Modulation of liver X receptor signaling as a prevention and therapy for colon cancer

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Liver X receptors (LXRα and LXRβ) are members of the nuclear receptor family and are important regulators of cholesterol, fatty acid, and glucose homeostasis. LXR agonists are effective for treatment of murine models of atherosclerosis, diabetes, and Alzheimer’s disease. Recently we and other groups observed that LXR agonists suppressed proliferation of multiple human cancer cell lines in vitro as well as suppressed the growth and progression of prostate tumor xenografts in nude mice. LXR agonists appear to cause G1 cell cycle arrest in cancer cells by reducing the protein expression level of Skp2, cyclin A2, cyclin D1, and the phosphorylation of Rb, while increasing the protein expression level of cell cycle inhibitor p27Kip1 and p53. LXR agonist also suppressed the oncogenic activity of β-catenin, an important regulator in Wnt signaling, as well as the proliferation in human colon cancer cells. Phytosterols, the plant equivalent of mammalian cholesterol, have been shown to be agonists for LXRs. Intake of phytosterol-rich diets reduced the incidence of colon cancer. We therefore propose that activation of LXR signaling via treatment with LXR agonists or intake of phytosterol-rich diets can reduce the incidence and suppress the tumor growth of colon cancer.

Introduction

Colon cancer and Wnt signaling

Colon cancer causes approximately 639,000 deaths per year. Colon cancer is the third leading cause of cancer-related death in the world and the fourth most frequently type of cancer for both men and women according to the 2009 report of World Health Organization. Although colon cancers acquire many genetic changes, the activation of the Wnt signaling pathway is regarded as the initiating event [1]. When Wnt is not present, Glycogen synthase kinase 3 (GSK-3) constitutively phosphorylates the β-catenin. β-Catenin is associated with axin complexed with GSK-3 and adenomatosis polyposis coli (APC). Once β-catenin becomes phosphorylated, it will be targeted for degradation. When Wnt binds to Frizzled family receptors, Dishevelled family proteins (Dsh) are recruited to the membrane. GSK-3 is inhibited by the activation of Dsh. β-Catenin then starts accumulating in the cytosol and can subsequently translocate into the nucleus. In the nucleus, β-catenin interacts with TCF/LEF family transcriptional factors to perform a variety of functions [2]. Constitutively activation of β-catenin can be oncogenic. The tumor suppressor gene APC degrades β-catenin and inhibits its nuclear localization. Mutation of APC is also found in 80% of all colon adenomas and carcinomas and is one of the earliest mutations in colon cancer progression [2]. In the absence of functional APC, Wnt signaling is inappropriately and constitutively activated, thus promotes the development of sporadic colon adenomas and cancers. A recent study showed that treatment with a synthetic liver X receptor (LXR) agonist T0901317 suppressed the transactivation activity of β-catenin and suppressed cell proliferation of HCT-116 human colon cancer cells [3].

LXR signaling and cancer suppression

Liver X receptors (LXRs) are ligand-activated transcriptional factors that belong to the nuclear receptor super family. LXRs are important regulators of cholesterol, fatty acid, and glucose homeostasis [4]. There are two LXR isoforms, LXRα and LXRβ. LXRα and LXRβ share high similarity in their DNA- and ligand-binding domains [4]. LXRα mRNA and protein is mostly expressed in liver, kidney, intestine, adipose tissue, macrophages, lung, and spleen [5–7], while LXRβ mRNA and protein is ubiquitously expressed [8]. LXRs regulate intestinal absorption and biliary excretion of cholesterol by inducing the expression of target genes such as the ATP binding cassette (ABC) transporters ABCA1, ABCG5, and ABCG8 [3]. LXRα and LXRβ form heterodimers with the obligate partner 9-cis retinoic acid receptor (RXR) [5,8–10]. The LXR/RXR heterodimer can be activated with either an LXR agonist (oxysterols) or a RXR agonist (cis-retinoic acid). Oxysterols are oxygenated derivatives...
of cholesterol. Oxysterols, such as 22(R)-hydroxysterol, 20(S)-hydroxysterol, 24(S)-hydroxysterol, bile acid, and cholestenoic acid, are natural ligands for LXR [4,11,12]. A few potent synthetic LXR agonists have been developed, including non-steroidal LXR agonists T0901317 [13] and GW3965 [14], and steroidal LXR agonists ATI-829 [15], hypolchomide [16] and YT-32 [17]. LXR agonists have been developed as potential drugs for treatment of cardiovascular diseases and metabolic syndromes and are effective for treatment of murine models of atherosclerosis, diabetes, and Alzheimer’s disease [4].

Previously we and other groups reported that treatment of synthetic LXR agonists (T0901317 and GW3965) and natural LXR agonists (22(R)-hydroxysterol and 24(S)-hydroxysterol) suppressed the proliferation of several human cancer cell lines, including prostate [4,18,19], breast [4,18,20], colon [3], lung [4], bone [4], skin [4], cervical [4], liver [4], ovarian [21] and leukemia [22] cancer cells. In xenograft study, gavage of LXR agonist T0901317 (10 mg/kg) suppressed the growth of LNCaP prostate cancer xenografts [18] and delayed the progression of androgen-dependent prostate tumors towards androgen independency in cancer xenografts [19]. LXR agonists suppressed the proliferation of several human cancer cell lines and LXR agonist T0901317 treatment [18].

Hypothesis

According to the following facts: (1) activation of the Wnt signaling pathway is the most common initiating event in colon cancer [2] LXR agonist suppress the transactivation activity of β-catenin, a key molecule in Wnt signaling (3) LXR agonists suppress the proliferation of several human cancer cell lines and LXR agonists mRNA and protein expression is relatively high in intestine tissue, we hypothesize that activating LXR signaling will suppress the development of colon cancer in people with APC gene deletion or mutation and inhibit the tumor growth in patients with colon cancer. In order to prove this hypothesis, we suggest to start clinical trials providing LXR agonists as an adjuvant therapy combined with standard therapy in patients with different stages of colon cancer to determine if activation of LXR signaling may enhance the treatment for colon cancer.

Phytosterols, LXR signaling, and colon cancer

Phytosterols, the plant equivalents of mammalian cholesterol, are essential components of all plants. The most common phytosterols include β-sitosterol, campesterol, and stigmasterol. Phytosterols and phytostanols from the 4-desmethylerol family (e.g., sitosterol and sitostanol) have been shown to activate LXR and LXR agonist T0901317 with EC50 at 30–150 nM [25]. Agonistic activity of β-sitosterol with LXRs is much stronger than campesterol or stigmasterol [25]. Phytosterol-rich diets were reported to decrease the incidence of gastric [26], breast [27], lung [28], and prostate [29] cancer. β-Sitosterol and other phytosterols were shown to suppress the proliferation of HT-29 human colon cancer cell [30–32] and other cancer cell lines [33–35]. Since β-sitosterol and campesterol are effective LXR agonists, it is possible that phytosterols suppress tumor growth partially through activation of LXR signaling. According to our hypothesis, we predict that phytosterol-rich diets, such as soy, can reduce the incidence of colon cancer. In support of our hypothesis, a research with seven case-control studies (a total of 2008 cases) evaluated the association between soy intake and colon adenoma or colon cancer. Point estimates suggested an inverse association between higher unfermented soy consumption (but not fermentsed soy products) and colon cancer onset or colon adenomas [36].

Conclusion

We provide several evidences to support the hypothesis that modulation of LXR signaling may be an effective therapy for colon cancers. In murine models, LXR agonists have been shown as potential drugs for treatment atherosclerosis, diabetes, and Alzheimer’s disease [4,13–15]. Therefore, colon cancer patients with cardiovascular diseases or metabolic syndromes may also benefit from LXR agonist treatment. Finally, since sitosterol and sitostanol are agonists for LXRs [25], phytosterol- and phytostanol-rich diets may be an affective way to prevent colon cancer.

Conflicts of interest statement

No potential conflicts of interest were disclosed.

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