone oxytocin, IFN-γ, and CD4+CD25+ immune cells. Likewise, mice supplemented orally with the same bacteria were resistant to both western diet-induced and ErbB2 oncogene-associated mammary carcinogenesis later in life [8].

Optimizing Gut Bacteria and Host Animal Signaling to Prevent Cancer

Earlier evidence for microbe-immune interactions in cancer was provided more than a decade ago by Erdman et al (2003) showing that immune-deficient Rag-knockout (KO) mice colonized with commensal bacteria exist in a chronic, smoldering pro-inflammatory and pro-tumorigenic proximal state [4]. By contrast, their wild-type immune-competent counterparts were resistant to neoplasms due to a competent adaptive immune system with potent anti-neoplastic properties [4]. Subsequent adoptive cell transfer experiments showed

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CD4+ T cells counteract carcinogenic processes, depending upon prior exposures and the composition of the host microbiome [4, 7, 8, 11, 13, 27, 31, 38]. Earlier infections may serve to reinforce immune system health to protect form cancer in a use-it-or-lose-it sort of way. Amazingly, killed sterile forms of microbes appear to convey similar anti-cancer benefits [7]. Emerging unpublished data from the same lab suggest that commensal bacteria serve to upregulate expression of epithelial Forkhead box protein [Fox]N1 and thus stimulate thymogenesis [39] culminating in CD4+ T cell-mediated immune balance. Interestingly, symbiotic microbiota such as human breast-milk borne *L. reuteri* appear to have transgenerational impact upon thymogenesis, with interesting implications in mammalian ontogeny [15]. In this way, exposures to bacteria may be used therapeutically for epigenetic control of resident immune cell populations in combating cancer [4]. In sum, these data from animal models raise the possibility of using synthetic microbe cocktails or sterile microbial products to stimulate immunity and lower risk of cancer [4].

Conclusions

Taken together, these findings offer exciting new microbe-based avenues for developing personalized or population-based medicine strategies to decrease the risk of malignancy. As the tumor microenvironment concept first put cancer cells into context within a lesion [2, 3], the notion of tumor macroenvironment puts carcinogenesis into a whole-body context that extends beyond the mammalian host to microbial passengers we may choose to engineer for our therapeutic benefit.

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Highlights

- Data reveal that the milieu of immune cells and factors in the whole host environment determine the fate of dysplastic and preneoplastic lesions toward carinogenesis or regression
- Clinically silent gastrointestinal tract immune networks and commensal microbiota may impart healthful phenotypes or alternatively stimulate distant smoldering carcinogenic processes in the mammary and prostate glands
- Microbes may thus be determining the fate of the distal cancer microenvironment
- Taken together, these results suggest that exposures to bacteria may be used therapeutically for epigenetic control of resident immune cell populations combatting cancer

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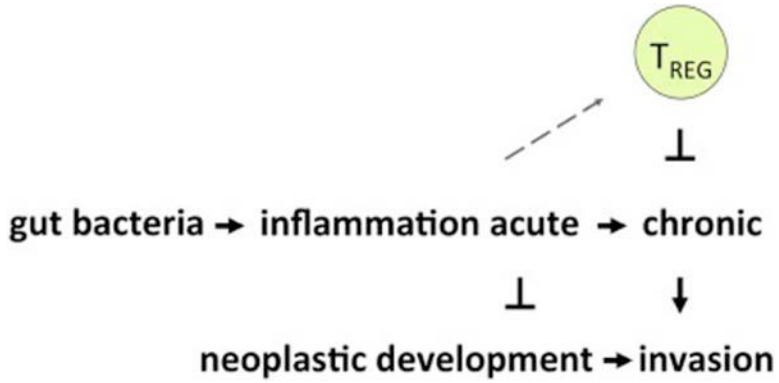

Figure 1.

The holobiont regulates neoplastic development, growth and invasion via bacterial interactions that modulate systemic inflammatory tone. Earlier microbe exposures stimulate the immune system culminating in robust yet tightly regulated host immunity to rapidly restore homeostasis with minimal collateral tissue damage. Thus, neoplastic development and growth is framed in the context of the holobiont, including native resident microbes or those we choose to engineer for personalized or public health goals.