Transcription

ISSN: 2154-1264 (Print) 2154-1272 (Online) Journal homepage: informahealthcare.com/journals/ktrn20

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To cite this article: Zhiyong Deng, Paul Cao, Mei Mei Wan & Guangchao Sui (2010) Yin Yang 1, Transcription, 1:2, 81-84, DOI: 10.4161/trns.1.2.12375

To link to this article: https://doi.org/10.4161/trns.1.2.12375

Transcription 1:2, 81-84; September/October 2010; © 2010 Landes Bioscience

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A multifaceted protein beyond a transcription factor

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As a transcription factor, Yin Yang 1 (YY1) regulates the transcription of a dazzling list of genes and the number of its targets still mounts. Recent studies revealed that YY1 possesses functions independent of its DNA binding activity and its regulatory role in tumorigenesis has started to emerge.

YY1 was discovered as a transcription factor and its transcriptional activity can be converted from a repressor to an activator by viral oncoprotein E1A.[1] As an ubiquitously expressed transcription factor, YY1 has been demonstrated to regulate cell proliferation and differentiation, and its deficiency in mice results in peri-implantation lethality during embryonic development.[2] However, YY1 has attracted the interest of researchers not only because of its essential role in normal cell growth, but also due to its aberrant expression and potential regulatory function in different cancers. YY1 has been reported to modulate a mounting list of genes, many of which are key players in different signaling pathways regulating cancer development and progression, such as c-myc, c-fos, ERBB2, E1A and p53.[3,4] Meanwhile, YY1 also physically interacts with a number of proteins regulating cell proliferation and apoptosis, such as p53, Mdm2, Ezh2, Rb, caspases and HDACs.[3] In addition, YY1 gene expression can be stimulated by several growth factors, while antiproliferative signals tend to antagonize its expression.[3] Therefore, as a multifunctional mediator of different signaling pathways, YY1 potentially acts as a critical regulator in cancer development and progression and likely plays a proliferative or oncogenic role in these processes.

YY1: Beyond a Transcription Factor

To date, most published data have demonstrated the activities of YY1 as a transcription factor. YY1 can either activate or repress gene expression, depending on the cofactors that it recruits. The promoters of these genes normally contain at least one of the two most frequent core binding elements of YY1: CCAT and ACAT.[5] YY1 plays an essential role in embryonic development.[2] Consistently, many YY1-targeted genes are key regulators of cell growth and differentiation, such as several mitochondrial proteins, Cdc6 and cyclin D1.[3] A major portion of these targets are key components of signaling pathways related to apoptosis and oncogenic transformation.[3,4]

Despite the well-established regulation of YY1 as a transcription factor, several reports, including ours, have demonstrated the role of YY1 as a transcription cofactor and its activity independent of its DNA binding. In our recent study, we observed YY1-dependent expression of prostate-specific antigen (PSA) in prostate cancer cells.[6] Due to the well-recognized function of YY1 as a transcription factor, we first tested whether YY1 directly regulates PSA transcription. When we mutated the only YY1 binding element in the PSA promoter, YY1-mediated transcription of PSA promoter was unaffected. Since androgen receptor (AR) is a well-studied transcription activator of PSA, we therefore asked whether YY1 is involved in AR-mediated transcription of PSA. Following this path, we discovered that YY1 directly interacts with AR and enhances the association of

Key words: Yin Yang 1, transcription factor, coactivator, protein modification, androgen receptor, prostate cancer

Submitted: 03/31/10

Revised: 05/13/10

Accepted: 05/14/10

Previously published online: http://www.landesbioscience.com/journals/transcription/article/12375

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AR with an androgen response element (ARE). Importantly, we observed that a YY1 mutant deficient of binding to AR lost the stimulating effect on the PSA promoter that wild type YY1 has. Hence, these studies suggest that YY1-AR interaction, but not YY1-DNA association, is essential to YY1-activated PSA expression. Therefore, instead of directly acting as a transcription factor, YY1 plays a role of a cofactor and its DNA binding activity is dispensable in mediating PSA expression. It is noteworthy that AR interacts with the C-terminal of YY1,[6] where its DNA binding domain, the zinc finger region, is located. Therefore, it is unlikely that YY1 molecule can associate with its DNA binding element and AR protein concurrently. The domain mapping studies indicate that the N-terminal of YY1 possesses transcriptional activation activity, and the N-terminal and middle region recruit many proteins with chromatin remodeling functions.[7,8] Therefore, with the C-terminal binding to AR, the N-terminal of YY1 will likely recruit other coactivators and consequently promote PSA gene transcription.

This is not the first observation of YY1 exhibiting activity independent of its DNA binding affinity. Our previous study also indicated that YY1 enhances the Hoxa11-DNA association and is required for the recruitment of HDAC2 by Hoxa11.[9] Moreover, we and others reported that YY1 stimulates Mdm2-mediated p53 ubiquitination and degradation.[10-12] In this study, both wild type YY1 and its DNA-binding deficient mutant promoted p53 ubiquitination. Importantly, this effect of YY1 on p53 could be visualized in a reconstituted ubiquitination system in vitro.[10] Additionally, the observation of altered translocation between nuclear and cytoplasm at different cell cycle stages also suggests that YY1 is involved in biological processes in addition to mediating gene transcription.[13,14]

The full length of YY1 protein has never been crystallized for structure analysis, except for the cocrystal study of its zinc finger region with the adeno-associated virus P5 promoter.[15] Therefore, the actual three-dimensional structure of YY1 activation domains at its N-terminal and middle region remains unclear. However, the amino acid composition of YY1 reveals some of its potential structural features. YY1 protein has two acidic regions at the N-terminal. Especially, an eleven-run of glutamic/asparatic acids is present at residues 43–53 and an eleven-run of histidines consists of residues 70–80 of human YY1, which are both well-conserved in its orthologs from rat, mouse and chick. The electronic charge of histidines may be altered with slight pH changes in the microenvironment. Therefore, the N-terminal of YY1 may employ electrostatic force to interact with different proteins, especially those with positive charges, such as histones. Between residues 150 to 200, there are four clusters of three- to five-runs of glycines that provide large flexibility to this region, which interacts with several proteins, including p300, HDACs, c-Myc, p53 and $p14^{ARF}$ (reviewed in refs. 3 and 7). Overall, these features may determine the potential of YY1 as a scaffold protein that recruits other transcription regulators to mediate gene expression when its C-terminal binds to either DNA or other transcription factors.

The discovery of YY1 as a cofactor of AR extended our understanding of YY1-mediated transcription. YY1 interacts with a number of protein modifiers that mediate various posttranslational modifications. Early studies by Shi and Seto demonstrated the association of YY1 with p300 and HDACs, regulating histone acetylation and deacetylation, respectively.[16,17] Studies by Sartorelli and Seto groups also revealed that YY1 recruits Ezh2 and PRMT1 to mediate histone methylation on lysine and arginine residues, respectively.[18,19] In addition, our recent studies demonstrated the association of YY1 with Mdm2, PIASy and Ubc9, which regulate protein ubiquitination and sumoylation, respectively.[10,20] Therefore, when binding to its own responsive element or recruited by another transcription factor, YY1 can likely provide a platform for the assembly of a scaffold with different transcriptional machineries where many other cofactors are recruited and assembled together. Especially, when a particular protein modifier binds to YY1, posttranslational modifications may occur to both histones and other recruited cofactors on a target promoter to modulate their functions. This interplay between the recruitment and modification will therefore determine the expression status of the regulated genes. Generally, p300-mediated histone acetylation and PRMT1-mediated histone H4-R3 methylation cause gene activation, while histone deacetylation by HDACs and H3-K27 tri-methylation by Ezh2 silence target genes (**Fig. 1A and B**). In addition, Mdm2 can cause histone ubiquitination and establishes transcriptional repression.[21] Most transcription factors, such as AR,[22] p53,[23] and YY1 itself,[3] also undergo various modifications, which differentially regulate their transcriptional activities. When YY1 acts as a transcription coactivator in AR-mediated PSA gene expression, it is likely that YY1 recruits other coactivators that are yet to be identified to promote transcription (**Fig. 1C**). It is noteworthy that, as a cofactor, the cellular levels of YY1 may determine the expression status of a target gene. Therefore, while a medium increase of YY1 stimulates AR-mediated transcription, further increases of YY1 can compromise this activation.[6] One possible reason for this phenomenon is that excessive YY1 associates with other coactivators to be recruited and therefore interferes with the transcriptional activation of a target gene, the so-called "squelching effect".[24]

YY1: Involvement in Prostate Cancer

YY1 has been suggested as a regulatory protein, a potential therapeutic target and a prognostic marker of cancers based on its aberrant expression in tumors and the properties of its target genes and interacting proteins.[3,25] YY1 overexpression has been detected in multiple cancers, including prostate cancer.[26] Bonavida group made a number of seminal discoveries that link YY1 to prostate cancer development and therapy.[4] They demonstrated a significant association between YY1 activity and the expression of both cytokine and death receptor. Mechanistically, YY1 negatively regulates the expression of both Fas and the death receptor 5 (DR5), and consequently endows prostate cancer cells with resistance to Fas-induced or TRAIL-induced apoptosis. Consistently, in a tissue microarray study, they observed that

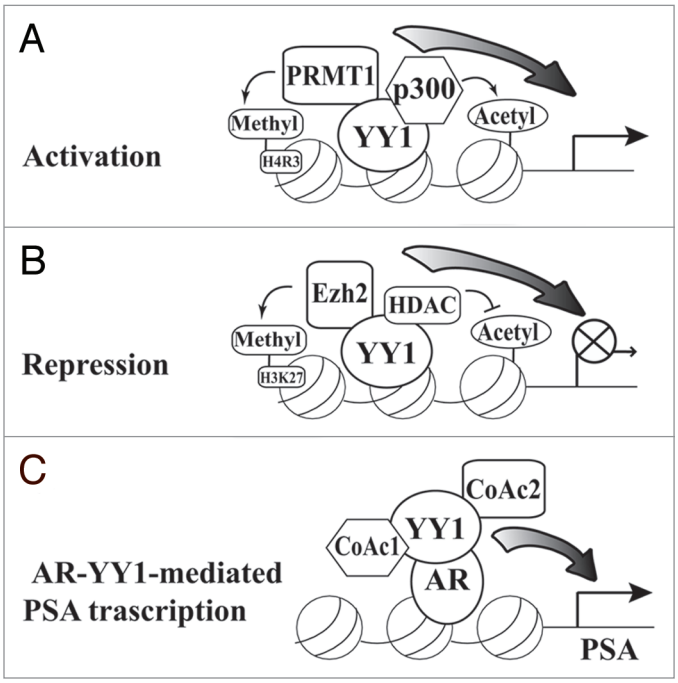

Figure 1. Schematic models of YY1 regulated gene expression. YY1 can act as transcription activator (A), repressor (B) and coactivator (C, with the PSA promoter as an example). Other coactivators (designated as CoAc1 and CoAc2) can be recruited by YY1 to facilitate AR-mediated PSA transcription.

elevated YY1 expression correlates with higher morphologic grades or malignant histological phenotypes in prostate cancer samples from 246 patients.[27] Our finding of YY1 as a coactivator of AR in promoting PSA transcription also implicates that YY1 potentially regulates prostate cancer development and progression through stimulating AR function. Especially, in the absence of androgen, we observed a modest activation by YY1 on AR-dependent transcription of the PSA promoter,[6] suggesting that, as a coactivator, overexpressed YY1 may be an essential regulator to the AR-signaling pathway in androgen independent prostate cancer.

Prostate cancer is a major public health problem among men of many countries. While locally confined prostate tumors can be treated by surgery and radiation therapy, advanced and relapsed prostate cancers are primarily handled by inhibiting the androgen signaling pathway. This can be typically achieved by androgen deprivation therapy including castration and administration of androgen antagonists. However, despite these therapies of androgen withdrawal, prostate cancer unavoidably progresses to the androgen-independent state. Even at low androgen levels, androgen-responsive genes in these tumors restore their expression nearly to the pre-treatment levels.[28] This strongly suggests that AR still plays an essential role in the growth and survival of recurred or advanced prostate cancers, even in androgen-deprived conditions. In fact, such prostate cancers retain high expression levels of AR and are still AR-dependent.[29] Therefore, AR is still a valid target for the therapeutic intervention of androgen-independent prostate cancers.

The aberrantly activated AR-signaling pathway in prostate cancer can be caused by different deregulations, including AR overexpression, AR mutation, increased sensitivity of AR to low androgen levels and ligand-independent AR activation.[30] Several mechanisms may lead to enhanced AR activity or sensitivity, including post-translational modifications and stimulation of overexpressed coactivators.[30] Our observation on that overexpressed YY1 enhances the transcriptional activity of AR suggests that YY1 and its interaction with AR or other transcription cofactors can be potential, alternative targets in the therapeutic treatment of androgen independent prostate cancer. Given the fact that many coactivators and corepressors interact with YY1, specific agonists or antagonists to these proteins can be designed and tested, and molecular agents, such as peptide inhibitors, can be used to attenuate AR activity. These studies can potentially lead to the development of new therapeutic strategies that are urgently needed to treat the fatal, advanced prostate cancer.

Acknowledgements

We thank Ms. Karen Klein (Research Support Core, Wake Forest University Health Sciences) for editing the manuscript. The support for the work came from grants of the Department of Defense (PC060490) and American Cancer Society (RSG-09-082-01-MGO) to Guangchao Sui. The NCI training grant 5T32CA079448-09 supports Paul Cao.

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