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The Regulation of YY1 in Tumorigenesis and its Targeting Potential in Cancer Therapy

Guangchao Sui

Department of Cancer Biology and Comprehensive Cancer Center, Wake Forest University School of Medicine, Winston-Salem, North Carolina

Abstract

Yin Yang 1 (YY1) is a multifunctional protein and regulates various processes of development and differentiation. Increasing evidence indicates an essential role of YY1 in tumorigenesis. As a transcription factor, YY1 regulates the expression of numerous genes that are mostly involved in cancers. YY1 can either activate or repress the target genes, depending on the cofactors that it recruits. Importantly, most studies to date suggest a proliferative or oncogenic role of YY1 in cancer development. Meanwhile, overexpression of YY1 has been observed in different types of cancers and YY1 has been proposed as a potential prognostic marker of these cancers. A reasonable hypothesis is that upregulated YY1 leads to unbalanced expression of its target genes and in turn initiates or arguments tumorigenesis. Ample studies indicate that YY1 exerts broad regulation in various epigenetic events, especially histone acetylation and methylation. Since most cancers exhibit deregulated epigenetics, overexpressed YY1 may contribute to these aberrant epigenetic statuses in cancer cells. The epigenetic processes regulated by YY1 are reversible. Therefore, it is possible that targeting YY1 may adjust various deregulated epigenetic events in cancer cells, restore the normal epigenetic conditions and consequently block cancer development. This review summarizes cancer-related studies of YY1 and discusses the potential of YY1 as a target of cancer therapy.

Keywords: Cancer therapy; Epigenetic regulation; Tumorigenesis; YY1

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Correspondence: Guangchao Sui, Ph.D., Department of Cancer Biology, Wake Forest University School of Medicine, Hanes 4052, Medical Center Boulevard, Winston-Salem, NC 27157, USA. Tel. 336-713-0052, Fax. 336-716-0255. email: gsui@wfubmc.edu

1. Introduction

Aberrant expression and function of transcription factors play vital roles in oncogenic transformation of cells in different tissues. These factors interact with specific DNA elements and other protein cofactors to form transcriptional machinery that can either activate or repress the expression of essential genes involved in tumorigenesis. The altered or enhanced functions of these factors contribute, either directly or indirectly through other downstream pathways, to some or all of the cancer hallmarks, including insensitivity to antigrowth or apoptotic signals, self-sufficient growth signals, sustained angiogenesis, limitless replicative potential and invasive or metastatic capability (1).

Yin Yang 1 (YY1) is a ubiquitously expressed protein in all tissues and highly conserved in many different species. YY1-related studies keep accumulating and have branched to almost all existing research areas with over 700 papers available to date. Therefore, it is unrealistic to embrace all of these publications and even every research field in this review. For a comprehensive understanding of YY1 gene, protein and its regulatory models, please refer to the two excellent review articles (2,3) from the pioneers of YY1 studies, Drs. Shi and Seto. Some other reviews also discussed the role of YY1 in cancer development (4-6). The focus of this article is the cancer-related function and regulation of YY1. The potential of YY1 as a therapeutic target of cancer therapy is also discussed.

1.1. Discovery of YY1

YY1 was initially discovered in 1991 by Shi et al as a transcriptional factor binding to the P5 promoter of adeno-associated virus (7). The inhibitory function of YY1 to this promoter can be converted to an activating effect upon association with a viral protein, E1A. By its very name, "Yin

Yang" represents its two opposite capabilities of either repressing or stimulating gene transcription, and both functions have been demonstrated in numerous studies. In addition, YY1 can act as an initiator to direct and activate gene transcription (8). Two subsequent studies also reported subcloning of YY1 cDNA (NF-E1 and delta, respectively) and observed the regulatory role of YY1 in gene transcription. One of the studies demonstrated that YY1 is a binding protein of the negative-acting segment of the immunoglobulin kappa E3' enhancer (9). The other study showed that YY1 acts as a transcription activator of two genes coding ribosomal proteins rpL30 and rpL32, since the deletion of YY1 binding elements dramatically reduced their expression (10). In 1992, YY1 (named as UCRBP) was identified as a binding protein of the upstream conserved region in Moloney murine leukemia virus (MuLV) and negatively regulated the MuLV promoter activity (11).

1.2. Expression and general function of YY1

YY1 is ubiquitously expressed in all tissues and highly conserved among different species. Currently, YY1 cDNAs have been cloned from many species, including human (7), mouse (10,12), rat (13), chicken (14), zebrafish (15) and xenopus (16). Drosophila has two orthologs of YY1, pleiohomeotic (*pho*) and *pho* like (*phol*) (17,18), which have high degrees of similarity in the zinc finger regions with those of human YY1. The Seto group discovered a protein called YY2 that has 65% similarity in DNA sequence and 56% similarity in protein sequence to human YY1 (19). Due to the pronounced similarity at the zinc finger regions of these two proteins, YY2 binds to the same consensus sequence as YY1 but with much lower affinity (20). A latter report suggested that YY2 is a retroposed copy of YY1 that has been inserted into another gene locus (21).

A number of studies demonstrated the essential roles of YY1 in normal biological processes, such as embryonic development and gene imprinting. Donohoe et al attempted to generate YY1 knockout mice, but discovered that YY1 deletion is lethal to mouse embryonic development (22). The complex of YY1 and a chromatin isolator, CTCF, regulates the X chromosome binary switch by binding to a non-coding locus, Tsix that controls chromosome pairing and counting (23). Meanwhile, YY1 has been shown as a critical regulator of early B-cell development (24), genomic imprinting (25), and neuron development and differentiation (26,27).

Affar et al presented a comprehensive study on the essential dosage-dependent functions of YY1 in embryonic development and cell cycle progression (28). They provided clear evidence that decreases of YY1 impair the growth and viability of mouse embryos in a dose-dependent manner. In addition, levels of YY1 tightly correlate with cell proliferation, and its depletion prevents cytokinesis and increases cellular sensitivity to various apoptotic stimuli.

2. YY1 as a transcription factor

The models of YY1-mediated gene repression and activation have been described in previous reviews (2,3). To repress the expression of a gene, the association of YY1 with a target promoter may cause activator displacement, interference with the activator's function or recruitment of corepressors. When activating a target gene, YY1 may directly act as an activator, inhibit the activity of repressors or recruit coactivators.

As a member of the GLI-Krüppel class of zinc finger proteins, YY1 has been reported to regulate the expression of a large cohort of genes and/or promoters. The four zinc fingers at the C-terminal of YY1 (Figure 1) are responsible for binding to its target promoters. The YY1 binding motif was initially recognized as having two types of cores,

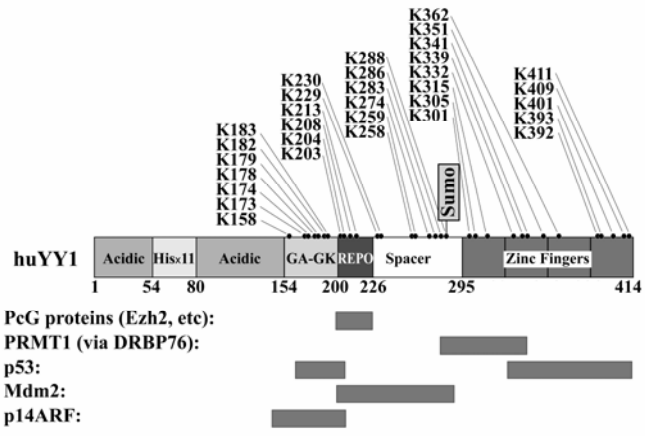

Figure 1. Domain structure of YY1 and interaction regions of histone methyltransferases and p53-related proteins. The YY1 sequence is based on the NCBI access number Z14077. All 32 lysine (K) residues are labeled on the top and the SUMO conjugation site, K288, is indicated. The REPO motif of YY1 is necessary and sufficient in recruiting PcG proteins, such as Ezh2, to YY1-targeted promoters to promote histone H3-K27 methylation and establish gene silencing (68). The residues 261-333 of YY1 are responsible for recruiting PRMT1 via DRBP76 to methylate histone H3-R4 (65). The interactions domains of p53, Mdm2 and p14ARF were mapped by *in vitro* protein binding experiments (47). For the binding domains of other YY1-interacting proteins, please refer to Seto's review (3).

ACAT and CCAT (29). Recently, longer DNA binding motifs were also identified (30). In an earlier report on the prevalence of YY1 binding sites, over 7% of vertebrate genes and 24% of viral genes contained YY1 binding elements (31), suggesting a ubiquitous regulation of YY1 in different biological processes. Interestingly, although YY1 was first recognized as a transcription factor, one report indicated that the localization of YY1 is cell cycle-dependent (32). In this report, the authors presented that YY1 mainly stayed in cytoplasm at G1 phase, but translocated into the nucleus at the early and middle S phases and then moved back to the cytoplasm at late S phase. The entry of YY1 into the nucleus coincided with increased YY1-DNA association and DNA/histone synthesis, suggesting a regulatory role of YY1 in cell division and proliferation. The function of YY1-regulated genes covers cell growth, proliferation, cytokinesis, apoptosis, development and differentiation, indicating that YY1 plays an essential role in coordinating multiple biological pathways through a complex transcriptional network (28).

In this review, I have categorized these targets into two groups based on the regulatory consequence of YY1: activation and repression. Because this review focuses on the genes involved in tumorigenesis, each group has also been divided into three subgroups based on the functions of the targeted genes or promoters (Tables 1.1 and 1.2).

2.1. YY1-activated gene expression

Many YY1-activated genes exert oncogenic or proliferative effects on cells (Table 1.1). The regulation of YY1 on some of these genes is reminiscent of its originally observed "Yin Yang" effects on the P5 promoter of adenovirus (7). c-Myc is the first oncogene that was demonstrated to be activated by YY1 (33). In this study, YY1 was shown to increase the levels of two major c-Myc mRNA transcript variants. A recent report further delineated the mechanism underlying this regulation and revealed that the viral oncogenic protein E1A plays a role in YY1-mediated activation of c-Myc expression. E1A disassociates the YY1-p300-HDAC3 complex, which initially inhibits c-Myc expression, and makes the c-Myc promoter more accessible by increasing regional histone acetylation (34). A similar scenario also occurs in the regulation of YY1 on another proto-oncogene, c-fos. Although YY1 can block c-fos gene expression through a direct interaction with the transcription complex ATF/CREB (35), this inhibition is also inverted by E1A, which disrupts the ATF-CREB-YY1 complex and changes YY1 from a repressor to an activator of c-fos gene (36). Consistently, YY1 stimulates the association of serum response factor (SRF) with the c-fos serum response element (37), suggesting an activating function to c-fos gene expression. These studies indicate that YY1 does not activate, or may even repress, these proto-oncogenes in normal conditions. However, when stimulated by oncogenic signals, YY1 will facilitate tumorigenic processes.

Among the targets of YY1, several other genes also code oncogenic proteins. YY1 is highly expressed in breast cancer and stimulates the expression of ERBB2 (38,39). ERBB2 (also known as Her2 and neu) is overexpressed in about 30% of breast cancers and generally correlated with a poor prognosis (40). Since overexpressed ERBB2 contributes to increased aggressiveness of cancer cells, it is a notable target of breast cancer therapy. Increased ERBB2 partly results from its gene amplification (41), which might put the physiological significance of its upregulation by YY1 in doubt. However, a recent study showed that YY1 protein levels are inversely correlated with ERBB2 gene amplification in breast tumors (39), suggesting that YY1 may play a role in ERBB2 upregulation when this gene is not amplified.

As a prosurvival endoplasmic reticulum (ER) chaperone, GRP78/BiP has been shown in multiple studies to possess oncogenic properties by stimulating tumor proliferation, survival, metastasis, and resistance to various therapies (42). Baumeister et al demonstrated that YY1 associates with the GRP78 promoter only in conditions of ER stress. YY1 acts as an essential coactivator of ATF6 and recruits histone H4 methyltransferase PRMT1 (Figure 1) to enhance GRP78 gene expression (43). This study revealed an important role of YY1 in regulating stress-induced modification of chromatin and promoting cell survival response to stress conditions.

Other oncogenic or proliferative genes activated by YY1 include COX-2 and OTX2 (Table 1.1). It is noteworthy that two studies suggested the contribution of YY1 to the epithelial-mesenchymal transition (EMT). EMT can be induced by multiple oncogenic pathways and is inhibited by the tumor invasion suppressor E-cadherin. A recent report demonstrates the regulation of YY1 to the transcription of Snail, a transcriptional repressor of E-cadherin (44). The association between YY1 and the 3' enhancer of Snail is essential to Snail expression in melanoma cells, since decreased levels

Table 1.1. YY1-activated genes/promoters linked to tumorigenesis.

Gene/promoter	Function of the gene product	References
A. Oncogenic, proliferative and/or overexpressed genes in cancer		
c-Myc	Transcription factor and oncogene of various cancers	[33,139]
ERBB2/Her2	Proto-oncogene in breast cancer	[33,39]
COX-2	Oncogene of various cancers	[112]
GRP78/BiP	Promoting tumor proliferation, survival, metastasis and resistance to cancer therapies	[42,43,140,141]
OTX2	Oncogene of medulloblastoma	[142,143]
Snail	Enhancing cell survival, movement and/or EMT	[44,144]
Msx2	EMT and tumorigenesis	[45,145]
Mitochondrial genes: Cyto C etc	Cell respiration	[46]
DR-α	Overexpressed in cancers	[146,147]
VASAP-60/ PRKCSH/80K-H	Elevated in breast cancer	[148]
B. Tumor suppression genes		
ERGIC-53	Transmembrane lectin facilitating the efficient export of a subset of secretory glycoproteins from the endoplasmic reticulum; induced by ER-stress	[99]
HLJ1	Tumor and invasion suppressor	[53]
p53	Tumor suppressor	[51]
p73	A member of p53 family proteins	[52]
Peg3 (via CSE2 binding element)	Imprinted gene with tumor suppression function	[149]
RIZ1	A histone methyltransferase Altered expression in cancers, maybe a tumor suppressor	[150]
C. Other regulatory proteins in tumorigenesis		
Epidermal growth factor receptor (EGFR)	Cell signaling molecules involved in diverse cellular functions, including cell proliferation, differentiation, motility, and survival, and in tissue development	[151]
Histone H3.2alpha	Aberrant modifications in cancers	[77]
Histone H4	Aberrant modifications in cancers	[78]
Line-1 (promoter)	Showing altered methylation in cancers	[152]
Myelin Proteolipid protein (PLP)	Primary constituent of myelin in the central nervous system	[153]
OTK18	Induced by HIV infection	[154]
PARP-1	Promoting poly(ADP-ribosyl)ation; related to DNA damage repair	[76]
PCNA	Involved in DNA synthesis and repair; cooperating with nucleophosmin/B23	[80,155]
RE-1 silencing transcription factor (REST) *or* neuron-restrictive silencer factor (NRSF)	Showing both tumor suppressor and oncogenic activities	[156,157]
gp91(phox)	Catalytic subunit of the NADPH oxidase; potential target of cancer therapy	[158,159]
B-type natriuretic peptide (BNP)	Related to patients' response to cancer therapy	[160]
Transferrin receptor (CD71)	Related to poor prognosis and resistant to tamoxifen in breast cancer	[161]

Table 1.2. YY1- repressed genes/promoters linked to tumorigenesis.

Gene/promoter	Function of the gene product	References
A. Oncogenic and/or overexpressed genes		
c-fos	Proto-oncogene	[162]
interferon β (IFN-β)	Potential target in cancer therapy	[87,163]
HOXB13	Promoting cancer progression	[63,164]
CREB	Transcription factor	
matrix metalloproteinase-9 (MMP-9)	Increasing expressed in various cancers	[69]
steroidogenic acute regulatory (StAR)	Related to some cancers, e.g. glial tumors	[165,166]
B. Tumor suppression genes		
microRNA-29	Tumor suppressor of rhabdomyosarcoma	[57]
p21	Leading to cell cycle arrest	[55]
p16(INK4a)	Tumor suppressor	[56]
Peg3 and Usp29 (via CSE1 binding element)	Peg3: tumor suppression; Usp29: ubiquitin-specific protease 29	[149]
Rb	Tumor suppressor	[54]
TGF-beta	Tumor suppressor	
C. Other regulatory proteins in tumorigenesis		
alpha3beta1-integrin	Contradictory role in cancer invasion	[117]
mu opioid receptor (MOR)	Cancer-related pain	[102]
CD30	A member of the TNF receptor family; related to lymphoma	[167]
CXCR4	Chemokine receptor; related to breast cancer cell migration	[168]
PPAR-delta	Nuclear receptor proteins regulating gene expression	[169]
ERCC5/XPG	DNA repair gene	[170]
OX40	A therapeutic target in the treatment of autoimmunity and cancer	[171,172]
Cdk4	Regulating Rb phosphorylation	[55]
Cyclin D1	Regulating Cdk4 function	[55, 173]
Involucrin	A marker of differentiation	[174]
Hoxd4	Regulating morphogenesis	[175]

of YY1 led to reduced Snail expression. Another group also reported that YY1 acts as a transcriptional activator of a homeobox gene, Msx2, which plays an important role in inducing EMT transition in different cell types (45).

In 2007, a comprehensive study by Cunningham and colleagues described the role of YY1 in mediating cell respiration through mitochondria (46). YY1-binding elements are highly enriched in mitochondrial genes, and siRNA-mediated YY1 depletion significantly reduces the expression of many mitochondrial genes and in turn decreases the oxygen consumption. Consistently, YY1 protein is required for the inhibition of the mitochondrial genes by rapamycin. Mechanistic studies suggested that the YY1-PGC-1α transcriptional complex is essential to the mitochondrial oxidative function, while mTOR interferes with this regulation through altering the YY1-PGC-1α complex. Overall, this study demonstrated that YY1 plays an essential role in maintaining the basal respiration of cells.

Although the research described above implicates a proliferative role of YY1, several studies also indicated that YY1 may promote genes with tumor suppression function. While most reports demonstrated that YY1 negatively regulates p53 at posttranslational level and inhibits p53 transcriptional activity (47-50), YY1

exhibited stimulating effects in a study using a p53-promoter reporter and overexpressed YY1, and this activation was further enhanced by cotransfected E1A (51), which seems to contradict the well-established oncogenic function of E1A protein. Another report also demonstrated the cooperative transcriptional activation of p73 by YY1 and E2F1 (52). Overexpressed YY1, together with activator protein 1 (AP-1), was shown to activate the transcription of HLJ1, a suppressor of tumor invasion (53).

2.2. YY1-repressed gene expression

YY1 represses several targets with potential tumor suppression function. YY1 exhibits an inhibitory effect on Rb expression. During myogenesis (muscle cell differentiation), the translocation of YY1 from the nucleus to the cytoplasm causes Rb gene activation, which leads to the exit of cell cycle and the consequent myogenesis (54). However, it is still unclear whether overexpressed YY1 during tumorigenesis can inactivate the Rb gene. One way in which YY1 antagonizes p53 function is through attenuating p53 target genes, including p21 (49). The same regulation was also observed in vascular smooth muscle cells (55). YY1 was reported to recruit HDAC3 and HDAC4 to the promoter of p16(INK4a) and repress its expression, which could release the cells from senescence (56). YY1, together with NF-kappaB, could inhibit microRNA-29 (miR-29) (57), which is a potential tumor suppressor through activating p53.

Other YY1-regulated genes involved in tumorigenesis are shown in Tables 1.1 and 1.2. Based on the regulation of YY1 and the function of these genes, some discrepancies still exist, which makes it impossible to exclusively define the role of YY1 in cancer development. However, the tumorigenesis promoting effects of YY1 clearly override its function of tumor suppression. It is reasonable to hypothesize that the overall outcome of YY1-regulated processes depends on the oncogenic stimuli, cell types and the interplay with its recruited cofactors, whose availability may be altered at different physiological conditions.

3. YY1 and protein post-translational modifications

Posttranslational modifications have largely increased the complicity of the regulation on protein functions. Among several modifiable residues, lysines are the major targets of post-translational modifications, including acetylation, methylation, ubiquitination and sumoylation. The high-lysine (8%) composition of YY1 has determined its liability as a target of multiple modifying groups. Interestingly, these lysine residues are mostly located in the middle region of the primary sequence of the protein, while none is among the first 157 residues (Figure 1). While YY1 itself is a target, it also regulates various protein modifications. A well established mechanism of YY1-regulated gene expression is through recruiting histone modifiers to the target promoters and modulating histone modifications. YY1 has been reported to interact with numerous proteins including many protein modifiers that promote acetylation, deacetylation, methylation, ubiquitination and sumoylation of histone or nonhistone proteins (Table 2).

3.1. Acetylation

The interaction of p300 and YY1 was initially demonstrated by Lee et al in 1995 (58). Interaction domain mapping experiments revealed that YY1 and E1A bind to distinct sites of p300, and the primary binding sites of p300 and E1A on YY1 do not overlap, suggesting that the three proteins potentially form a ternary complex. Hence, the molecular mechanism underlying the conversion of YY1 from a repressor to an activator by E1A is through recruiting p300 to acetylate histones on YY1 target promoters. One of the transcription-independent properties of YY1 is its inhibition of p300-mediated p53 acetylation (48). This is one of the multiple approaches employed by YY1 to antagonize p53 (Figure 2), since acetylation can both prevent p53 ubiquitination (59) and enhance p53 transcriptional activity by promoting p53-DNA association (60).

Another landmark study by Yang et al linked the regulation of YY1 to histone deacetylation (61). They discovered an YY1 binding protein, hRPD3, a homolog of yeast RPD3 that is the definition base of the Class I HDACs. This hRPD3, which was later determined to be HDAC2 (3), contributes to YY1-repressed gene expression. Many other reports confirmed the importance of HDACs in YY1-mediated gene repression. Luke et al revealed that YY1 interacts with a homeodomain protein, HoxA11, and recruits HDAC2 to HoxA11 target gene to abrogate HoxA11-mediated gene activation (62). Recently, YY1 was reported to recruit HDAC4 and repress the expression of HOXB13, which plays a role in growth arrest in androgen receptor-negative prostate cancer cells (63).

Table 2. YY1 interacting proteins

Protein	Function	References
A. Modifiers of histones and nonhistone proteins		
p300, CBP	Acetylation of histone and nonhistone proteins	[58]
HDAC1, 2, 3, 4, 5	Deacetylation of histone and nonhistone proteins	[61,63,64,176,177]
Ezh1	Histone methyltransferease	[66]
Ezh2	Histone methyltransferease on H3-K27 and H1-K26	[67,178]
PRMT1	Histone methyltransferease on H4-R3	[65]
Mdm2	Ubiquitination of p53 and histones	[47,48]
Ubc9	E2 conjugating enzyme of sumoylation	[72]
PIASy	E3 ligase of sumoylation	[72]
B. Other chromatin remodeling proteins		
Nucleophosmin (NPM)/B23	A histone chaperon involved in nucleosome formation	[79]
CtBP1	A corepressor involved in chromatin remodeling	[81,82]
RYBP	A repressor present in PcG complex	[83]
CTCF	Chromatin remodeling; its deregulation causes epigenetic imbalance in cancer	[23,179]
INO80	Chromatin remodeling and DNA repair	[88,89]
SAP30	Involved in LOH (Loss of Heterozygosity)	[86,87]
C. Tumorigenesis and apoptosis		
p53	Tumor suppression and genome stability	[47]
Rb	Tumor suppression and genome stability	[91]
p14ARF	Tumor suppression	[47]
E1A	Oncogene leading to tumorigenesis	[7]
Mdm2	Oncogene enhancing p53 degradation	[47,180]
c-Myc	Oncogene transforming cells	[181]
c-Jun	Protooncogene	[94]
Caspases* 1, 3, 5, 6, 7	Proteases activated during apoptosis	[95]
PARP-1	Posttranslational modification, DNA repair	[76]
E2F2, E2F3	Regulating Rb pathway	[84]
MBP1	c-Myc promoter binding protein 1 (MBP-1)	[139]
α-enolase	Tumor antigen in lung cancer	[139]
D. General and other regulation		
RNA Pol. II, TFIIB, Sp1, ATF/CREB, TAFII55	General gene transcription	[35,96-99]
Notch1 receptor	Cell fate determination during embryonic development	[139,182]
SFMBT2	A member of PcG proteins	[183]
YY1AP (HCCA2)	Hepatocellular carcinoma-specific protein	[184-186]
YAF2	Interacting with MycN in neuroblastoma	[187,188]
mTOR (FRAP1)	Key factor in transducing various stimuli to regulate a wide range of cellular functions	[46]
Raptor	Associate with mTOR, and regulate its expression and activity	[46]
PGC-1α	A co-activator of YY1 in regulating mitochondrial genes	[46]
SHDAg and LHDAg (σ-virus antigen)	Involved in TGF-beta and c-Jun-induced signaling cascade	[189]
Hoxa11	Regulating uterine development	[62]
AP-2 (activator protein 2)	Acting as a co-factor to stimulate ERBB2 promoter	[38]
CP2	Transcription factor; interacting with the HXPR motif of YY1	[190]
SMAD1/4	TGF-beta signal pathway	[191]

The transcriptional activity of YY1 is also regulated by acetylation (64). p300 and PCAF mediate the acetylation of the central region (residues 171-200) of YY1 and this modification augments YY1-mediated gene repression. The C-terminal of YY1 can also be acetylated by PCAF, which reduces the YY1-DNA association.

3.2. Methylation

As stated above, YY1 is an activator of c-Myc gene. Rezai-Zadeh et al demonstrated that the mechanism of this activation is through the YY1-recruited PRMT1, a histone methyl-transferase specific to the arginine 3 of histone H4 (H4-R3) (65). The recruitment of PRMT1 by YY1 on the promoter of GRP78, a prosurvival ER chaperone, also leads to histone H4-R3 methylation and GRP78 gene activation (43). YY1 interacts with two lysine-specific histone methyl transferases, Ezh1 (enhancer of zeste homologue 1) and Ezh2, both of which mediate the methylation of histone H3-K27, a hallmark of gene silencing (66,67). Caretti et al first demonstrated that YY1 is essential to Ezh2-mediated methylation on histone H3-K27 in mouse skeletal muscle cells (67). This finding supports a regulatory role of YY1 in prostate cancer development, since the essential role of Ezh2 in prostate cancer development has been well established. Both YY1 and Ezh2 are overexpressed in various cancers. Thus, the recruitment of Ezh2 by YY1 may contribute to the aberrant epigenetic status of cancers. Transgenic studies in Drosophila indicated that the REPO (REcruitment of POlycomb proteins) motif, consisting of residues 201-226 of YY1 (Figure 1), is necessary and sufficient in recruiting Ezh2 and other polycomb group (PcG) proteins to establish transcriptional repression (68).

3.3. Ubiquitination and sumoylation

The turnover of YY1 is likely through ubiquitination and proteasomal degradation, since the treatment of a proteasome inhibitor led to accumulated YY1 protein (47). In neuronal cells, ubiquitinated YY1 interacts with CtBP and HDAC3 to establish a repressive complex (69). Meanwhile, we and others discovered that YY1 plays a role in regulating p53 ubiquitination and degradation (47,48) (Figure 2). YY1 directly interacts with both p53 and Mdm2, a ubiquitin E3 ligase, and enhances the Mdm2-p53 interaction by forming a ternary complex with them. As a result, YY1 depletion leads to either apoptosis or cell cycle arrest, depending on the cell types (28,47). Importantly, this regulation is

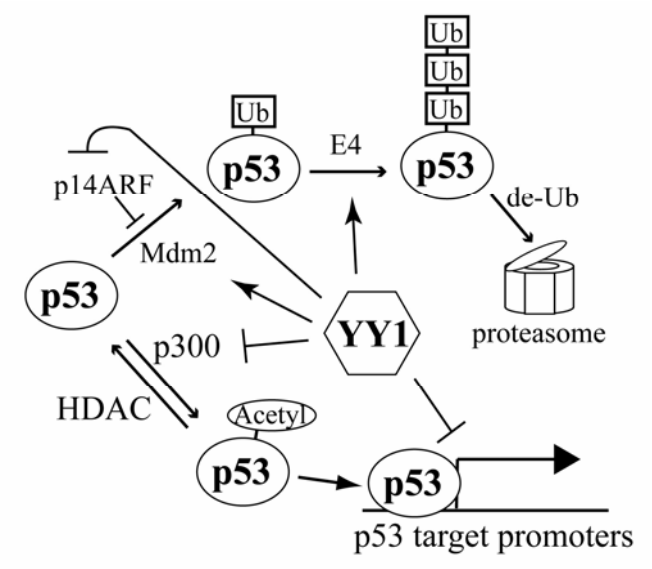

Figure 2. Schematic model of multiple mechanisms of YY1 to antagonize p53. YY1 inhibits p300-mediated p53 acetylation that endows p53 with increased stability and DNA binding affinity compared to deacetylated p53 [48]. YY1 also enhances Mdm2-mediated p53 ubiquitination and polyubiquitination, and interferes with p14ARF-mediated p53 stabilization [47]. In addition, YY1 also inhibits the transcription of p53 target genes, such as p21. Acetyl: acetylation; Ub: ubiquitination; de-Ub: deubiquitination driven by ubiquitin-specific proteases.

independent to the transcriptional activity of YY1, since an YY1 mutant deficient in DNA binding retains the ability of stimulating p53 ubiquitination, and YY1 protein purified from a bacterial expression system is capable of enhancing p53 ubiquitination *in vitro* (47).

The functional outcomes of protein sumoylation and ubiquitination are very distinct (70). SUMO (Small Ubiquitin-related MOdifier) conjugations are normally present in specific regions responsible for protein-protein interactions. Therefore, sumoylation may alter the function of a protein by changing its binding partners (71). We have demonstrated that YY1 can be conjugated by SUMO-1, 2 and 3, and Lys288 of YY1 is the primary conjugating site (Figure 1) (72). YY1 sumoylation, which is stimulated by PIASy, a SUMO E3 ligase, negatively affects the transcriptional activity of YY1. In addition, we also revealed a direct interaction of YY1 with Ubc9, the only conjugating enzyme of protein sumoylation. The interaction of YY1 with Ubc9 and PIASy suggests a potential role of YY1 in regulating the sumoylation of its interacting partners.

The interaction of YY1 with different transcription factors and protein modifiers also contributes to YY1-mediated gene expression. As

schematically shown in Figure 3, multiple studies demonstrated the regulation of YY1 to histone acetylation, deacetylation and methylation by p300, HDACs, Ezh2, Ezh1 and PRMT1, respectively. It is possible that these modifications occur on non-histone proteins in an YY1-recruited transcriptional complex. In addition, Mdm2 and Ubc9 may also be recruited by YY1 to its targeted promoters and modify these cofactors to regulate gene expression.

3.4. Other modifications

YY1 is also a subject of other modifications. Some of the YY1 present in nucleus appears to be O-GlcNAcylated regardless of the differentiation status of the cells, and glycosylated YY1 no longer interacts with Rb, although it still binds DNA (73). This study suggested that the glucose metabolism regulates YY1 protein by promoting its O-GlcNAcylation and consequently changing its activity. Although glycosylation frequently occurs to proteins expressed in cell membrane, it also plays an important role in regulating transcription. A number of transcription factors, such as Sp1 and RNA polymerase II, bear glycosylation that affects their transcriptional activity (74). Whether the glycosylation affects YY1-mediated transcription, in addition to its interaction with Rb, is still unclear. Moreover, YY1 interacts with poly (ADP-ribose) polymerase 1 (PARP1) and stimulates its function in catalyzing the synthesis of ADP-ribose polymers (75). Meanwhile, YY1 was reported to be transiently poly(ADP-ribosyl)ated after genotoxic treatment, which is coincides with the activation of PARP1 (76). Unlike glycosylation, the poly(ADP-ribosyl)ation decreased the DNA-binding affinity of YY1.

4. YY1-interacted proteins and their function

YY1 has been reported to interact with numerous proteins and most of these interactions are direct. One report suggested that YY1 may change its subcellular localization at different stages of the cell cycle (32). We observed that YY1 is predominantly localized in the nucleus but a small portion of YY1 also can be found in the cytoplasm, suggesting that its binding proteins are present in both compartments and YY1 possibly switches its binding partners during cell division and proliferation. The proteins that interact with YY1 can be categorized into four groups (Table 2), most of which possess regulatory function in tumorigenesis.

4.1. Protein modifiers

This has been discussed in Section 3 and summarized in Table 2.

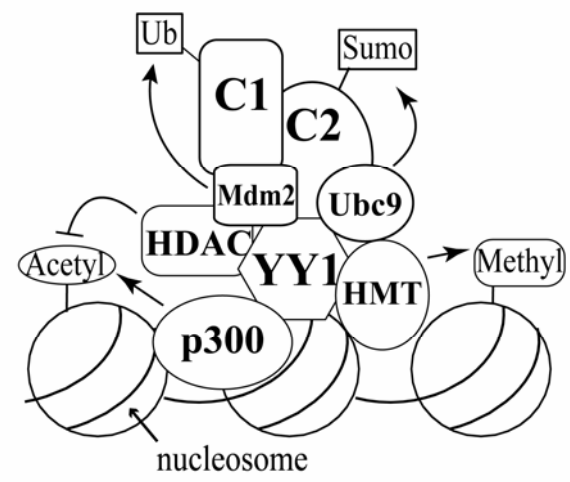

Figure 3. Schematic model of YY1-mediated protein modifications of histone and non-histone proteins on its target promoter. The interaction of YY1 with protein modifiers may mediate the modifications of the components in an YY1-recruited transcriptional complex. YY1 recruits p300, HDAC and histone methyltransferase (HMT, such as Ezh2, Ezh1 and PRMT1) to acetylate, deacetylate and methylate histones, respectively. Function of other cofactors (designated as C1 and C2) may also be altered by YY1-mediated modifications, such as ubiquitination and sumoylation.

4.2. Other chromatin remodeling proteins

In addition to these protein modifiers that directly regulate histone modifications, a number of other YY1-interacting proteins are also involved in chromatin remodeling. YY1 directly regulates the gene expression of histone H3.2alpha and histone H4 (77,78). These histone proteins are the primary components of the nucleosome. As a nucleolar protein and histone chaperone, nucleophosmin (NPM)/B23 regulates nucleosome formation. NPM forms a complex with YY1 both *in vivo* and *in vitro*. Interestingly, NPM relieves the transcriptional repression mediated by YY1 (79) and promotes the YY1-mediated activation of PCNA promoter (80). Among the polycomb group (PcG) proteins, YY1 is the only member that is known to directly and specifically bind DNA and recruit other PcG proteins to establish gene silencing. Using Drosophila as a model, the Atchison group demonstrated that the gene repression mediated by YY1 and other PcG proteins requires the co-repressor CtBP (81,82). A recent study in rat hippocampal cells indicated that CtBP specifically interacts with mono-ubiquitinated YY1 to repress matrix metalloproteinase-9 (MMP-9) gene transcription (69). Therefore, YY1 deubiquitination resulted from neuronal depolarization disrupts the repressive complex of

YY1-CtBP-HDAC3 and in turn activates MMP-9 expression.

RYBP (Ring1- and YY1-binding protein) was initially identified as a corepressor in PcG complex (83). A later study indicated that RYBP mediates the interaction of YY1 with E2F protein, which leads to activation of the Cdc6 gene (84). At the protein level, RYBP antagonizes Mdm2-mediated p53 ubiquitination (85), in opposition to the effects of YY1.

The interaction between YY1 and SAP30, a component of the human histone deacetylase complex, has been proposed as an alternative mechanism of YY1-mediated gene repression (86). SAP30 promotes the recruitment of HDAC1 by YY1 to repress gene expression. In addition, the recruitment of the Sin3A/NCoR/HDACs repressor complex by YY1 inhibits the expression of interferon beta (IFN-beta) gene (87).

INO80 is a subfamily of SWI2/SNF2 chromatin remodeling proteins and plays regulatory roles in gene transcription, DNA repair and DNA replication. Two recent studies demonstrated the functional interplay between YY1 and INO80. When YY1 activates transcription of its target genes, INO80 acts as an essential co-activator and helps YY1 to gain access to the target promoters (88). In addition, YY1 and INO80 are essential to homologous recombination-based DNA repair and therefore may regulate the cellular response to genotoxic stress (89).

4.3. Proteins involved in tumor suppression, oncogenesis, apoptosis and DNA damage

Besides p53 and Mdm2, YY1 also interacts with many other proteins that directly regulate tumorigenesis. YY1 binds to tumor suppressor retinoblastoma (Rb) *in vitro*. Either glycosylation of YY1 or phosphorylation of Rb disrupts this interaction (73,90). In cell-based experiments, only hypophosphorylated Rb interacts with YY1 and this interaction disrupts the YY1-DNA association (90), suggesting that Rb may be involved in YY1-mediated transcriptional regulation. Interestingly, the YY1-Rb complex was only observed in resting cells, but not in serum or lipopolysaccharide (LPS) stimulated cells (90,91), indicating their interaction is cell cycle-regulated. Another YY1-interacting tumor suppressor is p14ARF. Our functional study demonstrated that YY1 competes with p14ARF and therefore attenuates p14ARF-mediated p53 activation (47), which is another way in which YY1 antagonizes p53 function (Figure 2).

YY1 also interacts with many oncogene products, including E1A, c-Myc, c-Jun and Mdm2. As described above, viral oncogene E1A converts YY1 from a transcriptional repressor to an activator. As an YY1 interacting protein, c-Myc prevents YY1 from associating with its cofactors, but does not block its binding to DNA (92). YY1-c-Myc interaction mediates the stimulation of Surf-1 in the MAP kinase cascade (93). Similarly, c-Jun also interacts with YY1 and decreases the binding affinity of YY1 to its consensus binding element (94).

Krippner-Heidenreich et al provided direct evidence of the involvement of YY1 in apoptosis (95). Various apoptotic stimuli could promote rapid translocation of YY1 into cell nucleus and lead to cleavage of YY1 at Asp12-Gly and Asp119-Gly. Interestingly, one of these N-terminal truncated forms of YY1 could enhance Fas-induced apoptosis, suggesting YY1 plays a role in positive feedback during apoptosis. An *in vitro* study showed that YY1 was cleaved by caspase 1, 3, 5, 6 and 7 (95).

4.4. Other regulatory proteins

YY1 interacts with many general transcriptional factors and cofactors, such as RNA polymerase II, ATF/CREB, and Sp1 (35,96-99). This suggests that YY1 not only recruits other transcriptional cofactors to its target promoters, but also potentially acts as a cofactor recruited by others. Importantly, the presence of YY1 in a transcriptional complex creates an interface for these YY1-interacted protein modifiers that may alter the function of transcriptional machinery by modulating their posttranslational modifications (Figure 3). The interactions of YY1 with these general transcriptional factors and the regulatory proteins in Notch, TGF-beta, mTOR signaling pathways, as well as cell respiration (Table 2), once again indicate a critical role of YY1 in different biological processes.

5. YY1 being regulated

Although most reports have described how YY1 regulates the expression or modifications of other genes or proteins, some studies also demonstrated how YY1 expression and function are regulated (Table 3).

YY1 expression was shown to be upregulated by two growth factors, insulin-like growth factor-1 (IGF-1) and fibroblast growth factor-2 (FGF-2) (100,101). YY1 exhibited low or absent expression in NIH3T3 cells that were quiescent or cultured in serum-deprived medium. Consistently, YY1 expression could be equally stimulated by serum or

Table 3. Factors that regulate the function of YY1

Factor	Effect on YY1	References
Insulin-like growth factor-1 (IGF-1)	Activation	[100]
Fibroblast growth factor-2 (FGF-2)	Activation	[101]
TNF-alpha/NF-kappaB	Activation	[104,105]
Morphine	Stimulating YY1 expression	[102]
Lysophosphatidylcholine (lysoPC)	Enhancing YY1 expression	[103]
C/EBP-beta	Inducing YY1 activity	[192]
Prohibitin	Repressing YY1 expression	[107]
MicroRNA-29	Inhibiting YY1 translation	[57]
DETANONOate (nitric oxide donor)	Inhibiting YY1 mRNA synthesis and YY1-DNA association	[109,110]
Staphylococcal enterotoxin A (SEA)	Reducing YY1 expression by 15-fold in peripheral blood	[111]
Naloxone	Downregulating YY1 expression	[102]
RKIP	Down-regulating YY1 via NF-kappaB inhibition	[108]
Rituximab	Inhibiting YY1 expression	[106]
Lipopolysaccharide (LPS)	Inducing YY1 binding to COX-2 promoter	[112]
Sumoylation/PIASy	Enhancing YY1 sumoylation	[72]
Ubiquitination	Enhancing DNA binding and interaction with CtBP, HDAC3	[69]
Different apoptotic stimuli and DNA synthesis inhibitor	Causing YY1 translocation and cleavage	[32,95]
Myeloid nuclear differentiation antigen (MNDA)	Increasing YY1 affinity to DNA	[113]

IGF-1 (100). Injury of smooth muscle cells also led to an increase of YY1 expression; this stimulation was abolished by treatment with FGF-2 antibody (101). Proliferative drugs, such as morphine and lysophosphatidylcholine, also increased YY1 expression (102,103).

YY1 expression is stimulated by transcription factor NF-kappaB that directly binds to YY1 promoter through its subunit p50/p65 heterodimer (104). Consistently, PC-3 cells treated by TNF-alpha exhibited elevated levels and increased DNA-binding activity of YY1. On the other hand, genetic ablation of the p65 subunit of NF-kappaB in both cultured cells and adult skeletal muscle correlated with reduced YY1 transcripts and protein (105). A chimeric antibody against CD20, rituximab, which inhibits constitutive NF-kappaB activity and therefore sensitizes tumor cells in B cell non-Hodgkin's lymphoma and leukemias, represses YY1 expression (106).

Several mechanisms have been reported to downregulate YY1 expression. At the transcriptional level, YY1 expression is inhibited by prohibitin through E2F1 binding sites (107). While YY1 negatively regulates miR-29 expression, miR-29 also targets the 3'-UTR of YY1 mRNA and blocks its translation (57). The interplay between YY1 and miR-29 implicates their function in skeletal myogenesis and rhabdomyosarcoma development.

As a metastasis suppressor gene, Raf kinase inhibitor protein (RKIP) is poorly expressed in cancers. RKIP downregulates YY1 expression through inhibiting its transcription (108). Hence, RKIP overexpression increases tumor cell sensitivity to TRAIL via blocking YY1 expression. YY1 expression can also be inhibited by DETANONOate (a nitric oxide donor), naloxone (a drug used to counter the effects of opioid overdose) and staphylococcal enterotoxin (102,109-111).

In addition to regulating YY1 expression, some factors also affect YY1 function. Both lipopolysaccharide (LPS) and myeloid nuclear differentiation antigen (MNDA) enhance YY1 binding affinity to its target promoters (112,113). Mono-ubiquitinated YY1 recruits CtBP and HDAC3 to repress Mmp-9 gene expression (69), while PIASy-mediated sumoylation inhibits YY1-mediated gene transcription (72). Different apoptotic stimuli, including the DNA synthesis inhibitor aphidicolin, can translocate and cleave YY1 protein (32,95).

Overall, YY1 expression is stimulated by proliferative stimuli, while antiproliferative signals tend to antagonize YY1.

6. YY1 expression in cancers and its correlation with disease outcome

Most processes mediated by YY1 are cancer-related, while YY1 itself is also differentially regulated during apoptosis and tumorigenesis. Therefore, the studies summarized above provide unequivocal evidence for the essential role of YY1 in tumorigenesis. The regulatory role of YY1 in various signaling pathways may explain its aberrant expression in cancers. YY1 overexpression has been demonstrated in human breast cancer (38), prostate carcinoma (114), acute myeloid leukemia (115), osteosarcoma (116,117), cervical cancer (118), brain cancer (119), ovarian cancer (120), large B-cell and follicular lymphoma (121) and colon cancer (122). Currently, the mechanisms of YY1 increase in these cancers remain unclear. As discussed in Section 5, YY1 expression can be regulated by multiple pathways and its upregulation can be achieved by different proliferative stimuli. Therefore, it is unlikely that a universal mechanism can be applied to YY1 upregulation in all cancers.

In prostate cancer, elevated YY1 expression correlates with higher morphologic grades or malignant histological phenotypes (114). Similarly, YY1 overexpression in osteosarcoma is positively and strongly correlated with the degrees of malignancy (116,123). Consistently, YY1 is also upregulated in metastatic breast cancer (124) and its staining intensity in colon cancer is more pronounced in poorly differentiated tumors than in moderately or well-differentiated colon cancers (122).

As discussed above, the overall effect of YY1 on cells is proliferative or oncogenic, and YY1 overexpression is prevalent in most cancers. However, the expression of YY1 does not show a defined correlation with the susceptibility of cancer reoccurrence or length of patients' survival. In prostate, colon and ovarian cancers, YY1 expression positively correlated with the long-term survival periods of patients (114,120,122,125). In contrast, among patients with large B-cell and follicular lymphoma, high levels of YY1 were associated with poor outcome, including a shorter survival interval (121). The mechanisms of this apparent paradox remain unknown. A recent study by Matsumura et al investigated the positive correlation between YY1 expression and the length of survival in patients with ovarian cancer (125). Their results suggested that the overexpression of YY1 and E2F could sensitize ovarian cancer cells to the treatment of taxane, a class of drugs that disrupt the function of microtubules. As a result, patients with higher expression of YY1 exhibited better response to the therapy and therefore had longer survival.

Despite the fact that YY1 exhibits oncogenic function in cancer development, an *in vitro* study using colon cancer cells showed no evidence of gene amplification or chromosomal translocation of YY1 (122). However, two YY1 mRNA isoforms (7.5 and 2.9 kb) were substantially overexpressed and aneuploidy was also observed.

7. The role of YY1 in tumorigenesis and its potential as a target in cancer therapy

The essential regulation of YY1 in numerous cancer-related pathways and its increased expression in various cancers strongly implicate the importance of YY1 in cancer development and progression.

As a guardian of the genome, the tumor suppressor p53 plays a vital role in preventing malignant transformation of cells. Consistently, p53 mutations have been reported in over 50% of cancers. *In vitro* and *in vivo* studies also indicated that p53 inactivation can immortalize the cells and lead to deregulated cell proliferation or tumor formation. As described above, YY1 antagonizes p53 through several mechanisms (Figure 2), including enhancing p53 ubiquitination and degradation (47), blocking p53 acetylation (48), attenuating p14ARF-mediated p53 stabilization (47), and inhibiting p53-mediated transcription (49). These multiple and consistently negative effects of YY1 on p53 stability and function implicate p53 as a primary target of overexpressed YY1 in cancer cells and strongly suggest an oncogenic or proliferative role of YY1 in cancer development.

We hypothesize that YY1 coordinately regulates the function of Ezh2 and p53 to facilitate cancer development. Ezh2 has been identified as a bona fide oncogene (126) and used as a marker of cancers with aggressive and metastatic potential. Functionally, Ezh2 is essential to cancer progression and invasion (127,128), and its overexpression increases the likelihood of therapy failure (129). In prostate cancer, although p53 deficiency did not lead to prostate carcinoma in a mouse model, p53 deletion augments the cancer development in Pten null mice (130). Our proposed model is that the regulation of p53 and Ezh2 by YY1 may take place at different stages of cancer development (Figure 4).

Firstly, since nearly half of the cancers retain functional p53, especially at early stages, a developing phase must exist in the primary malignancy to defeat the genomic surveillance or tumor suppression function of p53 prior to its inactivation. We hypothesize that at this earlier stage, highly expressed YY1 plays a role to antagonize p53 function, which consequently initiates and/or promotes cell malignancy. Meanwhile, the suppression of Ezh2 expression by p53 (131) will also be released by YY1-mediated p53 inactivation and this in turn leads to increased levels of Ezh2 (Figure 4). Secondly, Ezh2 increase is always linked to tumor progression, invasion and metastasis (132-134), which are the later events of cancer development. We hypothesize that elevated YY1 expression is essential for Ezh2 to exert its methyltransferase activity and establish aberrant epigenetics, which augments cancer progression. At this stage, most of the cancers may already have acquired p53 mutations, which will augment the cancer progression. To these retaining functional p53, YY1 may still play a role in attenuating its function.

Noteworthily, our model suggests that YY1 antagonizes the functional p53 during the cancer development. This hypothesis does not conflict with the Vogelstein model for colorectal tumorigenesis (135,136), which proposed that the acquired p53 inactivation, mostly through gene mutations, is a frequent event at the late stages of cancers. Based on the published data, YY1 is likely an important negative regulator of p53 throughout the whole malignant process, especially in the cancers preserving functional p53 proteins. Certainly, we cannot exclude the possibility that the contribution of our model to tumorigenesis is more important in certain types of cancers than the others.

Several studies described the potential of YY1 as an effective target in cancer therapy. The Bonavida group extensively studied the role of YY1 in chemo- and immuno-resistance in cancer therapy and concluded that YY1 levels could be used to predict the therapeutic responsiveness (137). Since YY1 negatively regulates the expression of Fas, the inhibition of YY1 by nitric oxide or rituximab could upregulate Fas and sensitize the tumor cells to Fas-induced apoptosis (110,138). In addition, YY1 also inhibits the expression of DR5, a death receptor mediating the extrinsic pathway of apoptosis. Therefore, Raf-1 kinase inhibitor protein (RKIP) could decrease YY1 expression and consequently upregulate DR5 to sensitize the cells to TRAIL-induced apoptosis (108).

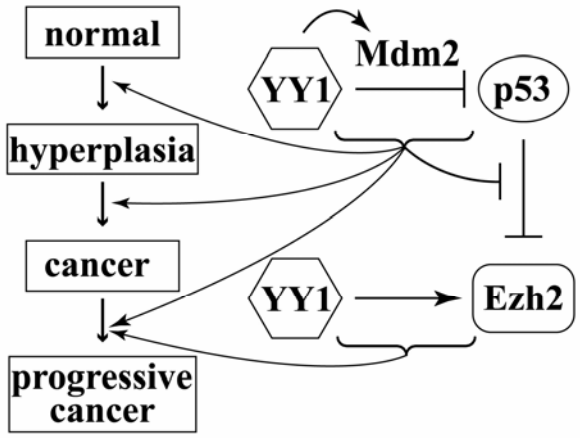

Figure 4. Schematic model of the regulation of p53 and Ezh2 by YY1 in cancer development. YY1 promotes Mdm2-mediated p53 degradation [47,48,55] and inhibits its transcriptional activity [49]. This leads to tumor initiation and cancer development. Moreover, the suppression of p53 on Ezh2 gene expression [131] will also be released by YY1's antagonism to p53, which results in increased Ezh2 expression. At the late stage of cancer, YY1 recruits Ezh2 for histone methylation and consequently promotes tumor progression. Meanwhile, overexpressed YY1 may also inhibit p53 activities in cancers retaining functional p53 proteins.

A recent report by de Nigris et al focused on the role of YY1 in cell invasion, angiogenesis and metastasis (123). Their study demonstrated that YY1 depletion significantly decreased cell invasion and metastasis growth, which was associated with reduced endothelial growth factor (VEGF) and angiogenesis. This finding clearly suggests that YY1 is a promising and effective target in the therapy of bone cancer.

As summarized above, although discrepancies still exist, the overall function of YY1 is understood as both inhibiting tumor suppression processes and promoting oncogenic events. Especially, YY1 is an essential regulatory factor of numerous epigenetic events and its expression may affect many different biological processes leading to tumorigenesis. Theoretically, simultaneously targeting several pathways related to cancer development should result in more efficient and prompt outcome than targeting each of them individually. If a regulatory protein contributing to the abnormality of several processes toward malignancy can be identified, targeting this key regulator may exhibit a substantial impact by reversing or adjusting

multiple pathways concurrently. Given its unique properties in mediating multiple epigenetic events and its causal links with various cancers, YY1 is likely one of these key regulatory proteins in cancer development and therefore can serve as an effective target in therapeutic treatment of cancers. Thus, targeting or adjusting YY1 in cancer therapy can potentially reverse the aberrant epigenetics of cancer cells and restore their normality. This will be especially important to the cancers in critical organs where radical surgery is not applicable.

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Conflicts of Interest

No potential conflicts of interest to disclose.

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