The Potential Role of Exercise and Nutrition in Harnessing the Immune System to Improve Colorectal Cancer Survival

Given the ever-increasing number of colorectal cancer (CRC) survivors, development of new approaches to improve patients' long-term survival outcomes is a high priority. Recent striking success of immunotherapies in specific clinical circumstances has motivated research to identify novel strategies based on immune modulation to more effectively harness the immune system to combat cancer. Increasing data indicate a considerable influence of diet and lifestyle on CRC prognosis. In turn, diet and lifestyle shape the gut microbiota, which has been associated with CRC incidence and progression and predicts responsiveness to immunotherapy.[1] Despite long-standing evidence that diet and lifestyle as well as the gut microbiome influences the host intestinal and systemic immune system,[2] the potential role of lifestyle modification in enhancing the anticancer immune response remains largely unknown. Herein, we review the most recent data regarding how exercise and diet may improve CRC survival via immune and microbial mechanisms (Figure 1), and identify critical questions for future research.

Role of the Immune System in CRC Survival

Spanning the evolution of the earliest concept of cancer immunosurveillance proposed by Paul Ehrlich in the 1950s to the cancer immune editing concept elucidated by Schreiber and colleagues in 2002, in the last several years, the field has grown to recognize a dual role of the host immunity, both as an extrinsic tumor suppressor and a facilitator of tumor growth and progression.[3] In parallel, whereas early clinical data have focused on the beneficial effect of the adaptive immune response (eg, tumor-infiltrating cytotoxic and memory T cells and T helper 1 cells [Th1]) for CRC survival, more recent data indicate the functional heterogeneity of certain immune cells (eg, Th17 cells[4] and regulatory T cells [Tregs][5]) in CRC depend on immune and microbial context, as well as the balance between cytotoxic T-cell lymphocytes and immune checkpoint expression in the prognosis of CRC.[6] These data highlight the plasticity of an immune system that may be modified to both activate antitumoral immunity and suppress immune evasion by tumors.

Exercise

Several observational studies have consistently identified a dose-dependent relationship between physical activity, both before and after CRC diagnosis, and lower risk of recurrence and mortality.[7] Moreover, CRC patients who increased their physical activity by any level from before diagnosis to after diagnosis showed decreased mortality compared with those who did not change their physical activity level or were inactive/insufficiently active before diagnosis. In addition, clinical evidence indicates the benefit of exercise for improving the efficacy of radiotherapy and chemotherapy as well as reducing cancer- and treatment-related adverse effects,

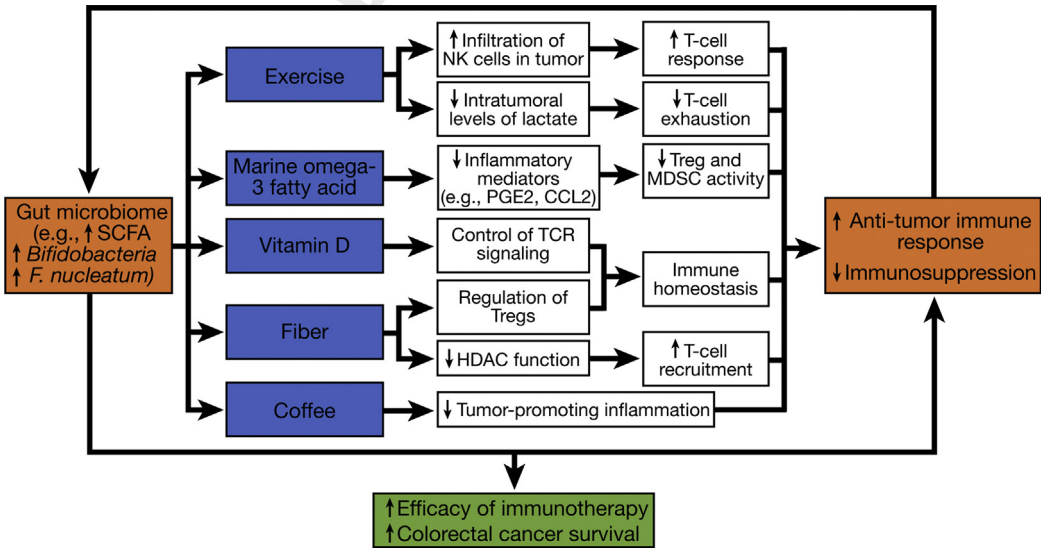

Figure 1. Potential immune and microbial mechanisms underlying the benefit of exercise and nutritional factors for colorectal cancer survival. In addition to the local effects, these lifestyle factors also reduce systemic inflammation induced by cancer and treatment. CCL2, C-C motif chemokine ligand 2; HDAC, histone deacetylase; MDSC, myeloid-derived suppressor cells; NK, natural killer; PGE_2, prostaglandin E_2; SCFA, short-chain fatty acid; TCR, T-cell receptor; Treg, regulatory T cells. histone deacetylase.

EDI 5.5.0 DTD ■ YGAST62022 proof ■ 1 August 2018 ■ 12:31 pm ■ ce

including cachexia, depression, anxiety, and cognitive problems. Preliminary results of a multicenter randomized controlled trial (RCT) indicate the feasibility of a structured exercise program in colon cancer survivors and the benefit of 1-year intervention for a variety of health-related fitness parameters.[8] Exercise may regulate tumor growth kinetics and metabolism through both physical (eg, increased blood flow, shear stress on the vascular bed, and sympathetic activation) and endocrine (eg, stress hormones and myokines) mechanisms. These effects may also contribute to exercise-induced enhancement of antitumor immunity by increasing mobilization and infiltration of innate and cytotoxic immune cells in the tumor microenvironment. For example, a recent study revealed that exercise increased accumulation of natural killer cells in an epinephrine- and IL-6–dependent manner, thereby decreasing tumor growth by >60% across different mouse tumor models.[9]

Moreover, given the close link between tumor metabolism and immunity, physical activity may also regulate tumor immunogenicity by reducing the production of metabolic byproducts. For instance, exercise has been shown to lower intratumoral levels of lactate, a byproduct of aerobic glycolysis that is enhanced in most tumors owing to metabolic reprogramming. Lactate may facilitate tumor growth through its immunosuppressive effects, including impaired activity of natural killer and T cells, disrupted T-cell motility, and increased tumor-permissive activity of tumor-associated macrophages.

In addition, exercise may improve immune and metabolic homeostasis by modifying the gut microbiota. Compared with healthy controls with similar body mass index, professional athletes have been found to have a more diverse fecal microbiota and enrichment of metabolic pathways related to production of secondary metabolites with immune benefits, such as short-chain fatty acid (SCFA).[10] SCFA, including butyrate, acetate and propionate, is a family of bacterial fermentation products of fiber and functions as a critical regulator of colonic Treg homeostasis and expression of numerous genes responsible for tumor growth and migration.

Finally, exercise may also improve systemic immunity and metabolic health of cancer patients through reductions in systematic low-grade inflammation, as indicated by lower levels of proinflammatory factors (eg, C-reactive protein, tumor necrosis factor alpha) in clinical intervention studies.

Marine Omega-3 Fatty Acid

Higher marine omega-3 fatty acid (MO3FA) intake after CRC diagnosis has been associated with lower risk of recurrence and overall and CRC-specific mortality.[11,12] Patients who increased their intake of MO3FA after diagnosis had a particularly longer survival than those who did not change or reduced their intake. The beneficial effect of MO3FA on CRC survival is supported by a RCT demonstrating that MO3FA supplement of 2 g/d before surgery reduced mortality among patients with CRC liver metastasis.[13] In addition, some clinical evidence indicates the benefit of MO3FA for abrogation of cancer cachexia, although the RCT data remain inconclusive.

The anticancer effect of MO3FA may be related to its anti-inflammatory activity mediated by increased incorporation of these fatty acids into cell membranes at the expense of arachidonic acid and alterations in lipid raft structure and function. These changes decrease the production of inflammatory eicosanoids (eg, prostaglandin E_2) and chemokines (eg, C-C motif chemokine ligand 2), reverting the immune suppression mediated by Tregs and myeloid-derived suppressor cells to enhance antitumor immunity. In support of these mechanistic data, our recent cohort study indicated that high intake of MO3FA was associated with a lower risk of CRC that is infiltrated with high density of $FOXP3^+$ T cells, but not tumors with low $FOXP3^+$ T cells.[14] FOXP3 is a prerequisite transcription factor for the immunosuppressive function of Tregs. Consistent with the human findings, our in vitro study indicated that MO3FA treatment decreased the suppressive activity of Tregs against proliferation of T effector cells. This effect may be mediated by alterations in the Treg cytokine repertoire (eg, lowering inhibitory cytokine IL-10) and the gut microbiota.

Compared with other fats, MO3FAs have been associated with higher intestinal microbiota diversity and amelioration of ω-6 fatty acid- or antibiotic-induced dysbiosis. MO3FA supplementation has been shown to increase the abundance of anti-inflammatory bacteria, such as SCFA-producing bacteria (mainly *Lactobacillus* and *Bifidobacteria*), and decrease the abundance of proinflammatory and tumor-permissive bacteria, such as lipopolysaccharide-producing bacteria (eg, *Escherichia coli*) and *Fusobacterium nucleatum*.[15] Lipopolysaccharide is a known trigger of chronic inflammation that may in turn promote CRC, and *F nucleatum* may support CRC development and metastasis by potentiating tumoral immune evasion, inhibiting antitumor defense by natural killer or T cells, and modulating the E-cadherin/β-catenin pathway. In contrast, commensal bacteria *Bifidobacteria* have been found to improve the efficacy of programmed death-ligand 1 blockade immunotherapy by modulating activation of dendritic cells and enhancing $CD8^+$ T-cell immune response.[16] These experimental and clinical data together support the potential of adjuvant or combinational treatment with MO3FA to improve CRC survival by abrogating immunosuppression and improving antitumor immune response.

Vitamin D

Higher levels of circulating 25-hydroxyvitamin D before and after diagnosis have been consistently linked to improved survival among CRC patients across different stages.[17] These observational data have been supported by a recent phase II RCT reporting the benefit of high-dose vitamin D treatment for