Obesity-associated cancer risk: the role of intestinal microbiota in the etiology of the host proinflammatory state

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Obesity increases the risks of many cancers. One important mechanism behind this association is the obesity-associated proinflammatory state. Although the composition of the intestinal microbiome undoubtedly can contribute to the proinflammatory state, perhaps the most important aspect of host–microbiome interactions is host exposure to components of intestinal bacteria that stimulate inflammatory reactions. Systemic exposures to intestinal bacteria can be modulated by dietary factors through altering both the composition of the intestinal microbiota and the absorption of bacterial products from the intestinal lumen. In particular, high-fat and high-energy diets have been shown to facilitate absorption of bacterial lipopolysaccharide (LPS) from intestinal bacteria. Biomarkers of bacterial exposures that have been measured in blood include LPS-binding protein, sCD14, fatty acids characteristic of intestinal bacteria, and immunoglobulins specific for bacterial LPS and flagellin. The optimal strategies to reduce these proinflammatory exposures, whether by altering diet composition, avoiding a positive energy balance, or reducing adipose stores, likely differ in each individual. Biomarkers that assess systemic bacterial exposures therefore should be useful to (1) optimize and personalize preventive approaches for individuals and groups with specific characteristics and to (2) gain insight into the possible mechanisms involved with different preventive approaches. (Translational Research 2017;179:155–167)

Abbreviations: BMI = body mass index; CRP = C-reactive protein; LAL = limulus amebocyte lysate; LPS = lipopolysaccharide; LBP = lipopolysaccharide-binding protein; PGE_2 = prostaglandin E_2; Th1 = T-helper cell type 1

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PROINFLAMMATORY PATHWAYS ASSOCIATED WITH OBESITY INCREASE RISK OF CANCER

Obesity is one of the factors that increase the risk of many cancers. The data are especially compelling for cancers of the endometrium, kidney, colorectum, esophagus, pancreas, and postmenopausal breast cancer.[1] More recently, gall bladder, liver, thyroid, and ovarian cancers have been identified to be among those cancers strongly affected by obesity.[2,3] Obesity-related cancer risks do vary by factors such as ethnicity, sex, and menopausal status, but nonetheless substantial increases in risk have been observed with body mass index (BMI) increases greater than the normal weight range.[2] For colorectal cancer,

risk increases with obesity in a dose-dependent fashion, with a risk that is increased by 32%–41% in obese vs normal weight individuals.[4,5]

Several mechanistic pathways are identified to be operative in this link between obesity and cancer. These include hormonal alterations (eg, leptin and estrogen), induction of insulin-signaling pathways, and activation of proinflammatory pathways.[6] More and more research is turning to the role of activated proinflammatory pathways in mediating obesity-associated risks of not only cardiovascular diseases and diabetes but also of cancer. Indeed, experimental data support the role of inflammation in the development of many cancers.[7] Although immune surveillance does have a role in eliminating tumor cells, chronic, low-level activation of immune pathways also can alter the homeostatic state to stimulate tumor growth.

Cytokines, acute-phase proteins, and cancer risk. Excess body fat accumulation results in polarization of immune cells, resulting in generation of proinflammatory cytokines and chemokines.[8] This activated immune state has been characterized by the presence of "classically activated," termed M1, macrophage-secreted factors, increased proinflammatory T-helper cell type 1 (Th1) cytokines, and decreased Th2, immune-regulatory cytokines.[9-13] Among the many functions of cytokines, they signal the production of acute-phase proteins secreted by the liver during injury or infection, including C-reactive protein (CRP) and serum amyloid A. Interestingly, one of the functions of CRP is to bind to components of microorganisms to assist in their removal by immune cells.[14,15]

Increased serum CRP is associated with increased risks of several cancers, including that of the colon and breast.[16-19] In the prospective European Prospective Investigation into Cancer and Nutrition study, increased CRP was associated with the increased risk of colorectal cancer.[20] A proinflammatory state also plays an important role in survival from cancer, and an increased proinflammatory state is a risk factor for breast cancer recurrence and survival.[21-29] In a meta-analysis of 10 studies, relatively high levels of CRP were associated with reduced overall survival, disease-free survival, and breast cancer–specific survival.[23] CRP also was predictive of cancer survival when measured at diagnosis or 2–3 years after diagnosis.[21,25,28] Unlike CRP, cytokines such as interleukin-6 have not been as consistently associated with cancer risk.[18,19,30,31]

Eicosanoids and cancer risk. In addition to cytokines, eicosanoid production may be of interest as a more rapidly responsive biomarker of the proinflammatory state of tissues because cytokines can take weeks to fully manifest via induction of T cells.[10] Eicosanoids are bioactive molecules formed from the metabolism of arachidonic acid. Eicosanoid formation is inextricably linked with activation and deactivation of immune cells. For example, inhibition of cyclooxygenases that produce eicosanoids using indomethacin decreased the proinflammatory cytokines interferon gamma and tumor necrosis factor α and increased the immunoregulatory cytokine interleukin-10.[32]

One of the most widely studied eicosanoids with regard to carcinogenic processes is prostaglandin E_2 (PGE_2). Increased PGE_2 concentrations have been linked with an increased risk of many cancers, including that of the colon, breast, and skin.[33-35] Eicosanoids, and especially PGE_2, have critical roles in the initiation and progression of cancer.[36-38] Eicosanoids can also indirectly affect cancer growth. For example, PGE_2 induces aromatase expression, which is relevant to survival from postmenopausal breast cancer,[39] in addition to the more direct effects of PGE_2 on driving breast cancer growth and metastases.[33,40,41] Eicosanoids can be measured in tissues, but in epidemiologic studies stable metabolites have more often been measured in urine. Increased concentration of the PGE_2 metabolite in urine was positively predictive of increased breast cancer risk and breast cancer metastases.[42-45] Nonsteroidal anti-inflammatory agents, which inhibit cyclooxygenases and PGE_2 formation, decreased breast cancer recurrence in overweight and obese women.[46]

In the colon, proinflammatory changes characterized by increased colonic production of PGE_2 also have been shown to increase the risk of cancer.[47-49] PGE_2 has an important repair role for resolving frank inflammatory conditions such as colitis, but in normal tissue, low-level, chronic increased PGE_2 promotes carcinogenic processes.[50,51] PGE_2 mediates colonic crypt cellular expansion that can subsequently result in adenoma formation.[52-56]

Data in human colon tissue are more sparse than in animal models, but one study of subjects with a history of polyps showed that PGE_2 in the rectal mucosa was significantly increased with increasing BMI.[57] In another study, expression of cyclooxygenase 2, an inducible form of the enzyme, was higher in the colonic mucosa adjacent to the tumor of obese vs normal weight subjects.[58]

Beneficial effects of weight loss on reversing obesity-associated inflammation. This obesity-associated, proinflammatory state likely is sensitive to the energy balance that drives metabolic processes toward either lipid synthesis or lipid oxidation. This could be one reason why proinflammatory states are not always associated with obesity; conversely, a proinflammatory state can occur in lean individuals.[59,60] A modest weight loss, in which case many obese individuals will remain in the obese state, appears sufficient for reducing inflammation. A weight loss of at least 5%–