MINI-REVIEW

Potential Targets for Prevention of Colorectal Cancer: a Focus on PI3K/Akt/mTOR and Wnt Pathways

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Abstract

Colorectal cancer (CRC) is one of the most common cancers in many parts of the world. Its development is a multi-step process involving three distinct stages, initiation that alters the molecular message of a normal cell, followed by promotion and progression that ultimately generates a phenotypically altered transformed malignant cell. Reports have suggested an association of the phosphoinositide-3-kinase (PI3K)/Akt pathway with colon tumorigenesis. Activation of Akt signaling and impaired expression of phosphatase and tensin homolog (PTEN) (a negative regulator of Akt) has been reported in 60-70% of human colon cancers and inhibitors of PI3K/Akt signaling have been suggested as potential therapeutic agents. Around 80% of human colon tumors possess mutations in the *APC* gene and half of the remainder feature *β-catenin* gene mutations which affect downstream signaling of the PI3K/Akt pathway. In recent years, there has been a great focus in targeting these signaling pathways, with natural and synthetic drugs reducing the tumor burden in different experiment models. In this review we survey the role of PI3K/Akt/mTOR and Wnt signaling in CRC.

Keywords: Colon cancer - PI3K/Akt - mTOR - Wnt/β-catenin - chemoprevention - flavonoids

Asian Pacific J Cancer Prev, **14 (4)**, 2201-2205

Introduction

Every year, there is more than 1 million new cases of colorectal cancer (CRC) are diagnosed throughout the world. CRC is the third most common malignancy and fourth most common cause of mortality worldwide (Tenesa and Dunlop, 2009). Despite of the familial basis of CRC, environmental factors such as food-borne mutagens, chronic intestinal inflammation, specific intestinal commensals and pathogens, which leads to the tumor development. CRC is considered to be linked with dietary habits like excess animal fat intake (Reddy, 1986). In contrast, a number of studies have suggested that high consumption of fruits and vegetables decreases the risk of CRC and other cancers (Giovannucci et al., 1992; Slattery et al., 2000; Pandurangan et al., 2012). In my observation a novel flavonoid inhibits ACF formation (Ashokkumar and Sudhandiran, 2008), inhibits cell proliferation (Ashokkumar and Sudhandiran, 2011), controls the levels of glucoproteins (Pandurangan et al., 2012b), modulates the status of thiols (Pandurangan and Ganapasam, 2013a) and induces apoptosis in colon carcinogenesis (Pandurangan and Ganapasam, 2013b).

Pathogenesis of CRC

The progression of the CRC from normal colonic epithelium to the malignant phenotype is accompanied by numerous genetic alterations (Figure 1). The stages start from ACF, polyps, adenomas, and carcinomas (Terzic et al., 2010). Loss of function of Adenomatous polyposis coli (APC) is an early event in the pathogenesis of CRC. During the progression of the adenoma, whereby increases in adenoma size, degree of dyplasia, and degree of villous histology takes place other genetic changes occur such as induction of *k-ras* oncogene. Loss of function of p53 gene occurs in the late stage of the disease *i.e*. adenoma to carcinoma stage (Itzkowitz and Yio, 2004).

PI3K/Akt/mTOR Pathway as a Target

Inhibitors of PI3K/Akt signaling have been suggested as potential therapeutic agents in CRC. Published reports suggested that the association of phosphoinositide-3-kinase (PI3K)/Akt pathway, in colon tumorigenesis

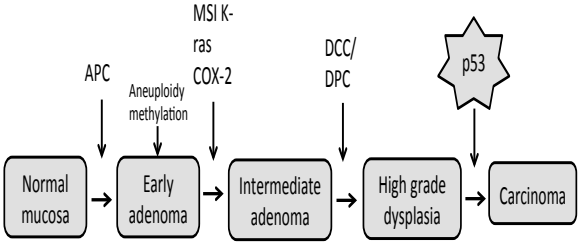

Figure 1. Molecular Pathogenesis of Sporadic Colorectal Cancer

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(Engelman, 2009; Palozza et al., 2009). Activation of Akt signaling and impaired expression of phosphatase and tensin homolog (PTEN) (a negative regulator of Akt) has been reported in 60-70% of human CRC (Colakoglu et al., 2008). Both catalytic (p110) and regulatory (p85) subunits of PI3K initiates a signal transduction cascade that promotes cancer cell growth, survival and metabolism (Rychahou et al., 2005; Engelman, 2009) which further keenly involved in protecting the cells from undergoing apoptotic mode of cell death (Jung et al., 2000; Lee et al., 2010) (Figure 2).

Mammalian target of rapamycin (mTOR) includes two functionally diverse protein complexes: mTOR complex 1 and mTOR complex 2 (Loewith et al., 2002; Sarnassov 2004). The mTORC1 signaling cascade is activated by pAkt. The serine/threonine kinase p70S6K1 is one of the most well-known downstream targets of mTORC1. 4EBP1 is another well-characterized mTORC1 target. 4EBP1 inhibits the initiation of protein translation by binding and inactivating eIF4E (eukaryotic translation initiation factor 4E) (Sonenberg et al., 1998). mTORC1 phosphorylates 4EBP1 at multiple sites to promote the dissociation of eIF4E from 4EBP1, relieving the inhibitory effect of 4EBP1 on eIF4E-dependent translation initiation (Pause et al., 1994). The inhibition of mTOR by rapamycin also causes 4EBP1 dephosphorylation, which prevents protein translation (Jastrzebski et al., 2007). Recent years the deregulation of mTOR pathway in CRC attains a considerable focus (Koehl et al., 2010).

Lycopene, a carotenoid present in tomato, could effectively inhibit the phosphorylation of Akt, glycogen synthase kinase-3β (GSK-3β) in colon cancer cells (Lin et al., 2011). Ellagic acid, shown to inhibit PI3K/Akt signaling their by modulating the apoptotic molecules such as Bcl-2, Bax and caspase3 in 1,2-DMH-induced colon cancer in rats (Umesalma and Sudhandiran, 2012). Wang et al. (2012) reported that silibinin suppresses the maintenance of colorectal cancer stem-like cells by inhibiting PP2A/AKT/mTOR pathways in colon cancer cells. The flavanols, such as epicatechin (EC), epicatechin-gallate (ECG) and procyanidin B2 (PB2) inhibits the phosphorylaytion of Akt in Caco-2 and SW480 colon cancer cells (Ramos et al., 2011). Fish oil and corn oil inhibits the phosphorylation of Akt in the post-initiation stage of colon cancer induced by 1,2-DMH in wistar rats (Kansal et al., 2012). Cannabidiol, a safe and non-psychotropic ingredient of Cannabis sativa, that reduces the p-Akt expression in AOM-induced colon cancer model (Aviello et al., 2012). A naturally occurring rotenoid, Deguelin is known to be an Akt inhibitor and to have an anti-tumor effect in HCT116 and COLO205 cells (Kang et al., 2012).

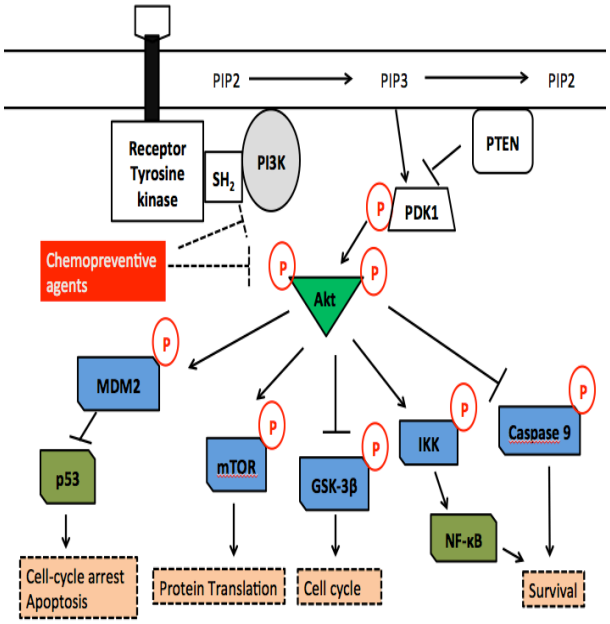

Figure 2. Regulation of Akt/mTOR Pathways

Vaish and Sanyal, (2012) reported that, NASIDs such as Celcoxib and Sulidac inhibits Akt by increased the expression of PTEN. Interestingly, ETP-46321, an imidazopyrazine derivative, as a potent inhibitor of PI3Kα in colon cancer cells (Granda et al., 2012). Piroxicam, a traditional non-steroidal anti-inflammatory drug and c-phycocyanin, a biliprotein from Spirulina platensis (cyanobacterium) both inhibits PI3K and Akt in 1,2-Dimethylhydrazine-induced colon cancer in mice (Saini and Sanyal, 2012). Aspirin inhibits mTOR signaling, activates AMP-activated protein kinase, and induces autophagy in colorectal cancer cells (Din et al., 2012). 3-Chloroacetyl-indole, a novel allosteric Akt inhibitor, suppresses cancer growth by inhibiting the Akt and mTOR pathway mediated by GSK3β inhibition, *in vitro* and *in vivo* model of colon cancer (Kim et al., 2011). Especially Rapamycin, an inhibitor of mTOR that reduces the tumor growth and oncogenic intestinal ion channels in $APC^{min/-}$ mice (Koehl et al., 2010).

Wnt/*β-catenin* Pathway as a Target

The Wnt family of secretory glycoproteins plays an important role in embryonic development, the induction of cell polarity, and in the determination of cell fate. A deregulation in the Wnt signaling pathway disrupts axis formation in embryos (Heasman et al., 1994; Funayama et al., 1995; Laurent et al., 1997) and is associated with multiple human malignancies (Polakis, 2000). Wnt signaling also plays an important role in the proliferation and differentiation of stem cells including human mesenchymal stem cells (Boland et al., 2004). β-catenin is the key component of wnt pathway, and it is a 97 kDa phosphoprotein plays a critical role in the regulation of cellular proliferation and in colon carcinogenesis (Behrens, 2000). Under basal circumstances, APC cooperates with GSK-3β to regulate β-catenin levels in the cytoplasm through phosphorylation sites in exon 3 of the β-catenin gene (Korinek et al., 1997) leads to ubiquitination in the cytoplasm (Figure 3).

Around 80% of human colon tumors possess mutations in the *APC* gene and rest of the half has *β-catenin* gene mutations (Sparks et al., 1998). When mutations are present in either the *APC* or *β-catenin* genes, accumulation of the β-catenin protein in the cytoplasm and nucleus is observed (Korinek et al., 1997). In the cytoplasm, the β-catenin protein forms a complex with the transcription factors, TCF and LEF, which migrates to the nucleus,

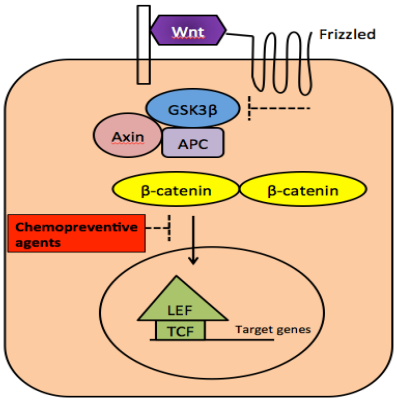

Figure 3. Regulation of Wnt/*β-catenin* Pathway

and co-activates transcription (Korinek et al., 1997). c-MYC, cyclin D1 and CD44 have been reported as targets of the wnt/β-catenin pathway (He et al., 1998; Tetsu and McCormick, 1999). Frequent mutations of the *β-catenin* gene were found in chemically induced colon tumors in both rat and mouse carcinogenesis models (Dashwood et al., 1998; Takahashi et al., 1998; Suzui et al., 1999), suggesting that the APC-β-catenin pathway plays an important role in the development of colon carcinogenesis in rodents, as seen in humans. Recent reports shown that activation of Wnt/β-catenin signaling is important for both initiation and progression of cancers of different tissues/organs, including liver (Lee et al., 2006; Ashokkumar and Sudhandiran, 2011), thus, Wnt/β-catenin signaling pathway is becoming a promising target for chemoprevention and chemotherapy in CRC (Herbst and Kolligs, 2007; Luo et al., 2007; Ashokkumar and Sudhandiran, 2011).

Sphingadiene (Kumar et al., 2012) and Enigmal (Symolon et al., 2011) a derivative of sphingolipid potentially reduces the expression as well as, controls the translocation of non-p-β-catenin in APC min mice and colon cancer cells through inhibiting pGSK3β. Similarly Luteolin, a flavone present in green pepper, perilla leaves and peanut inhibits the expression of non-p-β-catenin mediated by the inhibition pGSK3β in AOM-induced colon carcinogenesis. Kang et al. (2012) reported that, Magnolol, a neolignan from the cortex of *Magnolia obovata*, was identified as a promising candidate, as it effectively inhibited β-catenin/TCF reporter gene activity (Ashokkumar and Sudhandiran, 2011). Magnolol also suppressed Wnt3a-induced β-catenin translocation and subsequent target gene expression in HEK293 cells. Wu et al. (2012) reported that the, protein levels of β-catenin in the nucleus and cytoplasm were all reduced after treating the colon cancer cells with berberine. Published report from Lai et al. (2011) stated that, dietary curcumin and Tetrahydrocurcumin significantly decreased Wnt-1 and β-catenin protein expression, as well as the phosphorylation of GSK-3β in colonic tissue of AOM-induced mice model. Lycopene, a plant pigment could potentially inhibits the β-catenin protein expression in the xenograft model (Tang et al., 2011). Genistein a plant derived flavonoid, attenuates Wnt signaling by up-regulating sFRP2 (a Wnt pathway antagonist) in a human colon cancer cell line (Zhang and Chen, 2011). Triptolide, a diterpene triepoxide compound extracted from the traditional Chinese medicine herb *Tripterygium wilfordii Hook F*. potentially represses the expression of LEF/TCF (Liu et al., 2012).

Vaish and Sanyal, (2012) NASIDs such as Celcoxib and Sulidac inhibits the expression of non-p-β-catenin is mediated by the inhibition pGSK3β in 1,2-Dimethyl Hydrazine-induced colon cancer model. Similarly, Ibuprofen inhibits activation of nuclear β-catenin in human colon adenomas and induces the phosphorylation of GSKβ in colon cancer cell line (Greenspan et al., 2011). Brudivik et al. (2011) stated that, β-catenin nuclear translocation and expression of the β-catenin target genes such as c-Myc and COX-2 were significantly down-regulated upon treatment with Rp-8-Br-cAMPS (Protein Kinase A antagonist).

There are many potential targets were developed by many researchers all around the world to treat CRC. Among them Akt, mTOR and Wnt/β-catenin are the most promising targets were potentially targeted. Prevention of disease is an old and important concept. An essential consideration in cancer research today is that exposure to pharmacologically active chemicals may play an important role in blocking these signaling pathways resulting to reduce the risk of CRC.

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