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Targeting transcription factors in cancer: from "undruggable" to "druggable"

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Abstract

Deregulation of transcription factors is critical to hallmarks of cancer. Genetic mutations, gene fusions, amplifications or deletions, epigenetic alternations and aberrant posttranscriptional modification of transcription factors are involved in the regulation of various stages of carcinogenesis, including cancer initiation, progression, and metastasis. Thus, targeting the dysfunctional transcription factors may lead to new cancer therapeutic strategies. However, transcription factors are conventionally considered as "undruggable". Here, we summarize the recent progresses in understanding the regulation of transcription factors in cancers, and strategies to target transcription factors and co-factors for preclinical and clinical drug development, particularly focusing on c-Myc, YAP/TAZ and β-catenin due to their significance and interplays in cancer.

Keywords

Transcription factor; transcription co-factors; cancer; undruggable; druggable

1. Introduction

Transcription factors are proteins that bind to specific DNA sequences and regulate gene expression [1], which are essential for almost all aspects of cellular functions. Deregulation of gene expression is associated with hallmarks of various types of cancers [2]. Transcription factors themselves are often altered in cancers through genetic mutations, gene amplifications or deletions, epigenetic alternations and aberrant posttranscriptional modification [3], leading to deregulation of their functions and enhancing tumorigenesis. In the past decades, numerous transcription factors have been revealed as critical regulators of cancer cell proliferation, invasion, the epithelial-mesenchymal transition (EMT) and "stemness" [2, 3, 4]. These transcription factors and their co-factors include YAP/TAZ (YAP1/WWTR1) [5, 6], c-Myc [7, 8], β-catenin [9, 10], FOX (Forkhead box) proteins (FOXO1, FOXO3, FOXO4, FOXL2, FOXC1, FOXC2, FOXP3, FOXM1, FOXK2) [11–17], STAT3 [18], The nuclear factor kappa B (NF-κB) [19], RUNX family of transcription factors (RUNX1, RUNX2, RUNX3) [20], YY1 [21], Activator Protein-1 (AP-1) [22], p53 [23, 24], and NF-E2 p45-related factor 2 (Nrf2) [25] *etc*. Thus, targeting the deregulation

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of transcription factors at both transcriptional and post-transcriptional levels would lead to promising therapeutics for cancers. Traditionally, transcription factors are thought as “undruggable”, due to the challenge of using small molecules to disrupt protein-DNA or protein-protein interactions, or lack of defined ligand binding sites in transcription factors which allows inhibition of their functions (These features are well known in “druggable” targets, such as enzymes or receptors). With the progresses in elucidation of so-called “hotspot” amino acid residues contributing to the majority of the interaction energy, the leap from “undruggble” to “druggable” becomes reality [3, 26, 27]. At the same time, allosteric modulation of protein–protein interactions [28, 29] and gene therapy [30, 31] have provided alternative and additional approaches for curbing cancer.

In this review, we summarized strategies to directly or indirectly target the transcription factors designed with various approaches, such as targeting post-transcriptional regulation (phosphorylation, ubiquitination, acetylation), targeting protein-protein interaction, targeting new allosteric or ligand-binding site, targeting protein degradation, or targeting gene transcription.

2. Transcription factors involved in tumorigenesis

Over the last decades, the functions and mechanisms of transcription factors in the regulation of cancer initiation and progression have been progressively recognized (Figure 1). For example, in oral squamous cell carcinoma (OSCC), the transcriptional co-activators YAP and TAZ promote the pro-tumorigenic signals, and hyperactive YAP and TAZ contribute to the onset of OSCC through promotion of OSCC cell proliferation, survival, and migration *in vitro* and tumor growth and metastasis *in vivo* [32]. Similarly, the regulatory roles of YAP and TAZ in tumorigenesis have been confirmed in the tissues of liver [33], breast [34], uterine [35], lung [36] *etc*. Another critical oncoprotein, c-Myc, has been shown to be implicated in stimulating the progression of various cancers, mainly through its ability to promote cancer cell growth and cellular survival mechanisms and maintaining cancer stem cells [37, 38]. β-catenin plays vital roles in the development and tumorigenesis as the key mediator of Wnt signaling pathway [39]. In prostate cancer, activation of the Wnt/β-catenin pathway stimulates prostate cell proliferation, differentiation and the EMT, which is thought as the contributor for invasive behavior of tumor cells [40]. FOX proteins are a group of multifarious transcription factors implicated in initiation, development and progression of almost all kinds of cancers [41, 42, 43]. In colorectal cancer (CRC), metabolic stress and chemotherapy stimulate the translocation of FOXO3a into mitochondria to facilitate mitochondrial metabolism and cell survival in tumor cells [43, 44]. In gastrointestinal cancer, FOXM1 was implicated as a critical regulator in the proliferation, migration, and invasion of GI cancer cells and FOXM1 modulates EMT through its crosstalk with Wnt/β-catenin signaling pathway [45]. RUNX1, RUNX2, RUNX3 proteins are essential for tissue and organ developmental processes [46]. Disruption of the normal developmental processes has contributed to cancer cell survival, invasion and EMT [47, 48, 49, 50]. RUNXs have been demonstrated to interplay with Wnt/β-catenin signaling pathways. For example, RUNX could either directly modulates β-catenin/TCF-4 transcriptional activity, or indirectly targets on other Wnt/β-catenin signaling nodes. In a feedback regulation, β-catenin and its transcriptional cofactors could also control RUNX

gene expression [51, 52]. The nuclear factor kappa B (NF-κB) consists of a family of transcription factors involved in the regulation of oncogenesis, as well as inflammation and tumor immunity [53]. YAP/TAZ has been targeted by NF-κB through directly transcriptional regulation [54], suggesting that an extensive transcription factor network is involved in tumorigenesis.

Given the critical roles of YAP/TAZ, c-Myc and β-catenin in cancer development, progression and metastasis, and their extensive crosstalk with other transcription factors, we will focus on the discussion of: 1) the regulatory roles of YAP/TAZ, c-Myc and β-catenin in cancer, especially summarizing their aberrant expression and modulation in both transcriptional and post-transcriptional levels in cancers; 2) the therapeutic strategies developed in the recent years by targeting these transcription factors directly or indirectly.

3. Regulation of transcriptional factors in cancer development

3.1 c-Myc

The transcription factor c-Myc is a master regulator of cell proliferation, cell growth, cell differentiation and cell death, by binding to consensus DNA elements (5'-CACGTG-3') and driving the expression of target genes (*Cyclin D2*, *CDK4, p21, p15, CDH2* and *CEBP etc.*). Regulations of c-myc mRNA and c-Myc protein at transcriptional and post-transcriptional levels are tightly controlled. Deregulation of their levels will have critical impact on cell proliferation and cell fate. Numerous studies have indicated that the aberrant expression of the c-myc oncogene, either due to transcriptional overexpression (gene amplification, translocation, alterations in upstream signaling pathways) and/or c-Myc protein stabilization, have been implicated in various cancers, including breast, ovarian, prostate cancers, leukemia and lymphoma. Indeed, high c-Myc protein levels are not only able to drive tumor initiation and progression, but also essential for tumor maintenance: as sustained c-Myc overexpression is critical to cancer cells, and reduction in c-Myc levels leads to growth arrest, apoptosis and differentiation of cancer cells [55].

3.1.1 Transcriptional regulation of c-myc—Gene amplification of c-myc is the most common type of c-my deregulation in cancers. C-myc locates in Chromosome *8q24*, a region frequently amplified in cancers (in 18.92% cancers), including leukemia [56], neuroblastoma [57], small cell lung cancer [58], ovarian, breast, pancreatic, prostate, colorectal, and squamous cell lung cancers [59, 60].

The upstream transcription factors that directly bind with c-myc promoter have been widely studied and reviewed, for example, β-catenin and γ-catenin activate the c-myc promoter at its c-myc's TCF-4 (T-cell factor 4) binding sites and Wnt signaling, TGFβ signaling, NO (Nitric oxide), 1,25-$(OH)_2$-D_3 (1,25-dihydroxyvitamin D_3) signaling, estrogen-ER (estrogen receptor) signaling, Androgen-AR (androgen receptor) signaling, mTOR signaling all converge to β-catenin activation to drive c-myc expression [61]. In addition, E2F, Smads (Smad1, Smad2, Smad3, Smad4), METS, BMAL1, CYR1, C/EBPα, STATs (STAT1, STAT3, STAT4), FBP (FUSE binding protein), NF-κB, AP1, CTCF and FOXOs (FOXM1c, FOXO3) have been reported to directly bind to c-myc promoter and govern its gene

expression [61]. Therefore, signaling pathways that influence the activities of these upstream transcription factors could lead to c-myc upregulation in cancers.

Genetic mutations of c-myc are relatively infrequent, but some studies have found functional mutations in c-myc Homology Box I (HBI) region in Burkitt lymphoma [62, 63]. For example, T58A mutation increased the stability of c-Myc [64, 65, 66]. Additional mutations have been found on T244 and P245 residues in lymphomas, among which P245A mutation increased the turnover half-life and stability of c-Myc [67].

3.1.2 Post-transcriptional regulation of c-Myc—In addition to transcriptional regulation of c-myc gene expression, the post-transcriptional regulation of c-Myc protein was altered in cancers, including phosphorylation, ubiquitination and acetylation *etc*. c-Myc heterodimerizes with Max and then bind to specific E-boxes with the consensus gene sequence 5'-CACGTG-3' [68]. The post-transcriptional modification of c-Myc, such as phosphorylation and acetylation would affect its binding with Max and their regulatory roles in downstream gene expressions.

c-Myc phosphorylation: It was first reported that protein kinase CK2 phosphorylates c-Myc at the acidic domain and near the basic region to stabilize c-Myc protein [69]. Phosphorylation of c-Myc at the transactivation domain (TAD) on Thr58 and Ser62 are important for c-Myc stability and activity [70, 71]. GSK3 and proline-directed kinases respectively phosphorylate Thr58 and Ser62, and modulate c-Myc stability [72]. Moreover, Ser62 phosphorylation is prerequisite for GSK3-mediated phosphorylation, which promotes c-Myc ubiquitination and proteasomal degradation, mediated by the binding and recruiting of the SCFFBW7 ubiquitin ligase complex [70, 71]. In addition, mitogen-activated protein kinase (MAPK), c-JUN N-terminal kinase (JNK), and cyclin-dependent kinase 1 (CDK1) have also been implicated in c-Myc Ser-62 phosphorylation [73, 74, 75, 76, 77, 78, 79], suggesting that phosphorylation is a common regulation of c-Myc function.

c-Myc ubiquitination: Besides recruitment of the SCF(FBW7) ubiquitin ligase complex to direct c-Myc ubiquitination, c-Myc is also polyubiquitinylated by the SCF-SKP2 ubiquitin ligase complex [80, 81]. SKP2 and other subunits of the SCF-SKP2 complex initially interacted with c-Myc, which synergistically leads to c-Myc ubiquitination, proteasomal degradation and inhibition of its transcriptional activity, thereby governing its regulatory downstream under a tightly controlled fashion [82]. Accordingly, SKP2 is recognized as an oncogene, and amplified in a subset of cancers [83]. However, the direct evidence of SKP2 and c-Myc protein levels correlation is missing, which should be further explored.

c-Myc acetylation: Lys323, located within the nuclear localization sequence domain (NLS), is modified by both p300 and mGCN5 [84]. However, it remains unclear whether the lysine acetylation of c-Myc affects its binding sites for specific interaction partners, including TRRAP (transformation/transcription domain-associated protein), STAGA (SPT3-TAF9-GCN5L acetylase), and TIP60 (Tat-interactive protein 60 kDa, also termed KAT5) histone acetyltransferase complexes *etc*. Since lysine residue can be modified by both ubiquitination and acetylation, these two modifications can potentially interfere with each other. Indeed, activation of lysine acetylation reduces lysine ubiquitination of c-Myc and enhances its

stability [85, 86, 87]. Thus, ubiquitination and acetylation are tightly interconnected, not only in regulating c-Myc protein stability but potentially also in controlling its association of cofactors.

3.2 YAP/TAZ

The Hippo pathway plays significant roles in modulating cell proliferation, cell fate and organ size under normal physiological conditions [88, 89, 90]. It has been emerging as critical players of tumorigenesis. The deregulation of transcriptional coactivators YAP (Yes-associated protein) and WWTR1 (TAZ) is critical for cancers [91], and the hyperactivation and overexpression of YAP/TAZ have been tightly linked to various cancer types, including breast cancer [92, 93], bladder cancer [94], liver cancer [95], squamous cell carcinoma [96], Ovarian cancer [97], and non-small cell lung cancer [98] *etc.* Several mechanisms, including transcriptional upregulation and post-transcriptional activation, could lead to hyperactivation of YAP/TAZ.

3.2.1 Transcriptional regulation of YAP/TAZ—

It has been shown that NF-κB transcription factors directly bind to YAP and TAZ promoters and regulate YAP and TAZ transcription in U2OS cells [54]. However, additional evidence in other cancer types is needed to confirm that NF-κB could regulate YAP/TAZ expression. In addition, in pancreatic ductal adenocarcinoma (PDAC) cells, eIF5A-PEAK1 signaling has been shown to contribute to the elevated YAP/TAZ protein levels, but the intermediate factor responsible for YAP/TAZ gene expression remains unknown [99].

3.2.2 Post-transcriptional regulation of YAP/TAZ

YAP/TAZ phosphorylation: YAP/TAZ is post-transcriptionally phosphorylated and deactivated by kinases LATS1 and LATS2, which are phosphorylated and activated by MST1 and MST2, as the core regulation of the canonical Hippo pathway (Figure 2). Deregulation of these kinases lead to YAP/TAZ dephosphorylation and persistent accumulation in the nucleus [89, 100]. Once in the nucleus, YAP/TAZ binds to DNA-binding transcription factors, most notably TEADs (TEAD1, 2, 3, 4) [101], and could also associate with AP1 [102], RUNXs [90], p73, β-catenin and ERBB-4 (EGFR family member v-Erb-b2 avian erythroblastic leukemia viral oncogene homolog 4) (Figure 2) [103]. Several new upstream regulators of Hippo pathways have also been revealed recently, which might offer new targets as potential cancer therapeutics. For example, NUAK2 has been identified as a direct suppressor of Hippo pathway, and functions in a feed forward loop and promptly induces YAP/TAZ nuclear translocation, binding with transcriptional partners and concurrent cancer cell and tumor growth [6].

YAP/TAZ ubiquitination: YAP/TAZ has also been shown to be dynamically ubiquitinated and deubiquitinated. Ubiquitination of YAP/TAZ could direct the proteins for proteinase degradation. In human glioma cells, YAP is ubiquitinated by β-TrCP E3 ubiquitin ligase and the interaction could be disrupted by ACTL6A, which leads to YAP stabilization and nuclear accumulation [104]. Hence, the hyperactivation of YAP may be responsible for ACTL6A's role in promoting glioma cells proliferation, migration, and invasion [104]. OTUB2, a deubiquitinating cysteine protease, has been shown to deubiquitinate and activate

YAP/TAZ in RAS-transformed MCF10A cells, which is dependent on poly-SUMOylation of OTUB2 on lysine 233 (Figure 2) [105]. A yet-unknown SUMO-interacting motif (SIM) in YAP and TAZ was required for the association of YAP/TAZ with SUMOylated OTUB2. Importantly, EGF and oncogenic KRAS induce OTUB2 poly-SUMOylation and thereby activate YAP/TAZ. The study revealed a novel mechanism, in which YAP/TAZ activity is induced by oncogenic KRAS [105]. Furthermore, YAP undergoes nonproteolytic, lysine 63 (K63)-linked polyubiquitination by the SCF(SKP2) E3 ligase complex (SKP2) and deubiquitination by the deubiquitinase OTUD1 (Figure 2). The non-proteolytic ubiquitination of YAP induces its binding with transcription factor TEAD1, thereby retaining YAP's nuclear localization, transcriptional activity, and growth-promoting activity, which is independent of classical Hippo pathway [106].

3.3 β-catenin

Nuclear accumulation of β-catenin has been manifested in various tumors, and is inevitably associated with tumor progression and metastasis. Therefore, precise and highly orchestrated regulation of β-catenin at the transcriptional and posttranslational levels is critical for cancer.

3.3.1 Oncogenic mutations of β-catenin—

Gain-of-function mutations of β-catenin that lead to stabilized β-catenin have been frequently found in cancers of skin, prostate, ovary, liver, colon, and the endometrium [107, 108, 109, 110]. For example, in pilomatricomas, mutations in the N-terminal segment of β-catenin including S33F (TCT→ TTT), S33Y (TCT→ TAT), S37C (TCT→ TGT), S37F (TCT→ TTT) and T41I (ACC→ ATC) leads to the inhibition of GSK-3-mediated phosphorylation of β-catenin and its subsequent ubiquitination and degradation. Stabilized β-catenin leads to persistent accumulation in the cells [109]. In castrate-resistant prostate cancer (CRPC), β-catenin forms complex with AR, and potentiates AR signaling [111]. In addition, MDA PCa 118a, MDA PCa 118b prostate cancer cells carry β-catenin D32G mutation, which leads to enhanced nuclear localization of β-catenin and increase of its downstream target gene HAS2 (hyaluronan synthase 2) expression [110].

3.3.2 Posttranslational regulation of β-catenin

β-catenin phosphorylation: In the absent of WNT ligands, WNT receptor complexes (Fz/LRP/CKI γ/Axin/GSK3) fail to bind β-catenin, CK1 and GSK3α/β sequentially phosphorylate β-catenin (Figure 3) [112]. Phosphorylated β-catenin is then ubiquitinated by the F box/WD repeat protein β-TrCP, a component of a dedicated E3 ubiquitin ligase complex, subsequently leading to its rapid degradation by the proteasome (Figure 3) [112]. In contrast, in the presence of WNT ligands, β-catenin degradation is blocked, which leads to nuclear translocation of β-catenin and its binding with T-cell factor (TCF) and lymphoid enhancer-binding protein (LEF) and activation of their target gene transcriptions, including c-myc, cyclin D-1 and metalloproteinase, which are essential regulators of cell growth, proliferation and EMT transition [10, 109, 113].

3.4 Interplays among YAP/TAZ, c-MYC and β-catenin

β-catenin has been shown to induce c-Myc expression by activating c-myc promoter, which harbors several TCF-4 (T-cell factor 4) binding sites (Figure 4). It is also known that

Wnt signaling, TGFβ signaling, NO (Nitric oxide), 1,25-$(OH)_2$-D_3 (1,25-dihydroxyvitamin D_3) signaling, estrogen-ER (estrogen receptor) signaling, Androgen-AR (androgen receptor) signaling, and mTOR signaling all converge to β-catenin to regulate c-Myc expression [61]. Meanwhile, YAP/TAZ could bind to β-catenin, which is vital for β-catenin-TCF medicated c-myc transcription [103, 114, 115]. At the protein level, cytoplasmic YAP may directly sequester β-catenin into the cytoplasm (Figure 4). On the other hand, cytoplasmic TAZ may sequester DVL2 to impede its activity in promoting β-catenin accumulation in the condition of Wnt stimulation [116]. Additionally, YAP directly increased β-catenin level, which may due to the blocking of β-Trcp-dependent β-catenin degradation (Figure 4) [115]. Recently, we and others have shown that nuclear YAP/TAZ could interact with Groucho/TLE to inhibit T-cell factor (TCF)-mediated transcription in intestinal stem cells, suggesting that the crosstalk between these pathways are extensive and complicated [117].

Taken together, targeting these signaling nodes may lead to promising therapeutic strategies in cancer treatment. Traditionally, transcription factors were considered as “undruggable” due to the difficulties of targeting protein-DNA binding and protein-protein interaction where defined small molecule binding pockets might be lacking [2, 3]. With the elucidation of above-mentioned new knowledge of YAP/TAZ, c-Myc and β-catenin modifications and regulation, the inventions of potential therapeutic agents could be possible.

4. Targeting transcription factors for drug discovery

4.1 Targeting posttranslational regulation

4.1.1 YAP/TAZ—In renal cell carcinoma (RCC), dasatinib, a second-generation tyrosine kinase inhibitor suppressed RCC cell viability in *vitro* and decreased tumor growth *in vivo*. Mechanistically, dasatinib directly inhibits Src kinase, and subsequently activates Src-JNK-LIMD1-LATS signaling cascade, leading to YAP phosphorylation and suppression of YAP/TAZ-TEAD target genes, (such as CTGF, Cyr61, and AJUBA *etc.*) (Table 1) [118]. In MDA-MB-231, H1299 and HCT-116 cells, statins blocked YAP/TAZ nuclear localization and transcriptional responses via inhibition of HMG-CoA reductase, the rate-limiting enzyme of the mevalonate cholesterol biosynthesis pathway. Such inhibition leads to reduction of geranylgeranyl pyrophosphate levels, which is required for membrane localization and activation of RHO GTPases, a key upstream regulator of YAP [119, 120, 121]. Norcantharidin (NCTD) inhibited non-small cell lung carcinoma (NSCLC) progression and metastasis via cell cycle arrest, enhancing apoptosis and inducing senescence dependent on the modulation of YAP’s translocation between cytoplasm and nucleus (Table 1) [122]. In addition, the clinical drug dobutamine has been demonstrated to induce the YAP accumulation in the cytosol and YAP-dependent gene transcription in human osteoblastoma U2OS cells independent of Hippo pathway [123], which has been recapitulated in human gastric adenocarcinoma SGC-7901 cells [124].

4.1.2 β-catenin—In non-small-cell lung cancer A549/Wnt2 cells (with overexpression of human Wnt2), GDK-100017, a 2,3,6-trisubstituted quinoxaline derivative, suppressed cell proliferation via arresting cell cycle, which is associated with its reduction on β-catenin nuclear localization, β-catenin-TCF/LEF-dependent transcriptional activity and

target genes expression (cyclin D1 *etc.*) (Table 1) [125, 126]. In colorectal cancer cell line SW480, the natural flavonoid genistein inhibited cell proliferation via suppressing β-catenin/TCF transcriptional activity. Mechanistically, genistein promoted the ubiquitination and degradation of β-catenin through targeting the phosphorylation of AKT-GSK3β-β-catenin signaling cascade (Table 1) [127, 128]. In colorectal cancer HCT116 cells and associated xenografted tumor, isopropyl 9-ethyl-1-(naphthalen-1-yl)-9H-pyrido[3,4-b]indole-3-carboxylate (Z86) inhibited cell growth and tumor growth through suppression of GSK3β (Ser9) phosphorylation and activation of its activity and subsequently promoting the phosphorylation and degradation of β-catenin (Table 1) [129, 130].

4.2 Targeting protein-protein interactions

4.2.1 c-Myc—In a panel of neuroblastoma cell lines and xenograft tumor models, MYCMI-6 was identified as a potent and selective inhibitor of c-Myc/MAX interaction, binding exclusively to the c-Myc bHLHZip domain and suppressing c-Myc-driven transcription [131]. Phenotypically, MYCMI-6 inhibits tumor cell growth in a c-Myc-dependent manner and promotes massive apoptosis in tumor tissue. c-Myc inhibitor 10074-G5 (N-([1,1′-biphenyl]-2-yl)-7-nitrobenzo[c][1,2,5]oxadiazol-4-amine) targets a hydrophobic domain of c-Myc and perturbs the interaction of c-Myc and Max (Table 1). The ortho-biphenyl group 10074-G5 replaced by a para-carboxyphenyl group yielded the new inhibitor JY-3-094, which exhibits improved selectivity over Max–Max homodimers and physicochemical properties [132]. Another analogue of 10074-G5, named 3jc48-3, is 5-times more potent in blocking c-Myc–Max dimerization, leading to inhibition of the proliferation of c-Myc hyperactive human leukemia HL60 and Burkitt's lymphoma Daudi cells (Table 1) [133]. A novel small-molecule inhibitor of c-Myc, KJ-Pyr-9, has been identified from a Kröhnke pyridine library. KJ-Pyr-9 disrupted c-Myc–MAX complex formation in cells, leading to blockage of c-Myc-induced oncogenic transformation in cell culture and suppression of the growth of a xenotransplant of MYC-amplified human cancer cells (Table 1) [134]. In bladder cancer cells and xenograft tumor model, c-Myc/MAX binding inhibitor KSI-3716 decreased the expression of c-Myc target genes, such as cyclin D2, CDK4 and hTERT, exerted cytotoxic effects by inducing cell cycle arrest and apoptosis and blocked tumor growth [135]. In a Burkitt lymphoma P493-6 cell model, sAJM589, a novel small molecule c-Myc inhibitor, potently perturbs the formation of c-Myc–Max heterodimer, preferentially inhibits transcription of c-Myc target genes and inhibited proliferation of P493-6 cells (Table 1) [136]. However, all these inhibitors lack sufficient potency, selectivity and toxicity profile to be advanced to human clinical testing. Further efforts to develop specific inhibitors are still needed.

4.2.2 YAP/TAZ—In gastric cancer, downregulation of VGLL4 was correlated with upregulation of YAP and YAP/TEADs target genes, and VGLL4 directly competes with YAP for binding to TEADs. Importantly, VGLL4's tandem Tondu (TDU) domains are not only necessary but also sufficient for its inhibitory activity toward YAP. A peptide mimicking this function of VGLL4 (super-TDU) potently suppressed tumor growth *in vitro* and *in vivo*. Mechanistically, super-TDU disrupts of YAP-TEADs interaction and YAP-TEADs target genes, including *CTGF*, *Cyr61*, and *CDX2* (Table 1) [137]. In human hepatocellular carcinoma (HCC), verteporfin, a benzoporphyrin derivative, inhibited cell

growth of HCC cells via disruption of YAP-TEAD binding and expression of their target genes (Table 1) [138, 139]. In human retinoblastoma cell lines (Y79 and WERI), verteporfin dose-dependently suppressed cell proliferation and migration, and inhibited tumor angiogenesis through inhibition of YAP-TEAD binding and downstream target genes, such as c-myc, CTGF, Cyr61, and VEGF-A (Table 1) [140]. YAP/TAZ drives cancer cell survival and BRAF inhibitor resistance in melanoma [141, 142]. Compared with BRAF inhibitor (BRAFi) sensitive melanoma cancer stem cells (MCS cells), YAP1, TAZ and TEAD protein levels were significantly increased in BRAFi resistant MCS cells, which is accompanied by elevated cell survival, spheroid formation, invasion in matrigel assays, and tumor formation [143]. In xenograft tumor model, verteporfin mitigated YAP1/TAZ level induced by BRAFi resistance, restored BRAF inhibitor suppression of ERK1/2 signaling and reduced tumor growth in BRAFi-resistant tumors [143]. However, it remains unknown how verteporfin modulates YAP/TAZ and TEAD functions, which warrants future explorations before its further applications.

Most recently, our lab has identified a specific inhibitor of TEAD palmitoylation MGH-CP1, which attenuated the interaction between YAP and TEAD and its downstream regulatory events through inhibition of TEAD autopalmitoylation, which provided new insights of targeting these transcription factors [117].

4.2.3 β-catenin—ICG-001, a small molecule that down-regulates β-catenin-TCF signaling, specifically binds to cyclic AMP response element-binding protein (CBP) and disrupts the β-catenin/CBP interaction (Table 1) [144]. Phenotypically, ICG-001 induces apoptosis and reduces growth of human colon carcinoma SW480, SW620, and HCT116 cells, but not normal colon cells *in vitro*, and is efficacious in the xenograft mouse models of colon cancer. Likewise, KRAS activation has been found to induce the CBP/β-catenin interaction in pancreatic cancer, and ICG-001 sensitizes pancreatic cancer cells and tumors to gemcitabine (deoxycytidine analog) treatment, possibly through antagonizing CBP/β-catenin interaction [145]. NLS-StAx-h, a selective, cell permeable, stapled peptide inhibitor, suppresses the interaction between β-catenin and TCF/LEF transcription factors and inhibition of target genes transcription (Table 1). It showed good cellular uptake and profound inhibitory effects on proliferation and migration of colorectal cancer cell lines DLD-1 and SW-480 [146].

An RNAi-based modifier screening strategy was exploited for the identification of specific β-catenin responsive transcription (CRT) inhibitors without affecting degradation of β-catenin. These inhibitory compounds functioned specifically in antagonizing the transcriptional function of nuclear β-catenin, such as blocking β-catenin-TCF induced target genes and phenotypes in various mammalian and cancer cell lines (Table 1) [147]. It is of great interest to note that these CRT inhibitors are specifically cytotoxic to human colon tumor biopsy cultures as well as colon cancer cell lines with deregulated Wnt signaling. Novartis collections yielded eight compounds with a dose-dependent inhibition of β-catenin-TCF binding and target gene transcription from approximately 7000 natural products and 45000 synthetic compounds. Two structurally related compounds (PKF115-584 and CGP049090) proved to be effective in suppressing Wnt reporter gene activity and colon cancer cell proliferation, among which PKF115-584's inhibitory effect on Wnt signaling

was confirmed in xenograft models of human multiple myeloma (Table 1) [148]. Henryin, an ent-kaurane diterpenoid isolated from *Isodon rubescens* var. *lushanensis*, selectively inhibits the proliferation of human colorectal cancer HCT116 cells through inhibiting the association of β-catenin/TCF4 transcriptional complex and the transcription of target genes, such as Cyclin D1 and C-myc (Table 1) [149]. In 2019, a group of small molecule inhibitors specifically disrupting the β-catenin/TCF protein-protein interaction without affecting the β-catenin/E-cadherin and β-catenin/APC interactions have been synthesized and was reported to inhibit migration and invasiveness of Wnt/β-catenin-dependent cancer cells [150].

Peptoids, or poly-N-substituted glycines, are a series of peptidomimetic oligomers in which the side chains are presented to the nitrogen atom of the peptide backbone instead of the α-carbons as they are in amino acids. They have been proposed as capable of curbing protein-protein interactions through mimicking motifs of protein secondary structures [151]. Using the Rosetta suite of protein design algorithms, a small library of peptoid–peptide macrocycles has been designed *in silico*, based on the prediction of binding to β-catenin. Cell based luciferase assays were further used to test their inhibitory effects on Wnt signaling [152]. Interestingly, inhibitors which potently blocking β-catenin/TCF interaction has been identified and significantly inhibit the proliferation of prostate cancer cells *in vitro* and inhibit Wnt signaling *in vivo* in a zebrafish model [152].

4.3 Targeting new allosteric or ligandable site of TF

Allosteric modulation is generally recognized as one of the most direct and efficient ways to govern protein functions. Targeting allosteric or ligandable sites has attracted great attentions for drug development due to their high selectivity and potential to target many previously “undruggable” targets.

Most c-Myc inhibitors perturb the binding of c-Myc and its obligate heterodimerization partner Max through their respective bHLH-ZIP domains. However, the natural triterpenoid celastrol and its derivatives bind to and alter the quaternary structure of the preformed dimer and abrogate its DNA binding (Table 1). Phenotypically, the triterpenoids suppressed the proliferation of multiple myeloma, non-small cell lung cancer and breast cancer cell lines [153]. Using biophysical methods including NMR spectroscopy and surface plasmon resonance, novel, low-molecular-weight, synthetic α-helix mimetics have been designed, which could bind to helical c-Myc in its transcriptionally active coiled-coil structure in association with Max have been designed. These compounds disrupted the heterodimer’s binding to its canonical E-box DNA sequence without causing protein–protein dissociation, and blocked the proliferation of c-Myc-overexpressing cell lines (Table 1) [154].

4.4 targeting TF degradation

4.4.1 c-Myc—In colorectal cancer HCT116 cells, dihydroartemisinin (DHA), the main active metabolite of artemisinin, induced significant apoptosis through promoting the degradation of c-Myc protein (Table 1), which was mitigated by proteasome inhibitor MG-132 or GSK 3β inhibitor LiCl [155]. However, the precise mechanisms of how DHA induces c-Myc degradation require further studies.

4.4.2 β-catenin—Colon carcinoma cells with mutations in the APC (adenomatous polyposis coli) locus or in an allele of β-catenin, have been related to hyperactivation of Wnt signaling. JW55 (a novel TNKS inhibitor) has been identified to stimulate β-catenin degradation, which fulfilled through inhibition of the PARP domain of tankyrase 1 and tankyrase 2 (TNKS1/2) and induction of the β-catenin destruction complex (Table 1) [156]. In concrete, the inhibitory effect of JW55 on TNKS1/2 poly(ADP-ribosyl)ation activity contributes to stabilization of AXIN2 and increased degradation of β-catenin [156]. With a TCF-dependent luciferase-reporter assay, MSAB (methyl 3-{[(4-methylphenyl)sulfonyl]amino}benzoate) was identified as a selective inhibitor of Wnt/β-catenin signaling through its binding and targeting on β-catenin degradation, which is accompanied by downregulation of Wnt/β-catenin target genes and tumor inhibitory effects selectively on Wnt-dependent cancer cells *in vitro* and in mouse cancer models (Table 1) [157]. In colorectal cancer SW480 and SW620 cells and mice xenograft model, YW2065 (1c) exerted excellent anti-tumor effects by stabilizing Axin-1, a scaffolding protein that induces proteasome degradation of β-catenin [158].

4.5 Nucleic acids-based therapy

Genetic methods, such as antisense RNA, RNAi, or CRISPR/Cas based gene therapy can be achieved through inhibition or replacement of a mutated gene, inactivation or reconstruction of a deregulated gene to combat the disease. Due to its specificity, they have drawn great attentions in the past two decades for the treatment of a wide spectrum of cancers.

In human prostate cancer cell lines, such as LNCaP, PC3, and DU145, c-myc-antisense-oligonucleotide, c-myc-As-ODN treatment has shown to time-and dose-dependently reduces DNA synthesis and cell viability (Table 1) [159]. Similarly, in human prostate cancer cell lines, such as LNCaP, PC3, and DU145 cell lines, and PC-3 androgen-independent human prostate cancer xenograft murine model, a novel antisense phosphorodiamidate morpholino oligomer AVI-4126 directly targets c-myc mRNA and reduced its translation, leading to significant apoptosis and growth inhibition in prostate cancer cells and in subcutaneous tumor xenografts (Table 1) [160]. In the LLC1 syngeneic murine lung metastasis tumor model, AVI-4126, a neutral antisense phosphorodiamidate morpholino oligomer (PMO) specifically inhibits c-myc expression and decreased tumor burden, number of tumorlets formed in the lung, decreased mitotic activity but increased rate of apoptosis (Table 1) [161].

G-quadruplexes (G4s) are noncanonical DNA structures that frequently occur in the promoter regions of oncogenes, such as c-myc, and c-myc G4 stabilizer have been demonstrated to mitigate c-myc expression [162, 163, 164]. A core-modified expanded porphyrin analogue, 5,10,15,20-[tetra(N-methyl- 3-pyridyl)]-26,28-diselenasapphyrin chloride (Se2SAP) selectively binds with the c-myc G-quadruplex and inhibits its expression (Table 1) [165]. In multiple myeloma (MM) cells, DC-34, a small molecule significantly decreases c-myc transcription in a G4-dependent manner [166]. The specific contact responsible for affinity and selectivity of MYC G4 and DC-34 was confirmed by NMR spectroscopy. Furthermore, with the aid of structural modification of aryl-substituted imidazole/ carbazole conjugates, a brand-new, four-leaf clover-like ligand IZCZ-3 was synthesized to preferentially bind and stabilize the c-myc G-quadruplex and

suppress c-myc expression (Table 1) [167]. Cellular and physiological studies revealed IZCZ-3's promotive role in cell cycle arrest and apoptosis, thus inhibited cell growth in squamous cell carcinoma SiHa cells and suppressed tumor growth in SiHa xenograft model, mainly through curbing c-myc transcription by exclusive targeting on the promoter G-quadruplex structure.

Wnt/β-catenin signaling mediates cancer immune evasion and resistance to immune checkpoint therapy, in part by blocking cytokines that trigger immune cell recruitment. DCR-BCAT, a nanoparticle drug product containing a chemically optimized RNAi triggers silencing of β-catenin, which significantly increases T cell infiltration and potentiated the sensitivity of the tumors to checkpoint inhibition (Table 1). The combination of DCR-BCAT and immunotherapy yielded significantly greater tumor growth inhibition (TGI) compared to monotherapy in B16F10 melanoma, 4T1 mammary carcinoma, Neuro2A neuroblastoma, and Renca renal adenocarcinoma [168].

Thus, nucleic acid-based approach would be a promising strategy in curbing cancers due to its direct effects on silencing oncogenes. However, the challenge that to what extent an oncogene should be downregulated or upregulated in a controlled manner without side effect ought to be overcome before its clinical trial and application. In addition, delivery and stability of these agents need further improvement. Off-target effects of RNAi-based approach should also be very careful evaluated. With the advancement of cutting-edge gene technologies, like the state-of-the-art technology CRISPR (clustered regularly interspaced short palindromic repeats), specific and precise modulation of genes to antagonize cancers would prosper in the near future.

Conclusion

Transcription factors play vital roles in tumorigenesis. Although technically challenging, directly targeting these important proteins is critical for development of promising therapeutics. The current review summarized the deregulation of three leading transcription factors and co-factors, including YAP/TAZ, c-Myc and β-catenin, such as their transcriptional and post-transcriptional regulation in cancer, which provide insights to design drugs to target these traditionally "undruggable" spot and make it "druggable". However, future exploitation of their precise mechanisms of action, dosage and duration, effectiveness and efficacy in clinical settings are needed to further make them "druggable".

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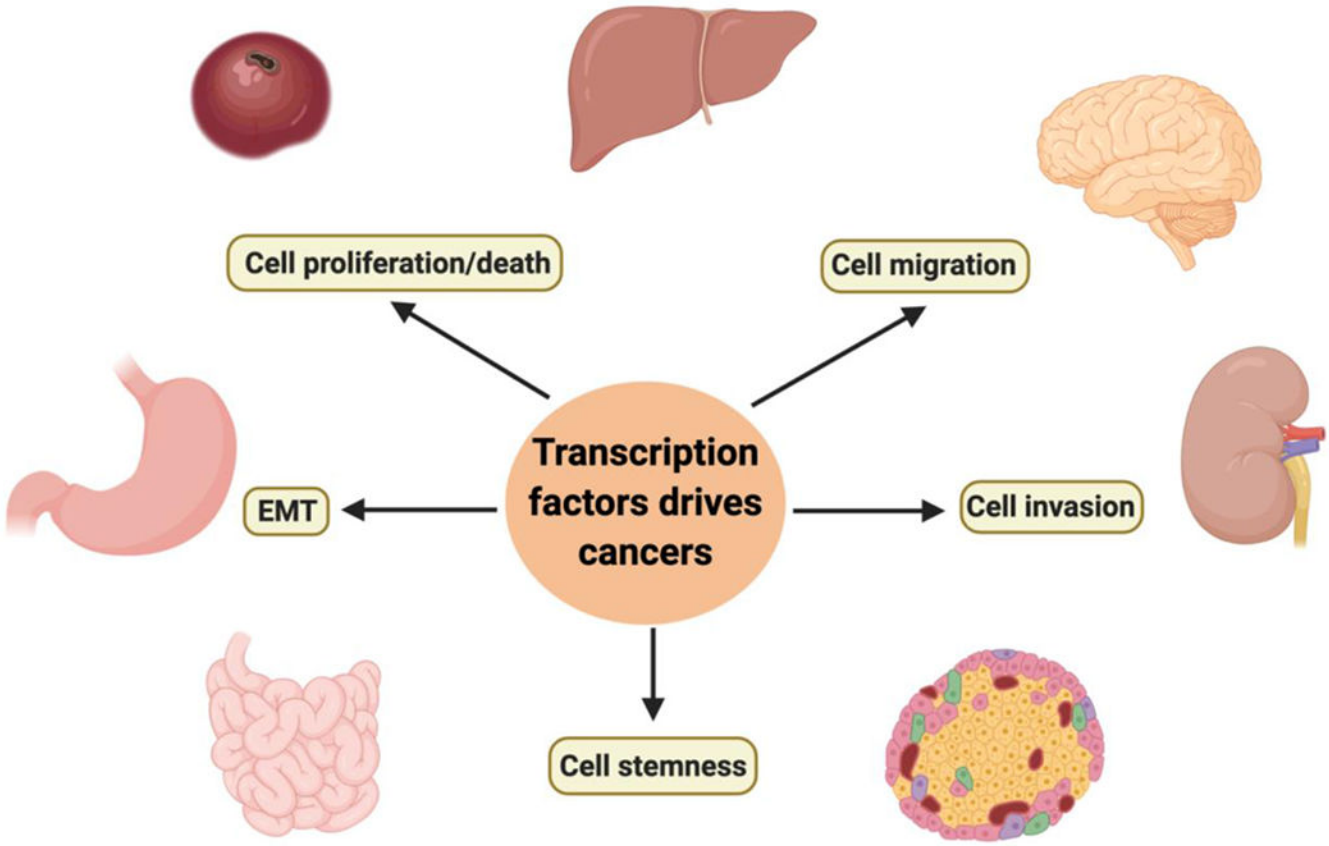

Figure 1. Transcription factors (TFs) drive cancer.

TFs are involved in tumorigenesis via various mechanisms including the regulation of cancer cell proliferation, apoptosis, migration, invasion and “stemness”.

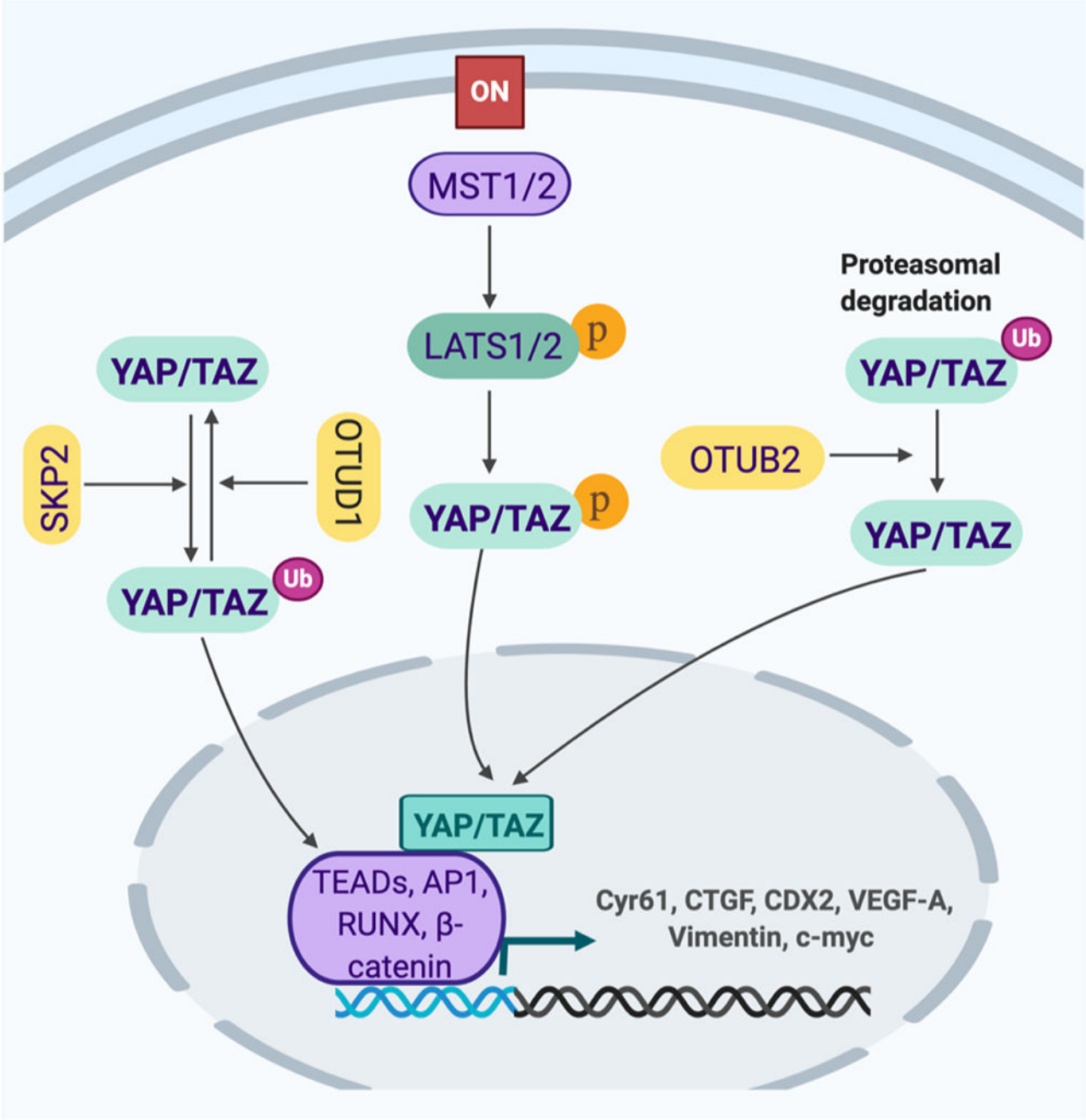

Figure 2. The regulation of YAP/TAZ.

YAP/TAZ could be phosphorylated by LATS1/2, which was controlled by upstream of Hippo pathway. Phosphorylation of YAP/TAZ affects its nuclear translocation and binding with transcription factors, including TEADs, AP1, RUNX and β-catenin, and their target genes, including Cyr61, CTGF, CDX2, VEGF-A, Vimentin, and c-myc *etc*. The ubiquitination of YAP/YAZ was dynamically controlled by SKP2, OTUD1 and OTUB2. Ubiquitination of YAP/TAZ affects its proteasomal degradation and translocation to nucleus.

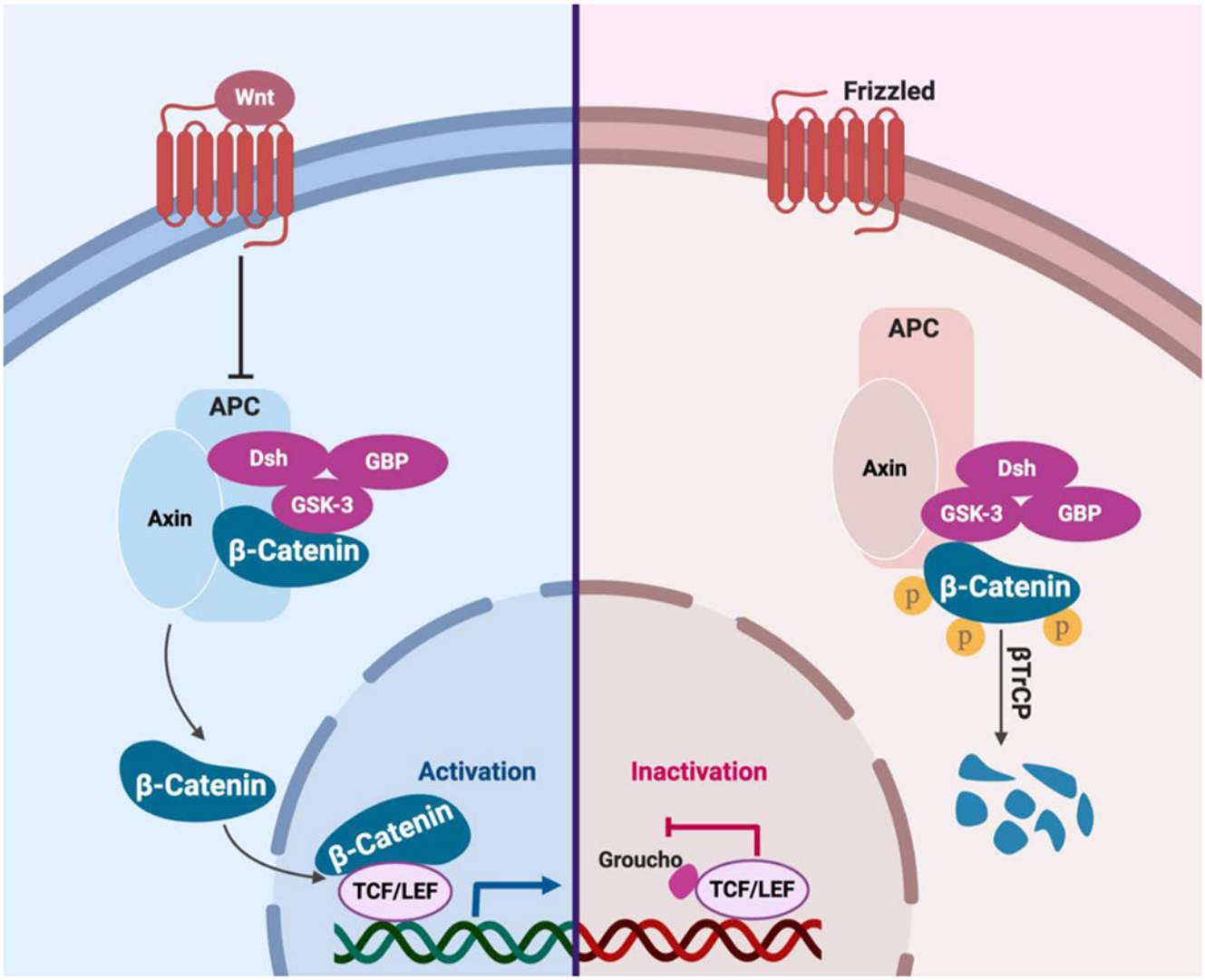

Figure 3. The regulation of β-catenin.

β-catenin was tightly controlled by Wnt signaling, which affects its association with complexes APC, Dsh, GBP, GSK-3. When Wnt signaling is triggered, β-catenin will be shuttled into nucleus to initiate its binding with transcription factors TCF/LEF and target genes expression. When Wnt signaling is frizzled, β-catenin will be phosphorylated and subjected to degradation.

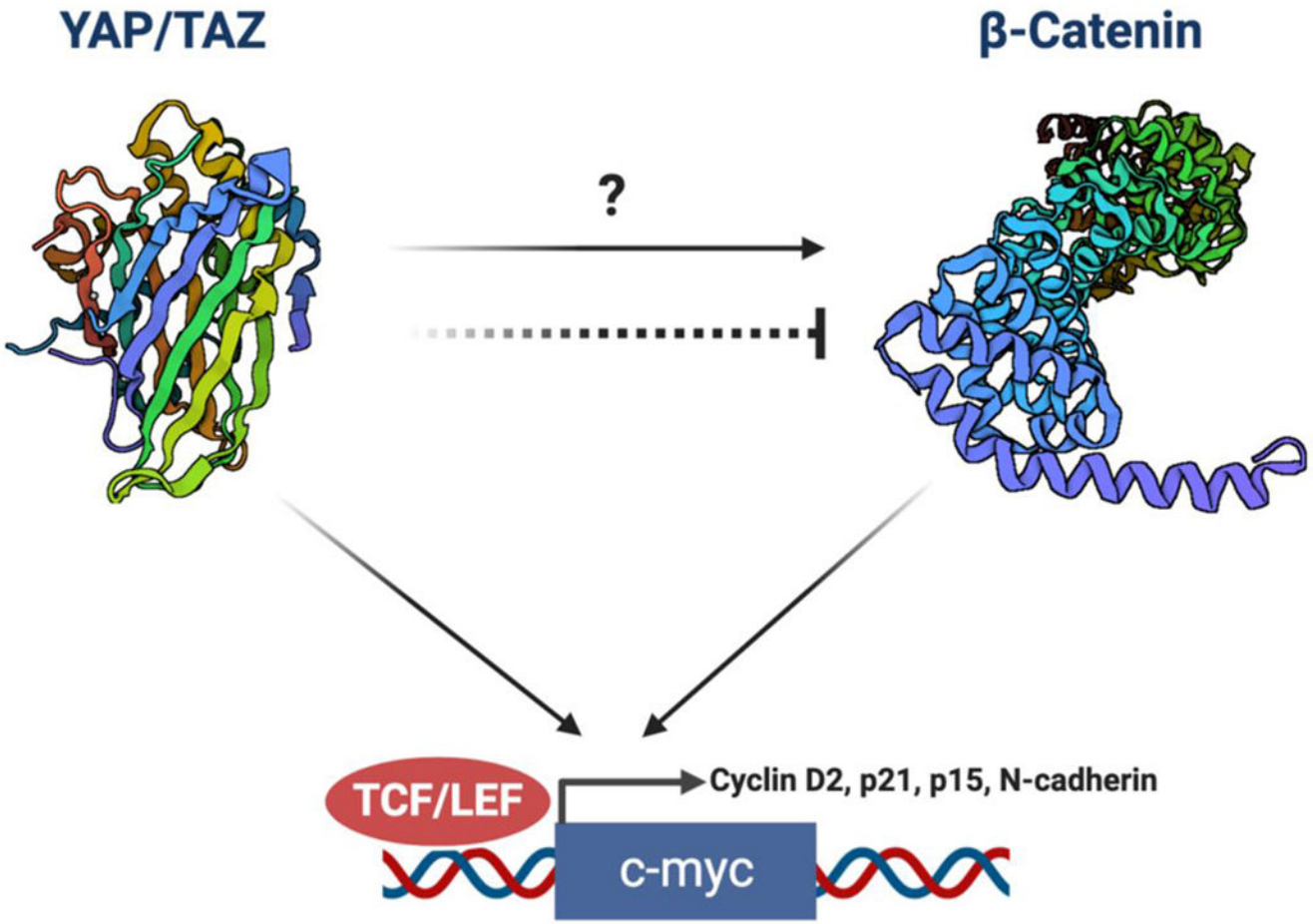

Figure 4. Interplays among YAP/TAZ, β-catenin and c-Myc.

YAP/TAZ could affect β-catenin protein levels, either promotion or suppression. However, the mechanism remains unknown, which has been labeled with question mark. At the same time, YAP/TAZ and β-catenin could promote c-myc gene expression.

Table 1

Summary of drugs targeting on YAP/TAZ, β-catenin and c-Myc

Inhibitors	Target	References
Targeting Posttranslational Regulation		
Dasatinib	YAP phosphorylation	118
statins	YAP phosphorylation	119,120,121
norcantharidin (NCTD)	YAP phosphorylation	122
dobutamine	YAP phosphorylation	123,124
GDK-100017	β-catenin phosphorylation	125,126
genistein	β-catenin ubiquitination	127,128
Z86	β-catenin phosphorylation	129,130
Targeting Protein-Protein Interactions		
MYCMI-6	c-Myc/MAX interaction	131
10074-G5	c-Myc/MAX interaction	132
JY-3-094	c-Myc/MAX interaction	133
3jc48-3	c-Myc/MAX interaction	134
KJ-Pyr-9	c-Myc/MAX interaction	135
KSI-3716	c-Myc/MAX interaction	136
sAJM589	c-Myc/MAX interaction	137
super-TDU	YAP-TEADs interaction	138
Verteporfin	YAP-TEADs interaction	139,140
MGH-CP1	YAP-TEADs interaction	117
ICG-001	β-catenin-CBP interaction	145
NLS-StAx-h	β-catenin-TCF interaction	146
CRT inhibitors	β-catenin-TCF interaction	147
PKF115-584	β-catenin-TCF interaction	148
CGP049090	β-catenin-TCF interaction	148
Henryin	β-catenin-TCF4 interaction	149
peptoid–peptide	β-catenin-TCF interaction	152
Targeting New Allosteric or Ligandable site		
celastrol	c-Myc-DNA interaction	153
α-helix mimetics	c-Myc-DNA interaction	154
Targeting TF Degradation		
Dihydroartemisinin	c-Myc	155
JW55	c-Myc	156
MSAB	β-catenin	157
YW2065	β-catenin	158
Nucleic Acids-Based Drugs		

Inhibitors	Target	References
c-myc-As-ODN	c-Myc	159
PMO	c-Myc	161
Se2SAP	c-Myc	165
DC-34	c-Myc	166
IZCZ-3	c-Myc	167
DCR-BCAT	β-catenin	168