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Transcription Regulator Yin-Yang 1: From Silence to Cancer

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Abstract

Yin Yang (YY) 1 represents the epitome of what is considered to be a "Swiss army knife" transcription factor and regulator. YY1 is a ubiquitous and multifunctional zinc-finger transcription factor member of the Polycomb group protein family, a group of homeobox gene receptors that can act as activators or repressors of transcriptional activity. Furthermore, YY1 can act as a redox sensor, adaptor molecule, and chromatin structure and function regulator. YY1's characteristic function as transcriptional activator and repressor relies on its C2H2 (x4) zinc-finger structural DNA-binding motifs tangled with 2 specific regulatory domains. This structural conformation will render the activity of YY1 susceptible to changes in cellular redox status. YY1 also has been shown to undergo chromatin remodeling via interactions with histone acetyl transferase and histone deacetylase complexes. Both groups modify histones, resulting in altered chromatin structure. Herein, we will discuss the multiple roles and mechanisms of YY1 in the regulation of gene expression, its genetic factor functions, epigenetic regulatory activity, and its role as a redox sensor in the context of malignant neoplastic diseases.

Keywords

transcriptional regulation; gene expression; nitric oxide; redox regulation; zinc-finger; oxidation

I. INTRODUCTION

Transcriptional regulation of gene expression is a complex and well-orchestrated process where many actors come to secure a timely and precise expression of a particular gene or group of genes. This organized process is not an isolated event and is the result of the interaction of a myriad of molecular signals that converge in the activation or repression of genes in response to the intracellular or extracellular environment. Transcription factors are molecules specialized in the interaction with regulatory regions on the deoxyribonucleic acid (DNA) that control either the activation or the suppression of gene expression by controlling the initiation of the transcription from DNA to messenger ribonucleic acid (RNA). Transcription factors perform this function alone or in association with other factors or molecules in a complex by promoting or blocking the recruitment of the transcriptional machinery –generally represented by the RNA polymerase– to regulatory regions of specific

genes. They can be modified by epigenetic elements or be disrupted in their functions by environmental and intracellular changes such as the oxidative state of the cell (redox status).

Yin Yang (YY) 1 is a transcription factor that can fulfill both functions—an activator or a repressor—of gene expression. It can bind DNA directly or indirectly through association with other transcription factors or adaptor molecules. It can mediate the epigenetic regulation by its association with proteins that control chromatin organization, and it varies its functional structure and DNA binding activity in response to temporal redox changes in the cell. YY1 epitomizes the “Swiss army knife” transcription factor and regulator (Fig. 1).

YY1 is expressed ubiquitously in many tissue types, and its mechanisms of activation/inactivation remain unclear. There is much experimental evidence suggesting that subtle changes in expression of YY1 might control its final activity. In addition, reversible posttranslational modifications leading to conformational changes or variations in protein stability have been implicated in the regulation of YY1 activity.

More than a decade ago, we reported a possible association between YY1 activity as a repressor of gene expression and the sensitivity of tumor cells to mechanisms of programmed cell death or apoptosis, implicating the role of YY1 in cancer. Since then, others and we have contributed to the increasing body of knowledge in which YY1 clearly is associated with malignant processes by either interfering with the sensitivity of tumor cells to apoptosis (resistance), increasing survival mechanisms, or promoting alterations in the control of the cell cycle. In addition, the expression of YY1 has been correlated with possible prognostic value in the state of disease or as an indicator of clinical behavior in cancer progression. However, its intimate molecular mechanisms of regulation and direct implication in cancer remain elusive.

In this review article, we attempt to put in perspective the fundamental aspects pertaining to the multiple functions of YY1 in the context of malignant neoplastic processes and the potential mechanism involved in it. We have examined the basic elements of the YY1 molecule such as its structure and the correlation with its multiple and sometimes opposing functions. Further, we present some of the fundamental elements that have been correlated to YY1 activity as a direct genetic factor and an epigenetic regulator by its association with proteins playing a major role in the chromatin plasticity and regulation. Finally, we analyze the role of YY1 as a redox sensor based on its characteristic structure, which exhibits 4 C₂H₂-type zinc-finger motifs on its DNA binding domain totally exposed as “antennas” that sense changes in the oxidative status of the cells that can be exploited therapeutically, as we have proposed and demonstrated in the case of using nitric oxide (NO)-releasing agents to sensitize cancer cells to apoptosis-mediated stimuli.

II. MOLECULAR SENSE AND FUNCTION

A. One Identity, Diverse Nomenclature

Two original studies sparked the cloning and molecular characterization of YY1. During the study of the adeno-associated virus (AAV) P5 promoter region and its activation by E1A gene products, Berns and Bohenzky¹ and Chang and colleagues² identified 2 elements associated with basal and E1A-induced P5 activity. Both elements had a negative effect in the absence of E1A oncoprotein, but was converted to transcriptional activators in its presence. Furthermore, simultaneous deletion of both elements reduced P5 promoter activity 25-fold, raising the possibility of the presence of the dualacting transcriptional factor YY1.

In 1991, 2 independent groups simultaneously reported the cloning and characterization of the multifunctional transcription factor YY1. Initially, Shi et al.³ described the identification

of 2 cellular proteins binding overlapping regions within the transcription control elements of the AAV P5 promoter. YY1 was found to be responsible for the repression of the promoter activity, whereas E1A relieved repression exerted by YY1 and further activated transcription through its binding site. Furthermore, Park and Atchison⁴ have isolated a human cDNA clone encoding a zinc finger protein termed *nuclear factor E1 (NF-E1)*, which binds to the negative-acting elements of the immunoglobulin κ enhancer. It was determined that NF-E1 was encoded by the same gene as the YY1 factor, which binds to the AAV P5 promoter. Hariharan and colleagues⁵ identified and cloned a protein, which they termed δ , based on its ability to bind to sequence elements downstream of the transcriptional start sites in ribosomal protein genes. It was determined that NF-E1 is also the human homologue of the mouse delta (δ) protein binding to ribosomal protein gene promoters.^{6,7} Subsequently, YY1 has been identified in other species and has been assigned alternate nomenclature by other authors, including upstream control region binding protein,⁸ nuclear matrix protein 1,⁸ and common factor 1.⁹

B. Yin Yang 1: The Molecule

YY1 is a multifunctional zinc-finger transcription factor with great sequence similarity in its finger domain to members of the GLI-Krüppel family of human zinc-finger proteins. This group of proteins encodes a zinc-finger protein with 4 zinc-finger domains repeated in tandem. The *Drosophila* Krüppel protein has been shown to hold the ability to both activate and repress transcription.^{10,11} Functionally, YY1 is a member of the Polycomb group proteins, a family of proteins that are characterized by their ability to remodel chromatin such that transcription factors cannot bind their cognates' responsive elements on the promoter region, such as in the case of preventing the expression of homeotic (Hox) genes in *Drosophila*.^{12,13}

C. Molecular Structure

The *YY1* gene has been mapped to the telomere region of human chromosome 14 at segment q14 in humans.^{14,15} The *YY1* gene consists of 5 highly conserved exons encoding a protein 591 amino acids in length and an estimated molecular weight of 62.8 kDa (pI 8.0).¹⁶ The sequence of the *YY1* gene is supported by 850 sequences from 781 cDNA. The human *YY1* gene produces 7 different transcripts (a, b, c, d, e, f, and g) generated by alternative splicing, encoding 7 different putative protein isoforms (2 complete and functional, 3 COOH-complete, and 2 partial).¹⁵ The function of these isoforms remains unclear. Two alternative promoters have been identified as controlling the expression of the 2 complete isoforms. Different transcripts differ by truncation of the 5' end, truncation of the 3' end, presence or absence of 4 cassette exons, and different boundaries on common exons due to variable splicing of an internal intron.

D. Regulation of Yin Yang 1 Activity

Despite all recent developments in the molecular characterization of the nature of YY1, very little is known about the regulation of YY1 activity. Transcriptional control of YY1 expression seems to be regulated constitutively. More evidence has been gathered on the regulation of YY1 based on its cellular localization, trafficking, and posttranslational modifications. It has been shown that YY1 is associated with the nuclear matrix. McNeil et al.¹⁷ have identified specific sequences that lead YY1 to nuclear targets. Progression through the cell cycle also induces a DNA replication-associated switch in YY1 subcellular localization. As a DNA binding protein, YY1 functions in the replication and regulation of the histone alpha complex, vital for proliferating cells.¹⁸

Histone deacetylases (HDACs) and histone acetyltransferases (HATs) are 2 groups of proteins, previously known to function as corepressors and coactivators, that have been

shown to modulate the function of YY1. These 2 types of enzymes modify histones, and this modification is proposed to alter chromatin structure with gene expression consequences. HATs typically are localized to active chromatin whereas HDACs colocalize with transcriptionally inactive chromatin. When these enzymes are directed to a promoter through a DNA binding factor such as YY1, that promoter can be activated or repressed.⁹

It has been shown that YY1 is a stable phosphorylated protein expressed ubiquitously regardless of cell cycle position or the differentiation status of the cell,¹⁹ suggesting that the activity of YY1 is regulated at the posttranslational level, possibly through interactions with other proteins. A wide variety of transcription factors have been shown to associate with YY1, including proteins of the basal transcription machinery, such as the TATA-binding protein¹⁹; TFIIB²⁰; sequence-specific DNA-binding transcriptional activators, such as Sp1,^{21,22} c-Myc,²³ activating transcription factor/ cyclic adenosine monophosphate response element binding (CREB),²⁴ CCAAT/enhancer-binding protein²⁵; and a series of transcriptional coregulators, such as E1A,²⁶ TAFII55,²⁷ p300, CREB protein,^{19,28} and HDAC1, HDAC2, and HDAC3.^{29,30} The YY1-p300 and YY1-HDAC interactions are of particular interest. p300 and CREB protein are 2 closely related transcriptional coactivators that have been shown to be HATs.^{31,32} Yao et al.³³ have demonstrated that YY1 activity is regulated through intricate mechanisms involving negative feedback loops, histone deacetylation, and recognition of the cognate DNA sequence affected by acetylation and deacetylation of the YY1 protein.

Direct proteolysis also has been implicated in the regulation of the activity of YY1. It has been shown that YY1 can be a substrate for cleavage by the calcium-activated neutral protease calpain II (m-calpain) and the 26 S proteasome.³⁴ In addition, transcription factor NF kappa (κ) B has been shown to regulate YY1 by direct binding of the Rel-B component of NF- κ B to YY1 and sequences at the HS4 enhancer region of B-cell lymphoma immunoglobulin H gene, thereby implicating this complex in the antiapoptotic response and the up-regulation of the proliferative potential of these lymphocytes *in vivo*.³⁵

III. Yin Yang 1 AND CANCER?

A. The Way We Met: In Search of Silence

Although there were several pieces of evidence suggesting the potential role of YY1 in cancer, none of those were direct implications of the participation of YY1 in the onset, development, or persistence of malignancies.

We have shown previously that the sensitization to Fas-mediated apoptosis in ovarian carcinoma cell exposed to interferon (IFN)- γ is in part due to the generation of NO or derivatives by the induction of NO synthase (NOS) type II enzyme (iNOS) by tumor cells. Inhibitors of NOS interfered with the observed sensitization. Furthermore, the use of NO donors mimicked the IFN- γ -mediated sensitization to a Fas-agonist antibody in cancer cells. In addition, a concurrent upregulation of Fas receptor was observed, either upon induction of iNOS by IFN- γ or by the treatment of cancer cells with NO donors. The observed up-regulation of the Fas receptor was abrogated by the use of NOS inhibitors, suggesting a strong correlation that might account for the sensitization to Fas-induced apoptosis.³⁶

Morimoto et al.³⁷ have demonstrated the influence of IFN- γ in the regulation of Fas receptor expression on the tumor cell surface. Studies searching for the role of NO in vascular smooth muscle cell apoptosis showed that NO induces upregulation of Fas antigen expression via a cyclic guanosine monophosphate-independent mechanism.³⁸ Further, NO primes pancreatic β cells for Fas-induced apoptosis by increasing the surface's CD95

receptor expression.³⁹ However, it was unclear how NO was affecting the transcriptional machinery to regulate Fas gene expression.

Characterization of the human Fas (CD95/Apo-1) gene promoter has revealed 3 major regions within 2000 base pair of the 5'-flanking region. Functional analysis has identified a silencer activity residing between nucleotide position -1781 and -1007 and a strong enhancer region between -1007 and -425 in the human Fas gene. The region between -425 and -1 retained basal promoter activity.⁴⁰ A subsequent study, aimed at identify the specific mechanisms by which NO could regulate the expression of Fas gene, demonstrated the direct effect of NO on the inactivation of negative regulatory trans-acting signals on the Fas promoter. This evidence suggested the possibility that a negative regulatory factor was suppressing the expression of Fas and most likely would be sitting on the silencer region of the promoter. Further in silico analysis of the silencer region of the Fas promoter revealed a cluster of putative responsive elements for YY1.

It was established that the mechanism by which NO up-regulates the expression of the Fas receptor on different tumor cells is caused by the specific inactivation of the transcription repressor YY1 DNA-binding activity to the silencer region of the Fas promoter.⁴¹ Similarly, it has been suggested the specific role of NO in the regulation of TRAIL receptor (DR5) gene expression via disruption of the repressor activity of YY1.⁴²

Further, it was determined that the mechanism of NO-mediated inhibition of YY1 DNA-binding activity was caused by S-nitrosylation of critical cysteines residues coordinated by Zn²⁺ residing at its 4 zinc fingers. This resulted in inhibition of the transcriptional repressive activity of YY1 and an increase in the expression of Fas and DR5 and subsequent tumor cell sensitization to Fas- and TRAIL-induced apoptosis.⁴³

Although its diverse functions allow for the context-specific paradoxical effects of transcriptional initiation, activation, and repression, the overwhelming evidence of the role of YY1 in tumor biology would support the hypothesis that YY1 functions to promote carcinogenesis and perhaps even confer cells with a mechanism for evading cell death in the face of cytotoxic stimuli, including chemotherapy and/or immunotherapy. Primary mechanisms seem to include perturbations in cellular surveillance systems as well as modulation of key genes involved in cell cycle regulation and programmed cell death.

B. Redox Sensing: Back to Structure

A distinguishing feature of YY1 is its exquisite sensitivity to cellular redox status. This can be explained based on the structural characteristics of its functional domains. The YY1 protein contains 4 C2H2-type zinc-finger motifs with 2 dedicated domains that characterize its dual function as an activator or repressor. Fusion protein analysis revealed repression of transcription by the C-terminus domain (amino acids 298–397).^{3,16} Two other domains contributing to its repression include sequences within the zinc-finger motifs and a glycine-rich residue between amino acids 157 and 201. The N-terminus region (amino acids 43–53), however, acts as a potent activation domain, which is followed by a glycine-rich domain and 11 consecutive histidine residues (amino acids 70–80).^{16,44} The role of this sequence remains unclear, although it has been considered that this basic histidine segment could neutralize the putative activating function of the neighboring acidic domain under repressing conditions.¹⁶

A partial crystal structure for YY1 has been reported, based on the zinc-finger domain bound to the AAV P5 promoter initiator element. The 2.5-Å resolution YY1-initiator element co-crystal structure revealed 4 zinc fingers recognizing a YY1-binding consensus sequence.⁴⁵ The YY1-initiator complex demonstrated many features of DNA recognition by

zinc-finger proteins. All 4 fingers bind to the major groove, using residues in positions within the finger similar to those responsible for stabilizing homologous proteins. Finger lengths and amino acid contacts are distributed along the DNA's major groove, exposing areas of zinc coordination within the finger to the outer part of the complex molecule. The observed pattern of protein-DNA contact also explains how YY1 can be modified structurally by the oxidation of its thiol-containing residues at the zinc-finger regions serving as sensing antennas for the cellular redox status (Fig. 2).

C. From Silence to Cancer

After the initial characterization of YY1 as one of the main transcriptional repressors controlling the expression of the Fas gene in tumor cells and, through this, regulating the sensitivity of tumor cells to apoptosis-mediated mechanisms, a myriad of investigations emerged to demonstrate the paradoxical role of YY1 in tumorigenesis.

There are several lines of evidence supporting the role of YY1 in tumorigenesis. An initial obvious starting point for this type of association is the implication of YY1 in molecules that regulate cell cycle. Direct association of YY1 with cell cycle signaling pathways has been suggested after observing that cyclin D1 gene promoter activation in estrogen-responsive human breast cancer is marked by release of the YY1 transcriptional repressor complex, leading to the accumulation of cyclin D1 in the cell and contributing to the long-lasting gene enhancement required to drive G1-phase completion and subsequent promotion of tumor cell proliferation.⁴⁶

YY1 may attenuate p53-dependent transcription from a subset of p53 target genes, a hypothesis that may be relevant for defining the role of YY1 in directing cells to arrest either growth or apoptosis upon p53 binding. YY1 interacts with p53 and inhibits its transcriptional activity by disrupting the interaction between p53 and its coactivator p300, thereby blocking p300-dependent p53 acetylation and stabilization and disabling this checkpoint mechanism.⁴⁷

The proto-oncogene c-Myc has been demonstrated to have a fundamental role in cellular processes such as proliferation, differentiation, apoptosis, and transformation. c-Myc activity has been implicated in the pathogenesis of malignancies such as breast, ovarian, prostate, hepatocellular, and colorectal carcinomas as well as lymphoma and plasma cell tumors.⁴⁸ YY1 can activate both endogenous and exogenous c-Myc promoters when overexpressed. In turn, c-Myc overexpression seems to alter the constitutive repressive role of YY1 by interfering with the association between YY1 and basal transcription proteins such as TATA-binding protein and transcription factor IIF, with altered transcription of target genes.⁴⁹ Hence, YY1 may serve constitutively to repress c-Myc-responsive antiapoptotic signals.⁵⁰

As mentioned in previous sections, another key cellular process in which YY1 plays a fundamental role in control is at the programmed cell death or apoptosis. The most relevant transcription factor participating in the regulation of genes involved in apoptosis is the NF- κ B promoting the expression of antiapoptotic genes, therefore conferring resistance to cell death stimuli.^{51–54} Several models have increased the amount of evidence by revealing the specific influence of YY1 in the regulation of antiapoptosis-related genes via direct or indirect control of NF- κ B. Vega et al.⁵⁵ have shown that inhibition of YY1 activity by either rituximab (chimeric anti-CD20 monoclonal antibodies), treatment with NO donors, or after silencing RNA-mediated gene knockout of YY1 in B non-Hodgkin lymphoma cells resulted in up-regulation of Fas expression and sensitization to Fas-mediated apoptosis, suggesting that the regulation of Fas resistance by NF- κ B is mediated via YY1 expression and activity. Further, these observations were confirmed in other tumor cell types and models, including

those involving TRAIL-mediated apoptosis and regulation of its cognate death receptors.^{56–63}

Raf-1 kinase inhibitor protein (RKIP) has been implicated in the regulation of cell survival pathways and metastases, and it is not highly expressed in tumors. RKIP overexpression in human prostate cancer and melanoma cells regulates tumor cell sensitivity to TRAIL via inhibition of YY1, upregulation of DR5, and modulation of apoptotic pathways.⁵⁸ Frequent alterations of the YY1:RKIP ratio were found in hepatocellular carcinoma. The ratio of YY1:RKIP messenger RNA constantly was inverted profoundly in the tumors compared with the adjacent nontumoral tissues. A similar result was shown to occur frequently at the protein level. Hyperactivation of YY1 in tumors was contrasted with its nuclear localization and the finding that in the tumors there were increases in YY1-associated protein, an YY1 coactivator not expressed in normal liver, and in survivin, a possible target of YY1. The frequent alteration in the YY1-RKIP balance might represent a marker of malignant progression.⁶⁴

In addition, YY1 has been implicated in the modulation of taxane response in epithelial ovarian cancer. YY1 knockdown in ovarian cancer cell lines results in inhibition of anchorage-independent growth, motility, and proliferation, but it also increases resistance to taxanes, with no effect on cisplatin sensitivity. These results, and the resulting augmentation of microtubule-related genes by E2F3, suggest that enhanced taxane sensitivity in tumors with high YY1/E2F activity may be mediated by modulation of putative target genes with microtubule function.⁶⁵

Differential nuclear YY1 expression has been demonstrated in human osteosarcoma cells in contrast to osteoid tissue. YY1 gene activation seems to be an early event in the process of osteoblastic transformation that can be associated with increased resistance to apoptosis.⁶⁶ In prostate cancer, YY1 expression and localization were examined by immunohistochemistry. Analysis of the data demonstrated that cancer cells show higher expression of YY1 than normal tissues. In addition, the data demonstrated the prevalence of a subset of patients whose YY1 expression predicted tumor recurrences. These studies suggested that YY1 expression might be considered a prognostic marker in prostate cancer, independent of other markers.⁶⁷ Furthermore, YY1 was uniformly highly overexpressed in a wide range of human cancer cell lines and in human colon cancer tissue samples. YY1 immunoreactivity in human colon tumor samples was shown to be more intense in poorly differentiated tumors than in moderately and well-differentiated colon cancers, and lower expression levels tended to be associated with shorter survival. YY1 was overexpressed in colon cancer in the absence of gene amplification and chromosomal translocation.⁶⁸

In contrast, there have been some reports high-lighting the positive role and implication of the overexpression of YY1 in tumor cells. Naidoo et al.⁶⁹ recently reported that YY1 expression predicts favorable outcome in follicular lymphoma. Expression levels of YY1 protein were increased significantly in live patients compared with dead patients after follow-up ($P = .025$). In this study, Kaplan-Meier analysis showed association of higher expression levels of YY1 with longer survival ($P = .01$; hazard ratio, 3.33; 95% confidence interval, 1.26–8.85). The multivariable analysis identified YY1 protein level as the strongest predictor of outcome ($P = .018$), with none of the other markers being significantly associated with outcome. Furthermore, Lee et al.⁷⁰ reported that YY1 positively regulates the breast cancer-associated gene 1 and inhibits mammary cancer formation.

IV. CONCLUSIONS

Our knowledge about the ubiquitous and multifunctional transcriptional regulator YY1 has evolved significantly since it was first cloned and identified in 1991. Moreover, the specific

role of YY1 in cancer is been reinforced by mounting evidence, triggered after initial identification, of YY1 as the key suppressor mechanism in the resistance of tumor cells to Fas-mediated apoptosis. Its transcriptional regulation functions correlate directly to its molecular structure and, possibly, to its myriad of interactions at the site of transcriptional control. Noteworthy is its capacity to sense the intracellular redox environment through its suited zinc-finger structures that are exposed to the outer part of the transcriptional complex.

YY1 is a central component intercalated between the 3 major elements determining the nature and potential regulation of the cell biology: (1) cell cycle/ proliferation, (2) oncogenes/tumor suppressor genes, and (3) apoptosis/survival (Fig. 3).

Although we are more aware of the elements that govern YY1 cellular activity, the precise mechanisms of control remain elusive. Subtle changes in its level of expression, posttranslational modifications, and/ or subcellular localization dictate the final outcome in the potential role of YY1 in oncogenesis. The overall account of correlations between increased cellular YY1 expression in tumor cells suggests—if not confirms—its tremendous diagnostic/prognostic value. In addition, it places YY1 as a plausible target for therapeutic intervention for the control of malignant cells.

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ABBREVIATIONS

YY1	Yin-Yang 1
HAT	histone acetyl transferases
HDAC	histone deacetylases
NO	Nitric Oxide
AAV	Adeno-Associated virus
NF-κB	nuclear factor kappa B
IFN-γ	Interferon gamma
NOS	Nitric oxide synthase
RKIP	Raf-1 kinase inhibitor protein
BRCA1	breast cancer-associated gene 1

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FIGURE 1.
Yin Yang 1: the “Swiss army knife” transcription factor and regulator.

FIGURE 2.

Co-crystal structure revealing 4 C₂H₂-type zinc-finger motifs recognizing a YY1-binding consensus sequence on the adeno-associated virus P5 initiator. A, Transversal view. B, Lateral view. Images were generated using Cn3D software version 4.3 (<http://www.ncbi.nlm.nih.gov/Structure/CN3D/cn3d.shtml>) and based on data from the Molecular Modeling Database⁴⁵ and the Protein Data Bank.⁴⁵

FIGURE 3.

Yin Yang 1 is a central component intercalated between the 3 major elements determining the nature and potential regulation of the cell biology: (1) cell cycle/ proliferation, (2) oncogenes/tumor suppressor genes, and (3) apoptosis/survival.