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Review

Colon carcinogenesis: Influence of Western diet-induced obesity and targeting stem cells using dietary bioactive compounds

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ABSTRACT

Colon cancer strikes more than 1 million people annually and is responsible for more than 500,000 cancer deaths worldwide. Recent evidence suggests that the majority of malignancies, including colon cancer are driven by cancer stem cells (CSCs) that are resistant to current chemotherapeutic approaches leading to cancer relapse. Wnt signaling plays a critical role in colon stem cell renewal and carcinogenesis. Leucine-rich repeat-containing G protein-coupled receptor 5 (*LGR5*), a Wnt target gene, and aldehyde dehydrogenase 1 B1 (ALDH1B1) are good markers for normal and malignant human colon stem cells. Diet contributes to 20% to 42% of all human cancers and 50% to 90% of colon cancer. Recent evidence shows that the Western diet has a causative link to colon cancer; however, mechanisms of action are not fully elucidated. Western diet-induced obesity elevates systemic insulin-like growth factor-1 and insulin levels, which could lead to elevated proliferation and suppressed apoptosis of CSCs through PI3K/AKT/Wnt pathway. Although conventional chemotherapy targets the PI3K/AKT pathways and can significantly reduce tumor size, it fails to eliminate CSCs and has serious side effects. Dietary bioactive compounds such as grape seed extract, curcumin, lycopene, and resveratrol have promising chemopreventive effects, without serious side effects on various types of cancers due to their direct and indirect actions on CSC self-renewal pathways such as the Wnt pathway. Understanding the role of CSCs in diet-induced colon cancer will aid in development of evidence-based dietary chemopreventive strategies and/or therapeutic agents targeting CSCs.

Introduction

Colon cancer strikes more than 1 million people every year and is responsible for more than 500,000 cancer deaths annually worldwide [1]. It is the second leading cause of cancer deaths in the United States with an estimated incidence of 142,570 (72,090 men and 70,480 women) and a mortality of 51,370 in 2010 [2,3]. Colon cancer incidence has been decreasing over the past 30 y in the United States largely due to medical advances in early detection; however, the survival of patients with advanced and metastatic colon cancer has not changed notably over the past several decades [4]. Despite these statistics, there is considerable promise in the cancer research field that new targeted therapies will dramatically improve the results of empirical therapeutics [4]. The ability to target specific pathways in carcinogenesis raises optimism for developing therapies with enhanced specificity and decreased toxicity [4]. As the capacity to target certain cellular events increases, a fundamental question remains, “Are we targeting the right cells”? Available evidence suggests that the majority of malignancies are driven by cancer stem cells (CSCs), or cancer-initiating cells, and these cells may be inherently resistant to current therapeutic approaches and may be the cause of cancer recurrence [4].

Historically, colon tumorigenesis has been viewed as a stochastic model where wide populations of abnormal colonocytes

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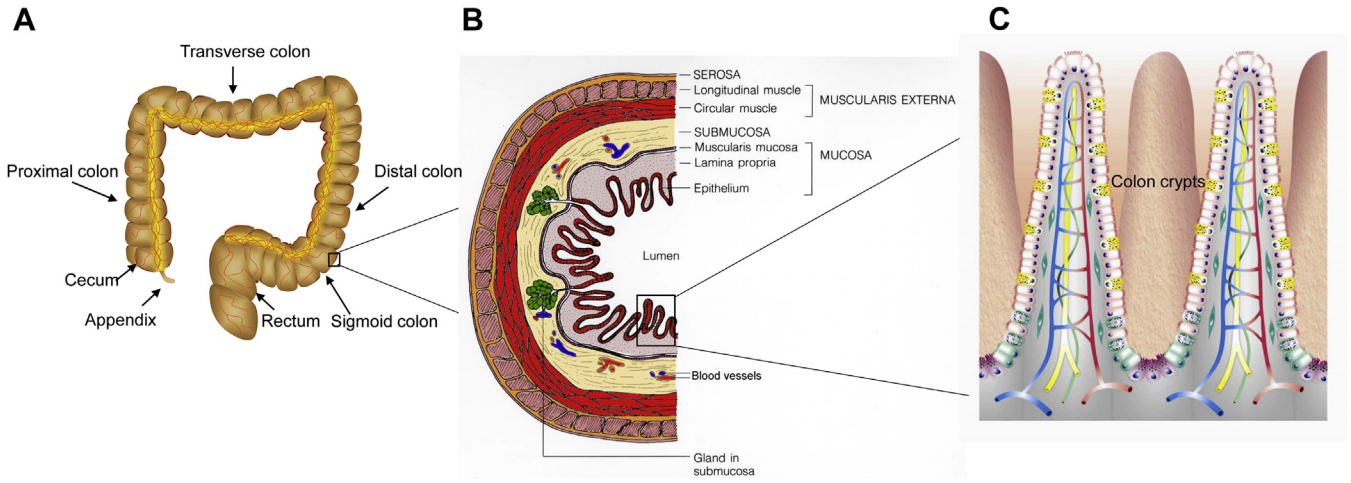

Fig. 1. Morphology of the colon. (A) The large intestine consists of the cecum, proximal colon, transverse colon, distal colon, sigmoid colon, rectum, and the anal canal. (B*) There are four layers of the colon wall; from inside to outside mucosa, submucosa, muscularis externa, and serosa. (C) The mucosa is composed of distinct crypt-like structures, which represent the functional unit of the colon. [Figures were drawn using Scienceslides Suite software (2010 edition)].*From [48].

have an equal propensity to initiate tumor growth [5]. In 1994, a Canadian research group reported evidence for cell-initiated acute myeloid leukemia (AML) in immunodeficient mice [6]. Most human AML cells have limited proliferative capacity; therefore this finding suggests that leukemic clone may be maintained by a population of stem cells (SCs). When putative human leukemia SCs were transplanted into healthy mice, it was found that these cells can initiate AML [6]. This observation implies that cancer, potentially colon cancer, may be initiated by SCs [7]. The CSC theory suggests that most, if not all, cancerous tumors are driven by CSCs probably through dysregulation of self-renewal pathways. This leads to an expansion of this cell population that may further undergo genetic or epigenetic changes to become fully transformed [4]. CSCs are capable of self-renewal, cellular differentiation, and maintain their SC-like characteristics even after invasion and metastasis [8]. Although the colon CSC research field is in its infancy and yet to come to an agreement on the best markers for identifying CSCs, the Wingless/Integrated (Wnt) target gene, leucine-rich repeat-containing G protein-coupled receptor 5 (*LGR5*) has emerged as a valid and putative marker in identifying and isolating CSCs [9]. More recently, aldehyde dehydrogenase (ALDH1B1), a mitochondrial ALDH isozyme, has been proposed as a marker for normal as well as malignant human colonic CSCs [10,11].

Accumulating evidence suggests that lifestyle factors are one of the predominant components that modulate susceptibility to colon cancer [12,13]. It is a concerning fact that the highest incidence rates of colon cancer are observed in developed nations, including the United States [14]. Moreover, risk for colon cancer is elevated within one generation in individuals who migrated from developing countries to developed countries. Colon cancer rates are rapidly rising in developing nations and could be due to adoption of several features of the Western lifestyle, as previously reviewed [14]. Diets rich in red and processed meats, refined starches, sugar, and saturated and trans-fatty acids but poor in fruits, vegetables, fiber, ω-3 fatty acids, calcium, vitamin D, and whole grains are closely associated with an increased risk for colon cancer. Other main features of the Western lifestyle, such as excess body mass and sedentary behaviors, are also strongly associated with higher risk for developing colon cancer [14–16].

Overweight/obesity is now established as a risk factor (second only to smoking) for colon cancer [12]. Two-thirds of Americans and an estimated 2.3 billion people worldwide are either overweight (body mass index [BMI] 25–29.9 kg/m^2) or obese ($\geq$30 kg/m^2) [12]. According to a recent meta-analysis, a 5 kg/m^2 increase in BMI raised colon cancer risk by 24% in men [17]. Obesity is a major determinant of insulin resistance. Elevated insulin and insulin-like growth factor (IGF-1) have been associated with colon carcinogenesis [12]. IGF-1 binding to its receptor, IGF-1R, activates the PI3K/AKT cascade, which promotes G_1 to S cell cycle progression [18] and elevates cell proliferation [19]. The Wnt/β-catenin pathway is one of the pathways activated by the PI3K/AKT signaling [20]. The Wnt/β-catenin pathway plays a central role in elevating colonocyte proliferation and suppressing apoptosis [21] in both humans and rodent models of experimentally induced colon cancer [22,23].

Diet contributes to 20% to 42% of all human cancers and 50% to 90% in colon cancer [24]. The fact that only 5% to 10% of all cancer cases are due to genetics and the remaining 90% to 95% are due to lifestyle factors, environmental toxins, and infections provide a major opportunity for the prevention of colon cancer [25]. Although the Western diet has causal link to colon cancer [26,27], very little is known about its effect on colon CSCs and approaches to eliminate colon CSCs. Thus, it is important to have a better understanding of the role of CSCs, particularly in Western diet-induced obese conditions, and develop evidence-based safe approaches for prevention and treatment.

It has been suggested that targeting CSCs could be achieved by several strategies including sensitizing them to chemotherapeutic agents, inducing differentiation, and inhibiting self-renewal signaling [28,29]. Conventional chemotherapies can significantly reduce tumor size, but they mostly fail to eliminate CSCs and can have serious side effects [8]. The search for a nontoxic chemotherapeutic regimen is fueled by epidemiologic studies that show correlation between plant-based diets and the reduced risk for various cancers [30]. The dietary bioactive compounds differ from macronutrients (carbohydrate, fat, and protein) and micronutrients (vitamins and minerals) in that they are not essential in the diet but provide extranutritional, health-promoting constituents.