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Convergence of Hormones, Inflammation, and Energy-Related Factors: A Novel Pathway of Cancer Etiology

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Abstract

Colorectal cancer (CRC) is a multifactorial disease with several hypothesized etiologic factors including inflammatory processes; hormones such as estrogen, androgen, and insulin; and energy-related factors. We present evidence that integrates these elements in a pathway we call the convergence of hormones, inflammation, and energy-related factors (CHIEF). First, given the physiology of the gut, substantial epidemiologic and molecular data support the hypothesis that activation of innate immunity in the normal gut mucosa by various environmental agents (commensal bacteria, dietary antigens, mucosal irritants, pathogens) and endogenous factors such as estrogen, androgens, and insulin levels provokes basal inflammation as an underlying factor of the association of insulin, estrogen, and energy-related factors with CRC. Second, critical genes involved in this pathway, e.g., phosphatase tensin homologue on chromosome 10 (PTEN) and serine threonine kinase 11 (STK11)/LKB1, are tumor suppressor genes often mutated in intestinal cancer or CRC. Third, laboratory experiments show that cellular PTEN and STK11/LKB1 tumor suppressor enzymes are vulnerable to inactivation by redox-active species, especially chemically reactive lipid mediators of inflammation and redox stress. Epidemiologic data further support the underlying proposal that CHIEF comprises important elements of CRC risk. Although this discussion of the CHIEF pathway focuses on CRC, we believe that this pathway may play an important role in the etiology of other cancers as well.

Epidemiology is devoted to understanding the causes and distribution of diseases within populations. Cancer epidemiology has focused on associations between specific cancers and environmental, nutritional, behavioral, physiologic, and molecular and genetic factors. Observations from these studies have been central to our current understanding of the causes of cancer and our efforts to control cancer through public health policy, interventions, and translational research. Percival Pott's observation in 1775 that soot exposure led to a high rate of scrotal cancer in chimney sweeps likely gave birth to the concept of chemical carcinogenesis, which was validated in preclinical studies of 1918 proving that soot caused scrotal cancer in animals (the cancer link to polycyclic aromatic hydrocarbons in soot was made in 1938; ref.

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1). Pott's observation led to important workplace measures for cancer prevention. The association between tobacco use and lung cancer is a more recent example of epidemiologic observations leading to public health measures to reduce cancer risk.

Not all associations between risk factors and cancer are as robust and singular as are the associations between chimney soot and scrotal cancer, or tobacco smoke and lung cancer. One of the challenges of contemporary epidemiology is to determine the common molecular processes through which risk factors operate. Epidemiologic observations of the present day emphasize the complexity of cancer etiology, comprising abundant data suggesting that cancers have multiple causes and usually both unique and overlapping risk factors. However, as in 1775, epidemiologic observations are crucial to our understanding of cancer etiology and continue to lay the foundations for cancer prevention and control.

In this review, we consider the associations of inflammation, hormones, and energy-related factors such as obesity, physical activity, and energy intake with colorectal cancer (CRC) and propose a mechanistic explanation for their convergent effects on colorectal carcinogenesis. We label our proposed pathway the convergence of hormones, inflammation, and energy-related factors (CHIEF) and provide epidemiologic and molecular evidence that supports the importance of this pathway to CRC. Although our discussion of the CHIEF pathway focuses on CRC, we believe that this pathway also may play an important role in the etiology of other cancers.

The Gut: A Lymphoid Organ Routinely Exposed to Inflammatory Stimuli

Inflammation, a core component of the CHIEF pathway, is an underlying feature of physiologic and pathologic processes that operate throughout the gut, particularly the intestinal tract and colon. Many pathologic aspects of gut inflammation, e.g., colitis, are well established and well understood. By contrast, physiologic aspects of inflammation are unknown and often not acknowledged. Conventional sources of inflammation—infectious pathogens and tissue injury—occupy one end of a continuum of pathologic processes that inaugurate inflammation. They disrupt vascular integrity and cause plasma proteins and leukocytes to accumulate at an affected tissue site, where they annihilate pathogens and eventually help restore morphologic and histologic integrity. Toward the other end of the continuum, tissue stressors or malfunction, such as premalignant lesions including adenomatous polyps, can provoke an adaptive response sometimes called “parainflammation.” This response may involve tissue-resident leukocytes (macrophages, eosinophils) and adjacent cells in the stroma (fibroblasts), and it is intermediate between the basal homeostatic state and a classic inflammatory response. Parainflammation is likely a major contributing factor to many modern human diseases including CRC. Parainflammation is inseparable from the role of the gut in human physiology.

The gut, particularly the large intestine, is one of the largest and most diversified lymphoid organs of the body (2) and is routinely exposed to immune and inflammatory stimuli. It contains gut-associated lymphoid tissues, mast cells, resident macrophages, lymphocytes, and eosinophils (3) in the lamina propria and submucosa of the intestine and colon (4), and specialized epithelial cells called M cells, which allow host immune cells to sample luminal antigens (5). All of these cells are close to the epithelial cells (colonocytes), suggesting that biochemical interactions between the stroma and epithelium could influence colorectal tumor progression. Basically, the gut mucosa and stroma are the first ramparts of a host's defense against swallowed matter, including bacteria, bacterial lipopolysaccharides, gut parasites, food antigens, particulates, chemical irritants, alcohol, dietary polyunsaturated fatty acids, carcinogens, and even certain drugs, which can activate innate and adaptive immune responses. Furthermore, anything that disrupts the mucosal barrier, e.g., ulcers or colorectal polyps (6),

can expose the lamina propria to bacteria, exacerbate immune activation, and necessitate repair or replacement of cells at the affected site of the gut.

Once thought to be a host response against tumors, localized stromal inflammation may actually worsen cancer risk and progression (7-10). Eosinophils are inflammation-related leukocytes with a special capability to counter parasitic infections in the gut (3,11), and mild-to-moderate eosinophilia occurs in the stroma of ~75% of colonic adenomas (12). Neutrophils, another inflammation-related group of leukocytes, are occasionally found in colorectal polyps (13). Eosinophils and neutrophils also can cause tissue remodeling and wound healing, not just tissue damage such as that associated with polyps. It is possible that eosinophils and neutrophils mediate both cell destruction and normalization and recovery from inflammation, and are potentially important modulators of intestinal tumorigenesis; they are the first inflammation cell types recruited in response to proinflammatory cytokines. Mast cells are then activated, stimulating the proinflammatory cytokines and chemokines such as the interleukin (IL) family, IFNs, and tumor necrosis factors (TNF; ref. 14). Macrophages derived from monocytes that have infiltrated the inflamed area provide a network of growth factors, cytokines, and prostaglandins.

The inflammatory loci are further influenced by interaction with epithelial and vascular endothelial cells and are closely linked with angiogenesis, which involves the growth of new blood vessels from preexisting vessels. Both angiogenesis and inflammation are hallmark features of tumorigenesis as well as other diseases such as Crohn's disease, diabetes, and obesity (14), and have related molecular events. Inflammatory cells that have infiltrated tissue are one of the factors that stimulate angiogenesis; the vascular endothelial growth factor (VEGF) is known to play an important role in angiogenesis (15). Without the recruitment of blood vessels during angiogenesis, tumors are limited in growth and in their ability to metastasize (16). In animal models, it has been shown that inflammatory cytokines such as IL-1 α and IL-1 β are required for angiogenesis and tumor growth (17,18), whereas cyclooxygenase (COX)-2 acts both as an proangiogenesis and proinflammatory agent (19,20).

Inflammatory processes seem to be a key element in colorectal carcinogenesis. The intestine must carefully balance immunity, which protects us from harmful microbes, and tolerance, which permits interactions with harmless commensal bacteria and dietary antigens. Disruptions that tilt the balance toward immune activation/inflammation could facilitate tumor progression in the intestinal tract. The loss of balance between anti-inflammatory and proinflammatory mediators may precipitate or aggravate neoplastic transformation in the intestinal epithelium. This concept is best thought of as a continuum. Illustrating the mild end of the continuum are mice held in germ-free environments, where there are fewer bacterial threats and, presumably, reduced mucosal immune activation; they do not develop intestinal tumors (21). At the severe end of the continuum, persistent inflammation in the colon is a strong independent risk factor for CRC (7). Ulcerative colitis lasting >20 years increases the risk for CRC as much as do inherited cancer syndromes such as familial adenomatous polyposis (22). The initial inflammatory insult in the gastrointestinal (GI) tract may originate from diet and carcinogenic exposures that lead to a state of low-level inflammation. Disruptions in the delicate balance between harmful microbes and harmless commensal bacteria in the GI tract that enable immune activation/inflammation could facilitate multistep tumorigenesis in the intestinal tract (Fig. 1).

Molecular Support for CHIEF, the Pathway of Convergence

The importance of the convergence of inflammation with pathways that involve hormones and energy-related factors suggests the necessity to examine the broad spectrum of these interrelated pathways rather than each pathway in isolation. This integrated approach is the essence of the CHIEF pathway (Fig. 2). The LKB1 \rightarrow AMP-activated protein kinase α \rightarrow

tuberous sclerosis 1&2 → mammalian target of rapamycin (mTOR) → ribosomal protein S6 kinase (S6K) component of our proposed pathway senses and responds to changes in cellular ATP levels, which may be governed in part by diet, physical exercise, or inflammation (23); therefore, this component integrates nutrient and insulin signaling. Cells with low ATP and excess AMP activate LKB (STK11) at the apex of this pathway (23-26) in repressing anabolic processes (ATP use) and enhancing catabolic processes (ATP generation). The signaling pathway senses and responds to changes in cellular energy balance (ATP levels; refs. 27,28). LKB1 is a tumor suppressor that causes Peutz-Jeghers syndrome, an autosomal dominant disorder that often manifests as hamartomatous polyps that increase the risk of intestinal cancer. LKB is an AMPK kinase and a tumor suppressor and therefore is a prominent link between metabolic signaling pathways and cell proliferation and polarity pathways (28-31). In cells with excess AMP due to altered energy homeostasis, LKB1 phosphorylates AMP-dependent kinase (PRKAA1&2; refs. 24-27), which in turn phosphorylates proximal substrates like acetyl-CoA carboxylase and tuberous sclerosis 1&2. Sequential phosphorylation of distal substrates in this kinase cascade, such as mTOR and S6K (also known as RPS6KA1&2), ultimately represses anabolic processes (ATP use) and enhances catabolic processes (ATP generation). This process restores the system to normal energy homeostasis. Overall, LKB1 is a prominent, widely expressed AMPK kinase that governs whole-body insulin sensitivity via this signaling pathway (32,33).

A different portion of the pathway that responds to insulin, estrogen, androgen, and certain proto-oncogene growth factors contains PTEN. PTEN is an unusual phosphatase enzyme which can preferentially remove phosphates from phosphatidyl inositol triphosphate 3, 4, and 5. Like LKB1, PTEN also has a dual role as a tumor suppressor and regulator of metabolic signaling. PTEN acts as a metabolic regulator by modulating the AKT1 kinase, which is downstream of the insulin receptor. This modulation ultimately affects the feedback inhibition processes [less insulin-receptor substrate (IRS) 1&2 transcription, more IRS1&2 phosphorylation] necessary to maintain normal insulin sensitivity. PTEN acts as a tumor suppressor by an analogous mechanism-negative regulation of the phosphatidyl inositol-3-kinase (PI3K)/AKT1 oncogenic signaling pathway. Loss of function from germ line mutations in the *PTEN* gene causes PTEN hamartoma tumor syndrome (34). This syndrome includes Cowden's disease, an autosomal dominant, complex disorder that manifests as malignant and benign (hamartomatous) lesions affecting breast, thyroid, uterus, brain, and mucocutaneous tissues. Because PTEN is both a tumor suppressor protein and a regulator of metabolic signaling, it is a candidate common factor in the development both of some types of cancer and insulin resistance.

Cytokines also represent the inflammatory process in the CHIEF pathway because inflammation is initiated by the synthesis and secretion of proinflammatory cytokines (e.g., TNF and IL-6 in macrophages) in response to an inflammation-provoking insult. The increased production of cytokines and subsequent elevation in reactive oxygen and nitrogen species are recognized hallmarks of inflammation. This process is regulated by a negative-feedback mechanism and closely followed by the secretion of anti-inflammatory cytokines (e.g., IL-10). As seen in Crohn's disease and ulcerative colitis, the cellular antioxidant defense system is activated to limit the development of chronic inflammation, which gives rise to a much higher-than-normal cancer risk. The binding of proinflammatory cytokines to their receptors triggers the activation of NFκB, which in turn activates the expression of a wide variety of genes including cytokines and COX-2. The unchecked activation of NFκB/COX-2 frequently occurs in colon tumor cells.

NFκB is an important nuclear transcription factor that regulates a large number of cytokines and is critical for the regulation of tumorigenesis, cell proliferation, apoptosis, response to oxidative stress, and inflammation. It plays a critical role in diseases associated with

dysregulated immune response and is an important regulator of insulin; inappropriate activation of NF κ B has been linked to inflammatory events. TNF α can activate the inhibitor of κ B kinase (IKK) complex and induce insulin resistance (35,36) and is thought to be one of the most important promoters of inflammation because it induces activation of at least two of the relevant major signaling pathways (IKK and NF κ B). The IKK complex is the key regulator of NF κ B's transcriptional activity.

NF κ B regulates the IL cytokines. IL-6 stimulates liver secretion of C-reactive protein, which is now considered to be an important biomarker for proinflammatory status in several diseases including cancer (37). Serum IL-6 is increased in many inflammatory diseases, but in contrast to other cytokines such as TNF, IL-6 can have both proinflammatory and antiinflammatory effects. Serum IL-6 has been shown to be elevated in several cancers, including prostate, bladder, colon, and breast cancer (38-40). IL-8 is a proinflammatory cytokine that primarily mediates the activation and migration of neutrophils into tissue from peripheral blood. IL-10 is an immunosuppressive cytokine and also is known as the cytokine synthesis inhibitory factor. Studies have shown that IL-10 may arrest chronic inflammatory responses in atherosclerosis (41) by responding to the secretion of proinflammatory cytokines such as IL-6 and TNF and by downregulating their activity. Circulating levels of IL-10 are elevated in obese women and decreased in metabolic syndrome (42,43).

Other cytokines with a potential impact on CRC risk through inflammation-related mechanisms include IL-1 (both IL-1 α and IL-1 β), IL-4, and IFN- γ . IL-1 α and IL-1 β are potent mediators of inflammation and immunity and have been associated with IL-6 and TNF levels in several diseases thought to have an inflammation-response element in their etiology (44,45). IL-1 β is an important element in the angiogenesis and invasiveness of several tumor cells (18). IL-1 receptor A is responsible for regulating IL-1 α and IL-1 β . IL-4 protects endothelial cells from the cytotoxic effects of the PI3K/Akt signaling pathway (46) and inhibits NF κ B and calcium signaling (47,48). IL-4 may have a direct effect on intestinal epithelial cells and upregulates the expression of suppressors of cytokine signaling (49,50). INF- γ is a proinflammatory cytokine that can activate the transcription factors NF κ B and c-Jun N terminal kinase (JNK).

Steroid hormones including estrogen, androgen, and progesterone have been shown to have both anti-inflammatory and proinflammatory properties (51,52) and, therefore, are components of an inflammation-related pathway. The receptors of the steroid hormones have been shown to interact with NF κ B in an antagonist manner (52-54). However, studies also suggest that the influence of estrogen may depend on cell type and form of estrogen (51,52,55). Estrogen receptor (ER) β , the most abundant ER in the GI tract, has been shown to have a dramatically beneficial effect in the HLA-B27 transgenic rat model of inflammatory bowel disease (56). Estrogen also has been shown to repress IL-6 expression as well as I κ B, potentially explaining its anti-inflammatory mechanism (52,57). It has been hypothesized that ER-negative breast tumors may metastasize through activation of NF κ B and I κ B due to loss of ER function (52).

It is hypothesized that inflammation-related mechanisms are associated with insulin through the axis connecting IRS1&2 \rightarrow PI3K \rightarrow AKT1 \rightarrow tuberous sclerosis 1&2 \rightarrow mTOR \rightarrow S6K1&2. The *VEGF* gene may influence CRC development through its action on tumor cells and angiogenesis; VEGF also regulates S6K and IRS-1 and may play an important role in regulating cell growth signaling within this pathway (58). PTEN restrains insulin signaling via this pathway. Chemical inactivation of PTEN also predisposes to polyp formation and the attendant risk for cancer.

Signal transduction and activation of transcription (STAT) and mitogen-activated kinases (MAPK) are involved in both inflammation and metabolic signaling associated with hormones and energy-related factors. STAT protein family members are phosphorylated in response to

cytokines and growth factors. Therefore, their involvement in convergent areas of multiple pathways makes them attractive candidate etiologic factors of CRC. STAT-1 is activated by NF κ B, IFN- γ , IL-1, and IL-6 and mediates the expression of a variety of genes; STAT-1–dependent transcription of proinflammatory genes is regulated by IFN- γ –activated PI3K and mTOR pathways (59). Data also suggest that STAT-1 activation can contribute to maintaining and expanding the local inflammatory response in celiac disease and may therefore have implications for CRC (60). STAT-6 plays a central role in IL-4–mediated biological responses that involve TNF α , IL-8, and NF κ B, and the STAT-6 pathway contributes to the hypercontractility of intestinal muscle in Crohn's disease (61). STAT-6 also is involved in signaling from the leptin receptor and may therefore be involved in obesity and energy balance (62).

MAPKs are a family of STKs that serve as an integration point for multiple biological signals and are involved in a variety of cellular processes such as proliferation, differentiation, and transcription regulation. JNK-1 or MAPK-8 is activated by TNF α and is necessary for apoptosis. NF κ B is required to terminate JNK signaling. JNK-1 activity is elevated in obesity, and an absence of JNK-1 results in decreased adiposity and improved insulin sensitivity (63). P38MAPK (also known as MAPK-14) is activated by environmental stresses and proinflammatory cytokines. *TP53* is mutated in roughly half of CRCs and is one of the substrates of P38MAPK, suggesting a role in cell cycle regulation. P38MAPK plays a role in multiple pathways that include the release of VEGF and is involved in the PI3K pathway related to *IL6* gene expression.

Epidemiologic Support for the CHIEF Pathway

Inflammation

Given the physiologic properties of the gut, the molecular properties of the CHIEF pathway, and the relevant epidemiology literature, it is reasonable to hypothesize that inflammation is the underlying determinant of CRC risk because it mediates the risk associated with many other factors. There is intriguing epidemiologic evidence of inflammatory mediators interacting with various metabolic, hormonal, and energy-related factors to alter the risk of CRC, suggesting that they may be central to explaining observed inconsistencies in the literature surrounding CRC risk factors. As previously noted, several inflammatory conditions predispose to CRC.

Epidemiologic and clinical data consistently support an association between aspirin and other nonsteroidal anti-inflammatory drugs (NSAID) and a reduced risk of CRC (64), suggesting that inflammation-lowering factors reduce CRC risk. NSAIDs also have been shown to modulate CRC risk associated with diet, life-style, and genetic factors (65). In laboratory settings, high doses of salicylates (salts and esters of salicylic acid, which is similar but not identical to the active ingredient of aspirin) inhibit NF κ B and its upstream activator IKK β , which regulate immune cell differentiation and survival (36). A 2- to 3-fold increased risk of colon cancer has been associated in some studies with high levels of C-reactive protein, a marker of systemic inflammation (37).

Although limited, epidemiologic studies of polymorphisms of genes thought to be involved in inflammation-related pathways provide additional support for inflammatory processes as a component of CRC development. Polymorphisms in *IL8* have been associated with inflammation levels and CRC development (66). In a study using hospital-based controls (66), associations between CRC risk and inflammation-related polymorphisms included a 50% reduction associated with the Ala variant of P12A peroxisome proliferator-activated receptor γ (*PPAR- γ*), a 70% increase associated with the C allele for *IL6*, and a 30% reduction in risk associated with the A allele of *IL8*. Another population-based study of CRC showed that ibuprofen-type drugs significantly interacted with the P12A *PPAR- γ* polymorphism to alter

rectal cancer risk (67). *SMAD7* single nucleotide polymorphisms have been shown to be associated with colon cancer risk in genome-wide association studies (68,69); *SMAD7* is involved in inflammation-related pathways and has been shown to modulate transforming growth factor β and wnt signaling (70). Confirmatory studies of the *SMAD7* association with colon cancer showed that aspirin and/or NSAID use modified the CRC risk associated with *SMAD7*.⁵ Polymorphisms of *IFN- γ* have been shown to influence survival in patients with pancreatic cancer and breast cancer (71) and may be an important mediator of inflammation-related processes. Most inflammation-related genes, however, have not been examined for potential associations with CRC.

Hormones

Androgenic and estrogenic steroids and insulin-related hormones have been identified as key risk factors in the etiology of CRC. Women taking hormone replacement therapy have been shown to have a reduced CRC risk in both observational studies and clinical trials (72,73); it seems that aspirin may modulate the risk associated with estrogen (74). Genetic polymorphisms in both the androgen receptor and *ER* genes are associated with altered CRC risk (75). Estrogen represses the production of IL-6 through an ER-dependent mechanism; serum levels of IL-6 increase following menopause in healthy women and with age in both men and women (76, 77).

An insulin-related pathway has been proposed as a unifying mechanism underlying several CRC risk factors including physical inactivity, obesity, and certain dietary factors such as glycemic index and dietary fiber (78,79). Polymorphisms of genes associated with insulin-related pathways, such as *IRS1*, are associated with colon cancer, and these associations can be modified by aspirin use (80). Insulin-like growth factor (IGF) 1 (*IGF1*), IGF binding protein 3 (*IGFBP3*), *IRS2*, and IGF receptor 1 (*IGF1R*) polymorphisms have not been consistently associated with CRC risk. Polymorphisms of the transcription factor 7-like 2 (*TCF7L2*) gene have been associated with insulin sensitivity and diabetes, and *TCF7L2* is involved in the Wnt/ β -catenin signaling pathway, all thought to be important factors in the etiology of colon cancer (81,82). Folsom et al. (83) showed a significantly increased CRC risk in association with the T allele of the rs7903146 *TCF7L2* polymorphism. A significant interaction has been found between the rs7903146 *TCF7L2* polymorphism and recent use of aspirin/NSAIDs ($P_{\text{interaction}} = 0.001$); an increased colon cancer risk associated with the T allele was restricted to people who had not recently used aspirin and/or NSAIDs [odds ratio, 1.65; 95% CI, 1.35-2.02] relative to recent (within 2 years before diagnosis) aspirin and/or NSAID users with the CC genotype; ref. 84]; and recent aspirin and/or NSAIDs use reduced colon cancer risk in people with the T allele (odds ratio, 0.78; 95% CI, 0.62-0.98) in a dose-response fashion ($P = 0.03$ for a linear trend across genotypes; ref. 84). These data provide additional support for aspirin and/or NSAIDs use, a crude potential surrogate for the inflammatory state of the GI tract, as an important mediator of hormone-related CRC risk.

The associations between insulin-related factors, including polymorphisms of genes in an insulin-related pathway, and CRC seem to be modified by aspirin use (80). Furthermore, salicylates have been shown to have a hypoglycemic effect (85-89), and high doses of salicylates can reverse hyperglycemia, hyperinsulinemia, and dyslipidemia by influencing insulin signaling (36). Epidemiologic studies show strong associations between systemic markers of inflammation (e.g., IL-6, TNF) and a heightened risk for obesity-related insulin resistance (90-93). Laboratory studies support a role for the inflammatory cytokine TNF and the NF κ B signaling pathway in the association between obesity, chronic inflammation, and insulin resistance (94,95). *TNF* has been reported to inhibit insulin-induced glucose uptake by

⁵M.L. Slattery, J. Herrick, K. Curtin, et al., unpublished data.

targeting components of the insulin-signaling cascade, one component of which is IRS-1 (96-100). Aspirin has been shown to protect insulin-induced glucose uptake in TNF-treated adipocytes by blocking TNF effects on IRS1 (96).

Although steroid- and insulin-related hormonal factors seem to be important in CRC etiology, it also seems that they do not reflect isolated pathways to cancer development; rather, they reflect an interrelated hormone-related pathway that operates on an underlying state of inflammation. Given the recurring theme of effect modification by aspirin and/or NSAIDs, it seems that the inflammatory state of the GI tract may be an important determinant of the CRC risk associated with estrogen and androgen and insulin-related factors.

Energy-Related Factors

Energy-related factors include factors related to energy balance, diet, physical activity, and obesity. These factors also have been proposed as key factors related to insulin signaling (79). Epidemiologic data show inconsistent associations between energy intake and CRC risk, and between energy-contributing nutrients (such as dietary fat) and CRC risk (101). Although physical activity has been consistently associated with a reduced risk of colon cancer, its association with rectal cancer risk has been inconsistent (102). Overweight and obesity have been identified consistently as important risk factors for colon cancer among men, premenopausal women, and postmenopausal women taking hormone replacement therapy (103-106); data suggest that body mass index (BMI)-related colon cancer risk also is modulated by aspirin and/or NSAIDs (107).

Diet, physical inactivity, and obesity are associated with inflammation as well as with insulin signaling. The finding that high-fat meals increase the coabsorption of enteric bacterial lipopolysaccharide endotoxin, causing low-grade endotoxemia and postprandial inflammation (108), links diet to an inflammation pathway. Studies suggest that aspirin use may modify harmful effects of dietary fat, and it has been suggested that a lower CRC risk associated with dietary fat in more recent years may relate to higher aspirin use in the general population (109,110), suggesting further that dietary fat effects on CRC risk may involve an inflammation-related mechanism. IL-6 is a “mytokine,” or a cytokine produced in muscle, and is elevated in response to muscle contraction (111). It is significantly elevated with exercise and precedes the appearance of other cytokines in the circulation. During exercise, IL-6 is thought to act in a hormone-like manner to mobilize extracellular substrates and/or augment substrate delivery (111). Therefore, inflammation-related mediators also may influence the effects of physical inactivity, a factor consistently associated with colon cancer risk.

Data on associations between body size and TNF α , IL-6, leptin, and adiponectin support obesity as an “inflammatory state.” Adipose tissue expresses mRNA for TNF α , and this expression is increased in healthy obese adults (112,113). IL-6 is produced by the stroma of adipose tissue, and serum IL-6 levels are increased in healthy obese individuals, independently of age or menopause (112). It is estimated that about one third of circulating IL-6 in a healthy individual derives from adipose tissue (114). Qi et al. (115) studied associations between the genetic variability of *IL6* and long-term changes in or related to BMI among 2,255 healthy women and 980 healthy men from two prospective cohorts. The *IL6* haplotype 222211 (comprising rs2069827, rs1800797, rs1800795, rs1554606, rs2069861, and rs1818879; 1 codes the common allele and 2 codes the minor allele) was consistently and significantly associated with a greater waist circumference ($P = 0.009$ in men and 0.0003 in women) and baseline BMI ($P = 0.01$ in men and 0.046 in women) compared with the most common *IL6* haplotype, 111112. A 5-prime polymorphism, rs2069827, also was consistently associated with significantly higher early-adulthood BMI, baseline BMI, and waist circumference in men and women. Adipose tissue secretes adipokines such as adiponectin and leptin. As members of the IL-6 family of cytokines, leptin and its receptor are considered to be proinflammatory

cytokines and to play a major role in modulating inflammation and immune response (116, 117). Epidemiologic data have shown a statistically significant interaction between recent use of aspirin and/or NSAIDs and leptin (*LEP*) polymorphisms and the risk of developing colon cancer (118).

Conclusions

The physiologic structure of the gut and supportive epidemiologic and molecular data led us to propose that basal immune activation—a repetitive, mild subclinical inflammation—is the underlying modulator of CRC risk and influences the CRC risk associated with insulin, estrogen, and energy-related factors. The CHIEF pathway integrates elements of angiogenesis, hormones, and energy-related factors with the underlying inflammatory state of the colon and rectum. Additional support for the importance of the CHIEF pathway comes from the fact that many of its genes are tumor suppressor genes, which frequently are mutated in CRC.

We believe that the CHIEF pathway of convergence resonates with other cancers including breast and possibly prostate cancer. Breast and prostate cancer risk assessments have revealed many of the same risk factors, with varying levels of risk and relative importance, as those identified for CRC. It is intriguing that obesity seems to increase colon cancer risk (119) and is associated with a reduced breast cancer risk (120) in premenopausal women. Hormone replacement therapy reduces the risk of colon cancer, whereas it increases the risk of breast cancer (73). Aspirin and NSAIDs reduce the risk of colon cancer, whereas their association with breast cancer risk is inconsistent (121-123). Inflammation-related factors may be pivotal for colon cancer risk, but the pivotal component of the pathway for breast cancer may be estrogen because the epidemiologic data suggest that menopausal status and estrogen are central effect modifiers of other risk factors. The pivotal pathway component is most likely determined by the underlying tissue structure. For CRC, we believe that the primary determinant of risk is inflammation. Given the close relationship of the key pathway elements, however, the ultimate pathway to carcinogenesis involves all of the elements of CHIEF.

Randomized clinical trials have reinforced the conclusions from over 40 observational studies that NSAIDs, which inhibit the COX enzymes, prevent colorectal adenomas as well as CRC (124,125). An understanding of key elements in the CHIEF pathway and their role in the carcinogenic process promises to lead to practical approaches for both prevention and treatment.

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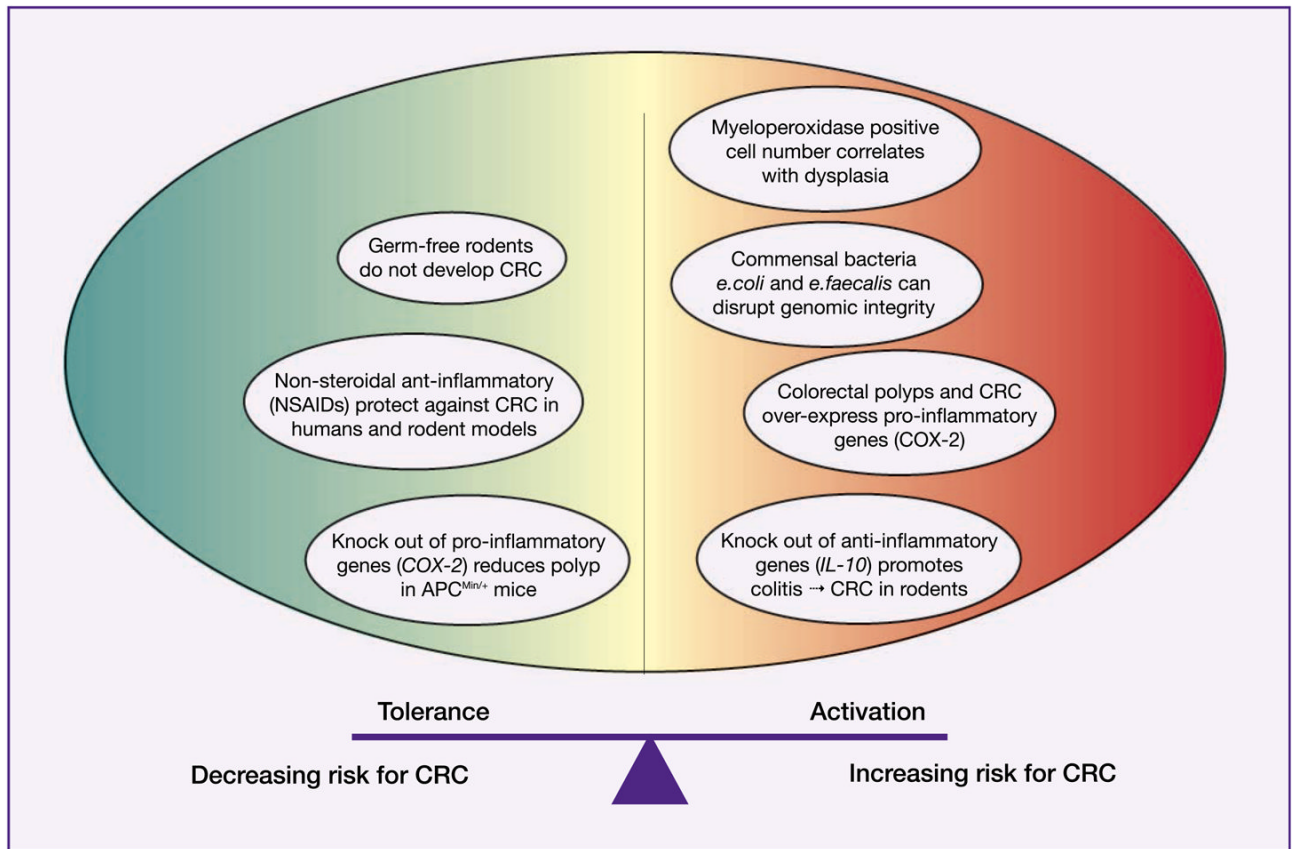


Fig 1. The balance between tolerance and activation of CRC risk. The intestine must carefully balance immunity, to protect us from harmful microbes, and tolerance, to permit interaction with harmless commensal bacteria and dietary antigens. Disruptions that tilt the balance toward immune activation/inflammation could facilitate multistage tumor progression in the intestinal tract.

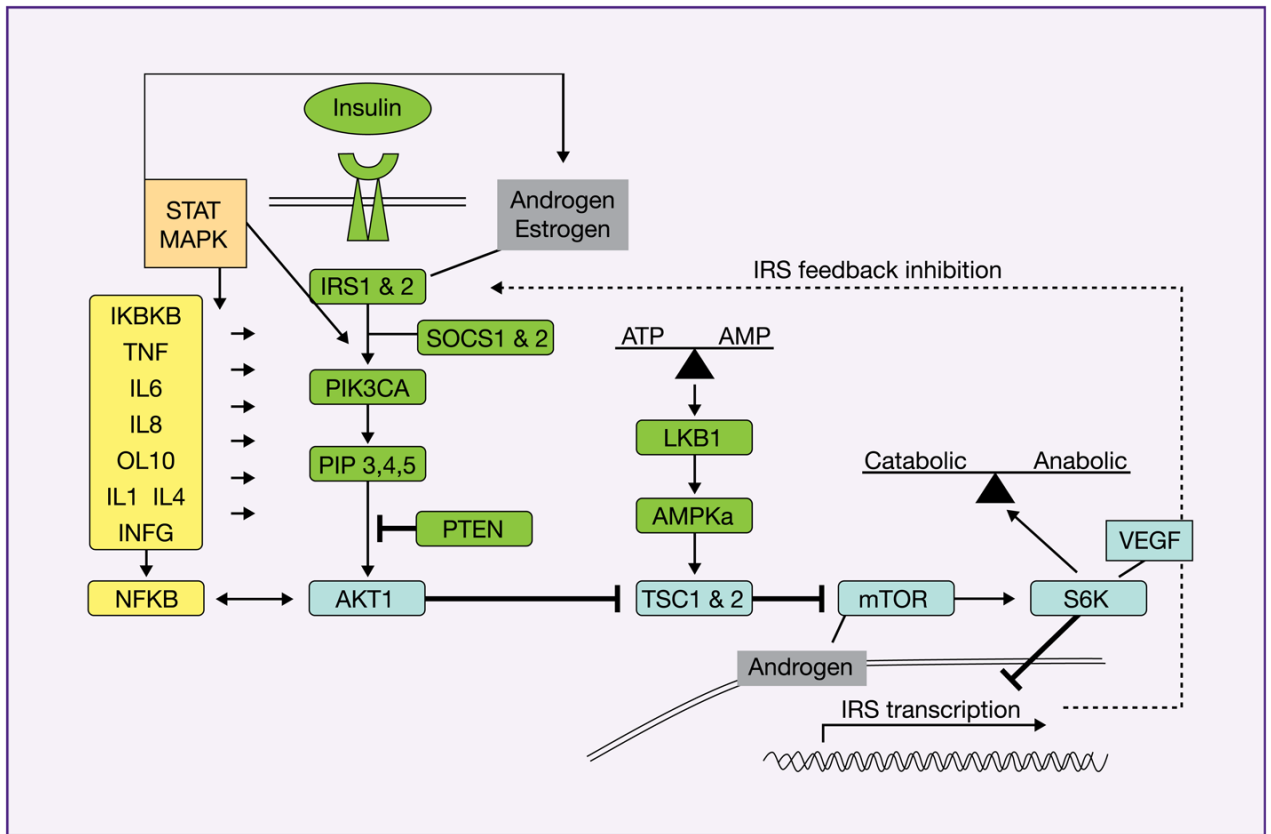


Fig 2. Convergent signaling pathways where inflammation and metabolic signaling intersect along the CHIEF pathway.