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REVIEW

Therapeutic aspects of c-MYC signaling in inflammatory and cancerous colonic diseases

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Abstract

Colonic inflammation is required to heal infections, wounds, and maintain tissue homeostasis. As the seventh hallmark of cancer, however, it may affect all phases of tumor development, including tumor initiation, promotion, invasion and metastatic dissemination, and also evasion immune surveillance. Inflammation acts as a cellular stressor and may trigger DNA damage or genetic instability, and, further, chronic inflammation can provoke genetic mutations and epigenetic mechanisms that promote malignant cell transformation. Both sporadical and colitis-associated colorectal carcinogenesis are multi-step, complex processes arising from the uncontrolled proliferation and spreading of malignantly transformed cell clones with the obvious ability to evade the host's protective immunity. In cells upon DNA damage several proto-oncogenes, including *c-MYC* are activated in parelell with the inactivation of tumor suppressor genes. The target genes of the c-MYC protein participate in different cellular functions, including cell cycle, survival, protein synthesis, cell adhesion, and micro-RNA expression. The transcriptional program regulated by c-MYC is context dependent, therefore the final cellular response to elevated c-MYC levels may range from increased proliferation to augmented apoptosis. Considering physiological intestinal homeostasis, c-MYC displays a fundamental role in the regulation of cell proliferation and crypt cell number. However, *c-MYC* gene is frequently deregulated in inflammation, and overexpressed in both sporadic and colitis-associated colon adenocarcinomas. Recent results demonstrated that endogenous c-*MYC* is essential for efficient induction of p53-dependent apoptosis following DNA damage, but *c-MYC* function is also involved in and regulated by autophagy-related mechanisms, while its expression is affected by DNA-methylation, or histone acetylation. Molecules directly targeting c-*MYC*, or agents acting on other genes involved in the c-*MYC* pathway could be selected for combined regiments. However, due to its context-dependent cellular function, it is clinically essential to consider which cytotoxic drugs are used in combination with c-*MYC* targeted agents in various tissues. Increasing our knowledge about MYC-dependent pathways might provide direction to novel anti-inflammatory and colorectal cancer therapies.

Key words: c-MYC; Therapy; Apoptosis; Autophagy; Colon; Inflammation; Colorectal cancer

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Core tip: The c-*MYC* gene is frequently deregulated in colonic inflammation, and overexpressed in both sporadic and colitis-associated colon adenocarcinomas. Endogenous c-*MYC* is essential for efficient induction of p53-dependent apoptosis following DNA damage, moreover its function is also involved in and regulated by autophagy-related mechanisms, and its expression is affected by DNA-methylation, or histone acetylation. Increasing our knowledge about MYC-dependent pathways might provide direction to novel colonic anti-inflammatory and anti-cancer strategies.

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INTRODUCTION

Chronic, non-infectious inflammatory and cancerous colonic diseases currently represent a major threat to human health worldwide. Inflammation is required to fight microbial infections, heal wounds, and maintain tissue homeostasis, however, it could lead to cancer. As the seventh hallmark of cancer it may affect all phases of tumor development, including tumor initiation, promotion, invasion and metastatic dissemination, and also evasion immune surveillance[1]. Inflammation acts as a cellular stressor and may trigger DNA damage or genetic instability, and, further, chronic inflammation can provoke genetic mutations and epigenetic mechanisms that promote malignant cell transformation[1,2]. Both sporadical and colitis-associated colorectal carcinogenesis are multi-step, complex processes arising from the uncontrolled proliferation and spreading of malignantly transformed cell clones with the obvious ability to evade the host' s protective immunity[3,4]. Therefore to develop more effective therapeutic strategies for colorectal cancer (CRC) it is quite challenging due to its heterogeneity and phenotypic diversity.

The *MYC*-family of cellular proto-oncogenes encodes three highly related nuclear phosphoproteins, namely c-MYC, N-MYC, and L-MYC[5]. c-MYC is a basic-helix-loop-helix-leucine zipper protein with a proto-oncogene function, being involved in cell proliferation, transformation, and death[6]. Data from chromatin immunoprecipitation studies demonstrate that c-MYC protein occupies regulatory regions of up to 15% of all genes, and can both activate or repress the expression of several target genes[7,8] (Figure 1A). The target genes of c-MYC participate in different cellular functions, including cell cycle, survival, protein synthesis, cell adhesion, and microRNA (miRNA) expression[7] (Figure 1B). The transcriptional program regulated by c-MYC is context dependent, therefore the final cellular response to elevated c-MYC levels may range from raised proliferation to augmented apoptosis[7]. In the absence of c-MYC cell cycle kinetics is strongly reduced[9].

As a result of synergistic or sequential damage of DNA in normal colonic epithelial cells, several proto-oncogenes, including *c-MYC* are activated in parallel with the inactivation of tumor suppressor genes, leading finally to the alteration of DNA repair systems and apoptosis regulation. Accumulation of the damaged DNA may ultimately cause cellular transformation. In this article we try to summarize the complex interactions of *c-MYC*-signaling within physiological intestinal epithelial homeostasis, inflammatory and cancerous colonic diseases, and the related therapeutic aspects.

CONTROL AND EFFECTS OF *MYC* GENE EXPRESSION

During recent years, several basic cellular functions of MYC have been established[10]. MYC plays a master regulator role of cell growth and proliferation, and it also controls stemness by maintaining pluripotency and self-renewal. On the other hand, MYC can sensitize cells to apoptosis, regulate cellular senescence, and is involved in DNA damage responses[10].

As a central, dual-faced regulator gene, *MYC* is controlled by several different mechanisms. Growth factor-dependent signals have been identified to control *MYC* expression. Growth factors like Ets-1 or E2F1 enhance transcription from the *MYC* promoter[11]. The β-catenin/TCF site also mediates the induction of the *MYC* promoter in regards to the Wingless type (Wnt)-signaling pathway[12]. Additionally, growth factor-dependent pulse of phosphoinositol (PI)3-kinase protects c-MYC protein from proteosomal degradation[13]. In contrast, the Smad and E2F4 containing repressor complex which forms on the *MYC* promoter after transforming growth factor (TGF)-β stimulus suppresses *MYC* expression and enhances the anti-proliferative effects of TGF-β[14,15].

Elevated levels of c-MYC protein strongly sensitize epithelial cells toward proapoptotic stimuli like DNA damage[16]. As a result, downregulation of c-*MYC* is necessary for cell cycle arrest, and survival of cells in response to DNA damage[17]. Since in the presence of strong mitogenic signals the downregulation of *MYC*-expression is required for proto-oncogene-induced cellular senescence[18], c-MYC may be involved in tumor-suppressive mechanisms as well. In case of epithelial and mesenchymal stem cells, however, *MYC*-

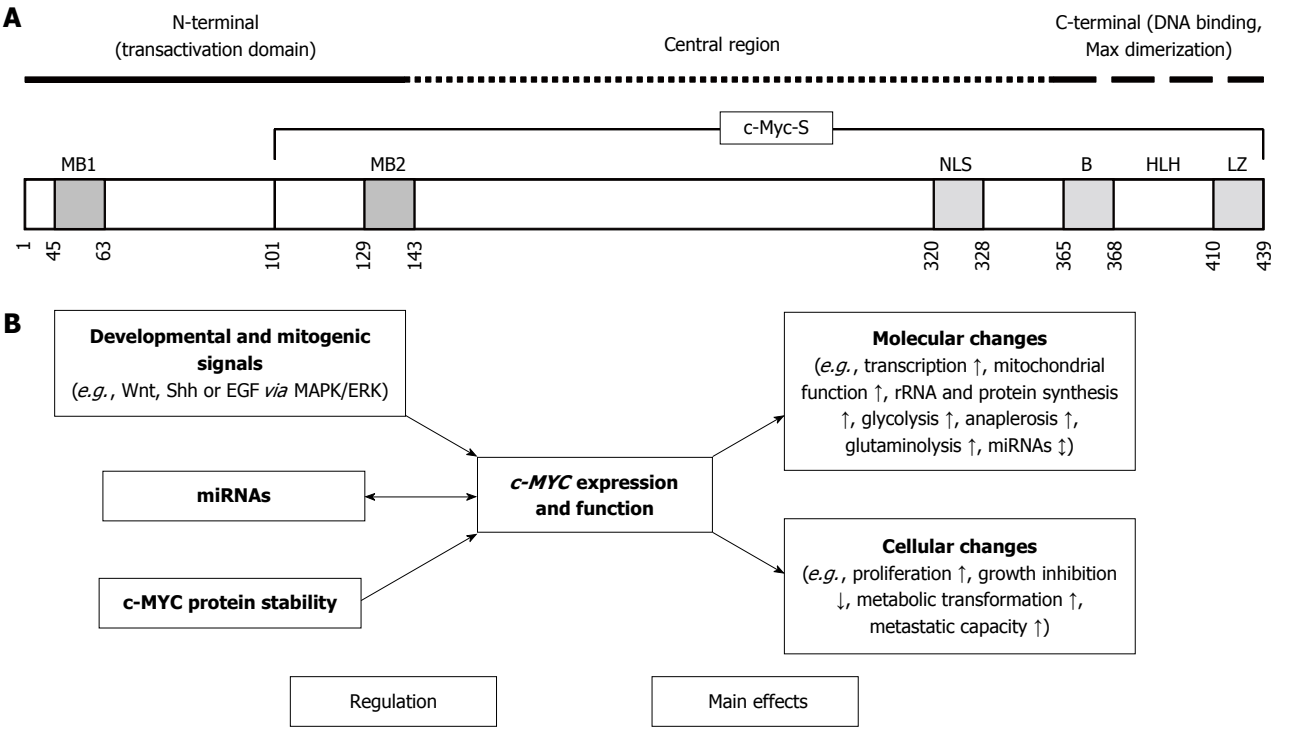

Figure 1 Schematic representation of the structure, regulation and main effects of c-MYC. A: The c-MYC protein consists of three domains: N-terminal, Central region, and C-terminal. The Central region and the C-terminal domain of c-MYC are responsible for protein-protein interactions that result in transcriptional repression by c-MYC. The C-terminal domain contains a basic (B) helix-loop-helix (HLH)-leucine zipper (LZ) motif that is necessary for interaction with different proteins (such as Max), and physiological recognition of DNA target sequences[7,58]; B: Developmental and mitogenic signals tightly regulate *c-MYC* gene expression both in normal (nontransformed) and in transformed cells *via* the MAPK/ERK pathway. MicroRNAs display a dual-faced role in the c-MYC regulatory network; both as regulators and as targets of c-MYC. The stability of the c-MYC protein also represents a particularly effective mechanism of gene regulation. c-Myc-S: Truncated c-Myc protein; MB1 and MB2: Evolutionarily conserved Myc Box sequences; NLS: Nuclear localization signal; Shh: Sonic hedgehog; EGF: Epidermal growth factor; MAPK: Mitogen-activated protein kinase; ERK: Extracellular signal-regulated kinase.

expression can be restricted even in the presence of several growth factors and cytokines[19]. These observations indicate that *MYC*-expression plays a dual-faced role regarding cellular survival and tissue homeostasis.

In physiological circumstances, negative feedback regulatory loops also play an important role in decreasing cellular c-MYC levels[20]. Negative feedback regulation is frequently disturbed in the course of tumorigenic transformation, permitting transformed cells to overexpress *MYC*[20]. Epigenetic factors, such as miRNAs, are also involved in downregulation of *MYC* in response to DNA damaging agents[17].

Regarding the colon, the protein kinase MK5 have been also identified as a negative regulator of *MYC* expression[15]. Expression of MK5 itself is regulated by MYC, since MYC binds to the promoter of the *MK5* gene, therefore activates its expression. As a result, MYC and MK5 form a negative feedback loop, in which FoxO proteins have been identified as key mediators[15].

c-MYC IN PHYSIOLOGICAL INTESTINAL HOMEOSTASIS

Considering intestinal homeostasis, c-MYC expressed in the entire intestinal tract displays a fundamental role[21]. In the small intestine c-MYC regulates the appropriate number of epithelial cells within the crypts[9]. Muncan *et al*[9] reported that upon conditional deletion of *c-MYC* gene crypt epithelial cells become smaller as compared to normal ones. Moreover, in the absence of c-MYC protein epithelial cell proliferation became reduced[9]. On the other hand, it was unexpectedly found in mice that conditional deletion of c-*Myc* in adult intestinal epithelium by utilizing a *Cre*-estrogen receptor fusion transgene driven by the intestine-specific villin promoter did not induce an overt phenotype[22]. According to this result the proliferation and expansion of intestinal epithelial progenitors can occur in a *Myc*-independent manner, as well. The difference between the studies of Muncan *et al*[9] and Bettess *et al*[22] most likely relates to deletion efficiency accomplished with the different Cre transgenes in the earliest crypt progenitors. Regarding apoptotic cell death, c-MYC does not influence epithelial apoptotic rate in the small intestine, it induces apoptosis only in the colon[9,23].

In the intestine cell proliferation and differentiation are under the tight control of the Wnt/β-catenin signaling[24]. In mice c-MYC is a critical downstream effector of cellular proliferation induced by the Wnt/β-catenin pathway[25,26]. Following epithelial injury,

the *c-Myc* 3'Wnt responsive DNA elements (WRE)-dependent regulation of the expression of the *c-Myc* gene seems to be essential for maintaining intestinal homeostasis and regeneration[27].

In colonic epithelial cells, c-MYC-induced apoptosis can be either p53-dependent or independent[28-30]. Basically, in cells the level of p53 expression is low, but its expression is elevated upon stress responses[31,32]. By promoting proteosomic degradation mouse double minute (Mdm)-2 is a negative regulator of the p53 protein[33]. As a regulatory loop, p53 transcriptionally upregulates Mdm2[33]. Alternative reading frame (Arf) also has a role in this regulatory mechanism, since it inhibits the function of Mdm2 and c-MYC[33,34]. By increasing Arf expression, c-MYC protein displays a prominent role in p53 regulation leading finally to p53-dependent apoptosis[35]. The crosstalk between c-MYC and p53 is essential in inducing pro-survival or pro-death responses to apoptotic stimuli.

Upon modulating apoptotic signals c-MYC is able to regulate intrinsic apoptosis independently from p53, as well[36,37]. c-MYC can also alter the balance between the pro- and antiapoptotic members of the Bcl2 (B-cell/lymphoma 2)-family[16,38]. Bcl2 can inhibit c-MYC mediated apoptosis, however, on the other hand, *c-MYC* overexpression suppresses the antiapoptotic Bcl2 protein and mRNA levels[39]. To suppress the antiapoptotic Bcl2 expression the DNA-binding activity of c-MYC is required[40]. In mice, c-MYC may induce apoptosis *via* the activation of the proapoptotic protein, Bax[41]. c-MYC also participates in the extrinsic apoptotic pathways[38,42,43]. Therefore, it is difficult to predict which c-MYC target genes are responsible for the final biological effects. It is likely that the current status of cell physiology ultimately influences the outcome of *c-MYC* overexpression, and affects c-MYC regulating the apoptotic process in colonic epithelial cells.

c-MYC IN COLONIC INFLAMMATION

As a hallmark of cancer, inflammation may lead to tumor formation. Acute and chronic colonic inflammation disrupts the integrity of the epithelial layer, moreover can lead to regenerative cell proliferation, and even fibrosis. In animal colitis models the use of glycogen synthase kinase (GSK)3β inhibitors mitigated disease symptoms by reducing pro-inflammatory immune response[44]. It has been shown, that during the recovery phase of dextran sulfate sodium (DSS)-induced colitis GSK3β inhibition by lithum chloride promotes colonic regeneration. The explanation of this effect is that lithium treatment increased the expression of *Myc* transcripts, MYC proteins, and the expression of several Wnt/MYC target genes in the colonic epithelium[45].

Additionally, in humans the steady-state levels of several nuclear proto-oncogenes including c-*MYC* and N-*MYC* were demonstrated to be lower in epithelial cells from involved or uninvolved inflammatory disease bowel (IBD) samples than in normal epithelial cells from either sporadic colon cancer or diverticulitis patients[46]. In active inflammation the downexpression of c-MYC in IBD epithelium may result in attenuated cell proliferation, therefore may contribute to mucosal ulceration. On the other hand, c-MYC may also be involved in epithelial regeneration after inflammatory damage by altering apoptotic cell death.

It is a known fact, that patients with chronic, longstanding IBD have an increased risk for developing colitis-associated cancer (CAC). By using whole-exome sequencing analysis it has been recently demonstrated that -among others- the *MYC* genomic locus is more frequently amplified in CAC than sporadic colorectal cancers[47]. Moreover, genomic alterations observed in CAC are distinct form those found in sporadic CRCs, and vary by type of IBD[48]. Proteomic network analyses have identified proteins related to mitochondria, oxidative activity, calcium-binding proteins, and c-MYC that play roles in early and late stage colitis-associated neoplastic progression, respectively[49]. *c-MYC* is often overexpressed in dysplastic cells in chronic longstanding ulcerative colitis, the precursor to CAC[50,51]. Taking together these data, it seems that the complex role and final effects of c-MYC in inflammatory colon mucosa are context- and microenvironment dependent.

c-MYC IN COLORECTAL CANCER

The *c-MYC* oncogene is frequently deregulated in human cancers and is overexpressed in up to 70%-80% of colon adenocarcinomas[52]. Since *c-MYC* is a downstream target of the *APC* (adenomatous polyposis coli) gene, and *APC* itself is inactivated in most colorectal cancers[53], it is not surprising that in early and advanced stages of colorectal carcinogenesis *c-MYC* is overexpressed at both the mRNA and protein levels[54,55].

The imbalance of cell proliferation and apoptosis is a key component in initiation of colorectal tumorigenesis. Basically, overexpression of *c-MYC* could lead to apoptosis[38], indicating its crucial role for determining cell survival and/or apoptotic pathways[36]. Under pathological conditions deregulated Wnt/β-catenin signaling promotes CRC by activating the expression of *c-MYC*[56]. Moreover, c-MYC-triggered apoptosis provides an inherent "fail-safe" program to check unlimited cell growth. The extent of apoptotic cell death is in correlation with the level of *c-MYC* expression[57].

In case of early to late colorectal adenomas significant correlation of nuclear β-catenin and c-MYC nuclear expression was found with the size of colon adenomas, but not with their cellular proliferative activity[58]. This phenomenon implies a dose-dependent function of β-catenin. Without nuclear β-catenin, T-cell factor family (TCF) proteins are bound by a co-

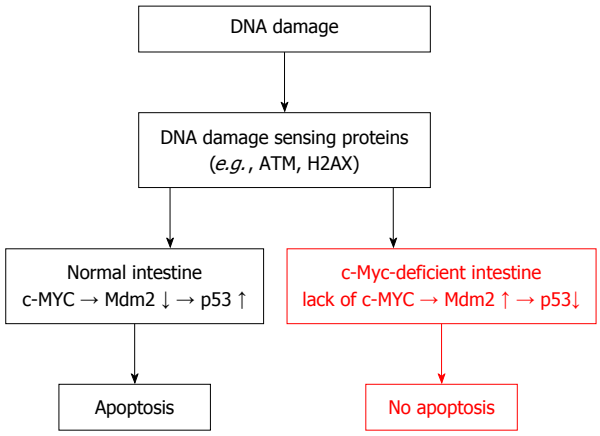

Figure 2 Schematic illustration of the relation of c-MYC to p53 following DNA damage in the intestine.

repressor, and this complex acts as transcriptional repressor of the target genes[59,60]. Nuclear β-catenin competes with the co-repressor for TCF binding in a dose-dependent manner. In colorectal cancer cells the disruption of β-catenin/TCF-4 activity induces a rapid G1 arrest and blocks the physiologically active genetic program in the proliferative compartment of colonic crypts. Simultaneously, an intestinal differentiation program is induced, in which c-MYC plays a switch role by direct repression of the p21CIP1/WAF1 promoter. Following disruption of β-catenin/TCF-4 activity, the decreased expression of c-MYC results in p21CIP1/WAF1 transcription, which in turn mediates G1 arrest and differentiation[12].

Though several *in vitro* studies proved that c-MYC has the ability to sensitize or induce apoptosis[61,62], its role in apoptotic cell-death is not well established and unclear *in vivo.* In a recent article, Phesse *et al*[63] demonstrated for the first time in an *in vivo* model that endogenous c-MYC is essential for efficient induction of p53-dependent apoptosis following DNA damage. It has been long known that p53 serves a key element in the development of sporadic colorectal cancer[64], and further, it is also involved in colitis-associated carcinogenesis[65]. Until now, in the gut *c-MYC* was considered as a fundamentally expressed gene responsible for epithelial regeneration and the regulation of the number of crypt cells. Phesse *et al*[63] concluded that c-MYC serves as a universal regulator of apoptosis in *in vivo* systems suggesting an important and new aspect of colorectal carcinogenesis (Figure 2). On the other hand, the exact mechanisms linking c-MYC levels to Mdm2 expression still remain unclear. In accordance with recent results[63,66,67], one can speculate that c-MYC may directly inhibit Mdm2 transcription. The induction of the c-MYC-dependent apoptosis program requires *c-MYC* expression to exceed a threshold, which is defined by Bcl2 family proteins in a cell-, tissue type and milieu-specific fashion[23]. In the colon, however, the different behaviour of the apoptosis regulator Bax, controlled by c-MYC may suggest the existence of a different apoptotic program of epithelial cells.

A recent report has demonstrated a role of AMBRA1 (activating molecule in Beclin-1 regulated autophagy) in both the autophagic pro-survival response and Beclin-1-dependent autophagy in embryonic stem cells[68]. AMBRA1 has been shown to be a crucial regulator of autophagy and apoptosis in colorectal cancer cells that maintains the balance between these cellular mechanisms[69]. AMBRA1 promoted dephosphorylation and degradation of c-MYC, and favors the interaction between c-MYC and PP2A (a c-MYC phosphatase), leading finally reduced cell divison rate[70]. AMBRA1 has been recently characterized as a target of mTOR (mammalian target of rapamycin) in the autophagy process[71]. Furthermore, the AMBRA1/PP2A-mediated regulation of c-MYC is also under mTOR control[70], indicating the key role of mTOR in regulating cellular fate by interfering with its metabolic status (Figure 3).

The MK5 kinase regulates the translation of c-MYC, since it is required for the expression of miR-34b/c that bind to the 3'UTR of *MYC*. The MK5-MYC negative regulatory feedback loop has been found to be disrupted during colorectal tumorigenesis[15]. Two changes may explain the disruption of this regulatory circuit. First, silencing of the miR-34B/c gene promoters by DNA methylation[72]. Second, the expression of MK5 is downregulated in colorectal tumors by a currently unknown mechanism[15]. Depletion of MK5 regulates *Ephrin B1*, a MYC-repressed gene that is involved in the progression of p53-deficient colorectal tumors[73].

ANTI-INFLAMMATORY THERAPEUTIC ASPECTS OF c-MYC IN THE COLON

Mesenchymal stem cell transplantation (MSCT) has been reported effective in the treatment of IBD as it can restore epithelial barrier integrity, induce immune suppression, and stimulate regeneration of endogenous host progenitor cells[74-78]. Mesenchymal stem cells can be engrafted into the damaged mucosa and even differentiated into colonic interstitial cells[79]. The pathobiologic background of this reparative process, however, is not well known. In an IBD-MSCT rat model, when intestinal epithelium was inflamed, the canonical Wnt signaling was found to be activated by Wnt3a and inhibited by GSK-3β and APC[78]. Shortly after MSCT, the elevated *c-Myc* and downregulated *Apc* gene expressions facilitate mesenchymal stem cell proliferation, and then differentiation into intestinal epithelial cells in the anaphase, by reducing the expression of *c-Myc*. These changes promoted intestinal stem cell proliferation and repaired the intestinal mucosa. Though, MSCT is a useful therapeutic possibility in IBD models, the parallel use of GSK3β inhibitors after MSCT may be therapeutically useful to enhance MYC-signaling, hence promoting reparative cell proliferation[45].

Traditionally, the pathomechanism of Crohn's

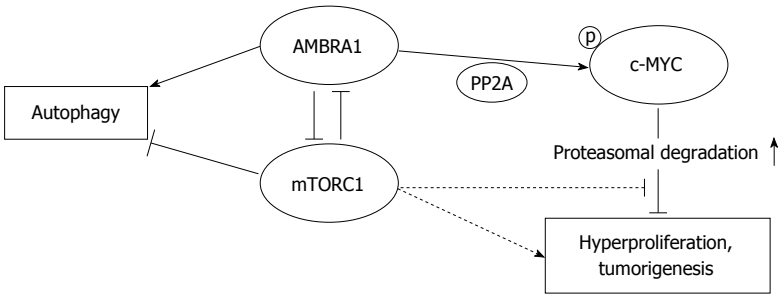

Figure 3 Interplay of AMBRA1, c-MYC and mTOR in colorectal cancer cells. AMBRA1 links autophagy to cell proliferation by facilitating c-MYC demolition. AMBRA1 promotes c-MYC phosphorilation and proteasomal degradation, therefore prevents hyperprolifearion and tumorigenesis. mTORC1 negatively controls the function of AMBRA1, thus finally supporting c-MYC-driven cell proliferation. Arrows represent stimulation or increase; blocked arrows represent inhibition; broken lines represent indirect effects. AMBRA1: Activating molecule in Beclin-1 regulated autophagy; mTORC1: Mammalian target of rapamycin complex 1; PP2A: Protein phosphatase 2A.

Table 1 Therapeutic options based on c-MYC targeting are represented by various strategies in inflammatory and cancerous colonic disorders

Main mode of action	Potential pathways/agents
Inflammatory colonic disorders	
Upregulation of c-MYC expression	GSK inhibitors ± MSCT
Inhibition of c-MYC signaling (suppression of Th1 function)	BET inhibitors ± c-MYC inhibitors
Cancerous colonic diseases	
Downregulation of c-MYC expression	dose-dependent gene and protein expression suppression; PPAR-γ (5-ASA, mesalazine)
	suppressing protein expression by UDCA
	crosstalk with integrins
	E2F1 inhibition (downregulatin GCN5 expression)
	FGFR kinase inhibition
	epigenetic regulation by miR-320b
	siRNA blocking of ABC-transporters
	lncRNAs (blocking of PARROT or CCAT1-L)
	siRNAs using PEI-PGMA platform
	modified ODC promoter
Promoting c-MYC degradation	26S proteosomal pathway (aspirin)
	SIRT2 inhibition
Inhibition of c-MYC signaling	Omomyc
	BET (+ Wnt/MAPK) inhibitors

GSK: Glycogen synthase kinnase; MSCT: Mesenchymal stem cell transplantation; PPAR-γ: Peroxisome proliferator-activated receptor-γ; 5-ASA: 5-aminosalicylate; UDCA: Ursodeoxycholic acid; E2F1: E2F Transcription factor 1; GCN5: Histone acetyltransferase; FGFR: Fibroblast growth factor receptor; miR-320b: Micro-ribonucleic acid-320b; siRNA: Small interfering ribonucleic acid; ABC: Adenosine triphosphate-binding casette; lncRNA: Long noncoding ribonucleic acid; PARROT: Proliferation associated RNA and regulator of translation; CCAT1-L: Longer isoform of colon cancer associated transcript 1; PEI-PGMA: Polyethileneimine-polyglycidal methacrylate; ODC: Ornithine decarboxylase; SIRT2: Sirtuine2; BET: Bromo- and extra-terminal domain; MAPK: Mitogen-activated protein kinase.

disease has been associated with Th1 cytokine profile. In an experimental autoimmune inflammation model it was demonstrated that inhibiting the functions of BET (bromo and extra-terminal domain)-family proteins during early T-cell differentiation resulted in long-lasting suppression of the pro-inflammatory functions of Th1 cells[80]. These effects were mimicked by an inhibitor of c-MYC function, as well, implicating reduced expression of c-*Myc* as one avenue by which BET-inhibitors suppressed the inflammatory functions of T-cells. hypothetically, BET and c-MYC inhibition may have therapeutic potential in Crohn's disease (Table 1).

ANTI-CANCER THERAPEUTIC ASPECTS OF c-MYC IN THE COLON

Cancer cells have been reported to display cell cycle arrest, differentiation, senescence or cell death after MYC inhibition *via* different molecular mechanisms (Table 1).

5-aminosalicylic acid has been identified as an agonist of peroxisome proliferator-activated receptor (PPAR)-γ[81]. Activation of PPAR-γ induces apoptosis by downregulating *c-MYC*[82,83]. Regrading aspirin the involvement of the 26S proteasomal pathway has been found in decreasing *c-MYC* expression in a concentration-dependent fashion[84]. Due to its oncogenic activities including cell growth, proliferation, angiogenesis, genomic instability and blocking differentiation, the downregulation of *c-MYC* would be expected to have important clinical implications[85].

Ursodeoxycholic acid (UDCA) displays chemo-preventive action against chemical and colitis-associated colonic carcinogenesis[86]. One possible explanation of this effect is the inhibition of cell proliferation by suppressing c-MYC protein expression and, as a consequence, cell cycle regulatory molecules including cyclin-dependent kinase-4 and -6[86]. According to this result, c-MYC is a target molecule of UDCA in colon carcinoma cells. However, mapping the benefits of UDCA administration for CRC chemoprevention at population level needs further studies.

Integrins, containing noncovalently associated α/β heterodimers provide dynamic cell to cell linkage and cell attachment to matrix molecules. While in normal human intestinal epithelium α1β1 integrins are usually expressed in the lower third of crypts[87],

in colorectal cancers and colon cancer cell lines integrin-α1 is expressed up to 65% of cases[88]. c-MYC regulates several integrin subunits, thus influences various functions of integrins regarding colon cancer cell proliferation, migration, and survival[89-92]. A combination of anti-MYC and -integrin targeted therapies hence may represent novel aspects of anti-tumor strategies in colon cancers.

Aberrant kinase activation originated from mutation, amplification, or translocation can drive growth and survival in several human cancers[93,94]. In gastric cancer, the crosstalk between fibroblast growth factor receptor (FGFR)2 and CD44 has been found to maintain cancer stemness by reciprocically regulating their expression *via* differentially regulating *c-MYC* transcription[95]. Since FGFR2 has been found to be amplified in the NCI-H716 colorectal cancer cell line[96], this result suggests that emerging FGFR inhibitor therapeutics may have efficacy in a subset of colon cancer driven by FGFR2 amplification.

It has been shown that the inhibition of BET protein family impairs the proliferation of several cancer cell lines[97-99]. These effects are partly mediated by *c-MYC* repression[98]. In a recent study of Tögel *et al*[100] the authors investigated the effect of BET inhibitors on proliferation and *c-MYC* expression within 20 CRC cell lines. They have found that JQ1, a BET inhibitor, administered together with Wnt or MAPK inhibitors sufficiently downregulates the expression of *c-MYC*, thus inhibits CRC cell proliferation. Based on these results, this kind of combined therapy seems to be effective in CRC treatment.

Upon recent results, targeting c-MYC can also be considered as a promising anti-cancer therapeutic strategy[23,101-104]. c-MYC inhibition with a protein fragment called Omomyc has been shown to be very effective to regress epithelial cell-derived tumors in mice models[23,105]. Omomyc has been found to be a pan-MYC family (c-, N- and L-MYC) inhibitor, potentially useful for cancers carrying any MYC family member amplification[106].

In case of cancers in which cell growth is not dependent on amplified *MYC* family genes, *MYC* suppression alone is not enough for a sufficient therapeutic effect. In animal models of *Myc*-driven cancers, reversion of the tumor by *Myc* suppression has been impeded by the parallel repression of TP53 or retinoblastoma-1 proteins underlining the relevance of these pathways to be intact for the treatment of cancers by MYC targeting[107-109].

Using a focused RNA interference library for genes involved in epigenetic regulation, sirtuin2 (SIRT2), an NAD(+)-dependent deacetylase, has been identified as a modulator of the therapy response to EGFR inhibitors in colon and lung cancers[110]. Thiomyristoyl lysine compound (TM), a SIRT2 inhibitor with high potency and specificity, has broad anti-cancer activity. SIRT2 inhibition was found to promote c-MYC ubiquitination and degradation, hence it may be a potential target for c-MYC-driven cancers including colorectal carcinoma[111].

Recent studies have suggested that the elevated expression of general control nonrepressed protein 5 (GCN5), a histone acetyltransferase can often be detected in human cancers[112]. GCN5 expression is elevated in colon cancer, and its overexpression is regulated by c-MYC[113]. By suppressing GCN5 human colon cancer cell growth can be inhibited. Furthermore, the suppression of the proapoptotic transcription factor E2F1-induced GCN5 transcription facilitates E2F1-induced cell death, implying a negative feedback in apoptosis regulation[113]. According to these results, GCN5 seems to be a potential therapeutic target for human colon cancers.

Regarding transcription factor-based therapies of tumorous diseases inhibition of c-MYC may also represent a promising option[101,114]. Numerous cytotoxic agents, and ionizing radiation have been shown to induce apoptosis following DNA damage. Since most of the anti-cancer drugs are used in combination with the potential of genotoxicity, it is of importance to further assess the role of c-MYC in response to DNA damage.

Therapeutic approaches that would allow the reprogramming and returning of altered c-MYC activity within tumor cells are also promising therapeutical strategies. RNA interference technology is one of these modalities. MiRNAs are key post-transcriptional regulators of genetic networks. Single-stranded mature miRNAs associated with Argonaute proteins form the core of a gene regulatory complex [*i.e.* RNA-induced silencing complex (RISC)]. MiRNA-RISC-mediated gene inhibition can be materialized by three processes: (1) site-specific cleavage; (2) enhanced mRNA degradation; and (3) translational inhibition[115]. Evidences indicate that post-transcriptional miRNA-mediated gene expression regulation can act as tumor suppressor or onogene in CRC[116]. Currently, miR-320b has been found to be significantly down-regulated in CRC tumor tissues. In addition, miR-320b overexpression has been found to correlate with decreased cell growth both *in vitro* and *in vivo*. Moreover, it has been also demonstrated that miR320b directly targets *c-MYC*, and its overexpression in SW-480, SW-620, HCT-116, LoVo, and HK293 CRC cell lines decreases *c-MYC* expression at gene and protein level as well[117]. According to these results, increasing miR-320b gene expression may represent a potential therapeutic approach in CRC.

Colorectal cancer stem cells (CSCs) has an important role in tumor initiation, progression, and recurrence. c-MYC was found to be highly expressed in CD133+ colon CSCs[118]. The overexpression of ATP-binding casette (ABC) transporters in cancer cells can result in therapy resistance by exporting anti-tumor drugs[119]. Recently, *c-MYC* expression has been effectively blocked on mRNA and protein level by *c-MYC* small interfering RNA (siRNA), moreover *c-MYC*

silencing sensitized CD133+ CSCs to chemotherapy-induced cytotoxicity by downregulating the expression of ABC transporter proteins[120].

In eukaryotic cells a vast number of noncoding RNA species are transcribed. Among them, long noncoding RNAs (lncRNAs) have been widely implicated in post-transcriptional gene expression regulation. The expression level of lncRNAs is usually very low and tissue-specific[121]. c-MYC can regulate the expression of lncRNAs, some of these may also contribute to the transcription of c-MYC target genes[122]. It has been reported that proliferation associated RNA and regulator of translation (PARROT), an lncRNA dynamically expressed in both transformed and normal cells contributes to proliferation in senescence and cancer. PARROT has been also identified as an upstream regulator of c-MYC. Its depletion results in the depletion of *c-MYC* mRNA and protein expression, subsequently altering cell growth and proliferation[121]. In gastric cancer c-MYC activates the expression of colon cancer associated transcript 1 (CCAT1) lncRNA, leading to an increased proliferation and migration of cancer cells[123]. CCAT1-L, a longer isoform of CCAT1, has been reported to regulate *MYC* expression in colon cancer. It is supposed that CCAT1-L allows the interaction between the enhancer and the *c-MYC* promoter thus promotes tumorigenesis[124].

Achieving effective intracellular delivery of therapeutic RNA interfering molecules such as siRNAs or short hairpin RNAs (shRNAs) is quite challenging. In a recent study, spherical nucleic acid-gold nanoparticle conjugates have been shown to selectively induce apoptosis in glioma cells *in vivo*[125]. However, the used 21 base siRNA duplexes were quite unstable. ShRNAs with a transient period of expression are better suited for long-term effectiveness, due to their ability to produce siRNAs continuously within cancer cells, thus resulting in prolonged suppression of target genes[126]. Until today, shRNAs have been delivered effectively *in vivo* using viral vectors. Among nonviral vectors, polyethileneimine (PEI) is the most widely used, gold-standard agent[127]. However, the major disadvantage of PEI is its cytotoxicity[128]. On the other hand, it has been demonstrated that anchoring multiple PEI chains to macromolecule polyglycidal methacrylate (PGMA) nanoparticles dramatically reduces their cytotoxicity, while achieving efficient nanoparticle endocytosis[129]. Using the PGMA platform effective delivery of small oligos (anti-miRs and mimics) and larger encoding shRNAs were performed in a wide variety of cancer cell lines including colorectal ones. Furthermore, the effectiveness of this therapy was validated for *in vivo* tumor suppression using transgenic mouse models. It was found that oral delivery of the *c-Myc*-conjugated nanoparticles to an *Apc*-deficient crypt progenitor colon cancer model resulted in an increased host survival and re-entered intestinal tissue to a non-*Wnt*-deregulated state[126]. According to these results, it seems that careful design of nonviral nanoparticles may help to made RNA interference technology an affordable and amenable therapy for CRC.

Regarding tumor-specific cytotoxicity, viral-directed enzyme prodrug therapy may also represent an ideal alternative[130]. However, the viruses used to deliver cDNAs encoding prodrug-activating enzymes can transduce normal cells, not just tumor cells. To achieve tumor-specific expression of the delivered cDNAs is to regulate transcription of the prodrug-activating enzyme with a promoter that is preferentially activated by tumor cells. *MYC*-responsive, modified ornithine decarboxylase (ODC) promoter/enhancer sequences have been identified that upregulate target protein expression in SW480 an HT29 colon cancer cells overexpressing the c-MYC protein. The modified ODC promoter may be useful in achieving tissue-specific expression of target proteins in cancers overexpress *c-MYC*[131].

CONCLUSION

The incidence of inflammatory colonic disorders is increasing worldwide. Though inflammation is required to heal infections, wounds, and maintain tissue homeostasis, as the seventh hallmark of cancer, however, it may affect all stages of tumor development. c-MYC, with its dual-faced role in cell proliferation and death, is implicated in several aspects of inflammatory tissue damage and repair. Since the therapeutic potential of c-MYC influencing therapies has not studied yet in the clinic, additional studies are needed to determine whether long-term treatment with c-MYC targeting agents can therapeutically suppress ongoing inflammation.

Colorectal carcinogenesis is a complex, multistep process that is driven by the accumulation of multiple genetic alterations. *c-MYC* is overexpressed in several types of malignant tumors including colorectal cancer, and is necessary for the uncontrolled proliferation of cancer cells. Single or combined therapies based on c-MYC targeting are represented by various strategies. Molecules directly targeting c-MYC, or agents acting on other genes involved in the c-MYC pathway could be selected for combined regiments. However, due to its context-dependent cellular function, it is clinically essential to consider which cytotoxic drugs are used in combination with c-MYC targeted agents in various tissues. Noncoding small RNAs have been recently implicated in anti-cancer therapies[132]. Regardless of the therapy applied, it is important to first determine the molecular pathways underlying the agents to inform the therapy design. Combining c-MYC-targeting agents with specific noncoding RNAs may lead to the development of novel colorectal cancer therapies.

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