

REVIEW

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

Ashok Kumar Pandurangan¹, 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)- κ B, 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 effects 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- κ B - cytokines - MiRNA

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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- κ B, 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

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

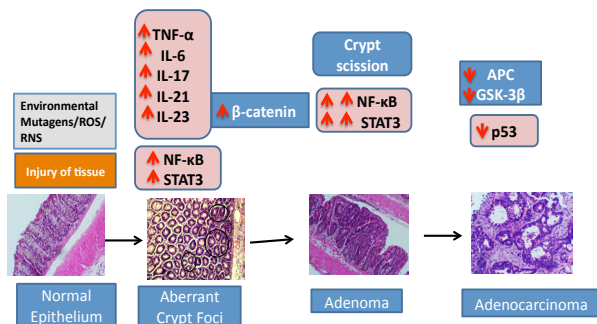


Figure 1. Mechanism of Colitis Associated Cancer Development. (A): The stages of cancer development, including formation of aberrant crypt foci, polyps, adenomas, and carcinomas, are similar between non-inflammatory CRC and CAC. However, some different pathogenic sequences have been proposed for CAC, 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- κ B 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 transcribes 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-transsignaling. 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- κ B 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.

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- κ B, PI3/Akt/mTOR pathway, Notch pathway, Wnt/ β -catenin and many cytokines.

Nuclear Factor - κ B

Nuclear factor (NF)- κ B is a transcription factor, under basal condition it resides in the cytoplasm as a heterotrimer consisting of p50, p65, and I κ B α . On activation, the I κ B α protein, an inhibitor of NF- κ B, 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 I κ B α is called I κ B α kinase or IKK. Whereas IKK β mediates the classic/canonical NF- κ B activation pathway, IKK α mediates the non-canonical pathway. The reason behind the activation of IKK is not well-understood. More than a 12 different kinases have

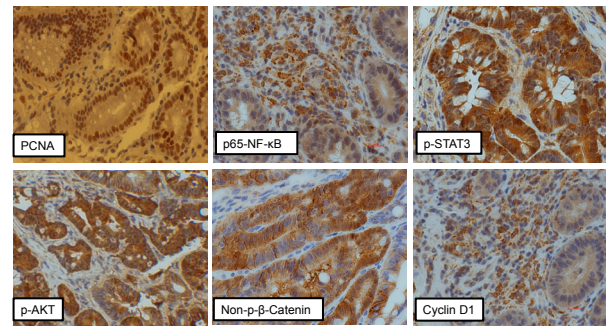


Figure 2. Immunohistochemical Expression of PCNA, p-STAT3, pAkt, non-p- β -catenin, p65-NF- κ B and Cyclin D1 in CAC. Mice were induced with AOM/DSS for the period of 62 days, after that the colon was excised and fixed in 10% buffered formalin. After processing the tissues were embedded paraffin and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

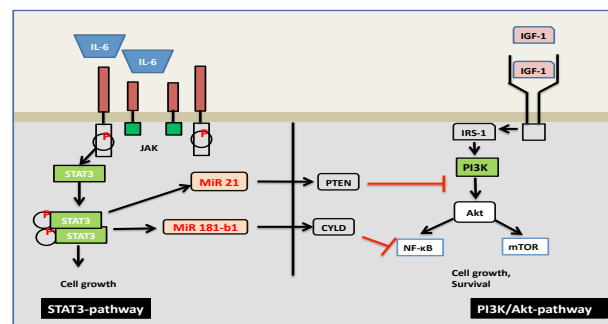


Figure 3. Regulation of Intracellular STAT3. The ubiquitous expression of gp130 and the capacity of STAT3 to stimulate its own transcription as well as that of gp130 ligands (in particular IL-6) also provide numerous amplification loops between the different cell types. Furthermore, limited responsiveness 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

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- κ B-activating kinase, NF- κ B-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- κ B (Aggarwal et al., 2009).

NF- κ B 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- κ B 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- κ B 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- κ B 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- κ B 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- κ B at several levels in a highly context-dependent manner. For example, several inflammatory factors encoded by NF- κ B 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- κ B family member RelA, trapping it in the nucleus and thereby contributing to constitutive NF- κ B activation in tumor (Lee et al., 2009). Ultimately, STAT3 and NF- κ B 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- κ B-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 γ t, 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 ROR γ t and IL-17. As a key transcription factor associated with the Th17 cells, ROR γ t 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 PKB α (Akt1), PKB β (Akt2) and PKB γ (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 phosphoinositide-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, IKK α , NOS, TSC2, PRAS40, p27, MDM2, and GSK3 β (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). Everolimus (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/RBPJ κ /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; Grivennikov 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-3 β 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-3 β . The phosphorylated form of GSK-3 β 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- κ B, 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-1 β , 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-1 β (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.

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