REVIEW

# Signal Transducer and Activator of Transcription 3 - A Promising Target in Colitis-Associated Cancer

**Ashok Kumar Pandurangan[1], Norhaizan Mohd Esa[1,2]***

## Abstract

**Colorectal cancer (CRC) is the third most common malignancy and fourth most common cause of cancer mortality worldwide. Untreated chronic inflammation in the intestine ranks among the top three high-risk conditions for colitis-associated colorectal cancer (CAC). Signal Transducer and Activator of Transcription 3 (STAT3) protein is a member of the STAT family of transcription factors often deregulated in CRC. In this review, we try to emphasize the critical role of STAT3 in CAC as well as the crosstalk of STAT3 with inflammatory cytokines, nuclear factor (NF)-κB, PI3K/Akt, Mammalian Target of Rapamycin (mTOR), Notch, Wnt/β-catenin and microRNA (MiR) pathways. STAT3 is considered as a primary drug target to treat CAC in humans and rodents. Also we updated the findings for inhibitors of STAT3 with regard to effeects on tumorigenesis. This review will hopefully provide insights on the use of STAT3 as a therapeutic target in CAC.**

**Keywords:** Colitis associated cancer - STAT3 - NF-κB - cytokines - MiRNA

*Asian Pac J Cancer Prev,* **15 (2)**, 551-560

## 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, leads development of CRC. Chemically-induced cancer models are very useful in understanding the consequences of colon cancer in rodents (Ashokkumar and Sudhandiran, 2008; Pandurangan et al., 2012; Pandurangan et al., 2013; Shafie et al., 2013). A myriad of signaling events were altered during the progression of the colon cancer was reported (Pandurangan, 2013). In this review we try to expose the STAT3 crosstalk with signaling pathways in CAC along with the current drugs that inhibit CAC through STAT3 pathway.

## Inflammatory Bowel Disease

The inflammatory bowel diseases (IBD), including ulcerative colitis (UC) and Crohn's disease (CD), are chronic inflammatory disorders of the intestine. CD affects all parts of the gastrointestinal tract, from mouth to anus, but most commonly involves the distal part of the small intestine or ileum, and colon. UC results in colonic inflammation that affects the rectum (proctitis) or can cause continuous disease from the rectum proximally, to involve part of or the entire colon. Clinical symptoms include diarrhea, abdominal pain, gastrointestinal bleeding, and weight loss. Chronic inflammation associated with malignancy has been proposed to be a major contributor to a multitude of cancers (Coussens and Werb, 2002; Kundu and Surh, 2008; Danese and Mantovani, 2010; Solinas et al., 2010). Chronic inflammation during UC or CD leads to increased risk of colon carcinogenesis (Bernstein et al., 2001; Itzkowitz and Yio, 2004; Ullman and Itzkowitz, 2011). CD is also associated with an increased risk of small bowel adenocarcinoma, due to chronic inflammation of the small intestine.

In this review, the pathogenesis of CAC and emerging role of STAT3, the cross talk between the other participants of CAC such as NF-κB, PI3K/Akt/mTOR pathway, Wnt/*β-catenin* and many cytokines will be reviewed.

## Pathogenesis of CAC

Chronic inflammation in the intestine and colon leads to damage of the epithelium. Locally produced cytokines cause inflammation and stimulate the proliferation of crypt cells to compensate the loss of epithelial cells. This chronically stimulated state of the epithelium may eventually lead to the development of CAC (Sartor, 2006; Schottelius and Dinter, 2006; Rubie et al., 2007). The stages of cancer development, including formation of aberrant crypt foci, polyps, adenomas, and carcinomas, are similar between non-inflammatory CRC and CAC (Figure

*[1]Department of Nutrition and Dietetics, Faculty of Medicine and Health Sciences, Serdang, Selangor, [2]Laboratory of Molecular Biomedicine, Institute of Bioscience, Universiti Putra Malaysia, Malaysia *For correspondence: nhaizan@upm.edu.my*

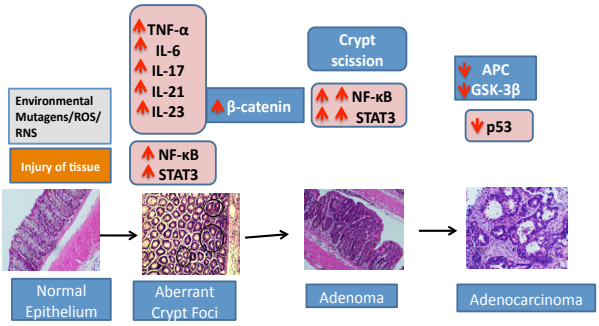


**Figure 1. Mechanism of Colitis Associated Cancer Development.** (A): The stages of cancer development, including formation of aberrant crypt foci, polyps, adenomas, and carcinomas, are similar between non-inflammatory CRC and CAC. However, some different pathogenic sequences have been proposed for CAC, including chronic inflammation and injury-dysplasia carcinoma that arises without the formation of well-defined adenoma. Common genetic and signaling pathways, such as Wnt/β-catenin, K-ras, p53 and TGF-β are altered in sporadic CRC and CAC, although the timing of p53 and APC inactivation and K-Ras activation can be different between CRC and CAC

1). However, some different pathogenic sequences have been proposed for CAC, including chronic inflammation and injury-dysplasia carcinoma that arises without the formation of well-defined adenoma. Common genetic and signaling pathways, such as Wnt/*β-catenin*, K-ras, p53 and transforming growth factor (TGF)-β are altered in sporadic CRC and CAC, although the timing of p53 and *adenomatous polyposis coli (APC)* inactivation and K-Ras activation can be different between CRC and CAC (Sheng et al., 1998; Lakatos and Lakotas, 2008). Aberrant activation of inflammatory cytokines, transcription factors such as NF-ϰB and STAT3 were in the early stage of CAC (Sakamoto et al., 2009; Yu et al., 2009).

## Animal Models of CAC

The classic and widely using model to induce CAC in rodents is azoxymethane (AOM) and dextran sodium sulfate (DSS). Many researchers use AOM, 1,2-dimethylhydrazine (DMH, a precursor of AOM) , and/or methyl azoxy methane (MAM) acetate in the animal models of CRC (Ward, 1974). The spectrum of AOM-induced epithelial lesions resembles those of the various types of neoplastic lesions in human CRC. In addition, AOM-induced CRC appears to follow the concept in which tumor initiation is followed by tumor promotion and progression in a sequential manner. Specifically, AOM induces the onset of ACF, as the precursor lesion and Mucin depleted foci (Ashokkumar and Sudhandiran, 2008; Norazalina et al., 2010; Pandurangan et al., 2012) followed by the onset of adenocarcinoma (Ashokkumar and Sudhandiran, 2011; Shafie et al., 2013) most often of the distal colon, and, finally, metastasis to mesenteric lymph nodes and liver (Reddy, 2004).

AOM is metabolized in the liver into MAM and this reaction is catalyzed by the enzyme cytochrome P450 E1 (Sohn et al., 1991). Metabolic activation of MAM to a highly reactive electrophile (methyl diazonium ion) occurs in liver and colon, which is known to elicit oxidative stress. This ultimate electrophile can methylate cellular nucleophile, such as DNA, causing alkylating damage (Fiala et al., 1987). These acquired mutations to DNA, then accumulate to cause cell proliferation leading to CRC.

DSS is a synthetic sulfate polysaccharide, and it was reported that repeated DSS exposure can cause chronic inflammation, thereby it resembles like IBD. Administration of DSS after AOM injection; strongly promotes tumorigenesis in colon. Experimental animal will be given a single intraperitoneal injection of AOM (10 mg/kg initial body weight) on Day 1 to induce colon cancer. Experimental mice will be given three cycles of 2% DSS in drinking water for 7 days followed by 2 weeks of consumption of free water. Mice will be sacrificed 7 days after the final 2% DSS administration (Okayasu et al., 1996).

## Oxidative Stress

Chronic inflammation is linked to cancer development in a number of organs. Chronic inflammatory conditions of the gastrointestinal tract, such as Barrett esophagus, chronic gastritis, and chronic pancreatitis confer a predisposition to malignancy (Genta, 2003; Zhang et al., 2009; McKay et al., 2008). One mechanism whereby inflammation may contribute to the development of cancer is through the production of reactive oxygen and nitrogen species that can cause oxidative damage to DNA, proteins, and lipids. A study of multiple inflammation linked cancers, including CAC, found increased levels of oxidative damage specifically at cancer sites (Kawanishi et al., 2006). Continuous cytokine exposure induces an iNOS dependent up-regulation of ROS production and DNA instability (Seidelin and Nielsen, 2005), that leads to cancer. Hence, Oxidative stress plays a crucial role in the development of CAC from chronic inflammation.

## Regulation of STAT3 Pathway

The STAT3 protein is an important member of the STAT family of transcription factors that are initially located in the cytoplasm of the cell in their inactive form. After stimulation by extracellular signals, such as cytokines, Janus kinases (JAKs), growth factors and hormones, are activated and then induce the phosphorylation of STAT3 at tyrosine residue 705 (Y705) (Buttner et al., 2002). Phosphorylated STAT3 (p-STAT3) proteins dimerize via their Src-homology(SH)-2 domains, and translocate into the nucleus and transcripts the expression of several critical genes involved in cell cycle progression, proliferation, migration and invasion, and cell survival (Buttner et al., 2002).

Inflammation and cancer are functionally linked by intrinsic, STAT3-dependent autocrine feedback loops in neoplastic epithelium and extrinsic, feed forward and often reciprocal interactions between tumor, stromal and inflammatory cells that collectively make up the microenvironment. The ubiquitous expression of gp130 and the capacity of STAT3 to stimulate its own transcription as well as that of gp130 ligands also provide several amplification loops between the different cell types. Furthermore, limited responsiveness to IL-6 and IL-

11 imposed by restricted expression of the ligand-specific receptor α-subunits can be overcome by IL-6-trans-signaling. Excessive cell-intrinsic STAT3 activation is also triggered by oncogenic events from (epi-genetic activation of positive regulators such as receptor Tyrosine kinases) and loss of function mutations of negative regulators such as SOCS3. Epithelial NF-κB and STAT3 are activated in response to the copiously present inflammatory cytokines IL-1, Tumor Necrosis Factor (TNF)-α and IL-6 which is released from Toll Like Receptor (TLR)-activated myeloid cell (macrophages), with IL-6 and IL-11 also contributed by tumor-associated stromal fibroblast and myo-epithelial cells. Meanwhile, release of IL-17 and IL-22 from mature Th17 cells provide an additional extrinsic link which results in excessive STAT3 activation in tumor cells.

The constitutive activation of STAT3 is frequently discovered in clinical samples from a wide range of human carcinoma and established human cancer cell lines, such as multiple myeloma, glioblastoma, colorectal and hepatocellular carcinoma (Buttner et al., 2002; Corvinus et al., 2005; Kusaba et al., 2005; Carlett-Falcone et al., 1999). The expression of STAT3 in colon adenoma was shown in Figure 2. The activated level of STAT3 was remarkably elevated in patients of CAC; along with STAT3 phosphorylation actively induced the anti-apoptotic genes including Bcl2 and Bcl-xl that also correlated with the tumor invasion, metastasis, and worse prognosis in CAC (Corvinus et al., 2005; Kusaba et al., 2005; Kusaba et al., 2006; Lassmann et al., 2007). Due to the remarkable role played by the STAT3 signaling pathway in intestinal inflammation and CRC, the STAT3 pathway was suggested to be primary and specific targeting pathway in selective therapeutic approach to CAC (Atereya and Neurath, 2008). Figure 3 shows the regulation of STAT3 with other key signaling pathways.

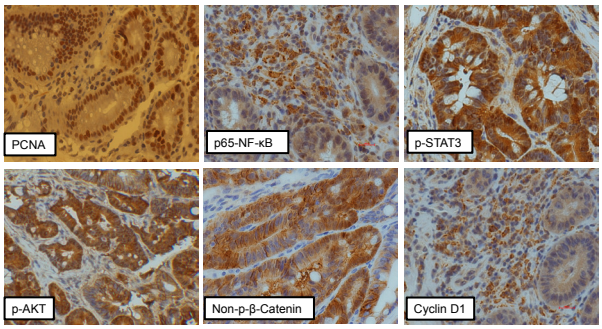


**Figure 2. Immunohistochemical Expression of PCNA, p-STAT3, pAkt, non-p-β-catenin, p65-NF-κB and Cyclin D1 in CAC.** Mice were induced with AOM/DSS for the period of 62 days, after that the colon was excised and fixed in 10% buffered formalin. After processing the tissues were embedded paraffin and cut into 4 μM thick. Dewaxed slides were stained with respective primary antibodies (PCNA, p-STAT3, pAkt, non-p-β-catenin, p65-NF-κB and cyclin D1) and counter stained with hematoxylin. After dry, slides were photographed in a microscope attached with camera at different magnifications

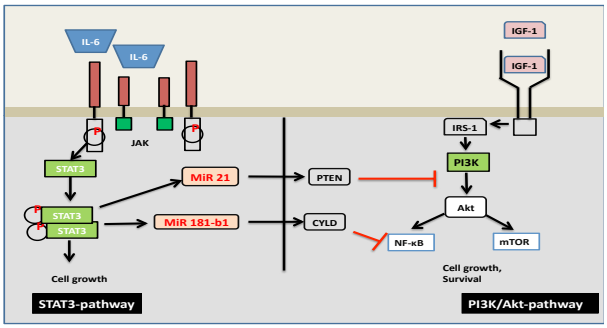


**Figure 3. Regulation of Intracellular STAT3.** The ubiquitous expression of gp130 and the capacity of STAT3 to stimulate its own transcription as well as that of gp130 ligands (in particular IL-6) also provide numerous amplification loops between the different cell types. Furthermore, limited responsiveness to IL-6 imposed by restricted expression of the ligand-specific receptor α-subunits can be overcome by IL-6-transsignaling. Excessive cell-intrinsic STAT3 activation is also triggered by oncogenic events from (epi-genetic activation of positive regulators and loss of function mutations of negative regulators. The activated STAT3 cross talk with Akt/mTOR, miRs and stimulates the cell growth

## STAT3 Cross Talks

STAT3 play a critical role in CAC by cross talk with other key signaling pathways involved in mediating inflammation and oncogenesis. Especially, NF-κB, PI3/Akt/mTOR pathway, Notch pathway, Wnt/*β-catenin* and many cytokines.

## Nuclear Factor -κB

Nuclear factor (NF)-κB is a transcription factor, under basal condition it resides in the cytoplasm as a heterotrimer consisting of p50, p65, and IκBα. On activation, the IκBα protein, an inhibitor of NF-κB, undergoes phosphorylation, ubiquitination, and degradation. The subunits p50 and p65 are released to be translocate into the nucleus, and to the bind specific DNA sequences present in the promoters of various genes, and initiate transcription of its downstream targets. The kinase that causes the phosphorylation of IκBα is called IκBα kinase or IKK. Whereas IKKβ mediates the classic/canonical NF-κB activation pathway, IKKα mediates the non-canonical pathway. The reason behind the activation of IKK is not well-understood. More than a 12 different kinases have been described that can activate IKK including Akt, mitogen-activated protein/extracellular signal-regulated kinase kinase kinase 1 (MEKK1), MEKK3, transforming growth factor-activating kinase 1, NF-κB-activating kinase, NF-κB-inducing kinase, protein kinase C, and the double-stranded RNA-dependent protein kinase. Various gene products that have been shown to mediate inflammation, cell survival, cell proliferation, invasion, angiogenesis, and metastasis are regulated by NF-κB (Aggarwal et al., 2009).

NF-κB has the ability to induce the expression of a large array of inflammatory mediators and its role as a core transcription factor in diverse immune responses, and NF-κB signaling has been recognized as a major pathway responsible for both inflammation-induced carcinogenesis (Figure 2) and anti-tumor immunity (Mantovani et al.,

2008; Karin and Greten, 2005; Pikarsky et al., 2004; Baud and Karin, 2009). Given their central roles in inflammation and cancer (Karin and Greten, 2005; Baud and Karin, 2009; Yu and Jove, 2004; Yu et al., 2007; Zhong et al., 1997; Bromberg et al., 1999) among other signaling STATs, particularly STAT3, is highly interconnected with NF-κB signaling (Lu and Stark, 2004; Bollrath et al., 2009; Grivennikov et al., 2009; Lee et al., 2009). There are striking parallels, as well as contrasts, between NF-κB and STAT3. Both proteins are not only persistently activated in cancer and essential for transducing cytoplasmic signals from extracellular stimuli, but they also function as nuclear transcription factors required for regulating genes involved in tumor proliferation, survival, angiogenesis and invasion, in addition to genes encoding key cancer-promoting inflammatory mediators (Karin and Greten, 2005; Baud and Karin, 2009; Yu and Jove, 2004; Yu et al., 2007; Darnell, 2002). NF-κB and STAT3 play a critical role in many cancers including, hepatic (He and Karin, 2011), prostate (Shanmugam et al., 2011), Lung (Tyagi et al., 2009) and breast cancer (Seo et al., 2012) which was evident from the previous reports.

It is mechanistically relevant that STAT3 interacts with NF-κB at several levels in a highly context-dependent manner. For example, several inflammatory factors encoded by NF-κB target genes, most notably IL-6, are important activators of STAT3 (Zhong et al., 1994; Ogura et al., 2008; Catlett-Falcone et al., 1999; Bollrath et al., 2009; Grivennikov et al., 2009). In tumors, STAT3 directly interacts with the NF-κB family member RelA, trapping it in the nucleus and thereby contributing to constitutive NF-κB activation in tumor (Lee et al., 2009). Ultimately, STAT3 and NF-κB also co-regulate numerous oncogenic and inflammatory genes (Darnell et al., 2002; Yu and Jove, 2004; Yu et al., 2007; Ogura et al., 2008; He and Karin, 2011). Continuous deregulation of these genes in tumor cells and the tumor microenvironment by persistently activated STAT3 and NF-κB-in contrast to their tightly controlled regulation in normal physiology is crucial for inflammation and malignant progression.

## Cytokines

Cytokines are key signaling molecules in the intestinal immune system, and are known to participate in the disruption of the so called normal state of controlled inflammation (Jump and Leivine, 2004). They are small peptide proteins produced mainly by immune cells that enable communication between cells, stimulate the proliferation of antigen specific effector cells, and mediate the local and systemic inflammation in an autocrine, paracrine and endocrine pathways (Neuman, 2007).

## IL-6 and STAT3

IL-6 is a pleiotropic cytokine that exerts its pro-inflammatory effects largely by mediated through its soluble IL-6 receptor (sIL-6R). The combination of soluble IL-6 receptor (sIL-6R) and IL-6 stimulates cells that only express gp130 and not IL-6R, a process known as trans-signaling. IL-6 signaling through STAT3 has been extensively studied (Suzuki et al., 2001; Mudter and Neurath, 2007; Tian et al., 2011). This system plays a central role in several immunologic reactions during the development of IBD, and circulating levels of IL-6 and sIL-6R correlate with many clinical features of CD and UC (Mitsuyama et al., 1995; Van Kemseke et al., 2000; Scheller et al., 2006; Rose-John et al., 2009). Blocking of IL-6 trans-signaling causes T-cell apoptosis, indicating that the IL-6-sIL-6R system mediates the resistance of T cells to apoptosis in CD (Van Kemseke et al., 2000).

IL-6 protein and mRNA are also often upregulated in serum and tumor samples of humans and mice suffering from breast, prostate, lung, liver and colon cancer (Heikkila et al., 2008). IL-6 enhances the proliferation of human colon carcinoma cells *in vitro* and interference with IL-6 signaling during late stages of CAC development slows down tumor growth (Becker et al., 2004; Becker et al., 2005). There are extensive reports are stating the IL-6 and STAT3 are required for survival of intestinal epithelial cells and development of CAC (Grivennikov et al., 2009) and blocking this will inhibit the tumor formation in CAC (Wang et al., 2009; Tian et al., 2011).

## Interleukin-17

IL-17A is an important pro-inflammatory cytokine that is secreted by CD 41 T cells that produce IL-17 (IL-17A) and express a specific transcription factor, retinoid-related orphan receptor -γt, have been distinguished from other Th1 and Th2 cells, and termed Th17 cells (Korn et al., 2007), while the monocyte/macrophage lineage also produces this cytokine (Fujino et al., 2003). In mice, IL-17A is furthermore secreted by NKT-like cells as well as CD T cells. The IL-17 receptor A (IL-17RA) is ubiquitously expressed on a variety of cell types and essentially involved in the IL-17A and IL-17F signaling (Korn et al., 2007). IL-17 plays a key role in animal models of chronic inflammation and several human chronic inflammatory diseases (Koyabayashi et al., 2008; Brand, 2009; Maynard and Weaver, 2009; Kanai et al., 2009; Abraham and Cho, 2009). IL-17 has been reported to be important in the initiation and/or progression of several inflammatory diseases through the recruitment of neutrophils or other cells in the immune system and amplifies the inflammation (Steinman, 2007; Korn et al., 2009; McGeachy and Cua, 2008).

STAT3 mediates IL-6-induced Th17 cell differentiation leading to the production of IL-17A (Hyun et al., 2012) and Activation of STAT3, as this transcription factor is required for IL-17 expression and Th17 dependent autoimmunity and has been implicated in promoting chronic inflammation in colitis (Atreya et al., 2000; Harris et al., 2007). IL-6 could directly promote the development of Th17 by activating the T cell gp130-STAT3 pathway through induction of RORγt and IL-17. As a key transcription factor associated with the Th17 cells, RORγt is critical for inducing IL-17 expression in a STAT3-dependent manner (Ivanov et al., 2006).

## Interleukin-21

IL-21 is a member of large family of cytokines and is made by a range of activated CD4+ Th cells, including Th1, Th17 and activated natural killer cells (De Nitto et al., 2010). An IL-21 protein level is elevated in the intestinal inflamed patients with CD and patients of UC as compared to normal controls (Monteleone et al., 2005). Excessive evidence supports that, elevated levels of IL-21 in the gut has deleterious consequences for the host. DSS or TNBS-induced wild-type colitis mice produce high level of IL-21; also IL-21-knockout mice are largely protected against disease in both models (Fina et al., 2008; Stolfi et al., 2011). IL-21 was highly expressed in human CRC patients and IL-21-deficient mice were resistant to CAC induced with AOM and DSS. IL-21, like IL-6 and IL-17A, is a powerful activator of the transcription factor STAT3 (Caprioli et al., 2008; Hirahara et al., 2010), which is a critical modulator of chronic inflammation (Atreya et al., 2008). Absence of IL-21 reduced STAT3 Activation and reduced the expression of Bcl-xL, a STAT3-induced anti-apoptotic protein in tumor and stromal cells (Stolfi et al., 2011).

## PI3K/Akt/mTOR Pathway

The serine/threonine protein kinase B (Akt) belongs to the AGC family of protein kinases. Akt consists of three homologous members known as PKBα (Akt1), PKBβ (Akt2) and PKBγ (Akt3). Akt is a growth factor regulated protein kinase that contains three functionally different sites: a pleckstrin homology domain, a central catalytic domain, and a C-terminal hydrophobic motif (Robertson, 2005). Binding of PI3K products to the pleckstrin homology domain results in Akt translocation to the plasma membrane where it is activated via phosphorylation by upstream kinases such as the phosphoinoside-dependent kinase 1 (PDK1). Researchers have identified some of the key roles of Akt. Among its myriad of cellular responsibilities, Akt is implicated in cellular processes such as cell survival, proliferation and growth, glucose metabolism, apoptosis, angiogenesis, transcription and migration (Scheid and Woodgett, 2003).

Recent studies support the notion that one of the major functions of Akt is to promote growth factor-mediated cell survival and to block apoptosis, as observed in most types of cancers. Akt indirectly activates mTORC1 via the phosphorylation of TSC2, this keeps TSC2 from activating Rheb; resulting in accumulation of Rheb-GTP complex. Rheb-GTP then activates mTORC1, which phosphorylates other downstream targets such as S6 kinase and 4-EBP-1. Akt substrates include Bad, Caspase 9, IKKα, NOS, TSC2, PRAS40, p27, MDM2, and GSK3β (Johnson et al., 2008). Akt mediated phosphorylation of these proteins leads to their activation or inhibition. Regulation of these substrates by Akt contributes to activation of various cellular processes.

Deregulation of mTOR signaling has been found in many cancers (Petroulakis et al., 2006). The crosstalk between STAT3 and mTOR is vital in several physiological and malignant conditions (Riemenschneider et al., 2006; Zhou et al., 2007; Kim et al., 2008; Wang et al., 2008; Thiem et al., 2013). STAT3 and mTOR are highly activated in epithelial and tumor cells in the inflamed colon. Also mTOR acts as an upstream regulator for the activation of STAT3 in epithelial cells in the human IBD and CAC model (Deng et al., 2010). Eveolimus (a derivative of rapamycin) inhibitor of mTOR complex 1 -treated STAT3 knockout mice showed a pS6 expression similar to that of control. These above said evidences clearly emphasize the cross talk of mTOR and STAT3 signaling (Deng et al., 2010).

## Notch Signaling

Notch signaling is triggered through the binding of a ligand (Delta/Delta-like/Jagged/Serrate) on the membrane of one cell to a receptor (subtypes Notch1/Notch2/Notch3/Notch4) on the membrane of the contacting cell. This causes proteolytic cleavage of Notch receptors to release the cytoplasmic tail of Notch (Notch intracellular Domain (NICD)) (Schroeter et al., 1998). NICD translocates to the nucleus and associates with CSL transcription factors (CBF1/RBPJκ/Suppressor of Hairless/Lag-1) and coactivator Mastermind to turn on transcription of target genes (Bray, 2006). The best-characterized targets of Notch are hairy/enhancer of split (HES) family of transcription factors, particularly HES1 in the intestine (Jensen et al., 200; Heitzler et al., 1996). Notch signaling was reported to deregulated in many types of cancers such as Liver (Villanueva et al., 2012; Dill et al., 2013), lung (Yang et al., 2013), prostate (Zhu et al., 2013), breast (Jin et al., 2012), and colorectal cancer (Reedjik et al., 2008). Matrix metalloproteinase-9 acts as a tumor suppressor in CAC, likely through its effect on the Notch signaling pathway. The absence of matrix metalloproteinase-9 is connected with defective Notch-1 activation, suppressed p21WAF1/Cip1 expression, and reciprocal activation of Wnt signaling and increased proliferation (Garg et al., 2010). Reports from previous studies have suggested that expression of Jagged ligands and Notch1 as well as Notch receptor activation are constant features of human colon cancers, thus application of GSIs and other anti-Notch therapeutics may benefit patients with this disease (Reedjik et al., 2008).

Notch plays a critical role in the initiation of the CRC but not progression in mice (Fre et al., 2009). The Notch signaling pathway is involved in the process of normal cell self-renewal and differentiation in a variety of tissues, and is involved in human cancer stem cells self-renewal capacity and tumorigenicity (Dontu et al., 2008; Griveniikov and Karin, 2008). It is actively involved in the stem cell growth and survival in the colon. Notch (subtypes 1, 3, 4) is considered as a downstream target gene of IL-6/STAT3 pathway. Blocking STAT3 by FLLL32 (an analog of curcumin) suppressed cancer stem-like cell growth (Lin et al., 2011).

## Wnt/β-Catenin Pathway

Wnt signaling pathway is essential in many biological process and their downstream effectors were shown to be conserved (Wodarz and Nusse, 1998). The vital component of the Wnt signaling is the cytoplasmic protein

*β-catenin*, which plays a critical role in the regulation of cellular proliferation in CRC. Under basal conditions, *Adenomatous polyposis coli (APC)* co-operate 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; Gregorieff and Clevers, 2005). In the nucleus, the *β-catenin* protein forms a complex with the transcription factors, T cell factor (TCF) and lymphoid enhancer factor (LEF), and co-activates transcription (Korinek et al., 1997; Sparks et al., 1998). Both *c-Myc* and *cyclin D1* have been identified as targets of the *β-catenin*/APC signaling 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 (Takahashi et al., 1998; Dashwood et al., 1998; Suzui et al., 1999).

The expression of *β-catenin* was downregulated by some chemopreventive agents during chemically induced CRC and *in vitro* (Ashokkumar and Sudhandiran, 2011; Kaur et al., 2010; Shafie et al., 2013). Aberrant activation of both STAT3 and Wnt/*β-catenin* (Figure 2) often occurs in malignancies, and the two pathways regulate each other in different cancer cell lines (Armanious et al., 2010; Kawada et al., 2006; Yan et al., 2008). STAT3 and Wnt/*β-catenin* signaling is functionally associated by GSK-3β. The phosphorylated form of GSK-3β positively regulates the level of non-p-*β-catenin*. STAT3 transmits extracellular signals from the environment of the periphery of cancer tissues, and accelerates nuclear accumulation of non-p-*β-catenin* in CRC cells (Kawada et al., 2006).

## MicroRNAs

MicroRNAs (miRNAs or miRs) are endogenously encoded short non-coding RNAs (20-23 nt), are pivotal players in posttranscriptional gene silencing of target mRNAs. In mammals, incomplete complementarity binding of the mature miRNA to the 3'UTR of target mRNA results in target gene silencing via translational repression, or in some cases via mRNA degradation (Bartel, 2004).The robust focus on miRNA research in current years has led to an exponential growth in the number of identified miRNAs, which exceed more than 1000 in humans (Kozomara and Griffiths-Jones, 2011) and regulate over 60% of human genes (Friedman et al., 2009). Importantly, miRNAs are involved in the regulation or fine-tuning of numerous crucial biological processes commonly de-regulated in cancer, including cell proliferation, differentiation, cell-cycle and apoptosis, among others (Carthew, 2006; Lima et al., 2011). Now it is well known that miRNAs are aberrantly expressed in several forms of human cancer, including colon cancer (Sarvar et al., 2009; Iliopoulos et al., 2010; Oberg et al., 2011).

In CAC, STAT3 activation directly triggers transcription of miR-21 and miR-181b-1 during the transformation process. Remarkably, transient expression of either miR-21 or miR-181b-1 is sufficient to induce a stable transformed state, and this occurs by direct targeting of the phosphatase and tensin homolog (PTEN) and cylindromatosis (CYLD) tumor suppressor genes, respectively. The resulting inhibition of PTEN and CYLD expression leads to the activation of NF-κB, which is required to maintain the transformed state. Thus, STAT3 is not simply a downstream effector of IL-6 but, together with miR-21, miR-181b-1, PTEN, and CYLD, is part of the epigenetic switch that links inflammation to cancer (Iliopoulos et al., 2010).

On the other hand, in murine macrophages expression of miR-223 was significantly decreased during activation by lipopolysaccharide (LPS) or poly (I:C) stimulation. The inducible miR-223 down-regulation resulted in the activation of STAT3, which is directly targeted by miR-223, thus promoting the production of pro-inflammatory cytokines such as IL-6 and IL-1β, but not TNF-α. Interestingly, IL-6 was found to be a main factor in inducing the decrease in miR-223 expression after LPS stimulation, which formed a positive feedback loop to regulate IL-6 and IL-1β (Chen et al., 2012). So, STAT3 cross talks with multiple MiRs during CAC thereby promote tumorigenesis.

## Inhibitors of STAT3

Triptolide, a diterpenoid triepoxide from the traditional Chinese medicinal herb *Tripterygium wilfordii Hook. f.*, that downregulates Rac1 and the JAK/STAT3 pathway and inhibits colitis-related colon cancer progression (Wang et al., 2009). Aspirin, a non-steroidal anti-inflammatory drug, has an ability to inhibit STAT3 activation in CAC (Tian et al., 2011). A curcumin derivative small molecule inhibits STAT3 phosphorylation and DNA binding activity and exhibits potent growth suppressive activity *in vitro* and *in vivo* model (Lin et al., 2010). Prohibitin 1 attenuates colitis associated CRC by modulating STAT3 apoptotic responses (Kathira et al., 2012). Kargl et al. (2012) reported that O-1602, an atypical cannabinoid, inhibits tumor growth in CAC through modulating the signaling of STAT3.

## Conclusion

CAC is considered as a major threat in developed and developing countries. The recent research is focusing on the finding of new drug targets in CAC. There number of reports stating that activated STAT3 was accumulated in tumors and surrounded tissues of human colon cancer and animal models of CAC. STAT3 play a central role in CAC, and cross talk with other oncogenic signaling pathways. Since, STAT3 play an important role in CAC, developing drugs which targets STAT3 will be worth in control of the disease.

## References

Abraham C, Cho J (2009). Interleukin-23/Th17 pathways and inflammatory bowel disease. *Inflamm Bowel Dis*, **15**, 1090-100.

Aggarwal BB, Vijayalekshmi RV, Sung B (2009). Targeting inflammatory pathways for prevention and therapy of cancer: short-term friend, long-term foe. *Clin Cancer Res*, **15**, 425-30.

Armanious H, Gelebart P, Mackey J, et al (2010). STAT3 upregulates the protein expression and transcriptional activity of beta-catenin in breast cancer. *Int J Clin Exp Pathol*, **3**, 654-64.

Ashokkumar P, Sudhandiran G (2008). Protective role of luteolin on the status of lipid peroxidation and antioxidant defense against azoxymethane-induced experimental colon carcinogenesis. *Biomed Pharmacother*, **62**, 590-7.

Ashokkumar P, Sudhandiran G (2011). Luteolin inhibits cell proliferation during Azoxymethane-induced experimental colon carcinogenesis via Wnt/ beta-catenin pathway. *Invest New Drugs*, **29**, 273-84.

Atreya R, Mudter J, Finotto S, et al (2000). Blockade of interleukin 6 trans signaling suppresses T-cell resistance against apoptosis in chronic intestinal inflammation: evidence in crohn disease and experimental colitis in vivo. *Nat Med*, **6**, 583-8.

Atreya R, Neurath MF (2008). Signaling molecules: the pathogenic role of the IL-6/STAT-3 trans signaling pathway in intestinal inflammation and in colonic cancer. *Curr Drug Targets*, **9**, 369-74.

Bartel DP (2004). MicroRNAs: genomics, biogenesis, mechanism, and function. *Cell*, **116**, 281-97.

Baud V, Karin M (2009). Is NF-kappaB a good target for cancer therapy? Hopes and pitfalls. *Nat Rev Drug Discov*, **8**, 33-40.

Becker C, Fantini MC, Schramm C, et al (2004). TGF-beta suppresses tumor progression in colon cancer by inhibition of IL-6 trans-signaling. *Immunity*, **21**, 491-501.

Becker C, Fantini MC, Wirtz S, et al (2005). IL-6 signaling promotes tumor growth in colorectal cancer. *Cell Cycle*, **4**, 217-20.

Bernstein CN, Blanchard JF, Kliewer E, et al (2001). Cancer risk in patients with inflammatory bowel disease: a population-based study. *Cancer*, **91**, 854-62.

Bollrath J, Phesse TJ, von Burstin VA, et al (2009). gp130-mediated Stat3 activation in enterocytes regulates cell survival and cell-cycle progression during colitis-associated tumorigenesis. *Cancer Cell*, **15**, 91-102.

Brand S (2009). Crohn's disease: Th1, Th17 or both? The change of a paradigm: new immunological and genetic insights implicate Th17 cells in the pathogenesis of Crohn's disease. *Gut*, **58**, 1152-67.

Bray SJ (2006). Notch signalling: a simple pathway becomes complex. *Nat Rev Mol Cell Biol*, **7**, 678-89.

Bromberg JF, Wrzeszczynska MH, Devgan G, et al (1999). Stat3 as an oncogene. *Cell*, **98**, 295-303.

Buettner R, Mora LB, Jove R (2002). Activated STAT signaling in human tumors provides novel molecular targets for therapeutic intervention. *Clin Cancer Res*, **8**, 945-54.

Caprioli F, Sarra M, Caruso R, et al (2008). Autocrine regulation of IL-21 production in human T lymphocytes. *J Immunol*, **180**, 1800-7.

Carthew RW (2006). Gene regulation by microRNAs. *Curr Opin Genet Dev*, **16**, 203-8.

Catlett-Falcone R, Landowski TH, Oshiro MM, et al (1999). Constitutive activation of Stat3 signaling confers resistance to apoptosis in human U266 myeloma cells. *Immunity*, **10**, 105-15.

Chen Q, Wang H, Liu Y, et al (2012). Inducible microRNA-223 down-regulation promotes TLR-triggered IL-6 and IL-1beta production in macrophages by targeting STAT3. *PLoS ONE*, **7**, 42971.

Corvinus FM, Orth C, Moriggl R, et al (2005). Persistent STAT3 activation in colon cancer is associated with enhanced cell proliferation and tumor growth. *Neoplasia*, **7**, 545-55.

Coussens LM, Werb Z (2002). Inflammation and cancer. *Nature*, **420**, 860-7.

Danese S, Mantovani A (2010). Inflammatory bowel disease and intestinal cancer: a paradigm of the Yin-Yang interplay between inflammation and cancer. *Oncogene*, **29**, 3313-23.

Darnell JE, Jr (2002). Transcription factors as targets for cancer therapy. *Nat Rev Cancer*, **2**, 740-9.

Dashwood RH, Suzui M, Nakagama H, et al (1998). High frequency of beta-catenin (ctnnb1) mutations in the colon tumors induced by two heterocyclic amines in the F344 rat. *Cancer Res*, **58**, 1127-9.

De Nitto D, Sarra M, Pallone F, et al (2010). Interleukin-21 triggers effector cell responses in the gut. *World J Gastroenterol*, **16**, 3638-41.

Deng L, Zhou JF, Sellers RS, et al (2010). A novel mouse model of inflammatory bowel disease links mammalian target of rapamycin-dependent hyperproliferation of colonic epithelium to inflammation-associated tumorigenesis. *Am J Pathol*, **176**, 952-67.

Dill MT, Tornillo L, Fritzius T, et al (2013). Constitutive Notch2 signaling induces hepatic tumors in mice. *Hepatology*, **57**, 1607-19.

Dontu G, Jackson KW, McNicholas E, et al (2004). Role of Notch signaling in cell-fate determination of human mammary stem/progenitor cells. *Breast Cancer Res*, **6**, 605-15.

Fiala ES, Sohn OS, Hamilton SR (1987). Effects of chronic dietary ethanol on in vivo and in vitro metabolism of methylazoxymethanol and on methylazoxymethanol-induced DNA methylation in rat colon and liver. *Cancer Res*, **47**, 5939-43.

Fina D, Sarra M, Fantini MC, et al (2008). Regulation of gut inflammation and th17 cell response by interleukin-21. *Gastroenterology*, **134**, 1038-48.

Fre S, Pallavi SK, Huyghe M, et al (2009). Notch and Wnt signals cooperatively control cell proliferation and tumorigenesis in the intestine. *Proc Natl Acad Sci U S A*, **106**, 6309-14.

Friedman RC, Farh KK, Burge CB, et al (2009). Most mammalian mRNAs are conserved targets of microRNAs. *Genome Res*, **19**, 92-105.

Fujino S, Andoh A, Bamba S, et al (2003). Increased expression of interleukin 17 in inflammatory bowel disease. *Gut*, **52**, 65-70.

Garg P, Sarma D, Jeppsson S, et al (2010). Matrix metalloproteinase-9 functions as a tumor suppressor in colitis-associated cancer. *Cancer Res*, **70**, 792-801.

Genta RM (2003). The gastritis connection: prevention and early detection of gastric neoplasms. *J Clin Gastroenterol*, **36**, 61-2.

Gregorieff A, Clevers H (2005). Wnt signaling in the intestinal epithelium: from endoderm to cancer. *Genes Dev*, **19**, 877-90.

Grivennikov S, Karin E, Terzic J, et al (2009). IL-6 and Stat3 are required for survival of intestinal epithelial cells and development of colitis-associated cancer. *Cancer Cell*, **15**, 103-13.

Grivennikov S, Karin M (2008). Autocrine IL-6 signaling: a key event in tumorigenesis? *Cancer Cell*, **13**, 7-9.

Harris TJ, Grosso JF, Yen HR, et al (2007). Cutting edge: An in vivo requirement for STAT3 signaling in TH17 development and TH17-dependent autoimmunity. *J Immunol*, **179**, 4313-7.

He G, Karin M (2011). NF-kappaB and STAT3 - key players in liver inflammation and cancer. *Cell Res*, **21**, 159-68.

He TC, Sparks AB, Rago C, et al (1998). Identification of c-MYC as a target of the APC pathway. *Science*, **281**, 1509-12.

Heikkila K, Ebrahim S, Lawlor DA (2008). Systematic review of the association between circulating interleukin-6 (IL-6) and cancer. *Eur J Cancer*, **44**, 937-945.

Heitzler P, Bourouis M, Ruel L, et al (1996). Genes of the

Enhancer of split and achaete-scute complexes are required for a regulatory loop between Notch and Delta during lateral signalling in Drosophila. *Development*, **122**, 161-71.

Hirahara K, Ghoreschi K, Laurence A, et al (2010). Signal transduction pathways and transcriptional regulation in Th17 cell differentiation. *Cytokine Growth Factor Rev*, **21**, 425-34.

Hyun YS, Han DS, Lee AR, et al (2012). Role of IL-17A in the development of colitis-associated cancer. *Carcinogenesis*, **33**, 931-6.

Iliopoulos D, Jaeger SA, Hirsch HA, et al (2010). STAT3 activation of miR-21 and miR-181b-1 via PTEN and CYLD are part of the epigenetic switch linking inflammation to cancer. *Mol Cell*, **39**, 493-506.

Itzkowitz SH, Yio X (2004). Inflammation and cancer IV. Colorectal cancer in inflammatory bowel disease: the role of inflammation. *Am J Physiol Gastrointest Liver Physiol*, **287**, 7-17.

Ivanov, II, McKenzie BS, Zhou L, et al (2006). The orphan nuclear receptor RORgammat directs the differentiation program of proinflammatory IL-17+ T helper cells. *Cell*, **126**, 1121-33.

Jensen J, Pedersen EE, Galante P, et al (2000). Control of endodermal endocrine development by Hes-1. *Nat Genet*, **24**, 36-44.

Jin S, Mutvei AP, Chivukula IV, et al (2012). Non-canonical Notch signaling activates IL-6/JAK/STAT signaling in breast tumor cells and is controlled by p53 and IKKalpha/IKKbeta. *Oncogene*, **26**, 517.

Johnson GE, Ivanov VN, Hei TK (2008). Radiosensitization of melanoma cells through combined inhibition of protein regulators of cell survival. *Apoptosis*, **13**, 790-802.

Jump RL, Levine AD (2004). Mechanisms of natural tolerance in the intestine: implications for inflammatory bowel disease. *Inflamm Bowel Dis*, **10**, 462-78.

Kanai T, Nemoto Y, Kamada N, et al (2009). Homeostatic (IL-7) and effector (IL-17) cytokines as distinct but complementary target for an optimal therapeutic strategy in inflammatory bowel disease. *Curr Opin Gastroenterol*, **25**, 306-13.

Kargl J, Haybaeck J, Stancic A, et al (2013). O-1602, an atypical cannabinoid, inhibits tumor growth in colitis-associated colon cancer through multiple mechanisms. *J Mol Med,* **91**, 449-58.

Karin M, Greten FR (2005). NF-kappaB: linking inflammation and immunity to cancer development and progression. *Nat Rev Immunol*, **5**, 749-759.

Kathiria AS, Neumann WL, Rhees J, et al (2012). Prohibitin attenuates colitis-associated tumorigenesis in mice by modulating p53 and STAT3 apoptotic responses. *Cancer Res*, **72**, 5778-89.

Kaur M, Velmurugan B, Tyagi A, et al (2010). Silibinin suppresses growth of human colorectal carcinoma SW480 cells in culture and xenograft through down-regulation of beta-catenin-dependent signaling. *Neoplasia*, **12**, 415-24.

Kawada M, Seno H, Uenoyama Y, Set al (2006). Signal transducers and activators of transcription 3 activation is involved in nuclear accumulation of beta-catenin in colorectal cancer. *Cancer Res*, **66**, 2913-7.

Kawanishi S, Hiraku Y, Pinlaor S, et al (2006). Oxidative and nitrative DNA damage in animals and patients with inflammatory diseases in relation to inflammation-related carcinogenesis. *Biol Chem*, **387**, 365-72.

Kim JH, Kim JE, Liu HY, et al (2008). Regulation of interleukin-6-induced hepatic insulin resistance by mammalian target of rapamycin through the STAT3-SOCS3 pathway. *J Biol Chem*, **283**, 708-15.

Kobayashi T, Okamoto S, Hisamatsu T, et al (2008). IL23 differentially regulates the Th1/Th17 balance in ulcerative colitis and Crohn's disease. *Gut*, **57**, 1682-9.

Korinek V, Barker N, Morin PJ, et al (1997). Constitutive transcriptional activation by a beta-catenin-Tcf complex in APC-/- colon carcinoma. *Science*, **275**, 1784-7.

Korn T, Bettelli E, Oukka M, et al (2009). IL-17 and Th17 Cells. *Annu Rev Immunol*, **27**, 485-517.

Korn T, Oukka M, Kuchroo V, et al (2007). Th17 cells: effector T cells with inflammatory properties. *Semin Immunol*, **19**, 362-71.

Kozomara A, Griffiths-Jones S (2011). miRBase: integrating microRNA annotation and deep-sequencing data. *Nucleic Acids Res*, **39**, 30.

Kundu JK, Surh YJ (2008). Inflammation: gearing the journey to cancer. *Mutat Res*, **659**, 15-30.

Kusaba T, Nakayama T, Yamazumi K, et al (2005). Expression of p-STAT3 in human colorectal adenocarcinoma and adenoma; correlation with clinicopathological factors. *J Clin Pathol*, **58**, 833-8.

Kusaba T, Nakayama T, Yamazumi K, et al (2006). Activation of STAT3 is a marker of poor prognosis in human colorectal cancer. *Oncol Rep*, **15**, 1445-51.

Lakatos PL, Lakatos L (2008). Risk for colorectal cancer in ulcerative colitis: changes, causes and management strategies. *World J Gastroenterol*, **14**, 3937-47.

Lassmann S, Schuster I, Walch A, et al (2007). STAT3 mRNA and protein expression in colorectal cancer: effects on STAT3-inducible targets linked to cell survival and proliferation. *J Clin Pathol*, **60**, 173-9.

Lee H, Herrmann A, Deng JH, et al (2009). Persistently activated Stat3 maintains constitutive NF-kappaB activity in tumors. *Cancer Cell*, **15**, 283-93.

Lima RT, Busacca S, Almeida GM, et al (2011). MicroRNA regulation of core apoptosis pathways in cancer. *Eur J Cancer*, **47**, 163-74.

Lin L, Deangelis S, Foust E, et al (2010). A novel small molecule inhibits STAT3 phosphorylation and DNA binding activity and exhibits potent growth suppressive activity in human cancer cells. *Mol Cancer*, **9**, 217.

Lin L, Fuchs J, Li C, et al (2011). STAT3 signaling pathway is necessary for cell survival and tumorsphere forming capacity in ALDH(+)/CD133(+) stem cell-like human colon cancer cells. *Biochem Biophys Res Commun*, **416**, 246-51.

Lu T, Stark GR (2004). Cytokine overexpression and constitutive NFkappaB in cancer. *Cell Cycle*, **3**, 1114-7.

Mantovani A, Allavena P, Sica A, et al (2008). Cancer-related inflammation. *Nature*, **454**, 436-44.

Maynard CL, Weaver CT (2009). Intestinal effector T cells in health and disease. *Immunity*, **31**, 389-400.

McGeachy MJ, Cua DJ (2008). Th17 cell differentiation: the long and winding road. *Immunity*, **28**, 445-53.

McKay CJ, Glen P, McMillan DC (2008). Chronic inflammation and pancreatic cancer. *Best Pract Res Clin Gastroenterol*, **22**, 65-73.

Mitsuyama K, Toyonaga A, Sasaki E, et al (1995). Soluble interleukin-6 receptors in inflammatory bowel disease: relation to circulating interleukin-6. *Gut*, **36**, 45-9.

Monteleone G, Monteleone I, Fina D, et al (2005). Interleukin-21 enhances T-helper cell type I signaling and interferon-gamma production in Crohn's disease. *Gastroenterology*, **128**, 687-94.

Mudter J, Neurath MF (2007). IL-6 signaling in inflammatory bowel disease: pathophysiological role and clinical relevance. *Inflamm Bowel Dis*, **13**, 1016-23.

Neuman MG (2007). Immune dysfunction in inflammatory bowel disease. *Transl Res*, **149**, 173-86.

Oberg AL, French AJ, Sarver AL, et al (2011). miRNA expression in colon polyps provides evidence for a multihit

model of colon cancer. *PLoS ONE*, **6**, 620465.
Ogura H, Murakami M, Okuyama Y, et al (2008). Interleukin-17 promotes autoimmunity by triggering a positive-feedback loop via interleukin-6 induction. *Immunity*, **29**, 628-36.
Okayasu I, Ohkusa T, Kajiura K, et al (1996). Promotion of colorectal neoplasia in experimental murine ulcerative colitis. *Gut*, **39**, 87-92.
Pandurangan AK (2013). Potential Targets for Prevention of Colorectal Cancer: a Focus on PI3K/Akt/mTOR and Wnt Pathways. *Asian Pac J Cancer Prev*, **14**, 2201-5.
Pandurangan AK, Ananda Sadagopan SK, Dharmalingam P et al (2013). Luteolin, a bioflavonoid inhibits Azoxymethane-induced colorectal cancer through Nrf2 signaling. *Toxicol Mech Methods*, **24**, 13-20.
Pandurangan AK, Dharmalingam P, Ananda Sadagopan SK, et al (2012). Effect of luteolin on the levels of glycoproteins during azoxymethane-induced colon carcinogenesis in mice. *Asian Pac J Cancer Prev*, **13**, 1569-73.
Petroulakis E, Mamane Y, Le Bacquer O,et al (2006). mTOR signaling: implications for cancer and anticancer therapy. *Br J Cancer*, **94**, 195-9.
Pikarsky E, Porat RM, Stein I, et al (2004). NF-kappaB functions as a tumour promoter in inflammation-associated cancer. *Nature*, **431**, 461-6.
Reddy BS (2004). Studies with the azoxymethane-rat preclinical model for assessing colon tumor development and chemoprevention. *Environ Mol Mutagen*, **44**, 26-35.
Reedijk M, Odorcic S, Zhang H, et al (2008). Activation of Notch signaling in human colon adenocarcinoma. *Int J Oncol*, **33**, 1223-9.
Riemenschneider MJ, Betensky RA, Pasedag SM, et al (2006). AKT activation in human glioblastomas enhances proliferation via TSC2 and S6 kinase signaling. *Cancer Res*, **66**, 5618-23.
Robertson GP (2005). Functional and therapeutic significance of Akt deregulation in malignant melanoma. *Cancer Metastasis Rev*, **24**, 273-85.
Rose-John S, Mitsuyama K, Matsumoto S, et al (2009). Interleukin-6 trans-signaling and colonic cancer associated with inflammatory bowel disease. *Curr Pharm Des*, **15**, 2095-103.
Rubie C, Frick VO, Pfeil S, et al (2007). Correlation of IL-8 with induction, progression and metastatic potential of colorectal cancer. *World J Gastroenterol*, **13**, 4996-5002.
Sakamoto K, Maeda S, Hikiba Y, et al (2009). Constitutive NF-kappaB activation in colorectal carcinoma plays a key role in angiogenesis, promoting tumor growth. *Clin Cancer Res*, **15**, 2248-58.
Sartor RB (2006). Mechanisms of disease: pathogenesis of Crohn's disease and ulcerative colitis. *Nat Clin Pract Gastroenterol Hepatol*, **3**, 390-407.
Sarver AL, French AJ, Borralho PM, et al (2009). Human colon cancer profiles show differential microRNA expression depending on mismatch repair status and are characteristic of undifferentiated proliferative states. *BMC Cancer*, **9**, 401.
Scheid MP, Woodgett JR (2003). Unravelling the activation mechanisms of protein kinase B/Akt. *FEBS Lett*, **546**, 108-12.
Scheller J, Ohnesorge N, Rose-John S (2006). Interleukin-6 trans-signalling in chronic inflammation and cancer. *Scand J Immunol*, **63**, 321-9.
Schottelius AJ, Dinter H (2006). Cytokines, NF-kappaB, microenvironment, intestinal inflammation and cancer. *Cancer Treat Res*, **130**, 67-87.
Schroeter EH, Kisslinger JA, Kopan Rn (1998). Notch-1 signalling requires ligand-induced proteolytic release of intracellular domain. *Nature*, **393**, 382-6.
Seidelin JB, Nielsen OH (2005). Continuous cytokine exposure of colonic epithelial cells induces DNA damage. *Eur J Gastroenterol Hepatol*, **17**, 363-9.
Seo HS, Choi HS, Kim SR, et al (2012). Apigenin induces apoptosis via extrinsic pathway, inducing p53 and inhibiting STAT3 and NFkappaB signaling in HER2-overexpressing breast cancer cells. *Mol Cell Biochem*, **366**, 319-34.
Shafie NH, Mohd Esa N, Ithnin H, et al (2013). Prophylactic Inositol Hexaphosphate (IP6) inhibits colon cancer through involvement of Wnt/β-catenin and COX-2 pathway. *BioMed Res Int*, **2013**, 681027.
Shanmugam MK, Rajendran P, Li F, et al (2011). Ursolic acid inhibits multiple cell survival pathways leading to suppression of growth of prostate cancer xenograft in nude mice. *J Mol Med*, **89**, 713-27.
Sheng H, Shao J, Williams CS, et al (1998). Nuclear translocation of beta-catenin in hereditary and carcinogen-induced intestinal adenomas. *Carcinogenesis*, **19**, 543-9.
Sohn OS, Ishizaki H, Yang CS, et al (1991). Metabolism of azoxymethane, methylazoxymethanol and N-nitrosodimethylamine by cytochrome P450IIE1. *Carcinogenesis*, **12**, 127-31.
Solinas G, Marchesi F, Garlanda C, et al (2010). Inflammation-mediated promotion of invasion and metastasis. *Cancer Metastasis Rev*, **29**, 243-8.
Sparks AB, Morin PJ, Vogelstein B, et al (1998). Mutational analysis of the APC/beta-catenin/Tcf pathway in colorectal cancer. *Cancer Res*, **58**, 1130-4.
Steinman L (2007). A brief history of T(H)17, the first major revision in the T(H)1/T(H)2 hypothesis of T cell-mediated tissue damage. *Nat Med*, **13**, 139-45.
Stolfi C, Rizzo A, Franze E, et al (2011). Involvement of interleukin-21 in the regulation of colitis-associated colon cancer. *J Exp Med*, **208**, 2279-90.
Suzui M, Ushijima T, Dashwood RH, et al (1999). Frequent mutations of the rat beta-catenin gene in colon cancers induced by methylazoxymethanol acetate plus 1-hydroxyanthraquinone. *Mol Carcinog*, **24**, 232-7.
Suzuki A, Hanada T, Mitsuyama K, et al (2001). CIS3/SOCS3/SSI3 plays a negative regulatory role in STAT3 activation and intestinal inflammation. *J Exp Med*, **193**, 471-81.
Takahashi M, Fukuda K, Sugimura T, et al (1998). Beta-catenin is frequently mutated and demonstrates altered cellular location in azoxymethane-induced rat colon tumors. *Cancer Res*, **58**, 42-6.
Tenesa A, Dunlop MG (2009). New insights into the aetiology of colorectal cancer from genome-wide association studies. *Nat Rev Genet*, **10**, 353-8.
Tetsu O, McCormick F (1999). Beta-catenin regulates expression of cyclin D1 in colon carcinoma cells. *Nature*, **398**, 422-6.
Thiem S, Pierce TP, Palmieri M, et al (2013). mTORC1 inhibition restricts inflammation-associated gastrointestinal tumorigenesis in mice. *J Clin Invest*, **123**, 767-81.
Tian Y, Ye Y, Gao W, et al (2011). Aspirin promotes apoptosis in a murine model of colorectal cancer by mechanisms involving downregulation of IL-6-STAT3 signaling pathway. *Int J Colorectal Dis*, **26**, 13-22.
Tyagi A, Singh RP, Ramasamy K, et al (2009). Growth inhibition and regression of lung tumors by silibinin: modulation of angiogenesis by macrophage-associated cytokines and nuclear factor-kappaB and signal transducers and activators of transcription 3. *Cancer Prev Res*, **2**, 74-83.
Ullman TA, Itzkowitz SH (2011). Intestinal inflammation and cancer. *Gastroenterology*, **140**, 1807-16.
Van Kemseke C, Belaiche J, Louis E (2000). Frequently relapsing Crohn's disease is characterized by persistent elevation in interleukin-6 and soluble interleukin-2 receptor serum levels

during remission. *Int J Colorectal Dis*, **15**, 206-10.
Villanueva A, Alsinet C, Yanger K, et al (2012). Notch signaling is activated in human hepatocellular carcinoma and induces tumor formation in mice. *Gastroenterology*, **143**, 1660-9.
Wang B, Xiao Z, Chen B, et al (2008). Nogo-66 promotes the differentiation of neural progenitors into astroglial lineage cells through mTOR-STAT3 pathway. *PLoS ONE*, **3**, 1856.
Wang Z, Jin H, Xu R, et al (2009). Triptolide downregulates Rac1 and the JAK/STAT3 pathway and inhibits colitis-related colon cancer progression. *Exp Mol Med*, **41**, 717-27.
Ward JM (1974). Morphogenesis of chemically induced neoplasms of the colon and small intestine in rats. *Lab Invest*, **30**, 505-13.
Wodarz A, Nusse R (1998). Mechanisms of Wnt signaling in development. *Annu Rev Cell Dev Biol*, **14**, 59-88.
Yan S, Zhou C, Zhang W, et al (2008). beta-Catenin/TCF pathway upregulates STAT3 expression in human esophageal squamous cell carcinoma. *Cancer Lett*, **271**, 85-97.
Yang Y, Yan X, Duan W, et al (2013). Pterostilbene Exerts Antitumor Activity via the Notch1 Signaling Pathway in Human Lung Adenocarcinoma Cells. *PLoS ONE*, **8**, 62652.
Yu H, Jove R (2004). The STATs of cancer--new molecular targets come of age. *Nat Rev Cancer*, **4**, 97-105.
Yu H, Kortylewski M, Pardoll D (2007). Crosstalk between cancer and immune cells: role of STAT3 in the tumour microenvironment. *Nat Rev Immunol*, **7**, 41-51.
Yu H, Pardoll D, Jove R (2009). STATs in cancer inflammation and immunity: a leading role for STAT3. *Nat Rev Cancer*, **9**, 798-809.
Zhang HY, Spechler SJ, Souza RF (2009). Esophageal adenocarcinoma arising in Barrett esophagus. *Cancer Lett*, **275**, 170-7.
Zhong Z, Wen Z, Darnell JE, Jr (1994). Stat3: a STAT family member activated by tyrosine phosphorylation in response to epidermal growth factor and interleukin-6. *Science*, **264**, 95-8.
Zhou J, Wulfkuhle J, Zhang H, et al (2007). Activation of the PTEN/mTOR/STAT3 pathway in breast cancer stem-like cells is required for viability and maintenance. *Proc Natl Acad Sci U S A*, **104**, 16158-63.
Zhu H, Zhou X, Redfield S, et al (2013). Elevated Jagged-1 and Notch-1 expression in high grade and metastatic prostate cancers. *Am J Transl Res*, **5**, 368-78.