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Oncogenic Potential of Yin Yang 1 Mediated Through Control of Imprinted Genes

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Abstract

The transcription factor Yin Yang (YY) 1 is one of the most evolutionarily well-conserved DNA binding proteins that is ubiquitously expressed among different tissue types. YY1 functions as a critical regulator for a diverse set of genes, making its role in the cancerous environment elusive. Recent studies have demonstrated that clusters of YY1 binding sites are overrepresented in imprinted gene loci. These clustered binding sites may function as a molecular rheostat with respect to YY1 protein levels. YY1 levels were documented to be altered in various tumor tissues in conjunction with the transcriptional levels of the imprinted genes it regulates. This review highlights the unexplored mechanism through which fluctuations in YY1 protein levels alter the transcriptional status of imprinted genes containing clustered YY1 binding sites, which potentially could affect cancer development and/or progression.

Keywords

YY1; imprinting; cancer; imprinting control region; paternally expressed gene three; guanine nucleotide binding protein; alpha stimulating

I. INTRODUCTION

Yin Yang (YY) 1 is a transcription factor that is present in multiple species, ranging from flying insects to placental mammals. It was identified almost 20 years ago by 3 independent groups and was originally named YY1, DELTA1, or nuclear factor-E1.^{1–3} According to numerous studies conducted during the past 2 decades, YY1 can function as an activator, repressor, or initiator of gene transcription,^{4–8} and bioinformatic estimates suggest that YY1 might regulate approximately 10% of the total human gene set.⁹ It is interesting to note that many of the genes bound by YY1 are involved in cell cycle regulation, including *p21*, *p57*, *cdc46*, *cyclin B1*, and *cyclin B2*.¹⁰ YY1 also interacts with numerous proteins to perform diverse cellular functions. In particular, YY1 is known to interact with several histone-modifying complexes, including histone deacetylase 1/2, p300, and proteinarginine N-methyltransferase 1, which may provide a molecular basis for its activator or repressor role.^{5,7} Consistent with these observations, a number of studies have reported that YY1 often is overexpressed in various types of cancers.¹¹ In addition, YY1 has been shown to control a large fraction of imprinted genes in mammals.^{12,13} The exact dosage (i.e., expression levels) of imprinted genes is critical for organism survival, thus misregulation of these imprinted genes often is observed in various disease states of mammals, including imprinting-related genetic disorders and cancers.^{14,15} In this short review, we will discuss a

possible route through which YY1 can cause cancers or disease states via control of imprinted gene transcription. We will discuss (1) how YY1 and vertebrate genomes have evolved, (2) how YY1 is involved in the regulation of several imprinted genes, and, finally, (3) describe several known cancer-related cases where imprinted genes are misregulated, possibly through changes in YY1 regulation.

II. EVOLUTION OF YIN YANG 1 AND VERTEBRATE GENOMES

YY1 is one of the few DNA binding proteins that has remained well-conserved during animal evolution.¹⁶ Mammalian YY1 proteins consist of 414 amino acids and are divided into several protein domains based on the presence of known protein motifs and unusual amino acid compositions.^{4,5} Among these domains, 2 are particularly well-conserved throughout all species of animals: a 25 amino acid recruiting Polycomb complex domain and a 120 amino acid Gli-Kruppel zinc-finger domain (Fig. 1A).¹⁷ The recruiting Polycomb complex domain interacts with YY1 associated factor 2, which is responsible for joining YY1 to RING1B, a component of Polycomb repression complex 1.¹⁸ This domain also has been demonstrated to be crucial for YY1's repressive functionality.^{17,18} The zinc-finger domains of YY1 are responsible for binding to DNA. This DNA binding domain displays very unusual levels of sequence conservation during evolution, producing an almost 100% amino acid sequence identity between insects and vertebrates (Fig. 1B).¹⁶ This conservation implies that the YY1 proteins from different species all bind to similar DNA sequences, a fact confirmed independently by several groups.^{19–21} Overall, YY1 has been well-preserved throughout different vertebrate species and flying insects, which represents a very unique case of gene evolution in the higher eukaryotes' genomes.

Despite the evolutionary conservation of YY1 at the protein structure level, the function of YY1 is predicted to have diversified tremendously during animal evolution based on multiple observations. First, the temporal expression pattern of YY1 shows a dramatic difference between insects and vertebrates. In flying insects, Pho, the homolog of YY1, is expressed only during early embryogenesis, which is a typical pattern for developmental regulators.²² In contrast, the expression patterns of vertebrate YY1 are both temporally and spatially ubiquitous.²³ This observed expression pattern shift suggests that the stage-specific developmental regulator role of Pho (YY1) in flying insects may have adapted into a more general transcription factor role in vertebrates. Second, the size of vertebrate genomes has increased significantly relative to that of insects. The main cause for this increase is believed to be the accumulation of a large number of repetitive DNA elements. Many of these repetitive elements have YY1 binding sites within their DNA sequences, thus adding a large number of potential YY1 binding sites into the vertebrate genome.^{24,25} Although the exact function of YY1 at these repetitive elements currently is unknown, it is likely that YY1 functions by silencing any "transcriptional noise" from these elements through a surveillance-type mechanism.⁴ In addition to this large number of newly added YY1 binding sites in the vertebrate genome, the number of actual genes bound by YY1 has increased dramatically when compared with the number of Pho's bound genes in the flying insects' genome. This increase in the number of YY1 target genes in vertebrate genomes also is consistent with the changes in both its expression pattern and functional shift to a general—versus development-specific—transcription factor.

According to genome-wide surveys, YY1 has maintained a predominantly single-copy gene status during animal evolution.¹⁶ This result is in stark contrast to the evolution pattern of other DNA binding proteins with similar evolutionary ages, such as SP1 and E2Fs. For most evolutionarily ancient genes, the number of gene copies has increased when the genome size and complexity has become larger.^{26,27} This increased number of gene copies for DNA binding proteins probably was necessary to help the vertebrate genome cope with new and

diverse functional demands. YY1's only 2 duplicated copies, REX1 and YY2, are recent evolutionary events that occurred only in placental mammals.¹⁶ Thus, the evolutionary significance of these duplications cannot be correlated to an increase in genome size or complexity and have remained relatively unstudied. Overall, the evolutionary constraint on YY1 genomic copies suggests it has developed fundamental cellular functions; thus the protein levels of YY1 likely are monitored and controlled tightly to maintain essential gene regulatory and signaling pathways. Consistent with this prediction, recent studies have revealed that the genomic locus of YY1 in all vertebrates contains a unique cluster of its own binding sites within the first intron (Fig. 2A).²⁸ Interestingly, this cluster of YY1 binding sites was shown to regulate the transcription rate of the YY1 locus as a molecular rheostat (Fig. 2B). The clustered YY1 binding sites promote gene activation when there are lower-than-normal levels of YY1 protein available. However, when cellular levels of YY1 protein are higher than normal, these multiple binding sites stimulate gene repression. Thus, this cluster of YY1 binding sites is thought to be important for the homeostasis of the YY1 protein. This observation further supports the theory that YY1 protein levels are critical for basic cellular survival, thus requiring tight control within a very narrow range of tolerable fluctuations.

III. YIN YANG 1 AND GENOMIC IMPRINTING

A small subset of mammalian genes are expressed mainly from one allele because of repression of the other allele through epigenetic modification, such as DNA methylation and/or histone modification. These "imprinted" genes occupy specific chromosomal regions, creating larger imprinted domains ranging from 500 kilobases to 2 megabases.²⁹ The imprinting (allele-specific expression) and transcription for a given domain typically are controlled by smaller genomic regions, 2 to 4 kilobases long, termed *imprinting control regions* (ICRs).²⁹ Several ICRs were confirmed to contain clusters of YY1 binding sites, similar to those in the YY1 locus depicted in Fig. 2. The list of these loci includes the ICRs of the paternally expressed gene (PEG) 3, guanine nucleotide binding protein, alpha-stimulating (GNAS) complex locus, and X (inactive)-specific transcript (XIST) domains.^{12,13} ICRs are known to have 2 main functions: They obtain allele-specific DNA methylation during gametogenesis and maintain this methylation in somatic cells. ICRs also control the transcription of nearby imprinted genes through a long-distance *cis* regulatory mechanism.²⁹ Given that YY1 binding sites are located within ICRs, the 2 main functions of ICRs likely are mediated through YY1. Results derived from previous *in vivo* and *in vitro* studies confirm this prediction. Reducing cellular levels of YY1 protein can alter the DNA methylation levels at specific ICRs, such as those for PEG3 and XIST, confirming YY1's role in establishing and/or maintaining allele-specific DNA methylation at ICRs.³⁰⁻³² Similar RNA interference-based YY1 knockdown experiments produced global changes in the expression levels of multiple imprinted genes within an imprinted domain, also confirming YY1's role as a *trans* factor controlling the transcription of imprinted genes.^{30,31}

Genome-wide surveys indicate that a small number of genomic loci (fewer than 10) contain clusters of YY1 binding sites similar to those in ICRs and the YY1 locus itself.¹³ The reason these loci need to maintain clusters of YY1 binding sites currently is unknown. Given all the known information about YY1 and genomic imprinting, we predict that the following scenarios most likely influence this cluster maintenance: (1) Clustered YY1 binding sites may be designed for securing a sufficient amount of YY1 protein, locally, around ICRs for their functional needs, such as DNA methylation during gametogenesis or transcriptional control in somatic cells. YY1's involvement in many diverse cellular pathways places a high demand on its total protein levels; thus, securing sufficient amounts of YY1 protein likely is critical for the functional needs of imprinted genes. (2) Clustered YY1 binding sites inside ICRs also could function as individual molecular rheostats, similar to the binding clusters in

the YY1 locus itself (Fig. 2B). It has been well-established that genomic imprinting is essentially a gene dosage control mechanism; thus, even slight changes in the expressed amount of imprinted genes are not tolerable for the survival of cells or organisms.^{14,15} Imprinted genes might use clusters of YY1 binding sites to control their transcription rates in response to fluctuating cellular conditions. In this case, subtle changes in cellular YY1 protein levels may function to modulate temporarily the transcriptional activity of imprinted genes. These possibilities remain to be investigated, but we strongly believe that one or both of these scenarios may be responsible for the presence of clusters of YY1 binding sites for these loci. In summary, the clusters of YY1 binding sites found within ICRs are unique, and we predict that the cellular levels of YY1 protein play a critical role in regulating the transcriptional rate of imprinted genes, possibly through the clusters of YY1 binding sites.

IV. ONCOGENIC POTENTIAL OF YIN YANG 1 THROUGH IMPRINTED GENES

Literature reviews have established that gene expression of YY1 generally is higher in many tumor tissues compared with their normal counterparts.^{7,11,33} Increased YY1 expression can correlate with either positive or negative disease outcomes, based on both a given cancer type and the treatment regime employed. This disparity may result from increased YY1 expression inducing cell growth in some tumors while at the same time making other tumors more susceptible to established chemotherapeutics (such as treatment with taxanes).¹¹ This variability also may arise partially from YY1's ability to interact with multiple transcription factors to facilitate gene activation, repression, or suppression in different cellular contexts. Newly developed cancer treatment regimens have employed either trichostatin A (a histone deacetylase inhibitor) or 5-azacitidine (a DNA methyltransferase inhibitor) and have demonstrated a reversal in cancer growth or progression.^{34–38} Some of these studies also have tied this drug-induced reversal in cancer progression to changes in either YY1's protein complex recruitment abilities or its DNA binding properties. Thus, it is possible that a main function of YY1 in cancer is to modulate epigenetic marks at specific gene loci, ultimately to control gene expression. Although YY1 can regulate a diverse set of genes, its modulation of multiple imprinted gene loci may prove to have some of the more profound effects on its correlation to cancer outcomes.⁷

Originally, genomic studies from tumors of single-parent origin demonstrated that an imbalance of imprinted genes, through changes in gene dosage, could result in tumor formation.³⁹ More recent molecular studies have illustrated that changes at imprinted loci may be responsible for embryonic rhabdomyosarcoma and other childhood tumors.^{40,41} Imprinted genes, being expressed from only one allele, are exceedingly vulnerable to epigenetic and expression changes; thus, they are often altered in multiple cancer types. Although these alterations have been reported modestly in the scientific literature (Table 1), their mechanism of change has not been well established. Given that YY1 recently was shown to regulate directly 4 imprinted genes—*PEG3*, *GNAS*, small nuclear ribonucleoprotein N (*SNRPN*), and *XIST*—that also are altered greatly in cancer, it is possible that changes in this regulation are a mechanism for cancer growth and/or progression.

Loss of *PEG3* expression, well-documented in ovarian carcinoma and glioblastoma, was shown to be significantly correlated with increased DNA methylation of the paternal allele (from which *PEG3* is expressed) and not genomic mutation.^{42–47} This aberrant DNA methylation also was reversible by treatment with 5-azacitidine. Down-regulation of *PEG3* correlated significantly with advanced tumor stage in glioblastoma and increased tumor growth in ovarian cancer. Both overexpression of *PEG3* and knockdown of YY1 have been independently shown to inhibit growth in ovarian cancer cell lines. Although YY1

expression has not been analyzed thoroughly in glioblastoma, its overexpression in ovarian cancer is well documented.¹¹ Recent studies have established that YY1 interacts with only the unmethylated allele of PEG3 to repress directly its gene expression.¹³ This mechanism seems to be compromised in ovarian cancer, where PEG3 has become repressed irreversibly and YY1 consistently overexpressed. This fact also may be true for glioblastoma, breast, and colon cancers as well, though further research is needed to draw these conclusions.

Like PEG3, the imprinted gene *SNRPN* commonly is down-regulated in cancer through either increased DNA methylation or genomic deletion.^{48–54} Notably, only deletion of the paternal allele, from which SNRPN is expressed, is known to cause disease. Thus, down-regulation of SNRPN correlates with enhanced germ cell tumor development and an increased risk of myeloid leukemia. Unlike PEG3, YY1 was demonstrated to increase SNRPN expression through binding of the unmethylated paternal allele.^{30,55} YY1 expression was demonstrated to increase in various testicular germ cell tumors and in myeloid leukemia, though the significance of this remains elusive.^{11,33} Ultimately, the initial increased methylation of the *PEG3* and *SNRPN* genes in cancer could be caused by changes in YY1 protein levels. If consistent YY1 protein levels are responsible for protecting and maintaining the somatic DNA methylation status of these genes, changes in the intracellular conditions of cancer cells may alter YY1's ability to perform this function.

Another genomic location associated with YY1 binding, *GNAS*, demonstrates a more complex imprinting mechanism involving multiple, overlapping, imprinted gene transcripts. In contrast to both the PEG3 and SNRPN loci, the *GNAS* locus generally is expressed at higher-than-normal levels in many tumor types.^{56–59} *GNAS* overexpression was demonstrated to correlate with a worsening cancer phenotype for diseases such as ovarian cancer, melanoma, and intraductal papillary mucinous neoplasms. Although the main changes to *GNAS* expression in cancer tend to be mutation of the active allele, changes in its imprinting status or genomic amplification also have been observed. Given the complexity of the *GNAS* locus with respect to changes in YY1 binding, some transcripts become down-regulated whereas others are induced, and YY1 may function as a pure transcriptional activator/repressor of this genomic region.^{30,31} Thus, changes in YY1 protein levels in the cellular environment of cancer may be responsible for the alterations in expression at the *GNAS* locus through binding of the clustered YY1 sites in this locus. This type of mechanism also may be true for regulation of the *XIST* gene. *XIST* alterations in cancer tend to stem from either loss of the inactive X chromosome or gain of expression from the active X chromosome.^{60–63} Reduced YY1 levels were documented to cause loss of DNA methylation at the *XIST* allele, suggesting that altering YY1 levels may cause increased expression of *XIST*.³² Conversely, YY1's recently characterized ability to bind both *XIST* RNA and DNA during the process of X chromosome inactivation ultimately may be compromised in the cancer environment.⁶⁴ Thus, for imprinted genes that gain function in cancer cells, YY1's role in this change may originate from its ability to function as a transcription factor that has both repression and activation capabilities.

V. CONCLUSIONS

Given YY1's ubiquitous expression in multiple cell types, it has the potential to influence cancer progression in a variety of ways. Asserting its ability through modulation of imprinted genes seems likely, given that these genes are highly susceptible to changes in the cellular environment. Though the exact mechanism by which YY1 regulates imprinted genes is still poorly defined, understanding this mode of regulation may assist with defining YY1 as either an oncogene or tumor suppressor; it is quite possible that YY1 can be either, depending on the exact subset of genes it modulates within a specific tumor type. Moreover, the amount of YY1 in the cellular environment seems to be an increasingly important factor

with respect to YY1 function at clusters of YY1 binding sites. Given that the dosage of imprinted genes, many of which contain YY1 binding clusters, must be strictly maintained for cellular survival (and possibly genomic stability), fluctuations in YY1 protein levels may create or perpetuate a cancerous cellular environment through alterations in the transcriptional regulation of imprinted genes. Overall, uncontrolled alterations in YY1 protein levels may result in tumor growth and/or development.

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ABBREVIATIONS

YY1	Yin-Yang 1
ICR	imprinting control region
PEG3	paternally expressed gene three
GNAS	guanine nucleotide binding protein, alpha stimulating
REPO	recruiting polycomb complex
SNRPN	small nuclear ribonucleoprotein N
XIST	X inactive specific transcript

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FIGURE 1. Evolutionary conservation of Yin Yang (YY) 1. A, Schematic representation of the YY1 proteins of mammals (top) and flying insects (bottom) demonstrating the strict conservation of the entire protein. The YY1 proteins of mammals (414 amino acids long) and flies (520 amino acids long) are divided into 5 and 6 regions, respectively, based on their exon structures. B, Sequence comparison of the zinc-finger domains of YY1 from different species illustrating the limited amino acid changes in the YY1 zinc-finger domains. Conservative and nonconservative amino acid substitutions are indicated by green and red, respectively.

(A)

>Human **AAGCCATGTTT**TATGTGTGTGATGGGCGC**CGCCATCTT**CTTCGCCAGGGCA**AGTATGGCG**GCCCCAA**AAGATGGCG**GGGCCGTGCGGGCGGGCGGGGCG*****AAGATGGCG**GCA
>Mouse **AAGCCATGTTT**TATGTGTGTGATGGGCGC**CGCCATCTT**CTTCGCCCGGGCA**AGTATGGCG**GCCCCAA**AAGATGGCG**GGGGCGGGCGGGCGCGCG-----**AAGATGGCG**GCG
>Cow **AAGCCATGTTT**TATGTGTGTGATGGGCGC**CGCCATCTT**CTTCG-CGGGGCA**AGTATGGCG**GCCCCAA**AAGATGGCG**GGGGCGGGCGGGCGGGCGGGCGCGCG**AAGATGGCG**GCG
>Dog **AAGCCATGTTT**TATGTGTGTGATGGGCGC**CGCCATCTT**CTTCG-CAGGGCA**AGTATGGCG**GCCCCAA**AAGATGGCG**GGGCCGCGCGGGGGCGGGCGGG*****AAGATGGCG**GCG
>Opossum **AAGCCATGTTT**TATGTGTGTGATGGGCGC**CGCCATCTT**CTTCGCCAGGACA**AGTATGGCG**GCCCCAA**AAGATGGCG**GGGCCGTGTGCGGGCGGGGG*****AAGATGGCG**GCG
>Frog **AAGCCATGTTT**TGGGTTGTTGCTGGGCGC**CGCCATGTT**CA---CTGG-CC**AGTATGGCG**GCCCCGAA**AAGATGGCG**TGTGGGCGCGGG-----**AAGATGGCG**GCG

>Zebra_1 **AAGCCATGTTT**AAGTGTGGATGGGCGC**CGCCATATT**CCTCCAGACC---**ATTATGGCG**GCGGCCCCGA-**AACATGGCG**GTTGTGTGAGCGGGGA-**AAGATGGCG**
>Zebra_2 **AAGCCATGTT**GTGCGTGTGATGGGCGC**CGCCATGTT**CCCCGAGTCC---**ACTATGGCG**GCCCCGTA---**AAGATGGCG**TCGGTGCAGCGCTG--**AAGATGGCG**
>Fugu_1 **AAGCCATGTTT**TATGTGTCATGGGCGCG**CGCCATATT**CCCCCGGTCTGGAA**AGTATGGCG**GCCCCGAA---**AAATGGCG**TTTATTGGCCGAC--**AAGATGGCG**
>Fugu_2 **AAGCCATGTTT**TAGGCTTGTATGGGCGC**CGCCATATT**CCCCGAGAATAGTA**AGTATGGCG**GCGGCCCCGAA**AAATGGCAT**AGTCGGGTCACAGAC**AGATGGCG**

(B)

FIGURE 2.

The cluster of Yin Yang (YY) 1 binding sites in the YY1 locus and its potential role for the homeostasis of YY1 protein. A, Evolutionary conservation of the cluster of YY1 binding sites within the first intron of vertebrate YY1. DNA sequences for the 80-basepair genomic regions containing the clusters of YY1 binding sites are aligned. The YY1 binding sites in the forward direction are marked in blue, whereas the YY1 binding sites in the reverse direction are in green. B, The genomic structure of mouse YY1 is presented with closed boxes as exons. The YY1 binding sites within the first intron are indicated with circles (top). A schematic representation of the functional mode of the cluster of YY1 binding sites is shown below. At normal levels of YY1 protein (indicated by arrows), the YY1 protein occupies half of the YY1 binding sites with the normal transcription rate of YY1. However, the transcription rate of the YY1 locus can be either up- or down-regulated at lower or higher levels of the available YY1 protein, respectively. This switch between activator and repressor roles may be feasible by the different levels of occupancy on the cluster of YY1 binding sites by the YY1 protein (bottom panel).

TABLE 1**Changes in Imprinted Genes in Multiple Cancer Types**

Imprinted Gene	Expression Change/ Tumor Type	Reason for Expression Change	Tumorigenic Correlation	Reference
PEG3 (paternal expression)	Down/ovarian, cervical, endometrial cancers	Increased DNA methylation	Increased tumor growth and progression	42–44
	Down/glioblastoma	Increased DNA methylation	Grade 4 tumors	45–47
	Up/choriocarcinomas	Loss of maternal imprinting	?	42
	Down/breast, colon	Increased DNA methylation	Increased cell line growth (casual)	48
SNRPN (paternal expression)	Down/breast, colon	Increased DNA methylation	?	48
	Slightly up/uterian tumor	?	?	49
	Germ cell tumor	Change in genomic methylation; controversial role	Tumor development	50,51
	Down/central neurocytomas and glioblastoma	Genomic deletion	Older patient age at disease onset	52
	Down/AML	Increased DNA methylation	No obvious correlation to cancer	53
	Down/PWS	Genomic deletion	Increased myeloid leukemia risk	54
GNAS (maternal expression)	Up/ovarian cancer	Genomic amplification	Poor progression-free survival	56
	Up/pituitary adenomas	Activating mutation and loss of imprinting	Smaller size and better sensitivity to pharmacological treatment	57
	Normal expression/malignant melanoma	Somatic SNP	Tumor progression and metastasis	58
	Normal expression/intraductal papillary mucinous neoplasm	GNAS mutation	Progression to invasive carcinoma	59
XIST (X chromosome inactivation)	Up/breast cancer	Misregulation of messenger RNA	?	60
	Down/ovarian cancer	Loss of inactive X chromosome	Shorter disease-free period	61,62
	Up/breast and cervical cancer	Gain expression from active X chromosome	?	61,63

AML, Acute Myeloid Leukemia; GNAS, guanine nucleotide binding protein alpha stimulating; PEG3, paternally expressed gene 3; PWS, Prader-Willi Syndrome; SNP, Single Nucleotide Polymorphism; SNRPN, small nuclear ribonucleoprotein; XIST, X (inactive) specific transcript.