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Mini Review

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Inflammation Driven Activation of *Wnt* Pathway: A Potential Mechanism Responsible for Obesity-associated Colorectal Cancer

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ABSTRACT

Substantial evidence indicates that obesity, which has reached an epidemic proportion, is a robust risk factor for several types of cancer, particularly the colorectal cancer. As the worldwide obesity epidemic has shown no sign to decrease, whereas further increases in the scope of this problem are still projected, insight into the mechanisms of obesity-associated tumorignesis is urgently needed for the development of preventive approaches to block this process. Obesity is associated with multiple metabolic changes, and therefore a single mechanism is unlikely to be responsible for all obesity-associated tumors. A quite number of articles provided systemic reviews of the possible mechanisms for the association between obesity and the initiation and progression of cancers. In this mini-review, we focus on how obesity mediates colorectal cancer *via* inflammation driven *Wnt*-signaling pathway.

KEYWORDS: Obesity; Inflammation; *Wnt* pathway; Colorectal cancer.

ABBREVIATIONS: Apc: *Adenomatous polyposis coli*; BMI: Body Mass Index; CRC: Colorectal Cancer; DKK: Dickkopf family; Fzd: Frizzled; GSK3β: Glycogen synthase kinase-3 beta; SFRP: Secreted frizzled-related protein family; IL-1β: Interleukin-1 beta; IFN-γ Interferon-gamma; TNF-α: Tumor Necrosis Factor-alpha; WIF: *Wnt* inhibitory factor family; *Wnt*: Wingless/Int.

INTRODUCTION

Colorectal Cancer (CRC) is the third most common cancer and the third leading cause of cancer death in both men and women in the United States, and ~5% of the population will develop CRC in their life. Based on this lifetime probability, it can be estimated that ~140,000 new cases will occur in US per year.[1] Most colorectal cancers are due to lifestyle factors and increasing age, with only a small number (<5%) of cases due to a family history of genetic disorders.[2] Among these risk factors for CRC, obesity, defined as abnormal or excessive fat accumulation to the extent that health is impaired,[3] results in a 50~100% increased risk of CRC in men and a 20-50% increase in women.[4] Obesity is one the fastest growing diseases worldwide, and in the United States, the prevalence has reached an epidemic proportion,[4] with more than two-thirds of adults overweight or obese as defined as Body Mass Index (BMI) greater than 25.[5] As there are few effective strategies to prevent the occurrence of obesity, and even further increases in the scope of the problem are still projected.[5,6] It is appropriate to develop preventive approaches for obesity-associated CRC.

To define effective strategies to block the linkage between obesity and cancer, it is essential to understand how obesity mechanistically leads to the development of cancer. It is well understood that, in addition to the function of storing excess calories in the form of lipid, adipose tissue is also a metabolically active organ, which secrets numerous molecules, including a number of critical inflammatory cytokines and adipokines such as leptin and adiponectin.[7] These molecules are associated with a number of physiological changes and thereby lead to multiple medical complications, including the development of cancer. For instance, obese individuals normally develop insulin resistance and consequently insulin levels raise as pancreatic β-cells secrete more insulin to compensate for the resulting hyperglycaemia. Chronically increased insulin levels have been associated with CRC.[8]

Multi-mechanisms have been described to link insulin with CRC. For instance, insulin promotes DNA synthesis, suggesting a mitogenic effect.[7] Increased insulin levels lead to reduced liver synthesis and blood levels of insulin-like growth factor, which further signals to promote cellular proliferation and inhibit apoptosis in many tissue types including the organ of colorectum, and these effects contribute to tumorigenesis.[4] Another complication of obesity which recently emerges to contribute to the development of CRC is gut microbiota.[9] The gut microbiota directly influences the intestinal immune system, including both initiating inflammation as well as regulating immune cells.[10] With the consideration of multiple complications associated with obesity, there must be many theories that could explain the increased incidence of cancer in obesity. A large number of articles provided systemic reviews of the possible mechanisms for the association between obesity and the initiation and progression of cancers.[4,7,11] In this mini-review, we focus on how obesity mediates colorectal cancer *via* inflammation driven *Wnt*-signaling pathway (Wingless/Int).

The Increasing Prevalence of Obesity: Implications for the Societal Burden of Colorectal Cancer

The prevalence of overweight and obesity has reached an epidemic level in the United States[5,6] and also in many other industrialized and urban areas in developing countries throughout the world.[12,13] Obesity is among the fastest growing disease worldwide. For example, the prevalence of obesity among adults in Great Britain almost tripled between 1980 and 2002.[14] Among preschool children (2-6 years old) in urban areas of China, the prevalence of obesity increased from 1.5% in 1989 to 12.6% in 1997 and prevalence of overweight increased from 14.6 to 28.9% at the same period.[15] Among U.S. adults, the prevalence of obesity (BMI > 30.0) doubled between 1976 and 2008. Although it has levelled off since 2004, there has been no indication of a decrease from the overall prevalence of 34% of obesity and a combined prevalence of 68% for overweight and obesity (BMI ≥ 25.0).[5,16] Moreover, a 33% increase in obesity prevalence and a 130% increase in severe obesity prevalence is projected by 2030.[17]

A prospective cohort of nearly 1 million Americans demonstrated obesity is a critical risk factor for total cancer deaths in the United States.[18] It has been estimated that 15~20% of all cancer deaths in the United States are attributable to this problem: ~90,000 cancer deaths per year.[18] The evidence is particularly strong for cancers of the colorectum:[19-22] case-control and cohort studies indicate that obesity causes a 50-100% increase in the risk of CRC in men and a 20-50% increase in women.[4] Even overweight produces a discernible (20%) increase in risk,[18] underscoring how sensitive the development of colon cancer is due to this factor. A comprehensive review of the literature by the International Agency for Research and Cancer concluded that there is sufficient evidence to conclusively state that overweight/obesity increase the risk of CRC.[23] Therefore, understanding the pathophysiological mechanism underlying the association between obesity and CRC and accordingly defining interventional approaches that would block the mechanistic link will greatly contribute to reducing the incidence of CRC, the third most common cancer in incidence and mortality.

Inflammation: Bridging Obesity and Colorectal Cancer

Since the initial discovery of escalated expression of Tumor Necrosis Factor-alpha (TNF-α) in adipose tissue in 1993,[24] many other adiposity-related inflammatory molecules, such as interferon-γ, and Interleukins (IL) -1, -6, -8 and -10 have been identified.[25,26] It is now well-accepted that obesity is associated with a state of chronic low-grade inflammation.[27]

These cytokines are actually produced, in a majority of portion, not from adipocytes, but from immune cells, particularly the macrophages, that infiltrate adipose tissues in obesity.[28] It is clear that this increased secretion of cytokines causes chronic inflammation that affects the function of other tissues in the body and thereby associates with the etiology of a variety of diseases.[29]

Epidemiologic studies have long supported a link between chronic inflammation and development of certain solid tumors including CRC.[30] The most overt examples are patients with chronic inflammatory bowel disease, among whom the incidence of CRC increases progressively over time, reaching 19% after 30 years of disease.[31] Animal models closely recapitulate the findings of human studies, unambiguously proving a causal link between chronic inflammation and CRC.[32] The Dextran Sulfate Sodium (DSS)-induced colitis animal model represents an excellent preclinical system to characterize the molecular events required for tumor formation in the presence of inflammation. Based on this model, a number of animal studies have reported that the incidence of neoplasia is increased and its progression to invasive cancer is accelerated significantly by administering DSS in combination with a known colon carcinogen, azoxymethane.[32] Additionally, some nutrients which possess anti-inflammatory characteristics, such as vitamin D[33] and ω-3 fatty acids,[34] show promise as preventive agents for cancer.[35]

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Inflammatory responses play decisive roles at different stages of tumor development, including initiation, promotion, malignant conversion, invasion, and metastasis.[36] However, how inflammation lies on the causative pathway mechanistically linking obesity to CRC and what is the cellular mechanism(s) by which these anti-inflammatory nutrients work remains unclear.

The *Wnt* Signaling Pathway: A Pivotal Pathway in the Development of Colorectal Cancer

The vast majority (>90%) of colon cancers in humans possess over-activation of *Wnt* pathway and there is strong evidence that this activation plays a pivotal role in carcinogenesis.[37,38] This pathway is outlined in figure 1. In the absence of *Wnt* ligands bound to the Frizzled-related protein family (Fzd) receptor as well as with an intact *Adenomatous polyposis coli* (Apc)-Axin complex (Figure 1A), *Wnt*-signaling is blocked, because under these conditions, Glycogen synthase kinase-3 beta (GSK3β, a key component of the Apc-Axin complex) phosphorylates β-catenin, which is in turn degraded through the ubiquitin pathway in the proteasome. Alternatively, in the presence of a competent *Wnt* ligand or a defective Apc-Axin complex (Figure 1B), β-catenin cannot be phosphorylated, and therefore stabilized β-catenin accumulates in the cytosol and then translocates into the nucleus, where it initiates transcription of a large number of pro-carcinogenic *Wnt* target genes such as cyclin D1 and c-myc.

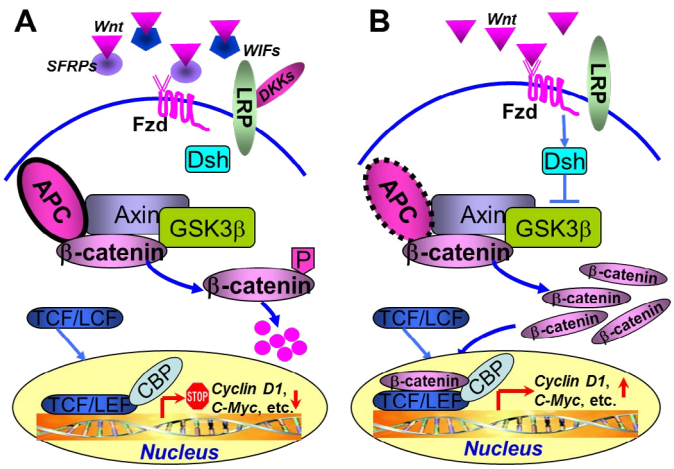

Figure 1: The activation of *Wnt* signaling. (A) In the presence of *Wnt* antagonists and with an intact Apc-Axin complex, GSK3β phosphorylates β-catenin and then phosphorylated β-catenin is rapidly degraded by ubiquination at the proteosome. (B) In the absence *Wnt* antagonists or with an altered Apc-Axin complex, β-catenin accumulates in the cytoplasm and form a complex with TCF/LEF in the nucleus, which initiates transcription of *Wnt* target genes.

Dysregulation of *Wnt*-signaling is traditionally attributed to mutations in Apc and β-catenin that lead to constitutive hyper activation of the pathway. Mutations in the tumor suppressor, Apc, are apparently the basis for familial *adenomatous polyposis*,[39] However, only a small fraction of CRC occur in an apparently inherited fashion with Apc mutation.[40] Activation of *Wnt*-signaling is not exclusively explained by mutations in the Apc gene. A significant amount of *Wnt*/β-catenin signaling alterations is modulated through other mechanisms.[41] For instance, inappropriate *Wnt*-signaling activation may also be produced by post-translational modification of its elements; it is now evident that epigenetic transcriptional silencing of components within the *Wnt* pathway cascade serves as an alternative mechanism for modulating *Wnt*-signaling in CRC.[42,43] Specifically, the epigenetic regulation of *Wnt* antagonistic genes, such as Secreted Frizzled-Related Protein family (SFRPs), Dickkopf Family (DKKs), and *Wnt* Inhibitory Factor family (WIFs) have been intensively investigated.[44] *Wnt*-signaling activation can also occur through phosphorylation of the negative regulatory element, GSK3β, which in turn causes β-catenin protein stabilization.[45] Obesity is associated with a state of low-grade inflammation and the development of CRC. The following section describes evidence that obesity is associated with the alteration of *Wnt* pathway, and particularly, some interesting studies that provided insight into the potential role of inflammatory cytokines in driving the activation of the critical *Wnt*-signaling tumorigenic pathway.

The Inflammation Driven Activation of *Wnt*-Signaling: The Potential Cellular Pathway Linking Obesity to the Development of Colorectal Cancer

Over the past several decades, the field of adipogenesis has demonstrated a number of regulators of preadipocyte differentiation, and one of the critical extracellular signaling pathways are the *Wnt*-signaling.[46] *Wnt* pathway exerts its role by signalling through multiple steps to control cell differentiation, proliferation, and apoptosis. As such, *Wnt*-signaling is highly pertinent to adipocyte biology, such as pre-adipocyte differentiation and fate determination.[47] The MacDougald laboratory first reported that *Wnt*/β-catenin signaling inhibits adipogenesis, by showing that over expression of *Wnt*1 or a GSK3β phosphorylation-defective β-catenin mutant, components within *Wnt* pathway cascade, inhibited adipogenesis.[48] Recently, Dr. Kenneth Walsh's laboratory showed a direct association between obesity and *Wnt* pathway: obesity induces a decrease in SFRP*5* production and an increased expression of *Wnt5a*, two upstream elements of the *Wnt* pathway, which collectively inhibit *Wnt*-signaling and lead to enhanced inflammatory signaling and insulin resistance.[49] In adipose tissue, *Wnt* pathway is now a well-established pathway as an inhibitory regulator in adipogenesis.

However, in addition to the role of *Wnt*-signaling in adipose biology, several striking studies recently indicate *Wnt* pathway plays as a critical regulator in linking obesity with its associated complications including cancer. Obesity is a predisposing factor for metabolic disorders, which are often associated with a systematically disrupted homeostasis of many metabolic molecules, including inflammatory cytokines. These cytokines have properties to activate *Wnt*-signaling. For instance, in a negative feedback mechanism, adipose tissue is associated with

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macrophage infiltration and increased local concentrations of inflammatory cytokines, such as TNF-α and IL-6, which inhibit adipogenesis *via* promoting *Wnt*-signaling.[50,51] More importantly, in gastrointestinal epithelial cells or colon cancer cell lines, it is reported that several inflammatory cytokines can activate *Wnt*-signaling. It has been shown that TNF-α possesses the function to phosphorylate the negative regulatory element GSK3β and in turn cause β-catenin protein stabilization in gastric cells.[45,52] We recently also demonstrated that obesity elevates TNF-α, in the mouse colon, and this occurs in parallel with alterations of several key components of the pro-carcinogenic *Wnt* pathway in a pattern that is indicative of its activation.[53] IL-1β, another critical inflammatory cytokines shown to be increased in obese state, also exhibits the function to phosphorylate GSK3β, stabilize β-catenin protein, enhance T-cell factor dependent gene activation and induced the expression of *Wnt* target genes in colonic tumor cells.[54] Nava P et al. reported that IFN-γ can regulate intestinal epithelial homeostasis through converging β-catenin signaling pathway.[55] These observations are very important since it is well-accepted that aberrant *Wnt*-signaling is a critical early event in CRC. Inflammation driven activation of *Wnt*-signaling may provide as a potential cellular pathway linking obesity to the development of CRC as shown in figure 2.

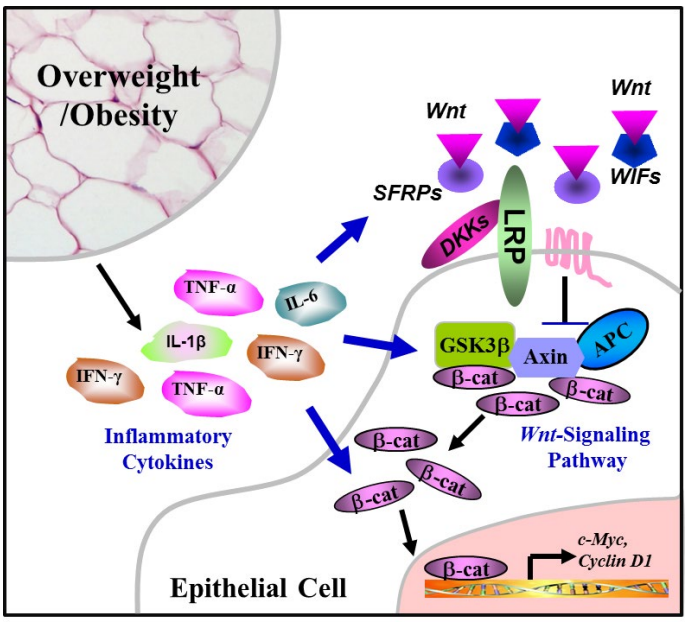

Figure 2: The scheme of the hypothesis: obesity increases the production of Inflammatory cytokines (TNF-α, IL-1β, IFN-γ, etc.), which target Wnt–signaling pathway elements in the colonic epithelial cells and thereby promotes the development of colorectal cancer.

In addition to the well accepted concept that a low-grade inflammatory response exists in the adipose tissue of obese individuals, and the adipose tissue-produced cytokines can circulate to other tissues and organs, as indicated by the elevated levels of inflammatory cytokines in the systemic circulation,[25,26] it is highly noteworthy that, in obese state, tissues and organs other than the adipose tissue also present a chronic inflammation. In addition to the increased TNF-α in the colon of obese mice reported by our group.[53] An inflammatory state in association with obesity also exists in other organs such as liver, pancreas, muscle and even brain.[56] The inflammatory cytokines produced locally may even have a more direct influence in modulating the local microenvironment, including the regulation of the *Wnt* pathway.

CONCLUSIONS

Our understanding of the biological mechanisms that link overweight and obesity to the pathogenesis and development of CRC is increasing. In this mini-review, we described inflammation driven activation of *Wnt*-signaling as a potential cellular pathway linking obesity to the development of CRC, but it is currently with only limited experimental support and further investigation is warranted. Given the lack of current effective strategies to diminish obesity epidemic, insight into the molecular mechanisms might lead to identification of new therapeutic targets for the development of efficient approaches to reduce the burden of obesity-associated CRC in our society.

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