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Chapter 23

The Function of YY1 and Its Oncogenic Role in Prostate Cancer

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Additional information is available at the end of the chapter

http://dx.doi.org/10.5772/53091

1. Introduction

Transcription factors regulate gene expression by interacting with specific DNA elements and other proteins to either activate or repress gene transcription. Aberrant expression and function of transcription factors are commonly observed in human cancers and play a pivotal role in oncogenic transformation. Ultimately, these affect downstream signaling pathways, resulting in acquisition of some or all of the hallmarks of cancer, such as insensitivity to antigrowth or apoptotic signals, production of self-sufficient growth signals, limitless replicative potential and invasive or metastatic capability [1].

Yin Yang 1 (YY1) is a highly conserved transcription factor across species and ubiquitously expressed in human tissues. YY1 has the ability to act as either an activator or repressor of its target genes, depending on the compositional difference of its recruited complexes. Through these complexes YY1 regulates epigenetic modifications, such as DNA methylation and histone acetylation, of its targeted promoters. Originally, YY1 was discovered as a transcription factor capable of binding to the P5 promoter of adeno-associated virus [2]. YY1 executed an inhibitory effect on this promoter, but this inhibition was reversed to activation by its association with a viral protein, E1A. Indeed, the name "Yin Yang" symbolizes these two opposing abilities. "Yin Yang" also represents the ongoing debate over what role YY1 plays in human cancers, although its oncogenic role is clearly more predominant than its tumor suppressive potential based on the current literature.

As discussed below, the evidence supporting the oncogenic role of YY1 has been obtained through its study in various human cancers. In this chapter, we will first describe the studies that suggest a proliferative role for YY1 in cancers, and then specifically discuss what is known to date about the function of YY1 in prostate cancer.

2. YY1 as a transcription factor

The YY1 protein consists of 414 amino acids and multiple functional domains (Figure 1). As a transcription factor, YY1 is capable of directly binding to DNA through the zing-finger domains at its C-terminus. YY1 recognizes and binds its DNA consensus sites with a core sequence of either CCAT or ACAT, and these consensus elements have been identified in over 7% of vertebrate genes, underscoring the importance of YY1 in gene regulation [3].

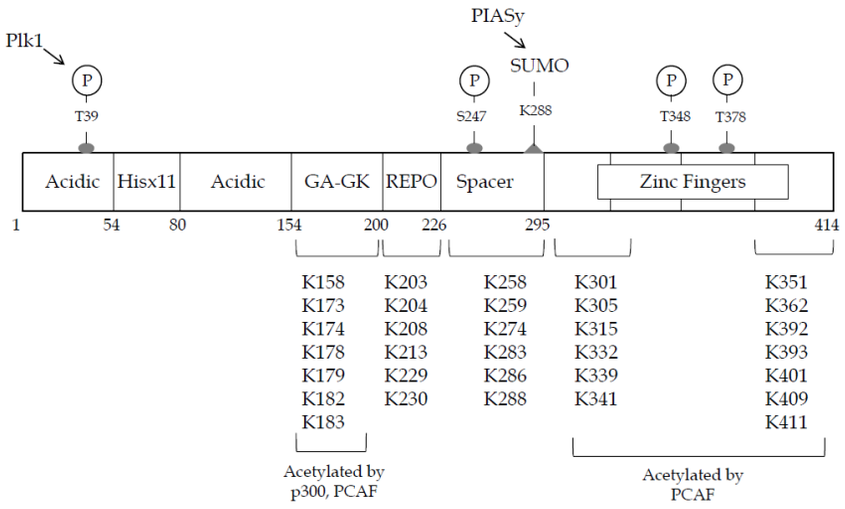

Figure 1. The Domain Structure of the YY1 Protein; YY1 is post-translationally modified at multiple sites. Polo-like kinase 1 (Plk1) phosphorylates T39, while protein inhibitor of activated STAT Y (PIASy) stimulates sumoylation of K288. PCAF and p300 mediate acetylation of residues 171-200, while p300/CBP associated factor (PCAF) also acetylates the C-terminus. All 32 lysine (K) residues are indicated in their respective domains of YY1. Phosphorylation of residues Thr348 and Thr378, but not Ser247, reduces DNA affinity of YY1. The REPO motif (201-226) is both necessary and sufficient for the recruitment of PcG proteins for the initiation and maintenance of gene silencing.

Most YY1 target genes are cancer-related, and can be either transcriptionally activated or repressed by YY1 and its associated factors. YY1-recruited proteins play a large role in determining whether YY1 will execute inhibitory or activating functions on a particular target gene. YY1 can recruit a variety of coactivators, including p300, cyclic adenosine monophosphate response element binding (CREB) protein (CBP), p300/CBP-associated factor (PCAF), and protein arginine methyltransferase (PRMT) 4 as well as corepressors such as histone deacetylases (HDACs), enhancer of zeste (Ezh) 2, and DNA methyltransferases (DNMTs) [4-11]. We will discuss these interaction partners and their effect on YY1-mediated gene regulation in detail below.

2.1. YY1-activated gene expression

We have listed cancer-relevant genes that are activated by YY1 in Table 1. In support of the predominance of YY1's oncogenic effects over its tumor suppressive potential, we note that the majority of its activated targets are oncogenes, which promote either proliferative or invasive phenotypes when overexpressed.

Gene/Promoter	Gene Product Function	Mechanism/Observation	Reference
A. Oncogenic, proliferative and/or overexpressed genes in cancer			
B23/nucleophosmin	Regulates nucleosome formation and inhibits tumor suppressors	HCV core, p300 and B23 itself are involved	[12, 13]
c-Myc	Oncogenic transcription factor in multiple cancers	E1A converts YY1 from a repressor to an activator; p300 and HDAC3 are also involved	[14, 15]
HER2/ERBB2/neu	Proto-oncogene in breast cancer	AP-2 transcriptional activity on the HER2 promoter is enhanced by YY1	[16, 17]
Cyclooxygenase-2 (COX-2]	Oncogene of various cancers	Proposed a model with YY1-mediated recruitment of p300 and HDAC1,2	[18]
c-Fos	Proto-oncogene	E1A converts YY1 from a repressor to an activator in this regulation	[19]
Glucose regulating protein 78/ binding immunoglobulin protein	Promotes tumor proliferation, survival, metastasis and therapeutic resistance	p300 and PRMT1 are recruited	[20-23]
Snail	Enhances cell survival, movement and/or EMT	YY1 binds a distal Snail 3' enhancer	[24, 25]
Msx2	EMT and tumorigenesis	Three YY1-binding sites are involved	[26, 27]
DR-α	Overexpressed in cancers	YY1 binding directly to the promoter	[28, 29]
TGF-β	Overexpressed in tumors; promotes invasiveness and metastasis	A polymorphism mutation in the TGF-β promoter creates a binding site of YY1 that activates the TGF-β gene	[30, 31]
B. Tumor suppression genes			
p53	Tumor suppressor	E1A and p300 can further induce p53 expression	[32]
p73	A member of the p53 family of proteins	YY1 and E2F1 cooperate to promote p73 transcription	[33]
RIZ1	A histone methyltransferase; altered expression in cancers; a potential tumor suppressor	Correlated with reduced H3-K9 dimethylation	[34]
C. Other regulatory proteins in tumorigenesis			
Epidermal growth factor receptor (EGFR)	Cell signaling molecule involved in diverse cellular functions, including cell proliferation, differentiation, motility, and survival	Sp1 and YY1 synergistically induce the EGFR promoter; p53 suppresses this activation	[35]
Histone H2a and H3	Aberrantly modified in cancers	Regulated by the cell cycle	[36]
Histone H4	Aberrantly modified in cancers	Multiple YY1 binding sites are involved	[37]
Poly(ADP-ribose) polymerase 1 (PARP1]	Promoting poly(ADP-ribosyl)ation; related to DNA damage repair	YY1 directly binds the promoter	[38]
Proliferating cellular nuclear antigen (PCNA)	Involved in DNA synthesis and repair; cooperates with nucleophosmin/B23	B23 is involved; accompanied by histone H4 deacetylation	[39, 40]

Table 1. YY1-Activated Genes and Promoters.

The first oncogene shown to be activated by YY1 is c-myc that drives cellular proliferation and leads to oncogenic transformation when constitutively activated [14]. Specifically, YY1 was found to increase levels of two c-myc mRNA transcript variants. It was later discovered that the viral protein E1A dissociates the YY1-p300-HDAC3 complex that normally inhibits c-myc transcription. Thus, with the presence of E1A and the dissociation of HDAC3, the c-myc promoter becomes more accessible due to regional histone hyperacetylation. YY1 acts similarly in regulating expression of c-Fos, another well characterized proto-oncogene driving cellular proliferation [41, 42]. Through interacting with the ATF-CREB transcription complex, YY1 inhibits c-Fos expression; however, this interaction is also disrupted by E1A, which changes the effect of YY1 from repressive to activating on c-Fos gene expression.

Another example of YY1-activated oncogene expression is its regulation of the protein B23. B23 is involved in nuclear export of ribosomes and chaperone activity and stimulates repression of multiple tumor suppressors. YY1 activates B23 in the presence of a viral gene product, the hepatitis C virus (HCV) core, which plays a pivotal role in liver oncogenesis [12]. The HCV core leads to YY1-mediated recruitment of p300 and B23 to the B23 promoter, activating its gene expression. In the absence of the HCV core, YY1 recruits HDAC1 to the B23 promoter to act as a transcriptional repressor. Thus, B23, like E1A, switches YY1 from a transcriptional repressor to an activator [43]. Other YY1-activated oncogenes include proliferating cell nuclear antigen (PCNA) and HER2 [17, 40, 44].

Several genes that directly promote cancer invasion and metastasis are regulated by YY1. Angiogenesis is important to cancer progression and tumor cell invasion. Vascular endothelial growth factor (VEGF) is a key mediator of angiogenesis in cancer. YY1 forms a complex with hypoxia-inducible factor (HIF) 1α to activate VEGF expression and consequently promotes angiogenesis [45]. YY1 also induces expression of cyclooxygenase (COX) -2, an inflammation-associated enzyme that mediates tumor cell bone metastasis [18].

Epithelial-to-mesenchymal transition (EMT) is one of the early and critical steps of the tumor metastatic cascade and characterized by tumor cells losing their epithelial architecture and adopting that of a mesenchymal cell. This morphological transition typically enhances the motile, migratory and invasive abilities of tumor cells [46]. The transcription factor Snail inhibits expression of the epithelial marker and EMT-inhibitor E-cadherin. YY1 binds the 3′ enhancer of Snail to upregulate its expression. Consequently, YY1 overexpression downregulates E-cadherin expression through activating Snail, leading to enhanced EMT and tumor progression [24].

The above studies, among others, demonstrate an oncogenic role of YY1 in human cancers through its transcriptional activation of a number of oncogenes. It is important to mention that YY1 has also been reported to activate several genes with tumor suppressive potential. The negative regulation of p53 activity by YY1 at the posttranslational level is well established [47-49]. However, ectopically overexpressed YY1 activated a p53 promoter driving expression of a reporter, and this activation was reversed in the presence of E1A [32]. Since YY1-mediated histone modifications are essential to its transcriptional activity and this modulation unlikely occurs on extrachromosomal DNA, such as transfected reporter plasmids, the results of this study may not truly reflect YY1's effect on the endogenous p53 promoter.

2.2. YY1-repressed gene expression

Cancer-related genes that are repressed by YY1 are listed in Table 2. Many of them encode gene products with tumor suppressive functions, a phenomenon consistent with YY1's predominantly oncogenic role in human cancers.

Gene/Promoter	Gene Product Function	Mechanism/Observation	Reference
A. Oncogenic and/or overexpressed genes			
Interferon β (IFN-β)	Potential target in cancer therapy	YY2 antagonizes the YY1-mediated repression, Sin3A/NCoR/HDACs complex is recruited by YY1	[50, 51]
Hypoxia-Inducible Factor 2α (HIF-2α)	Oncogenic role	PTEN released this repression	[52]
Matrix Metalloproteinase-9 (MMP-9]	Increasingly expressed in various cancers	Monoubiquitinated YY1 binds CtBP; HDAC3 is recruited	[53]
PVT1	Oncogenic role	A mutation leading to reduced YY1 causes PVT1 overexpression.	[54]
B. Tumor suppression genes			
CCAAT/enhancer-binding protein delta (CEBPD)	Tumor suppressor	Recruits Ezh2, DNMT1, DNMT3A, DNMT3B	[6]
Chondromodulin-I	Inhibitor of angiogenesis	YY1 recruits HDAC2	[55]
Death Receptor 5 (DR5]	A receptor in the extrinsic apoptosis pathway	Rituximab inhibits DNA binding of YY1 and relieves its repression of DR5	[56, 57]
KISS1	Metastasis suppressor	Sp1 is not involved.	[58]
microRNA-29	Tumor suppressor	Through binding to a conserved regulatory region	[59]
microRNA-206	Promotes cell apoptosis	YY1 regulation is antagonized by c-Jun and c-Fos	[60]
p21	Leads to cell cycle arrest	YY1 antagonizes p53-mediated transcription	[49, 61]
p16(INK4a)	Tumor suppressor	HDAC3 and HDAC4 are recruited	[62]
Retinoblastoma (Rb)	Tumor suppressor	GABP and HCF-1 are involved in this regulation	[63]
HOXB13	Inhibits prostate cancer cell growth by suppressing AR and TCF-4 signaling	YY1 recruits HDAC4 to promoter and inhibits transcription	[8]
PTEN	Tumor Suppressor and Antagonist of PI3K/Akt Signaling	MTA1 recruits HDAC4 and YY1 to PTEN promoter	[64]
C. Other regulatory proteins related to cancers			
CD30	A member of the TNF receptor family; related to lymphoma.	Directly binds the promoter	[65]
PPAR-δ	Nuclear receptor proteins regulating gene expression	Directly binds the promoter	[66]
Cyclin D1	Regulates Cdk4 function	HDAC1 is recruited	[61, 67]

Table 2. Y1-Repressed Genes and Promoters.

The tumor suppressor retinoblastoma (Rb) is transcriptionally inhibited by YY1 upon its binding to the Rb promoter [63]. YY1 also recruits HDAC3 and HDAC4 to repress the expression of tumor suppressor p16 that inhibits CDK4 to reduce cell proliferation [62]. YY1-mediated transcriptional repression of the cell cycle-regulator p21 is one of many examples of YY1's role in antagonizing p53 function [49]. Additionally, YY1 represses PTEN through associating with HDAC4 and the chromatin modifier MTA1 [64].

YY1 has been shown to inhibit genes encoding microRNA (miRNA) products with tumor suppressive potential. MiRNAs are critical players in a number of human diseases, including cancers. MiRNAs bind the 5′ UTRs of partially complementary mRNA transcripts, blocking their translation; they may also lead to mRNA degradation. MiR-29 exhibits tumor suppressive potential based on its activation of p53 through targeting its inhibitory proteins p85α and CDC42 [68]. YY1, in cooperation with NF-κB, can inhibit miR-29 transcription [59]. Ring1- and YY1-binding protein (RYBP) enhances YY1-mediated miR-29 silencing and enriches YY1-recruited Ezh2 at target loci [69]. YY1 has also been shown to negatively regulate miR-206, a known promoter of apoptosis [60].

YY1 binding elements are present in over a thousand vertebrate gene promoters. The effect of YY1 on the expression of a given target gene will depend on the extracellular stimuli available to the cell and the presence or absence of YY1-interaction partners that serve as coactivators or corepressors. The transcriptional activity of YY1 on its myriad of cancer-related target genes convolutes the task of determining its role in human cancers. However, the current evidence suggests that YY1 activity is primarily oncogenic, and these effects clearly override any YY1 tumor suppressive function.

2.3. YY1 as a transcription cofactor

Although most studies to date demonstrate the regulation of YY1 as a transcription factor directly binding to target promoters, recent reports have begun to reveal the role of YY1 as a transcription cofactor that is independent of its DNA binding ability.

In prostate cancer cells, YY1 interacts with androgen receptor (AR) and serves as its coactivator in mediating PSA expression. Thus, the putative binding site of YY1 is dispensable in YY1-promoted prostate specific antigen (PSA) expression [70]. YY1 represses RNA methyltransferase-like 1 gene expression, yet there is no YY1 binding site in its gene promoter [71]. In this instance, YY1 regulation depends on transcription factor ATF/CREB. Hypoxia-Inducible Factor (HIF) -2α is stabilized upon inactivation of tumor suppressor von Hippel Lindau (VHL). As a transcription factor, HIF-2α regulates the expression of genes responsible for angiogenesis and metastasis. YY1 acts as a corepressor of HIF-2α, but this repression is abolished by phosphatase and tensin homolog (PTEN) [52].

The recently appreciated function of YY1 as a transcription cofactor expands its role in mediating gene expression. As a cofactor, more or different YY1 functional domains are exposed and available to other proteins for binding or recruitment. This diversifies the interaction partners available to YY1 on its target promoters and extends its role in regulating gene expression [72].

3. YY1 as a regulator of post-translational modifications

YY1 was first identified as a transcription factor and has been shown to regulate the expression of many genes. However, our understanding of YY1 function has evolved with an increasing appreciation for its DNA-binding independent activities, many of which contribute to YY1-mediated gene expression.

Proteins undergo different types of post-translational modifications, including acetylation, methylation, ubiquitination and sumoylation that contribute to the complexity of protein stability, function and interactions. Many YY1-interaction partners mediate YY1-regulated gene expression through instigating post-translational modifications.

3.1. Acetylation

Acetylation is the addition of an acetyl group (CH_3CO) to a lysine residue and mediated by a class of proteins called histone acetyltransferases (HATs). These enzymes catalyze acetylation of both histone and non-histone proteins, and for this reason are more commonly referred to as lysine acetyltransferases (KATs) [73]. Acetylation of non-histone proteins modulates their activity and stablity, while histone acetylation is associated with a relatively loose or open chromatin conformation that is more accessible to transcriptional regulatory proteins, leading to active gene expression.

As we discussed above, YY1 interacts with the KAT p300 and this complex is disrupted in the presence of the viral protein E1A. Notably, YY1 and E1A bind to different domains of p300, and the binding sites of p300 and E1A on YY1 are also well separate [74]. Thus, it is very likely that these three proteins form a ternary complex. Such a complex would promote histone acetylation on promoters, such as P5, c-myc and c-Fos. This explains the role of E1A in converting YY1 from a transcriptional repressor to an activator to promote the expression of these target genes [2, 41, 75].

Acetylation of p53 by p300 both prevents its ubiquitination and subsequent degradation and enhances the p53-DNA interaction, thus promoting p53 transcriptional activity [76, 77]. YY1 inhibits p300-mediated p53 acetylation, thereby antagonizing the tumor suppressive function of p53 [47].

While histone acetylation is associated with active gene expression, histone deacetylation is a mark of gene repression and mediated by a family of proteins called histone deacetylases (HDACs). YY1 has been demonstrated to interact with a number of HDACs and recruit them to target promoters for gene repression. Indeed, YY1 recruitment of HDACs to tumor suppressor gene promoters is important for its role in prostate cancer, and will be discussed below.

3.2. Methylation

Like other modifications, methylation also modulates protein function. In this regard, the most studied activity is the contribution of histone methylation to gene expression. Al-

though DNA methylation usually inhibits gene expression, histone methylation can either activate or repress a target gene, depending on the methylated residues.

Protein arginine methyltransferase (PRMT) 1 catalyzes methylation of histone H4 at arginine 3 (H4-R3). YY1 recruits PRMT1 to the c-myc promoter to activate c-myc gene expression [9]. Similarly, YY1 has also been shown to activate the promoter of a pro-survival chaperone protein, GRP78, through recruiting PRMT1 [22]. YY1-mediated expression of these cell survival genes suggests its proliferative role in oncogenesis.

The proteins enhancer of zeste (Ezh) 1 and 2 are lysine-specific histone methyltransferases mediating methylation of lysine 27 on histone 3 (H3-K27), a hallmark of gene silencing in many cancer-related genes [78]. They are both members of the Polycomb group (PcG) of proteins and core components of the Polycomb repressive complex (PRC) 2, responsible for gene silencing in a number of tumor suppressor genes.

YY1 was first demonstrated to recruit Ezh2 in mouse skeletal muscle cells [4]. The Recruitment of Polycomb (REPO) domain of YY1 is both necessary and sufficient to recruit Ezh2 and other PcG proteins for the establishment of target gene silencing [79].

In addition to histone methylation, YY1 can also mediate DNA methylation. This multi-layered regulation by YY1 has been demonstrated on the promoter of CCAAT/enhancer binding protein delta (CEBPD). YY1 associates with both DNA methyltransferases and PcG proteins to execute gene silencing through modifications of both DNA and histones [80].

3.3. Ubiquitination

Ubiquitination is a modification executed cooperatively by a set of three ubiquitin enzymes (E1, E2, and E3). Protein monoubiquitination typically alters subcellular localization of a protein or modulates its function and additional types of modification, while polyubiquitination usually results in its proteasomal degradation.

In addition to the negative regulatory effects of YY1 on p53 discussed above, YY1 also promotes p53 polyubiquitination and degradation [47, 48]. YY1 directly interacts with both p53 and its E3 ligase Mdm2 and enhances the p53-Mdm2 interaction through the formation of a ternary complex. Both wild-type YY1 and its DNA-binding deficient mutant promote p53 polyubiquitination, indicating that this function of YY1 is independent of its transcriptional activity [48]. Consistently, YY1 depletion in cells leads to an increase in p53 stability and results in cell cycle arrest and apoptosis.

We recently identified negative regulation of the tumor suppressor p27 by YY1 through YY1-promoted ubiquitination [81]. YY1 overexpression enhanced both mono- and polyubiquitination of p27, while YY1 silencing markedly reduced p27 polyubiquitination, but not monoubiquitination.

In summary, the large number of YY1's interaction partners increases the complexity of its biological functions. Many of these proteins (e.g. p300, PRMT1, Ezh2, etc.) contribute to YY1-mediated gene expression and modulate its Yin Yang effects on target genes. This transcriptional modulation is typically executed through YY1-recruited complexes initiating the

addition or removal of different modifying groups on histone proteins. Other YY1-binding proteins contribute to the transcription-independent functions of YY1, such as Mdm2-mediated p53 ubiquitination and degradation.

4. Regulation of YY1 expression and activity

In addition to transcriptional regulation, YY1-mediated gene transcription and protein modifications, YY1 expression and function are also modulated at multiple levels.

4.1. YY1 is regulated by gene regulatory proteins

As a transcription factor, YY1 regulates the expression of itself through binding to consensus sequences in the first intron of the YY1 gene [82]. These YY1 binding sites are necessary for YY1 gene transcription. Interestingly, overexpressed exogenous YY1 inhibits the transcription of the endogenous YY1 gene, but the reduction of YY1 to normal levels restores this transcription, suggesting a negative feedback loop. Several other transcription factors regulate YY1 expression, including NF-κB, whose regulation of YY1 in prostate cancer will be discussed below.

Raf kinase inhibitor protein (RKIP) is a potential tumor suppressor gene based on its activity in suppressing metastasis and reduced expression in cancers. RKIP overexpression inhibits YY1 transcription and sensitizes cells to TRAIL-mediated apoptosis [83, 84].

In addition to transcription factors, other gene regulatory proteins also modulate YY1 expression. One example is G-quadruplex resolvase (G4R) 1 (also known as RHAU or DHX36], which upregulates YY1 expression by resolving secondary structures in the YY1 promoter. The G-quadruplex (G4) structure is a 4-stranded secondary DNA or RNA structure that is stabilized by non-canonical Hoogsteen hydrogen bonding of planar guanine quartets and their subsequent stacking [85]. G4 structures in gene promoters inhibit gene transcription, which can be relieved by G4 structure resolving helicases.

Both human and murine YY1 promoters have high contents of cytosine (C) and guanine (G) nucleotides that confer these promoters with the potential to form G4 structures [86, 87]. We recently demonstrated that the presence of G4 structures in the YY1 promoter inhibits YY1 expression [86]. High G/C content is a common feature of many proto-oncogenes, such as c-myc and Bcl-2, whereas the promoters of most tumor suppressor genes have reduced numbers of closely-linked guanosine runs [88]. The high G/C content of YY1 and the presence of G4 structures in its promoter and 5′ UTR are strong indicators of the oncogenic nature of YY1.

4.2. YY1 is regulated by post-translational modifications

Lysine residues are one of the major targets of post-translational modifications, acting as a substrate for the addition of acetyl, methyl, ubiquitin or small ubiquitin modifier (SUMO) groups. YY1 contains 32 lysines, equivalent to 8% of its total amino acids, making YY1 a vulnerable target of multiple modifications. Of the 414 amino acids that compose YY1, all lysine

residues are located within the 257 amino acids comprising the middle and C-terminal regions, but not in the first 157 residues (Figure 1).

YY1 recruits p300 and PCAF to mediate histone acetylation of target promoters. Meanwhile, both p300 and PCAF acetylate YY1 in the central region (residues 171-200), augmenting YY1-mediated gene repression [11]. PCAF also acetylates YY1 in the C-terminus and thereby interferes with YY1's ability to bind its DNA consensus sequence [11]. On the other hand, HDACs deacetylate YY1 residues in its central region but not at the C-terminus [11].

YY1 is modified by ubiquitin and SUMO groups. Treatment with a proteasome inhibitor led to an accumulation of YY1 protein, suggesting that YY1 degradation is likely regulated by ubiquitination [48]. However, YY1 mono-ubiquitination enhances its interaction with C-terminal binidng protein (CtBP) and HDAC3 to establish a repressive complex that inhibits the expression of matrix metalloprotease (MMP) -9, a protein promoting cell invasion [53].

PIASy, a SUMO-E3 ligase, promotes the conjugation of SUMO proteins to YY1. We reported that sumoylation exerts an inhibitory effect on YY1-mediated gene expression [89].

YY1 is also subject to other modifications that do not rely on lysine residues. Phosphorylation of YY1 at three particular sites modulates a number of YY1 activities [90]. Among them, serine 247 (Ser247) is located in the spacer region of YY1 while two other sites, threonines 348 and 378, are in YY1's DNA-binding domain (Figure 1). Phosphorylation of the two threonines, but not Ser247, abolishes the DNA binding ability of YY1. Threonine 39 of YY1 was recently identified to be phosphorylated by Polo-like kinase 1; however, its role in modulating YY1 activity remains undetermined [91].

Akt is a well-established oncogene and acts as a critical upstream signaling protein for cell proliferation and survival. YY1 was shown to interact with Akt and is likely a substrate of Akt-mediated phosphorylation. Specifically, YY1 phosphorylation decreased upon treatment with an inhibitor of phosphoinositide 3 kinase (PI3K) that mediates Akt activation [45].

4.3. YY1 is regulated by growth factors & other biomolecules

Oncogenesis involves the upregulation of multiple growth factors, some of which promote YY1 expression. Insulin-like growth factor-1 increases YY1 expression while its depletion significantly decreases YY1 levels [92-94]. Fibroblast growth factor (FGF) -2 also upregulates YY1 expression in vascular cells upon injury [95]. YY1 expression in prostate cancer cells is particularly sensitive to growth factors, which will be discussed below.

Other biomolecules, such as lipopolysaccharide and myeloid nuclear differentiation antigen (MNDA) can promote YY1 expression and modulate its activity through enhancing YY1-DNA association [18, 96]. Conversely, YY1 is negatively regulated by molecules that have anti-growth effects. For example, aphidicolin, the DNA synthesis inhibitor and apoptosis inducer, facilitiates YY1 translocation and cleavage [97, 98].

While YY1 negatively regulates miR-29, this miRNA also binds the 3' UTR of YY1 mRNA and inhibits its translation [59, 99]. The tumor suppressor miR-34a has also been shown to target YY1 and block its expression [100, 101].

Yin Yang (YY) 2 has 65% similarity to YY1 in the protein coding regions while their amino acid sequences share 56% similarity, which is mostly in their DNA binding regions [102]. Thus, YY2 binds the same consensus sequence as YY1, but with a much lower affinity [103]. Interestingly, YY2 exhibits opposing effects on shared YY1 transcriptional targets [104]. YY2 silencing reversed the antiproliferative effects of YY1 depletion [104]. Nonetheless, more studies are needed to delineate the mechanisms and interaction of YY1 and YY2.

Overall, YY1 is activated by different growth factors, whereas antiproliferative signals tend to antagonize YY1 activity. These data support an oncogenic role of YY1 in tumor development and progression.

5. Evidence of YY1's oncogenic regulation in prostate cancer

Many lines of evidence support an oncogenic role of YY1. Most functions of YY1 discussed above contribute to this role in prostate cancer. Importantly, the overexpression of YY1 in prostate cancer augments the oncogenic effects caused by its regulated pathways. We allocate the role of YY1 in prostate oncogenesis into two categories based on the different regulatory mechanisms.

5.1. Transcriptional regulation

As a transcription factor, YY1 generally activates the expression of oncogenic or proliferative genes and inhibits those with tumor suppressive functions [105].

The Rex1 protein is a marker of both mouse and human embryonic stem cells and exhibits reduced expression in prostate cancer cells compared to normal prostate epithelial cells [106]. YY1 positively regulates Rex1 expression in normal human prostate epithelial cells, but this regulation is not observed in prostate cancer cells, suggesting that YY1 transcriptional activity may be altered during transformation [106].

Prostate stem cell antigen (PSCA) is differentially regulated during prostate oncogenesis and its expression is correlated with the development of malignant human prostate cancer. YY1 cooperates with androgen receptor (AR) to regulate PSCA expression [107]. Two YY1 consensus sites have been identified in the PSCA promoter and YY1 is overall essential to androgen-mediated PSCA upregulation in prostate epithelial cell lines. This suggests that YY1 contributes to prostate cancer progression by modulating genes such as PSCA (Figure 2) [107].

YY1 can act as a transcription coactivator to promote gene expression. We demonstrated that the expression of prostate-specific antigen (PSA) in prostate cancer cells is dependent on YY1 [70]. This effect is unaltered when the YY1 binding site in the PSA promoter is mutated, but lost when the direct YY1-AR interaction is disrupted. Since YY1-DNA association is unnecessary for YY1-mediated PSA transcription, YY1 acts as a coactivator in promoting PSA gene expression. We mapped the AR binding domain to the C-terminus of YY1 where its DNA binding site resides, suggesting that YY1 unlikely interacts simultaneously with the

PSA promoter and AR [70]. Elevated PSA levels serve as a diagnostic marker of prostate cancer development, and androgen hormones, which bind to AR and stimulate its activity, are known to facilitate prostate cancer progression [108]. The positive regulation of PSA expression by YY1 suggests its diagnostic and prognostic value in prostate cancer therapies (Figure 2).

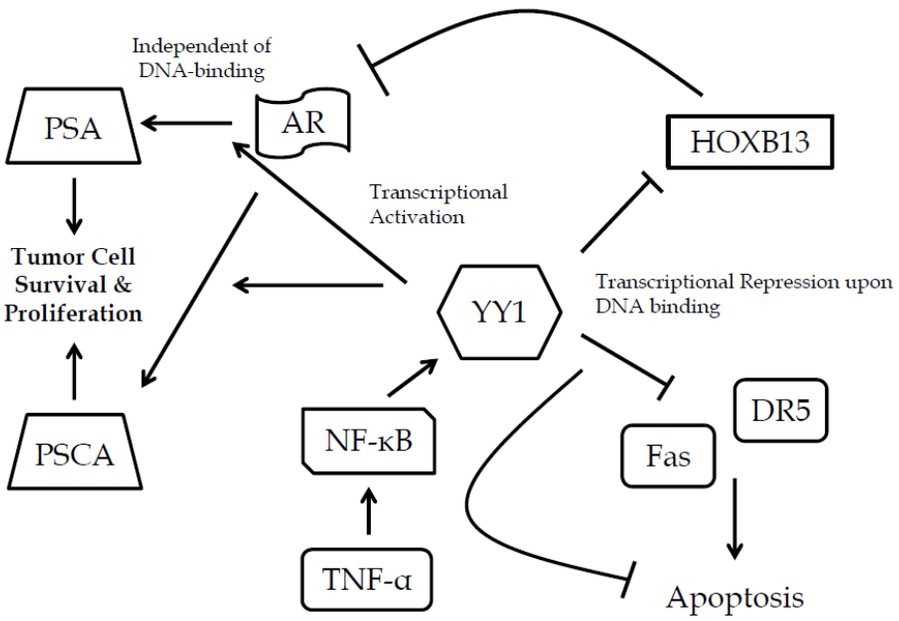

Figure 2. An Overview of Several YY1-Involved Signaling Pathways in Prostate Cancer; YY1 inhibits apoptosis by repressing DR5 and Fas receptors. YY1 and androgen receptor (AR) cooperate to activate expression of prostate specific antigen (PSA) and prostate stem cell antigen (PSCA), both of which contribute to prostate oncogenesis. HOXB13 inhibits prostate cancer cell growth by antagonizing AR signaling. YY1 represses HOXB13 transcription, thereby relieving growth suppression. The growth hormone tumor necrosis factor (TNF)-α enhances NF-κB-mediated YY1 expression and AR activity, promoting cell survival and growth. Overall, YY1 function and regulation support its oncogenic role in prostate cancer development and progression.

More evidence has been demonstrated to show how YY1-mediated transcriptional repression contributes to the oncogenic progression and therapeutic response of prostate cancer.

The homeobox gene HOXB13 suppresses prostate cancer cell growth by negatively regulating AR and T-cell factor (TCF) -4 signaling (Figure 2) [109, 110]. YY1 binds to the HOXB13 promoter and represses its expression through recruiting HDAC4, suggesting that YY1 releases HOXB13-mediated growth arrest of prostate cancer cells [8].

Fas receptor and DR5 are two death receptors regulating extrinsic apoptotic pathways. YY1 negatively regulates the expression of these two receptors (Figure 2) [111, 112]. Nitric oxide (NO) acts as an intracellular second messenger to modify gene expression, including upregulating Fas receptor. The underlying mechanism of this regulation is through NO-induced S-nitrosylation of YY1 and the consequently reduced YY1 DNA binding affinity. This abolishes YY1 mediated Fas receptor gene repression and sensitizes

prostate cancer cells to apoptotic stimuli [111]. A similar mechanism has also been reported in the regulation of YY1 by Rituximab, a synthetic antibody used in the treatment of multiple cancers, including prostate cancer [112]. YY1 inhibits DR5 expression; thus elevated YY1 levels in prostate cancer confer therapeutic resistance to tumor cells through downregulating DR5. Rituximab inhibits both DNA binding and expression of YY1, which consequently activates DR5 gene expression and sensitizes TRAIL-induced apoptosis.

5.2. The regulation of YY1 in prostate cancer-related mechanisms

In addition to the growth stimuli indicated above, YY1 expression is regulated by signaling pathways directly involved in prostate oncogenesis.

NF-κB contributes to prostate cancer development through its constitutive activation of AR expression and therefore serves as a prognostic marker of prostate cancer [113-115]. NF-κB directly binds to the YY1 promoter to enhance YY1 expression (Figure 2) [116]. Thus, genetic deletion of the p65 subunit of NF-κB was associated with decreased YY1 mRNA and protein levels [117]. Consistently, the growth hormone tumor necrosis factor (TNF) -α, an activator of NF-κB transcriptional activity, stimulates NF-κB-mediated YY1 expression in prostate cancer PC-3 cells (Figure 2) [117].

Transforming growth factor (TGF) -β3 is a commonly upregulated growth factor in cancers. A recent study revealed differential regulatory effects of TGF-β3 on YY1 expression in various prostate cell lines [118]. While TGF-β3 promotes YY1 expression in benign prostatic hyperplasia cells, this effect is diminished in LNCaP cells and reversed in DU145 cells. Consistent with other studies, these altered YY1 expression levels inversely correlated to p53 levels [47-49].

The contribution of Akt-mediated signaling pathways to prostate cancer development is well documented. Akt was reported to mediate YY1 phosphorylation and its cytoplasmic translocation, although the target residue(s) and whether the effect is direct or not remain unclear [45]. Tumor suppressor PTEN inhibits the proliferative regulation of Akt through antagonizing its phosphorylation [119-121]. Recent studies demonstrated PTEN-mediated YY1 downregulation through inhibiting PI3K/Akt signaling [52, 122].

Consistent with these mechanistic studies, YY1 was suggested as a biomarker of prostate cancer. A study using a prostate cancer tissue microarray consisting of 1364 representative tissues from 246 hormone-naive prostate cancer patients demonstrated that YY1 levels were increased in tumors of intermediate to high morphologic grades, indicating its upregulation throughout the progression of prostate cancer [3]. Interestingly, YY1 immunohistochemical staining was observed in both nucleus and cytoplasm in tissues of prostate cancer and prostatic intraepithelial neoplasia, consistent with the cytoplasmic localization of YY1 demonstrated in other cells [98]. In another study, YY1 was one of several differentially expressed proteins in prostate cancer in comparison to benign prostatic hyperplasia and contributed to upregulated transcriptional networks [76].

6. YY1 studies in the clinical applications of prostate cancer

Many biological functions of YY1 implicate its oncogenic role in human cancers. Further corroborating these observations is the frequent overexpression of YY1 in cancer cells, including prostate tumors [123]. These oncogenic properties confer YY1 with great potential as a therapeutic target in prostate cancer treatment.

YY1 antagonizes p53 function through multiple mechanisms, including facilitating Mdm2-mediated p53 ubiquitination and degradation, inhibiting p53-mediated transcription, blocking p53 acetylation, and attenuating p14ARF-mediated p53 stablization [47-49]. These suggest that p53 is a primary target of overexpressed YY1's role during prostate oncogenesis. Although p53 is most commonly deleted or mutated in prostate cancers, some tumors retain functional p53, especially at their early stages [124-126]. As a result, many tumors need to overcome p53 tumor suppression early in their cell transformation process, and it is reasonable to hypothesize that YY1 plays a role in overcoming this barrier to tumorigenesis in these developing prostate neoplasms.

YY1 is also implicated as a therapeutic target through its promotion of multiple oncogenes' function and expression. The bona fide oncogene Ezh2 has been used as a marker for aggressive prostate cancers and its overexpression is associated with decreased therapeutic efficacy [127]. Since YY1 is essential to Ezh2-mediated histone H3-K27 methylation, it is possible that YY1 augments the aberrant epigenetics in prostate cancer and contributes to tumor progression by recruiting Ezh2 to its target promoters.

The role of YY1 in prostate cancer therapies has been investigated in multiple studies. As indicated above, YY1 transcriptional activity and expression are negatively regulated by NO and rituximab. Thus, the treatment of the two anticancer drugs DETA/NONOate and rituximab releases YY1-mediated repression of the death receptors Fas and DR5, and sensitizes the ligand-induced apoptosis of prostate cancer cells [111, 112].

7. Summary

YY1 is a multifunctional transcription factor capable of either repressing or activating its target genes, depending on the cellular signals and composition of its recruited complexes. Additionally, YY1 modulates the activity and stability of its interaction proteins by mediating the post-translational modifications of these proteins. Several lines of evidence exist to suggest that YY1 acts as an oncogene in prostate cancer. First, YY1 activates the expression and function of oncogenes, while inhibiting tumor suppressor activity. Secondly, the activity of YY1 itself is promoted by oncogenes and growth factors, and inhibited by tumor suppressors. Third, YY1 is overexpressed in prostate cancers.

Epigenetics implicates reversible processes that do not involve any change of DNA sequence. In theory, simultaneously targeting several epigenetic, cancer-driving pathways should result in more efficient therapies than individually targeting each of them. Thus, if a

singular regulatory protein involved in the abnormality of multiple processes contributing to malignancy is identified, therapeutic targeting of this key regulator will display a substantial impact on disease progression or reversal. To date, no YY1 gene or protein mutation has been reported in any disease. YY1's regulatory role in multiple epigenetic processes coupled with its overexpression in prostate cancer lends YY1 therapeutic potential.

Many questions remain about the role of YY1 in prostate cancer-related biological pathways, and it is likely that such a promiscuous protein has more roles in prostate oncogenesis than what are currently known. Nonetheless, present evidence suggests that YY1 exerts a predominantly oncogenic function and therapeutic targeting of YY1 may result in substantial advances in prostate cancer treatment.

Acknowledgements

This work was supported in part by the Research Scholar Grants (116403-RSG-09-082-01-MGO) from the American Cancer Society and the National Institutes of Health R01 Grant (5R01CA106314-09) to GS. DBS was supported by the National Cancer Institute Training Grant 5T32CA079448.

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