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Targeting the Overexpressed YY1 in Cancer Inhibits EMT and Metastasis

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Abstract

There have been recent developments in the treatment of various cancers, in particular non-metastatic cancers. However, many of the responding patients often relapse initially through the development of spread micro-and macro-metastases. Unfortunately, there are very few therapeutic modalities for the treatment of metastatic cancers. The development of cancer metastasis has been proposed to involve the epithelial–mesenchymal transition (EMT), in which the tumor cells with the EMT phenotype exhibit various phenotypic markers and molecular modifications that are manifested to resist most conventional therapies. YY1 is a target of the hyperactivated nuclear factor-kappa beta pathway in cancer and it was reported that YY1 also regulates cell survival and cell proliferation in addition to its role in EMT and resistance. The overexpression of YY1 in the majority of cancers has been correlated with poor prognosis. It is hypothesized that targeting YY1 may result in several anti-tumor activities, including inhibition of cell survival and cell proliferation, inhibition of EMT, and reversal of resistance. This review discusses the potential therapeutic targeting of an overexpressed transcription factor, Yin Yang 1 (YY1), which has been implicated in the development of EMT and drug resistance. Several examples targeting YY1 in experimental models are presented.

Keywords

EMT; metastasis; NF- κ B; snail; RKIP; resistance; prognosis

I. INTRODUCTION

Endothelial–mesenchymal transition (EMT) is a biologic process that is inextricably linked to metastasis and growth in cancer. The underlying mechanisms of Yin Yang 1 (YY1) regulation are imperative to unraveling the role of EMT in cancer progression and developing new treatment modalities.^{1,2} EMT is the process through which epithelial cells lose their cell polarity and cell–cell adhesion to become migratory mesenchymal stem cells (MSCs).^{3,4} EMT is a process that is crucial for cell differentiation during distinct stages of embryogenesis such as gastrulation,⁴ but when dysregulated, can lead to negative outcomes

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in cancer due to the MSCs' enhanced migratory capacity, invasiveness, and higher resistance to apoptosis compared with normal cells.⁵

YY1 is a zinc finger transcription factor the particular function of which at a specific promoter is determined by its interactions with several key regulatory proteins.⁶ The transcription factor YY1 is key to understanding the progression of EMT in cancer due to YY1's participation in the established nuclear factor-kappa beta (NF- κ B)/Snail/YY1/Raf-1 kinase inhibitory protein (RKIP) circuitry loop that regulates EMT.^{7–13} Consistent with its various interactions, YY1 works to inhibit or to promote the expression of several targets such as *p53* and *ERBB2*.^{14,15} Interestingly, YY1 was found to be overexpressed in several types of cancer, including colon cancer,¹⁶ breast cancer,¹⁷ and prostate cancer.¹⁸

YY1 promotes EMT indirectly through the NF- κ B/Snail/YY1/RKIP loop via its transcriptional upregulation of Snail, a zinc finger protein that was found to induce EMT.^{2,7–13} This up-regulation of Snail induces EMT through the repression of the epithelial markers such as E-cadherin and claudins, both of which promote anti-invasive and anti-migratory properties in epithelial cells.^{19–21} The upregulation in Snail expression also causes the increased expression of the mesenchymal markers N-cadherin, vimentin, and fibronectin, which are involved in the regulation of EMT.^{22–24} However, it is not clear whether YY1 also regulates the EMT phenotype directly.

This review discusses the various manifestations that are mediated by the NF- κ B/Snail/YY1/RKIP loop and the indirect participation of YY1 in the induction of EMT through Snail. Importantly, we also discuss the potential mechanisms by which YY1 might participate directly in the regulation of the EMT phenotypic gene products (e.g., E-cadherin, N-cadherin, vimentin, fibronectin, and claudins).

II. DYSREGULATED NF- κ B/SNAIL/YY1/RKIP LOOP IN CANCER

Below, we briefly describe the underlying mechanisms through which NF- κ B regulates YY1 and YY1 regulates Snail in the NF- κ B/Snail/YY1/RKIP loop through published studies by us and others.

The presence of a dysregulated NF- κ B/Snail/YY1/RKIP loop that regulates cell survival, resistance, and EMT has been established in a variety of human cancers.^{8–13} The hyperactivated NF- κ B survival signaling pathway has been found in cancer cells, with downstream targets including YY1 and Snail.^{25–27} NF- κ B has been reported to upregulate EMT through the activation of the transcriptions of YY1 and Snail and the downregulation of the metastasis-suppressor cancer gene products RKIP and E-cadherin.^{19,26–31} Positively regulated by NF- κ B, Snail has been reported to induce EMT by playing an important role in the procurement of invasion and migratory properties by cancer cells.^{27,32} Similarly upregulated by NF- κ B, YY1 has been reported to activate the transcription of Snail and thus is also involved in the loop that regulates EMT during cancer metastasis.^{7,26} RKIP, a small, cytosolic protein, has been demonstrated to inhibit the expressions and activities of NF- κ B, Snail, and YY1 through its own overexpression.^{8,9,33} Overall, the above studies reported by

us and others clearly established a tightly controlled and dysregulated NF- κ B/Snail/YY1/RKIP loop in cancer cells through which EMT is, in large part, regulated (Fig. 1).

III. INDIRECT REGULATION OF EMT BY YY1 THROUGH THE NF- κ B/SNAIL/YY1/RKIP LOOP

Based on studies reported by us and others, YY1 up-regulates EMT indirectly by inducing Snail expression⁷ through the dysregulated NF- κ B/Snail/YY1/RKIP loop.^{2,8-13} In this loop, NF- κ B stimulates YY1 expression at the transcriptional level.² The activation of YY1, in turn, stimulates the expression of the transcription factor Snail, with overexpression of Snail inducing EMT and leading to cancer cells acquiring invasion and migratory properties characteristic of mesenchymal cells.^{7,32,34} Snail causes cells to undergo EMT by repressing metastasis-suppressor gene products such as E-cadherin¹⁹ and claudins^{20,21} directly and inducing metastasis-inducer gene products such as vimentin,²³ N-cadherin,²² and fibronectin.²⁴

Below, we briefly present the mechanisms by which YY1 regulates EMT indirectly by acting as a pivotal factor of the NF- κ B/Snail/YY1/RKIP loop.

A. Regulation of YY1 Transcription and Expression by NF- κ B

A protein complex involved in various signaling pathways, NF- κ B belongs to the Rel family of transcription factors that regulate a substantial number of genes, especially those linked with immune and inflammatory responses.³⁵ The hyperactivated NF- κ B signaling pathways have been observed in cancer cells, from which the dysregulated NF- κ B/Snail/YY1/RKIP loop was determined in cancer cells.² Wang et al.²⁶ reported that YY1 is a direct target gene of NF- κ B. In their study of the relationship between NF- κ B and YY1, Wang et al.²⁶ reported that, whereas YY1 expression in several cell types was increased by inducers of NF- κ B, lower levels of YY1 transcripts and protein corresponded with the genetic extraction of the RelA/p65 subunit of NF- κ B in cultured cells and adult skeletal muscle cells. Wang et al.²⁶ also demonstrated that two motifs similar to an NF- κ B consensus site could be found on the YY1 promoter and were, in fact, NF- κ B-binding sites. The inhibition of NF- κ B by NO donors was found to lead to the repression of anti-apoptotic target genes including *YY1*, further illustrating *YY1* as a direct target gene of NF- κ B.^{10,13} Likewise, reports by Karin et al.,³⁶ Hongo et al.,³⁷ and Kleinberg et al.³⁸ further corroborated that NF- κ B regulates the activation of YY1 and also other genes such as the *X-linked inhibitor of apoptosis protein (XIAP)* and the *B-cell lymphoma-extra large (Bcl-xL)* through direct targeting.

It is important to note that, aside from its role in the NF- κ B/Snail/YY1/RKIP loop, NF- κ B has also been found to have mechanisms through which it regulates EMT directly.²⁹ In a study by Huber et al.,²⁹ it was found that NF- κ B, along with transforming growth factor β (TGF- β), moderate EMT and signaling by NF- κ B is required for inhibition of apoptosis.

B. Snail is Activated Transcriptionally by YY1

Activated by NF- κ B, YY1 upregulates Snail, a transcription factor that inhibits EMT-suppressing gene products.^{7,14,26} Trask et al.³⁹ provided evidence of the regulation of Snail

by YY1 as Snail-null mouse embryos that do not complete gastrulation and have little E-cadherin expression, much like YY1-null cKO embryos, suggesting that YY1 and Snail expressions are linked. Likewise, Palmer et al.⁴⁰ reported a regulatory element located at the 3' enhancer of the Snail locus found in melanoma cells expressing Snail and absent in cells that did not express Snail. In a later study, Palmer et al.⁷ reported the binding of YY1 to the 3' enhancer in cells that expressed Snail and reported that knockdown of YY1 through siRNA led to the inhibition of Snail expression. Overall, YY1 can be found to participate in the NF- κ B/Snail/YY1/RKIP loop by regulating the expression of the EMT-inducer Snail.

C. Role of Snail in the Regulation of EMT Biomarkers (E-cadherin, N-cadherin, vimentin, fibronectin, and claudins)

1. E-cadherin—Induced by YY1, Snail acts to repress the metastasis-suppressor gene product E-cadherin directly.¹⁹ Cano et al.¹⁹ reported that E-cadherin expression was absent in invasive mouse and human carcinoma cell lines and tumors in which the endogenous Snail protein could be found. Poser et al.⁴¹ also reported similar findings with transient transfections of a Snail plasmid into human primary melanocytes resulting in the downregulation of E-cadherin and stable transfections of Snail into melanoma cells resulting in the repression of E-cadherin. By down-regulating the metastasis-suppressor E-cadherin at the transcriptional level, Snail causes cells to acquire migratory and invasive properties and concurrently induces EMT in cells.¹⁹

2. N-cadherin—Contrary to its effect on E-cadherin, Snail induces the expression of the EMT phenotype and the up-regulation of the gene product N-cadherin.^{22,42} ElMoneim et al.⁴³ reported that overexpression of Snail in breast carcinomas was correlated with overexpression of N-cadherin. Likewise, Hao et al.²² reported that a cadherin switch resulting in the re-expression of E-cadherin and the down-regulation of N-cadherin was regulated at the transcriptional level by Snail in malignant melanoma cells. By stimulating N-cadherin expression, Snail represses activities in cells including apoptosis and activates EMT.

3. Vimentin—Much like its effect on N-cadherin, Snail stimulates the expression of vimentin, a mesenchymal marker vital to cancer cells acquiring their characteristic migratory and invasive abilities.^{23,44} In a study by Usami et al.,⁴⁵ Snail expression was found to be correlated with high levels of vimentin expression through immunohistochemical analysis of human esophageal squamous cell carcinoma cells. Likewise, Kaufhold and Bonavida⁴⁶ reported the regulation of vimentin by Snail at the transcriptional level. Through Snail's effect of increasing vimentin expression, cells with overexpression of Snail are more inclined to undergo EMT and can be found to take on invasive and migratory properties.^{23,44}

4. Fibronectin—Snail has been reported to upregulate significantly the expression of fibronectin, a gene product commonly known as a mesenchymal marker.²⁴ Depletion of Snail has been reported to occur concurrently with a disrupted fibronectin layer in the heart region of zebrafish embryos.⁴⁷ In addition, transfection of Snail in HT29 cells has been shown to up-regulate the expression of fibronectin at the transcriptional level, as reported by Fan et al.⁴⁸ Because fibronectin is established as a mesenchymal marker and has been found

to promote disruption of epithelial cell adhesion, Snail stimulates EMT in cells by its up-regulation of fibronectin.²⁴

5. Claudins—Unlike its induction of fibronectin, Snail has been reported by Liu et al.²⁰ and Martinez-Estrada et al.²¹ to down-regulate claudin expression. The overexpression of Slug and Snail in Madin–Darby canine kidney cells resulted in claudin-1 down-regulation at both the protein and mRNA levels.²¹ In addition, Ohkubo et al.⁴⁹ and Findley et al.⁵⁰ have demonstrated that Snail regulates claudins directly by mediating translation initiation of claudins and without affecting transcription. Because claudins play a role in cell-to-cell adhesion, Snail down-regulation of claudins induces EMT, in which the epithelial cells lose their polarity and their characteristic adhesion.^{3,20,21,51}

Overall, the above reported studies clearly establish YY1 as an indirect inducer of EMT through its up-regulation of Snail and subsequent inhibition/induction of the gene products vimentin, claudins, N-cadherin, E-cadherin, and fibronectin.

IV. PUTATIVE DIRECT REGULATION OF EMT GENE PRODUCTS BY YY1: ANALYSIS OF YY1-BINDING SITES ON THE VARIOUS PROMOTERS

Although it has been established, by the studies discussed above and many others,^{7,14,19,20–24,42,44} that YY1 through Snail regulates indirectly the gene products E-cadherin, N-cadherin, vimentin, claudins, and fibronectin that induce/inhibit EMT, there exists little to no reported literature on potential mechanisms through which YY1 may regulate these gene products directly. Below, we examined reports by others and used Ensembl and TFBIND software to describe the known direct relationship that YY1 has with the gene products vimentin, claudins, N-cadherin, E-cadherin, and fibronectin. The promoter sequences of these gene products were retrieved from the online genome browser Ensembl.⁵² Built to find putative transcription-factor-binding sites (TFBS), the program TFBIND was used to find YY1-specific putative TFBS by analyzing the gene promoter sequences.⁵³

A. YY1 DNA-Binding Sites on the N-Cadherin Promoter

A total of 16 putative TFBS in the human N-cadherin promoter were found (Fig. 2), suggesting that YY1 may bind directly to the N-cadherin promoter and positively regulates N-cadherin expression positively at the transcriptional level.⁵³

B. YY1 DNA-Binding Sites on the E-Cadherin Promoter

Although it has been established that YY1 up-regulates the transcription of Snail⁷ and that Snail, in turn, represses the expression of the metastasis suppressor E-cadherin,¹⁹ little is known about the existence of a direct relationship between YY1 and E-cadherin. Wang et al.⁵⁴ reported in their study that tumor spheres of SC-M1 cells had levels of epithelial markers plakoglobin and E-cadherin increased by YY1 knockdown, leading them to investigate the mechanism by which YY1 may repress the expression of E-cadherin directly. However, YY1 was ultimately reported by Zhang et al.⁵⁵ not to regulate E-cadherin transcription directly, although a YY1-binding region was found in the E-cadherin promoter. Tong et al.⁵⁶ constructed in their study a primer (with products that had three putative YY1-binding sites)

to undergo chromatin immunoprecipitation assay and to establish whether YY1 in conjunction with Snail allowed for the recruitment of the Enhancer of zeste homolog 2 (EZH2) to the E-cadherin promoter. The report showed that, ultimately, Snail and not YY1 arbitrated EZH2 and HDAC1/2 induction to the E-cadherin promoter, discouraging the idea of a direct mechanism between YY1 and E-cadherin.⁵⁶

In addition to the above reports, an analysis of the human E-cadherin promoter through TFBIND investigated the direct relationship between YY1 and E-cadherin (Fig. 3). The analysis resulted in six YY1-specific putative TFBS on the E-cadherin promoter, suggesting that a direct regulation of E-cadherin by YY1 could exist, but requires further investigation.
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C. YY1 DNA-Binding Sites on the Vimentin Promoter

A protein associated with cell migration and EMT, vimentin can be found to be up-regulated by Snail expression.²³ Much like the relationship between YY1 and E-cadherin, the direct association between YY1 and vimentin has yet to be established clearly. This is due, in part, to vimentin retaining various complex mechanisms that regulate its transcription.⁵⁷ Sekimata et al.⁵⁷ reported a trial that further studied the relationship between YY1 and vimentin by investigating whether CpG methylation of the vimentin promoter could modify vimentin expression. Two subclones of rat C6 glioma cells were formed with (C6vim⁺) and without (C6vim^[minus]) vimentin and underwent bisulfite genomic sequencing, which showed that C6vim^[minus] cells retain acutely methylated transcription start sites within the vimentin promoter, whereas C6vim⁺ cells do not.⁵⁷ Once the C6vim^[minus] cells were treated with the demethylating agent, vimentin expression returned, indicating that a hypermethylated promoter region leads to transcriptional silencing of the vimentin gene.⁵⁷ By conducting electrophoretic mobility shift assay and transient transfection experiments, Sekimata et al.⁵⁷ established that YY1 is a transcriptional activator that regulates the expression of vimentin and can be kept from binding to the vimentin promoter through CpG methylation. The investigators suggested that the inability of YY1 to access the hypermethylated promoter may be one of the mechanisms that mediates vimentin down-regulation and, subsequently, infer the idea that a direct mechanism between YY1 and vimentin exists.

In addition to these reports, the human vimentin promoter sequence was examined through the software TFBIND to gauge the number of YY1-specific TFBS that could be found on the promoter (Fig. 4).⁵³ Four TFBS were found, further supporting the report by Sekimata et al.⁵⁷ that a direct mechanism between YY1 and vimentin may exist.

D. YY1 DNA-Binding Sites on the Claudin Promoter

Epithelial markers that play a role in cell–cell adhesion, claudins are gene products with expression that is down-regulated by Snail to induce EMT.^{20,21} In addition to the indirect regulation that YY1 has for claudin expression through YY1's up-regulation of Snail,^{20,21} a direct relationship between YY1 and claudin expression has been reported by Holloway et al.⁵⁸ These investigators demonstrated that the promoter regions of claudin-5 retain specific target sites for the Sp-family transcription factors TFIID and YY1, suggesting that YY1 could regulate claudin expression directly. The 5' promoter of claudin-5 was also found to

contain GC-rich segments with common sequence motifs, suggesting that this gene is regularly acted upon by common transcriptional factors such as YY1.⁵⁸

In addition, an analysis of several claudin promoter sequences was made through TFBIND to determine putative TFBS on claudin promoters that are YY1 specific (Figs. 5–7).⁵³ Analysis of the claudin-1 gene promoter resulted in five putative TFBS. Analysis of the claudin-5 and claudin-6 promoters resulted in two and five binding sites, respectively, inferring that a direct mechanism between YY1 and several claudins may exist.

E. YY1 DNA-Binding Sites on the Fibronectin Promoter

Much like YY1 and N-cadherin, the direct relationship between YY1 and fibronectin has not been reported. The fibronectin promoter was run through TFBIND, through which two YY1-specific putative TFBS were found on the promoter (Fig. 8).⁵³ However, neither of the putative TFBS sequences was able to be located on the promoter itself, leading to speculation as to whether they indicated a direct relationship between YY1 and fibronectin. Although the number of YY1-specific putative TFBS found is small, the possibility of YY1 regulating fibronectin directly needs validation.

V. POTENTIAL ROLE OF YY1 AS A THERAPEUTIC TARGET IN THE INHIBITION OF EMT

YY1 has been reported to act as an oncogene and to be overexpressed in many human cancers.⁵⁹ As discussed, YY1 has a pivotal role in cancer progression due to its indirect and direct regulation of several proteins that modulate cell proliferation, cell apoptosis, and EMT.^{7,14} Therefore, YY1 is strongly considered as a potential therapeutic target for inhibiting its various pro-tumorigenic activities including EMT and thus should result in reducing tumor progression and cell invasiveness in cancer. Several inhibitors of YY1 expression have been reported and are discussed in more details in a chapter by B. Bonavida in this issue (“Therapeutic Yin Yang 1 Inhibitors in Cancer: ALL in ONE”). Examples of YY1 inhibitors and their effects are presented briefly below.

A. Inhibition of YY1 by miRNAs

One of the more commonly found classes of gene regulatory molecules in multicellular organisms, microRNAs (miRNAs) regulate messenger RNA (mRNA) expressions post-transcriptionally through their binding of 3' untranslated regions of target genes.⁶⁰ Yang et al.⁶¹ have reported an association between miRNA-193a-5P and YY1 in endometrioid endometrial carcinoma, whereby knockdown of YY1 through increased levels of miRNA-193a-5P resulted *in vivo* and *in vitro* on both the inhibition of cell growth and migration. Zhang et al.⁶² similarly reported an association of miR-7 and YY1 in colon cancer, in which miR-7 was found to repress growth in several tumors, including glioblastoma and squamous cell carcinoma. In addition, Zhou et al.⁶³ reported a correspondence between miR-181 and YY1 in cervical cancer, with miR-181 regulating YY1 expression and EMT markers negatively.

The studies above demonstrate that specific miRNAs can be used as potential treatments, alone or in combination with drugs, to down-regulate YY1 expression and result in the inhibition of EMT in cancer cells.

B. Betalunic Acid

A naturally occurring triterpenoid found in bark extracts, betalunic acid has been reported to regulate YY1 expression negatively and, in turn, is considered to inhibit cell phenotypic properties that are markers of EMT.⁶⁴ Liu et al.⁶⁴ demonstrated that betalunic acid targets specificity proteins, many of which are overexpressed in cancer. They also reported that betulinic acid down-regulates the expression of sp1, sp3, and sp4, subsequently inhibiting YY1 as a downstream target.⁶⁴

C. NO Donors

In reports by us and others, the treatment of various cancer cells lines with NO donors resulted in the inhibition of EMT and cell proliferation through mechanisms that included the down-regulation of YY1.⁶⁵ The dysregulated NF- κ B/SNAIL/YY1/RKIP/PTEN loop was found to be altered significantly by NO donors.⁶⁵ In this loop, the NO donors inhibited YY1 through S-nitrosylation and also inhibited the YY1 inducer NF- κ B through S-nitrosylation of p50 and p65.⁶⁵

It is clear from the above examples that the inhibition of YY1 can be considered a significant therapeutic target for the inhibition of EMT. Therefore, potential treatments that seek to reduce EMT in cancer patients and that include inhibitors of YY1 should be further investigated and validated in cancer patients.

VI. CONCLUSIONS AND FUTURE DIRECTIONS

There have been several studies addressing the challenging topic of EMT in several cancers and investigations of the various molecular mechanisms leading to the development of the EMT phenotype. There are also several studies that have investigated various potential strategies to interfere with the EMT phenotype and the development of potential therapeutic targets to inhibit EMT. Clearly, these above studies have generated various enthusiasms, but there remains the clinical application and the demonstration of the clinical efficacy of these various therapeutic strategies. Various therapeutic strategies against cancer are, in general, primarily focused on particular properties such as viability, proliferation, invasion, metastasis, and reversal of resistance. Clearly, it will be of benefit if one were to develop and/or characterize a particular target in cancer cells that is involved in the regulation of all of these above characteristics of cancer cells.

We and others have reported the overexpression in cancer of the transcription factor YY1 and various analyses demonstrated that YY1 regulates various tumor properties that include proliferation, viability, invasion, EMT, resistance to both drug and immune therapies, as well as regulation of the cancer stem cell phenotype.^{5,14,16–18,66} These various activities that are mediated by YY1 clearly suggest that YY1 may be an ideal target the inhibition of which can lead to the reversal of the pleiotropic activities manifested by cancer cells. In this review, we have briefly discussed the regulation of YY1 and how YY1 regulates the various

properties in cancer cells. We also demonstrated that YY1 inhibition by various means (including siRNA, upstream inhibitors against NF- κ B, exogenous NO donors, proteasome inhibitors, etc.) have all led to similar end points in the inhibition of cancer cell proliferation and viability, the EMT phenotype, and their cancer-cell-sensitizing activities for the reversal of resistance when combined with conventional chemo- and immunotherapeutics.

Based on the above findings, we propose that all of the YY1 inhibitors that were used except siRNA YY1 are indirect and the application of siRNA *in vivo* is not yet a well-established and validated intervention. Although the various indirect inhibitors resulted in significant anti-tumor responses, they may also be modifying other gene products or pathways that might affect the expected overall response. Therefore, we stipulate that it might be important to design specific YY1 chemical inhibitors based on the structure and the catalytic subunit of YY1 and that such inhibitors, once tested, might have superior anti-tumor activities used alone or in combination with subtoxic doses of conventional therapeutics. Clearly, once those findings with these specific inhibitors are validated in cell culture, they will need to be corroborated in preclinical studies and eventually translated into clinical trials.

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ABBREVIATIONS

EMT	epithelial–mesenchymal transition
MSC	mesenchymal stem cell
miRNA	microRNA
RKIP	Raf-1 kinase inhibitory protein
siRNA	small interfering RNA
TFBS	transcription factor binding site
YY1	Yin Yang 1

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FIG. 1.

Inhibition of the dysregulated NF-κB/YY1/Snail loop. This figure represents the hyperactivated NF-κB pathway and downstream overexpression of YY1 and Snail that lead to the EMT phenotype. Treatment of cancer cells with various inhibitors of YY1 results in the reversal of the EMT phenotype.

>chromosome:GRCh38:18:27950366:28179446:-1
 CACTTCTGATTACTATATTAAGTGTTTCATCTCATCTTTTAAATTTAATTAACATAACCTTTCTTATTCTTTTGAAAAGAAAGAAA
 ATCCAGGAAAAATTTTGTTCATAAAAACTTACAATATTATGTTTAAATTAATTAAGCCTCCCTATGAATATTAAATT
 TTTAAAGCCTAGCCAGCAACAGTACATTATTAAGCTGTATCAGTTATGTCAAGAAATTAGTAGCTGTTTTTAAAGGTTCA
 TCATCAGATTCTTAAATGATCGGTATCTTGAAACTCAAATAAAGTTAATATTTCAAGTCACCCAAAGCAGAAAAAGCAAGCAATAA
 AGGCAGAAAAATATTCATTAAGTGAATGAAGTTCACCGATCTCCCAAGTGTTGAAAAGCTTACATAAAACGGATATTTCTATTT
 ACTTGTAAACCTTTCTTAAAAAGGTTCCGGAATTTATTACCTACCAGAAATTAGAAAAACAAAACTGCTCCCATCCC
 CCGCTCCATTCCACAAA TGCTTGTGACTCAAACCTGTAAAGTCTCTCACTGTGTTGCACTTGAAGTTCATGCCTTAAAGGAAGCC
 AGCAGAAATCCTTTACGTGGTGAGAAATCTGTATCAGTCATTTATCTTTTATATAATCCTATTTCTCAAGTTCGGCTTTTAGT
 TTCTCTCTTTTAAAAAATTGTTGTTAGGGGTGGTAGGAGAGGGTAAAAAGTACCCTGAAACTGTTGGCCCCAAATGTGAACAGT
 ACCACTAACAGGTAGTAATAGAAATAGAAAACGGGAGATTTCAAATAAAATAACAAACATGCACTCTCAAACCTCCAGAGGGG
 ACAAAGAAAAACAAACAAGAACACAAAACTTGGGCTGTTCCAGTACATCTCAAGGGTGGGAGCTGAAGGTGCGAGCTCC
 AGAGAGGAGCCGCGGCTCCGCCCTCCCCCGCCGAGGTGGCTCCCGGCGAGCGCTCAGACAACAATAGCTAGGATGAGCT
 TGGCCTGCGTCTTAGTTTGTGTGTCTGCCCTGCCAGGAAAGATTACCCATCTCCAAAGAATGACAAAATAAAGAAGCGTAC
 GTTAGGCTCCCAAGGAGACACCGCCCCCTTCCCCACCATTCTTCATCTCCATTAGATTCCCTACCGCGGACCAAAGATGAACC
 TGCTACCAATCAAGTTCCTGCCCAAGTTATTTATTTCCCGCAGCCCTCCACCTGCCGGGGCGGTGCTCGGCGCACTCTAGGCT
 TCCCTCCGGCGACCCCGCGGGCTGCAGCAAAATACGGGGCGCTTCGGCGGGGCGGGGGCGGGCGGTGCCGCGATCCGCG
 CGGTACAGCCGAGCTTGGTGGCTCCGATTGGCCACGACGCGGGCGGGGAGGCTCGGCGGAGGAGGGAGGCGGGGCGAG
 GGCGGCGGCGGGCGGGAGGAATAGGAGAGGGGAGCGGGCCGCGCAGCCAGGCAGCGCTGGGGCGAGCGCGGGGAGAGC
 GGCGGCGGCTCGCCAGGTGCGCGAGCGGAGGCCGAGCGGGGTGCGCGGTGCGCGACGAGGGGCGGCGCGCGAGTGAGCG
 GCGCAGGGCGAGGACCGCGGGCGGGTGCCGGTGCGCGGGCAGCAGGGCGGCTGCGGCAGCAGCTGCGCGGGACGGAGCCG
 CGGCGGGAGAGACCGCGCCGGCCCTCGCCTCACCCCTTGCGGCCGAGGCCGAGAACAGTCTCAACTCGCCGGGGGACCG
 GAAAGAGGAGCCGAGAAGCGCCCCCTCGGCCCCACGCAGCGGAGGCGGAGTGCGGGGACTGCTGCTCTTTGTGGGTGCAGC
 ACGCACGACCCGGAGCGCCCTCCCGCGGCGCTGTCCCGGCGTCTTCGTGCGCGCGAGCGGCCCTGGAGCGGGGACCCGG
 AGGAAGCAAAACCAGAGCCCGAAACCTCGCGTGCGGAGCTCTTGGGAGCGCCATCCG CTCCACTTCCACCTCCACAT

FIG. 2.

Promoter sequence of N-cadherin (CDH2) analyzed for YY1-specific putative transcription factor-binding sites with the software TFBIND.

```
>chromosome:GRCh38:16:68736625:68836148:1
TGCTAGCTCAGTGGCTCATGGCTCACACCTGAAATCCTAGCACTTTGGGAGGCCAAGGCA
GGAGGATCGCTTCAGCCCAGGAGTTCGAGACCAGGCTGGGCAATACAGGGAGACA CAGCG
CCCCACTGCCCCTGTCCGCCCCGACTTGTCTCTCTACAAAAAGGCCAAAAGAAAAAAAAA
TTAGCCTGGCGTGGTGGTGTGCACCTGTACTCCCAGCTACTAGAGAGGCTGGGGCCAGAG
GACCGCTTGAGCCCAGGAGTTCGAGGCTGCAGTGAGCTGTGATCGCACCACTGCACTCCA
GCTTGGGTGAAAGAGTGAGACCCCATCTCCAAAACGAACAAACAAAAAATCCCCAAAAAC
AAAAGAACTCAGCCAAGTGTAAAAGCCCTTTCTGATCCAGGTCTTAGTGAGCCACCGGC
GGGGCTGGGATTCTGAACCCAGTGAATCAGAACCGTGCAGGTCCCATAACCCACCTAGAC
CCTAGCAACTCCAGGCTAGAGGGTCACCGCGTCTATGCGAGGCCGGGTGGGCGGGCCGTC
AGCTCCGCCCTGGGGAGGGGTCCGCGCTGCTGATTGGCTGTGGCCGGCAGGTGAACCTC
```

FIG. 3.
Promoter sequence of E-cadherin (CDH1) analyzed for YY1-specific putative transcription-
factor-binding sites with the software TFBIND.

>chromosome:GRCh38:10:17227659:17238193:1
CTCTGCTCGTTACTAATATTGAAACAACAGCCCTTGAATTGAGTGATTTCCCTAGAAAGG
TTAAGGTGACCGAATCTGAACACTCCCTCCATGTCTTGGACACGAAGTTTTTTGCTGCGT
AGACAGTTTTATCCCCCTCACCCCAAGGTCAATTGCACGAATTCTTTTGGAAAACAGGAC
CTATGGCATTTCAGACAAATCACCGTGAACCCTGTACTGTGCATTGCTGTCCTAAAAT
TAACACATAAATCTATTGCCGCCAAAGATTCTGTCATTTGTGTTACATAATTGCCTTTCA
TTTGAATCATTAAATCAAATTGGGGTTTTTAAGCAACACCTAATTAATTCTTTAACTGGC
TCATATTATACCTTTAATGACTTCCACCAGGGTAAAAACCACTGATCACTGAGTTCTATT
TTGAAACTACGGACGTCGAGTTTCCTCTTTCACCCAGAATTTTCAGATCTTGTTTAAAAA
GTTGGGTGTGGTTTCATGGGGGGAGGGGGAAGAGCGAGAGGAGACCAGAGGGACGGGGGC
GGGGACTCTGCAAGAAAAACCTTCCCGGTGCAATCGTGATCTGGGAGGCCACGTATGGC

FIG. 4.

Promoter sequence of vimentin (VIM) analyzed for YY1-specific putative transcription-factor-binding sites with the software TFBIND.

>chromosome:GRCh38:3:190305101:190323075:-1
 TTGGGAGGGGAGCCAAGTACTGGATATGCTCCGTGCGTGAGTGTGTCTGTGTGTGTGTGT
 GTGTGTGTGTGTAAATCATGTTGCTCTCTGGGTCTGT**TTCCCAATCTGTAGAGT**GTAAAA
 GTCTCTGAGGCTCCTTGCAGAGACAAGTGATGGAACGACCTTGACAGAAGAGAGCAGAGA
 GAGGAAAGAAGGGGGAGGAAGCCAAGCAAAGG**AGAGAGAAATGGTGTGA**TGGGGGAGGAG
 ACGCGGAGTTGGGTAGAAATGCCTTTTAATAAGATATTGGGAAAAAAGTATTAAACCTAA
 AACTGCAGCTCTTG**AAGGATCATT**TTTTTCATCTTTGTGTTAGGATTTACAAGTACAGTGC
 ATAGTAATTT**TTGGATAATTGGAGTGA**ATGAATGAAAAGCGTGAAACGCCTTACAGGAGC
 GAGAAGATCCACGAGAGAAAGCGAGCAGGGACGCAGCTCTGGTGCCTGGTCCTGCCGGGT
 GGTCCCCACGCCGCCAGCCGCGCGTTCCCCAACCGGGCGCTCCCGGCGCCCTCTCGGTGA
 GCCGCCCTGAAACCGCCAGGGGGCGCTCCCCGGCTGCCGGGGCTGAGGCGGGCGGAGCTG

FIG. 5.

Promoter sequence of claudin-1 (CLDN-1) analyzed for YY1-specific putative transcription-factor-binding sites with the software TFBIND.

>chromosome:GRCh38:22:19522424:19528145;-1
TACCAGTGAGGAACTAAGGCAGAGAGGCCACCTCACTAGTCCAGAAAGTTTCTTGCTTGC
GGGAGCGAATCTGACTCCATGCCTGTGTTTAACCACAAAGAGTAACAACAATGCCCCGCAA
AACCGCCGAGTCTGGCACTGTCCACTCTGGATGCTGCTCACATCGTCACAGCCGCCCAGG
GGCCCCACACAGGGTGCCTCGGGCACCTGGTGCAGTGGTCAGGGATGCAGGAGGACCCCA
GCTGCTGCTCTCGGCCTGCAGGAGTACTGGCTTGTGTCAAGAAAGAGCACCAGGCCACAC
TGTGCTTGGAGGCTCTGCAAACATTTGCGGAAATAGAAGGACACATCCTTAAGTGTTC
AAACTGAAAGATAGAAGAAACGCTGTTCTTCACTTCCCCTGAAATCAAATCTGTAACTA
GGAGTTTCCCAAACCCAAATCCCCAGGAATCTTGAGCCTAAATTTAGCTTATCCTTGGAA
GGTCACGGGATTACCCTGGGGCAGGGTCAGCCAGCAGCTGCTCAAGATAAACTTGGCTTT
TCTGCAGACTCAGGCTCTTCTCACACACAATTAATGAGATCCTGCCATTCTTCCCCTGGG

FIG. 6.

Promoter sequence of claudin-5 (CLDN-5) analyzed for YY1-specific putative transcription-factor-binding sites with the software TFBIND.

```
>chromosome:GRCh38:16:3014112:3020671:-1
ATTGTGAATGAAGCTTGGAGAGTGATGGAAGTTCACAGCCGGGAGCGAGCTGTTTGAA
GGCCACCTGACCCAGATCCCCACATCCGCCTGTCCCCCAGTTCGGCGCTGTTCTCCAG
ACACCCAGTCCGGCTCCCGAGCCCCGGCCCGGGGTTCCCCGACCCGGAGTCCCGCGTAC
CTGGCGCTTGCTCCCCGGCCACGGAGCGCAGCAACGCCAGCCAGAGCCCCAGCACGAGGA
GCCGCAGCAACCGGCGCAGCGAGCCCCGAGCCATAGTGCACGTCCTGCGCCCGCCGCTGT
CTGCGCCCGCCGCGCCGGCAGGGACCCACGGCCGCGCCCGCCCCGCCCCCGCCCTT
CCGGGGCGGAGCTCTCGCCTCCGCCCCGCTTGAGGTCCGCTTCGGGACGCCCCGCCCCGC
GGCGCCCGCTCAGTTCAGTCATTCAACAAAGTCCTGGCGCGGGAGCTGCCAGGACC
CCGCAGGGACGCAGACCCCTTCCTTGCCAGCCGGTGATCTAGTCCAGCGTGCGTGGTG
TGGGGAATCAAAAATTAGACACGAGTGCTCGCTTCGGCAGCACATATAGAAATCAGACA
```

FIG. 7.

Promoter sequence of claudin-6 (CLDN-6) analyzed for YY1-specific putative transcription-factor-binding sites with the software TFBIND.

>chromosome:GRCh38:2:215359840:215436772:-1
CGTTCGCCCCGCTGGCCCTTTCTCAGAGCCAGACAGGCACAGCGCTGAGAAGGGAAGAAGT
CCGAACAGGGAGCTGTGAAGACAAAATAAGGGAGTCCCGAGTCAGTACCCTTTAGTCCAA
AGAAAGGGAGCGGGATGGGGGGAAAGGCAGCCCCGCCCTGGGACTGAAAAGTCTGGATTCT
TTAACAGCTGCAAGGTCGTGGATATTTTATGGGTTTCTTCCTCACAAAATACACTCCTA
TAAGCAGAGATTCCCCCCTCCACCCCGAAGAGAGGTGACGCAATGTCCTCAAACACTAC
CACCACCCCAATAAAAAAGAAAAGGGAAGGGGGAGCGTCTTGCAACCCCTTCGCTTCAC
ACAAGTCCAGCCACTCCCTTTCCTCCCAGCCGCTTCCCATCCCTTCCCCCATCCCTAAA
AAGTTTGATGACCGCAAAGGAAACCGAAAAAAGTTGTCTTGCCCCAGTCCTGGCGGGCC
ATCAGCATCTCTTTTGTTCGCTGCGAACCCACAGTCCCCCGTGACGTCACCCGGAGCCCG
GGCCAATCGGCGCGCGGTCTGGCTGCGGCGGCCGGCGGGCGGGCGGGCGGGTGGGGTGGGG

FIG. 8.
Promoter sequence of fibronectin (FN1) analyzed for YY1-specific putative transcription-
factor-binding sites with the software TFBIND.