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The microbiome modulates the tumor macroenvironment

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Earlier investigations of the tumor microenvironment unveiled systemic networks presenting novel therapeutic opportunities. It has been recently shown that gut microbes modulate whole host immune and neuroendocrine factors impacting the fate of distant preneoplastic lesions toward malignancy or regression. These findings establish a new paradigm of holobiont therapeutic engineering in emerging tumor macroenvironments.

The Tumor Environment School of Thought

At the dawn of the new millennium, Hanahan and Weinberg (2000) predicted that the future of cancer research would be shaped primarily by conceptual rather than technical advances.[1] The solidification and enrichment of the tumor microenvironment concept has proven this assumption to be valid.[2] It has become increasingly clear that neoplastic diseases cannot be entirely understood by examining stroma and genetics of cancer cells independently. The dynamic interrelationship of cancer with the host environment must be studied as well.[3]

The bulk of cancer research performed over the past decade has revealed that the tumor microenvironment contributes to neoplastic disease progression, invasion, and metastasis.[3] Recent findings in mice, however, take this notion further by showing that many tumors are less autonomous than previously thought. These include the surprising observations that expansive and invasive tumors regressed in the absence of systemic inflammatory stimuli.[4] Other intriguing findings have shown that the milieu of immune cells and factors in the whole host environment determine the fate of dysplastic and preneoplastic lesions toward tumorigenesis or regression.[4] This systemic modulation of neoplastic disease may be best described as the "tumor-macroenvironment."

The Immune System Shapes the Tumor Environment

Using Paget's "seed and soil" paradigm, whereby the "seed" is the initially transformed cancer cell and the "soil" is its tissue environment, the latter could either foster or attenuate the carcinogenic process. Neoplastic outcome has been found to largely depend upon coinciding systematic immune-related events.[3,4] Such correlations lead one to wonder about potential parallels between systemic immunity and the fact that people commonly bear early neoplastic lesions throughout their body, yet few actually develop cancer.[5] The high frequency of precancerous lesions with malignant potential is not surprising, since it has been estimated that each human gene could be mutated up to 10^{10} times during a person's lifetime, even in the absence of environmental mutagenic factors. It follows that since these seeds are inevitable, altering the soil remains as the viable target to affect cancer growth. The immune system, comprising cellular elements and secreted factors that convey powerful signals to preserve homeostasis, may rise to meet this objective. Indeed, the immune system of mice has been shown to influence the risk of developing sporadic cancers in various epithelia throughout the body.[4] The critical question, then, is whether efficient and biologically safe modalities harnessing the power of the immune system may serve to suppress carcinogenic processes throughout the body.

Gut Microbes Help Define the Tumor Macroenvironment

Interestingly, we have discovered that clinically silent gastrointestinal (GI) tract immune networks are integrated with gut microbiota to impart healthful phenotypes and suppress age-related pathologies and distal carcinogenic processes such as those occurring in the mammary and prostate glands.[4,6-8] These effects, achievable by feeding food-grade bacteria to mice, culminated from the interplay between the systemic immune system and metabolic processes (**Fig. 1**).[7,8] Consuming certain microbes and their products imparts downstream homeostatic health effects that overcome therapeutic limitations of exogenous

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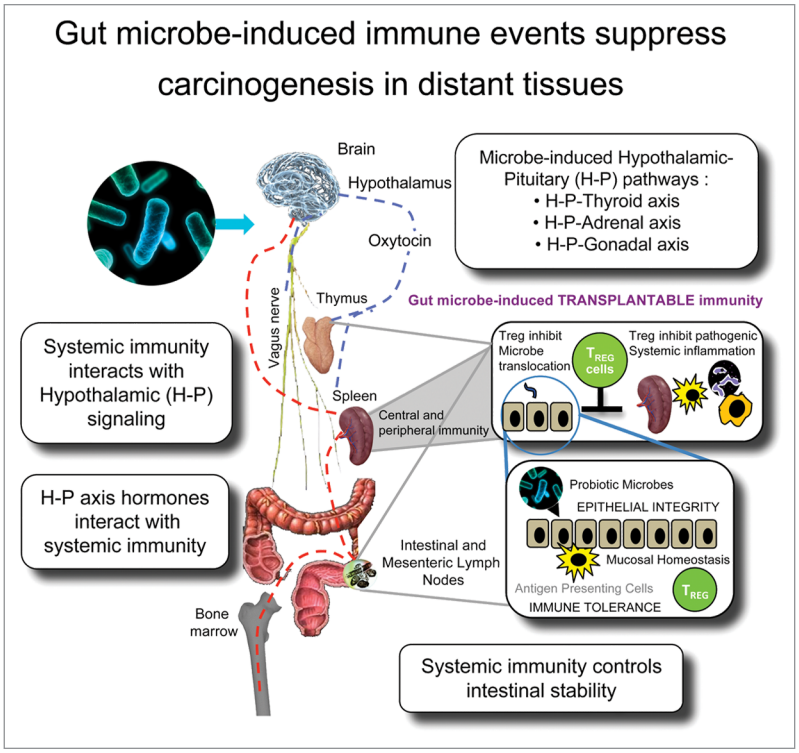

Figure 1. Gut bacteria-host crosstalk is continuous and reciprocal in the cancer macroenvironment. Beneficial microbes trigger IL-10-mediated gastrointestinal (GI)-tract immune and neuronal networks that lower systemic inflammatory tone and upregulate hypothalamic-hypophyseal targets, including the neuropeptide hormone oxytocin, constituting a systemic gut-immune-endocrine axis. Oxytocin upregulates systemic interferon-γ (IFNγ) expression culminating in robust yet tightly regulated host immunity. Thus, neoplastic development and growth is framed in the context of the holobiont, including native resident microbes or those we may choose to engineer, soliciting a new broader concept of the cancer macroenvironment.

administrations of discrete immune or hormonal factors. These findings open up new cancer prevention or therapeutic avenues. Further, our findings put cancer into a new broader context, the so-called "holobiont," comprised of the mammalian host plus resident microbes.[4,8]

GI Tract Bacteria Affect the Immunological and Metabolic Profile of the Host

The significance of the GI tract microbiota in the development of a potent and balanced immune system occurring during mammalian early life is now appreciated.[9,10] The "hygiene hypothesis" concept involves insufficient microbial exposures early in life that predispose the individual to uncontrollable inflammation-associated pathologies later in life.[4,9,10] Recent data suggest that this GI bacteria-host crosstalk is continuous and reciprocal throughout life, constituting a vast gut-immune-endocrine-brain signaling axis.[7-10] Our prior studies in mice using an opportunistic pathogen, *Helicobacter hepaticus,* a bacterium which colonizes the lower bowel, provided experimental evidence for the first 2 elements of this axis.[6] Indeed, *H. hepaticus* induced clinically silent systemic elevations of pro-inflammatory cytokines such as Interleukin (IL)-6 and IL-17 that fuel carcinogenesis in tissues distal from the colon, including mammary and prostate glands.[4] Our more recent studies using the probiotic microbe *Lactobacillus reuteri* completes the puzzle of the aforementioned axis to include the endocrine system and the brain by showing beneficial microbe-induced, IL-10-mediated GI-tract immune networks that lower systemic inflammatory tone[7,8] and upregulate hypothalamic-hypophyseal hormones including oxytocin.[7] Oxytocin modulates interferon-γ (IFNγ) and CD25 expression culminating in robust yet tightly regulated immunity. As a consequence of eating probiotic organisms, aged mice displayed superb wound healing capacity.[7,8] In this setting, mice were also resistant to both western diet-induced and ErbB2 oncogene overexpression-associated mammary carcinogenesis.[8]

Regulatory T cells Are Essential for Constructive GI Bacteria-host Signaling

Although immune-deficient mice colonized with *H. hepaticus* exist in a chronic, smoldering pro-inflammatory and pro-tumorigenic state, their wild-type immune-competent counterparts are more resistant to neoplasms due to microbe-induced regulatory T cells (Tregs) with potent anti-inflammatory and anti-neoplastic properties.[4] Elaborate adoptive cell transfer experiments have demonstrated similar beneficial outcomes with *L. reuteri* habitation involving IFNγ in an IL-10-dependent manner that counteracts carcinogenic processes.[4,7,8] These results suggest that exposures to bacteria may be used therapeutically for epigenetic control of resident Treg populations.[4]

Conclusions

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

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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