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Mechanisms of Yin Yang 1 in Oncogenesis: The Importance of Indirect Effects

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Abstract

Yin Yang 1 (YY1) is a ubiquitously expressed transcription factor that performs numerous functions including transcriptional regulation, cell growth control, apoptosis, large-scale chromosomal dynamics, and X-chromosome inactivation. YY1 clearly is able to control cell functions, including proliferation, by acting as a transcription factor either to activate or repress specific genes. Based on its ability to regulate cell growth control genes, it has been argued that YY1 can function as an oncogene that initiates oncogenesis. Although this is an attractive hypothesis, no reports indicate that YY1 can acutely transform cells in culture or form tumors within animals when overexpressed. Thus, it remains unclear whether YY1 is a "classic" oncogene. However, YY1 controls many diverse cell functions, and these functions may provide clues to its role in oncogenesis. We propose that in many cases YY1 may function in oncogenesis and disease progression through "indirect" effects by virtue of its role in either recruiting Polycomb group proteins to DNA, regulating mutator protein accumulation, controlling large-scale chromosomal dynamics or genomic integrity. Disruption of these functions may causally initiate cancer or may contribute to disease progression. Targeting YY1 functions provides possible avenues for clinical intervention.

Keywords

transcription; Polycomb; DNA repair; mutagenesis; genome stability

I. INTRODUCTION

Transcription factor Yin Yang (YY) 1 is a ubiquitous and multifunctional zinc-finger transcription factor that mediates multiple diverse functions. YY1 plays roles in a large array of diverse cell functions including transcriptional regulation, cell growth control, apoptosis, large-scale chromosomal dynamics, X-chromosome inactivation, and DNA repair. YY1 can act as a transcriptional activator, repressor, or initiator protein depending upon DNA binding site context or cell type.[1–3] It is implicated in lineage differentiation and cell growth control,[4–6] as well as in oncogenesis (discussed here) and other diseases such as dystrophic muscle disease.[4,7–9] A number of excellent reviews have covered some of the basic functions of YY1 in relation to function in transcription and possible role in disease.[2,3,10] In this review, we will briefly cover YY1 structure, gene regulation functions, role in development and chromosomal structure, and role in epigenetic phenomena. We then will assess what we perceive to be potential roles of YY1 in certain malignancies and possible therapeutic interventions targeting YY1.

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YY1 originally was purified and cloned based upon its ability to bind to the adeno-associated virus P5 promoter and to interact physically with adenoviral E1A protein. This interaction converts YY1 from a transcriptional repressor into an activator.[11] The YY1 complementary DNAwas cloned simultaneously based on its ability to bind to and repress the immunoglobulin kappa 3′ enhancer and termed *nuclear factor (NF) E1*,[12] or to bind to and activate the ribosome protein L32 promoter and named delta.[13] Shortly thereafter, YY1 was cloned based on its ability to bind to retroviral long terminal repeat sequences and named upstream control region binding protein.[14] The biphasic role of YY1 in transcriptional activation and repression, however, best matched the name YY1, and this name persists.

YY1 is greatly conserved in multiple species (the human and mouse proteins are 96% identical) and has functional orthologs even in insects (flies and honey bees).[15] Mammals have 2 additional YY1-related proteins, YY2 and Rex1, that are thought to have originated from YY1 via retrotransposition events.[16,17] YY2 is 56% identical to YY1 and shows overlapping DNA binding site specificity.[16] YY2 shows a more restricted expression pattern than YY1 and seems to regulate a subset of genes also regulated by YY1. YY1 also shows homology within its DNA binding domain with transcription factor Rex1.[17] The retention of YY1 and related proteins YY2 and Rex1 in mammals suggests functional divergence mediated by differences in DNA binding affinities or sites and specific protein interactions that may regulate distinct genes.[17]

II. YIN YANG 1 STRUCTURE

YY1 contains 4 zinc fingers at its carboxyl terminus (amino acids 298–414) and a region rich in alanine and glycine between amino acids 154 and 201. The amino terminal 100 amino acids of YY1 encode several notable features. Sequences 43 to 53 contain 11 consecutive acidic residues whereas amino acids 70 to 80 consist of 11 consecutive histidine residues. These 2 segments are separated by a region rich in glycine (residues 54–69). In addition, sequences 16 to 29 have the potential to form an amphipathic negatively charged helix, and sequences 80 to 100 are rich in proline and glutamine. Function of the histidine and acidic stretches are still unknown, but transcriptional activation function maps to sequences 16 to 29 and 80 to 100.[18–21]

Sequences near the YY1 carboxyl terminus (333–397) that overlap the zinc finger region, and sequences 170 to 200, have been reported to be involved in transcriptional repression.[1,11,18–20,22–24] These sequences are known to interact physically with a variety of transcriptionally important proteins including TATA binding protein, p300, c-Myc, and histone deacetylase (HDAC) 2.[2] The YY1 zinc-finger region also is capable of interacting with the nuclear matrix,[24,25] and C-terminal sequences seem to interact with and mask the transcriptional activation domain; YY1 transactivation function increases upon their deletion if YY1 is linked to a heterologous DNA binding domain.[20]

Interesting regions of homology exist between YY1 and its apparent *Drosophila* ortholog, pleiohomeotic (PHO). PHO is highly homologous to YY1 in 2 regions, which include YY1 sequences 296 to 414 and 205 to 226 (the corresponding segments in PHO are residues 357–475 and 148–169, respectively). Sequences 298 to 414 constitute the 4 YY1 zinc fingers. The homology over this region is extraordinary for organisms as diverse as flies and humans (112 identities out of 118; 95%). Within this segment, zinc fingers 2 and 3 are 100% identical. The 205 to 226 segment is also highly homologous. YY1 sequences 205 to 225 are 82% identical to the corresponding sequences in PHO and this region has been coined the “recruitment of Polycomb” (REPO) domain.[15] Other than the zinc-finger region, this is the most highly conserved segment of YY1 homologs in other species (see Fig. 1). This domain

will be discussed below with reference to its function in Polycomb group (PcG) protein DNA recruitment. Outside of these regions of high similarity (i.e., the zinc fingers and REPO domain), YY1 and PHO show no discernible similarity. PHO does not contain an obvious transcriptional activation domain and lacks YY1 structural features such as acid and histidine stretches. However, the 2 regions of high similarity between YY1 and PHO, and their similar spatial locations within the proteins, suggest that they might carry out some of the same functions in vertebrates and flies, respectively (discussed later). Notable sequence features and functional domains of YY1 are shown in Fig. 2.

III. GENES REGULATED BY YIN YANG 1

Because YY1 was first identified as a transcription factor, initial studies focused primarily on its ability to activate or repress transcription. Numerous genes are either repressed or activated by YY1, and it has been estimated that perhaps 7% of mammalian genes are regulated by this transcription factor.[26–28] In addition, some promoter sequences can bind to YY1 where it functions as an initiator protein.[29] Thus, YY1 mediates diverse roles in transcription and regulates a surprising array of genes. Genes regulated by YY1 include housekeeping genes and genes involved in cell cycle control, apoptosis, chromatin structure, cytokinesis, development, and differentiation.[1,2,10,30] YY1 binding sites are present in numerous promoters and enhancers, indicating its importance for the control of many genes. YY1-regulated genes have been reviewed previously[2,3,10,30] and will not be elaborated upon here.

IV. YIN YANG 1 FUNCTION IN DEVELOPMENT

The ubiquitous expression of YY1 and the large number of genes regulated by this protein suggest that YY1 might be crucial for cellular function and for development. Indeed, the Shi laboratory showed that YY1 is crucial for embryonic development because homozygous mutation of the YY1 gene in mice results in peri-implantation lethality.[31] Heterozygous knockout mice show growth retardation and some neurological defects, suggesting a YY1 dosage effect.[31] In addition, heterozygous mutant mice showed homeotic transformations of axial skeleton in mice,[32] consistent with YY1 PcG function (described more fully below). YY1 also is involved in eye development because ablation of YY1 enhances an anterior eye developmental abnormality caused by Ring1 knockout.[32]

Interestingly, reduction of YY1 levels impairs embryonic growth and viability in a dose-dependent manner.[33] The mechanism of this dosage effect is not clear, but there is a tight correlation between YY1 dosage and cell proliferation, with deletion of the *YY1* gene resulting in cytokinesis failure and cell cycle arrest.[33] Cellular levels of YY1 can determine whether YY1 functions as an activator or a repressor, indicating the YY1 levels in the cell can have a profound effect on function.[20]

YY1 also is crucial for B-cell development and immune function. B-cell development involves progression from $Lin^{-}Sca\text{-}1^{+}c\text{-}kit^{+}$ (LSK) progenitor cells through pro-B, pre-B, immature B, mature B, and plasma cell stages. The early stages of B-cell development can be delineated by the rearrangement status of the immunoglobulin (Ig) heavy and light chain genes. Both heavy and light chain genes are produced during early, antigen-independent B-cell development by a somatic rearrangement process that links together either V, D, and J segments (heavy chain), or V and J segments (light chain), to produce functional Ig genes.[34–36] The Ig loci are huge (2.4–3.2 Mb), and for rearrangement of distal variable region genes to occur, the loci must go through a physical contraction process. Although IgH D through J and proximal V to D rearrangements can occur without contraction, the distal V genes require locus contraction and looping for rearrangement.[37,38]

YY1 has long been believed to play some role in Ig gene regulation and B-cell biology because it associates with multiple Ig enhancer elements including the heavy chain intron and 3′ enhancers, as well as the Ig kappa 3′ enhancer.[12,39] The Shi laboratory at Harvard University provided some insight into the role of YY1 in B-cell development by demonstrating that conditional knockout of YY1 in the B-cell lineage (using mb1-CRE recombinase; expressed early after B lineage commitment) results in arrest at the pro-B cell stage.[40] Pro-B cells lacking YY1 have normal D_H-J_H recombination but reduced frequency of V_H-D_HJ_H recombination, with the defect being most severe for more distal V_H genes.[40] These knockout pro-B cells also show a defect in Ig locus contraction. Thus, conditional knockout of YY1 using mb1-CRE results in arrest at the pro-B cell stage, lost Ig locus contraction, and reduced rearrangement of distal V genes.

V. YIN YANG 1 EXPRESSION IN CANCER

Considerable data exist on the relative expression levels of YY1 in various cancers. The majority of this data is based on transcript analyses, although some include protein expression data. Collectively the data are somewhat diverse, with some cancers showing increased YY1 expression and some showing lowered expression. For instance, increased YY1 RNA or protein expression has been observed in cancers of the prostate,[41–45] colon,[42,46] ovary,[42,43] breast,[47–49] bone,[50,51] liver,[42] lung,[42] bladder,[42,43] cervix,[43] skin,[43,49] and blood (diffuse large B-cell lymphoma, acute myeloid leukemia, chronic myeloid leukemia, B and T acute lymphoblastic leukemia, Hodgkin lymphoma, Burkitt lymphoma, mantle cell lymphoma, chronic lymphocytic leukemia, and follicular lymphoma).[9,43,52,53] However, YY1 expression was found to be reduced in some melanomas, pediatric osteosarcomas, and urothelial carcinomas.[43] In addition, conflicting data exist on the survival outcome with relation to YY1 expression. In some cases, high YY1 expression correlated with poor prognosis (prostate, breast, and bone cancers),[47,51] whereas in other situations YY1 expression correlated with positive outcomes (ovarian cancer, colon cancer, follicular lymphoma).[46,54–56] In the case of ovarian cancer, small interfering RNA knockdown of YY1 resulted in reduced cell proliferation, reduced expression of cell division cycle6, reduced cell motility, and reduced growth in soft agar.[55] On the contrary, YY1 knockdown led to resistance to paclitaxel and docetaxel treatments in ovarian cancer cell lines.[55]

YY1 overexpression correlates with aggressive phenotype in osteosarcoma and this might be partially due to cooperation between Myc and YY1 silencing specific target genes.[50,57] To determine whether overexpression of YY1 was involved directly in osteosarcoma, the Napoli group used YY1 small interfering RNA treatment of sarcoma osteogenic 2 cells. YY1 knockdown caused dramatic growth differences including reduced cell growth, lack of growth in soft agar, reduced cell invasion in Matrigel filters (BD Biosciences, Sparks, MD), and reduced formation of new blood vessels.[51] On the other hand, YY1 can upregulate an invasion suppressor to inhibit cancer cell invasion.[58] Thus the data are complex and the role of YY1 in cancer is unclear.

VI. MECHANISMS OF YIN YANG 1 FUNCTION IN ONCOGENESIS

A. Identification of the Polycomb Group Function of Yin Yang 1

More than a decade ago, the Kassis laboratory cloned a *Drosophila* protein, PHO. We immediately were intrigued by homologies between the mammalian YY1 protein and the *Drosophila* PHO[59] (Figs. 1 and 2). Girton and Jeon[60] demonstrated that PHO is a PcG protein, a family of proteins involved in hematopoietic development, epigenetic chromosomal condensation, stable transcriptional repression, control of cell proliferation, as

well as stem cell self-renewal. This raised the exciting possibility that YY1 can function as a vertebrate PcG protein.

PcG proteins generate stable, heritable repression complexes on DNA.[61–64] The complexes assemble on Polycomb response element (PRE) sequences and repress transcription of nearby genes. Upon recruitment of complexes to DNA, the histones in the vicinity become deacetylated on H3 lysines 9 and 14 and become methylated on H3 lysines 9 and 27.[65–73] It is speculated that these modifications are part of the repression mechanism, but their precise functions are unknown. The molecular details of how PcG complexes are recruited to DNA are uncertain. The complexes bind to PREs apparently via interaction with sequence-specific DNA binding proteins. The current best candidates for these proteins are PHO (in *Drosophila*) and YY1 (in mammals). Many *Drosophila* PRE sequences contain PHO/YY1 binding sites, suggesting that this could be a common mechanism for PcG recruitment to DNA.[74]

Prompted by the possibility that YY1 functions as a PcG protein, we tested this hypothesis using a *Drosophila in vivo* transcription system as well as a phenotypic correction assay. Our results showed that human YY1 does indeed function as a PcG protein *in vivo*.[75–77] We found that YY1 can repress transcription in a PcG-dependent fashion, can phenotypically correct *pho* mutant flies, and can recruit PcG proteins to specific DNA sequences.[75–77] A number of mammalian DNA sequences have been identified that bind to PcG proteins *in vivo*.[78,79] Some of these DNA sequences also bind to YY1, and knockdown of YY1 expression in mammals can lead to loss of PcG DNA binding and loss of methylation on histone H3 lysine 27.[78] The demonstration that YY1 is a mammalian PcG protein with high affinity, sequence-specific DNA binding activity is particularly exciting because PcG proteins are known to contribute to a number of malignancies.[80–83] The ability of YY1 to control PcG DNA occupancy in mammals suggests that it could be a potential target for therapies against cancers that rely on PcG function (discussed below).[84,85] Thus, it would be advantageous to better understand YY1 PcG function and the YY1 sequences involved in PcG DNA recruitment.

B. The Yin Yang 1 Recruitment of Polycomb Domain

Using a fly transgenic approach, our laboratory identified the YY1 sequences involved in PcG function.[15] We found that a 26 amino acid segment (amino acid residues 201–226), when fused to a heterologous GAL4 DNA binding domain, was necessary and sufficient for PcG-dependent transcriptional repression. Amazingly, this small 26 amino acid segment also was necessary and sufficient for recruitment of PcG proteins to DNA.[15] Therefore, we named YY1 sequences 201 through 226 the REPO domain for their ability to recruit Polycomb.[zxsV Cxxxxxxc] A REPO domain YY1 mutant (Δ201–226) can mediate nearly all YY1 functions such as DNA binding, transcriptional activation, transient transcriptional repression, and interaction with histone acetyltransferase (HAT) and HDAC proteins. However, this mutant fails to carry out YY1 PcG functions and fails to recruit PcG proteins to DNA.[15]

We also identified biochemical interactions that link the YY1 REPO domain with PcG proteins *in vivo*. Using a yeast 2-hybrid screen approach, we found that the YY1 REPO domain interacts with the PcG protein YY1-associated factor 2 (Yaf2) and can recruit Yaf2 to DNA.[86] In turn, Yaf2 can recruit other PcG proteins to DNA, leading to transcriptional repression. As expected, loss of the *Drosophila* Yaf2 homolog, *Drosophila* Ring and YY1 binding protein, results in reduced PcG recruitment. Therefore, Yaf2 may provide a bridging function between YY1/PHO and other PcG complex proteins, and this too could be a target for therapy against malignancies caused by PcG dysfunction.

C. Polycomb Group Proteins in Hematopoietic Stem Cell Development

PcG proteins are involved in hematopoietic stem cell self-renewal and YY1 may play a role in this process.[80,87] PcG protein Bmi-1 is known to be necessary for hematopoietic stem cell self-renewal and can control cell proliferation.[88,89] Similarly, the PcG protein EZH2 can prevent hematopoietic stem cell exhaustion,[90] whereas Mel18 negatively regulates hematopoietic stem cell self-renewal.[91] Other PcG proteins implicated in hematopoietic development include Mph1/Rae 28 and extraembryonic ectoderm.[92–94] Based on the above PcG functions in stem cell biology, we hypothesize that YY1 also may be important for hematopoietic stem cell biology and may be involved in stem cell function.

Polycomb Group D. Proteins in Cancer

PcG proteins have long been associated with cancer biology and stem cell function.[80] The PcG protein Bmi-1 originally was identified as a protein that cooperates with c-Myc to promote B-cell and T-cell lymphomas.[95] EZH2 and extraembryonic ectoderm are involved in cell proliferation, and EZH2 provides proliferative advantage on cells, with high levels associating with breast cancer aggressiveness.[48,96] EZH2 also is overexpressed in hormone-refractory metastatic prostate cancer, leukemia, and breast cancer, and it directly contributes to the control of prostate cell proliferation and malignant behavior.[44,48,49,97–99] EZH2 or SUZ12 are overexpressed in a large variety of cancers,[83] and the high level of PcG gene expression in prostate, breast, and hepatocellular cancers can be considered a prognostic indicator for these diseases.[44,48,100] In some cases, PcG expression can be linked directly to disease phenotype. For instance, overexpression of EZH2 can cause anchorage-independent growth of breast epithelial cells.[48] In addition, EZH2 overexpressing cells can cause tumors in mice.[101] Similarly, high levels of EZH2 are observed in T-cell lymphoma/leukemia, and patients overexpressing YY1 have a worse prognosis.[102] The Oncomine database indicates overexpression of 4 PcGs (EZH2, Suz12, YY1, and RBB7) in brain tumors, and high levels of EZH2 correlate with the severity of the tumor.[103] Therefore, levels of PcG expression can be used as prognostic markers for cancer progression.

Although a definitive mechanism is not established for how PcG proteins contribute to oncogenesis, many PcG proteins regulate cell proliferation by negative regulation of the INK4A-ARF locus that encodes $p15^{INK4B}$, $p16^{INK4A}$, and $p19^{ARF}$ genes.[84,88,104–106] The PcG protein Bmi-1 also can regulate cell senescence[88] and can inhibit c-Myc–induced apoptosis.[107] In addition, PcG proteins can regulate p53 function, leading to cell cycle control.[108,109] It is not clear if the contribution of PcG proteins to cancer is directly due to their PcG repressive function, or if it is due to simple transcriptional repression, which is more transient in nature. However, it is clear in some cases that specific PcG proteins are directly involved in the malignant phenotype. The general assumption is that elevation of PcG proteins results in hyperrepression of a group of target genes involved in cancer, including tumor suppressor genes. Indeed, a group of PcG repressed genes correlates with poor outcome in prostate cancer patients.[110] Consistent with a role in cancer mechanism, reducing PcG protein EZH2 levels through RNA interference approaches reduces prostate cancer cell proliferation.[44] The role of EZH2 seems to depend upon its histone methyltransferase activity because pharmacologic disruption of PcG methyltransferase activity using 3-Deazaneplanocin A selectively induces apoptosis in breast cancer cells.[111] This is quite exciting because specifically targeting PcG function seems to be a viable approach for therapies against cancers dependent on aberrant PcG activity. Thus, inhibition of PcG function represents an important potential target for therapy against cancer.

Unfortunately, 3-Deazaneplanocin A is not specific for PcG methyltransferase activity because it inhibits S-adenosylhomocysteine hydrolase, resulting in accumulation of S-adenosylhomocysteine, which causes by-product inhibition of all S-adenosyl-L-methionine–

dependent methyltransferases. A more specific inhibitor for PcG function would be advantageous for treatment. Because most PcG proteins do not recognize specific DNA sequences, but instead require recruitment molecules such as YY1, targeting PcG DNA recruitment is a potential therapeutic target. As described above, we showed that the 26 amino acid YY1 REPO domain is necessary and sufficient for the recruitment of PcG complexes to DNA, for methylation of histone H3 on lysine 27, and for PcG-mediated silencing.15 We reasoned that disruption of REPO domain function might prove to be an effective approach to therapy against cancer. In this case, a REPO peptide could be used as a competitive inhibitor of YY1 recruitment of PcG proteins to DNA. We used 26 amino acid small peptide inhibitors (cell-penetrating peptides; cell-penetrating peptide inhibitors) that cross the cell membrane to show that the YY1 REPO domain peptide can indeed inhibit prostate cancer cell growth, as well as growth of an Abelson-transformed pro-B cell line.[112] We found that this inhibition is at least in part due to inducing cell death by stimulating apoptosis.[112] We propose that the REPO domain peptide functions to inhibit cancer cell growth by competitively inhibiting YY1 interaction with PcG proteins, thus ablating PcG-dependent repression (Fig. 3).

E. Cell Growth Control

YY1 clearly is able to control cell functions, including proliferation, by acting as a transcription factor either to activate or repress specific genes. Based on its ability to regulate cell growth control genes, it has been argued that YY1 likely can function as an oncogene that initiates oncogenesis.[3,10] For instance, YY1 can activate c-Myc P1 promoter activity in Burkitt lymphoma[113] and can enhance murine double minute 2-mediated p53 inactivation, thus potentiating cellular proliferation and tumorigenesis.[114] YY1 can control human immunodeficiency virus gene expression and viral titers, and deletion of YY1 binding sites in human papilloma viruses correlates with increased viral gene expression and the development of cervical cancer.[115–123] Thus, YY1 function is related to transcriptional regulation, embryonic development, oncogenesis, viral gene expression, and a growing list of diseases.

On the contrary, in human basal cell carcinoma, YY1 shows repressive activity at the glutathione S-transferase locus and may prevent tumor progression caused by the glutathione S-transferase M3 genotype.[124] Indeed, Lichy et al[125] found a marked decrease in YY1 binding in malignant HeLa/fibroblast somatic cell hybrids when compared to nontumor cells, whereas Austen and colleagues[126] showed that YY1 is a negative regulator of cell growth via potent inhibition of c-Myc transforming activity and possibly functions as a tumor suppressor. These diverse YY1 functions probably result from its ability to interact with numerous proteins and complexes.

A long list of proteins can interact physically with YY1 to control gene expression. It has long been known that YY1 interacts with various HATs and HDACs (reviewed by Thomas and Seto,[2] Gordon et al,[3] and Sui[10]). These proteins no doubt contribute to the role of YY1 in activating and repressing transcription, and YY1 itself is a target of acetylation.[127] For instance, YY1 interaction with the HAT protein p300 overcomes transcriptional repression,[19] and YY1 recruits the HDAC protein mRPD3 to DNA to repress expression.[23] YY1 also recruits histone H4 methyltransferase protein arginine N-methyltransferase to the *GRP78* gene to activate transcription.[128] On the other hand, YY1 recruits histone methyltransferase protein EZH2 to a variety of genes to repress transcription.[78,79] YY1 also interacts with proteins in the ubiquitinylation pathway and thus can control protein stability to regulate function.[114] YY1 also can bind to the retinoblastoma (Rb) protein to accelerate cell cycle progression to the S phase.[6,19] Hypophosphorylated Rb interacts with YY1, and this disrupts YY1-DNA association. The YY1-Rb interaction is observed in resting cells, but not in serum- or bacterial lipopolysaccharide-stimulated cells.[6,39] In addition, YY1 interacts

with murine double minute 2 and tumor suppressor p53, leading to enhanced p53 ubiquitinylation and subsequent degradation. As discussed above, overexpression of YY1 might therefore predispose cells to a transformed phenotype by inhibiting p53 tumor suppressor activity.

Although it is an attractive hypothesis that YY1 can directly participate in oncogenesis by regulating expression of growth control genes, no reports indicate that YY1 can acutely transform cells in culture (*viz.* 3T3 transformation assays; growth in soft agar) or form tumors within animals when overexpressed. Thus, it remains unclear whether YY1 is a "classic" oncogene. However, YY1 controls cell functions involved in DNA repair and genomic stability. These functions may provide clues to the role of YY1 in oncogenesis.

F. Role of Yin Yang 1 in Genomic Stability

YY1 can regulate large portions of the genome through imprinting mechanisms. Clusters of YY1 binding sites reside at imprinting control regions.[129,130] Knockdown of YY1 results in upregulation of many imprinted genes within the Peg3 region and a resultant loss of DNA methylation.[130] YY1 can function as a cofactor with CCCTC binding factor within the imprinting domain of Tsix. Loss of YY1 causes aberrant expression of Tsix as well as Xist.[131] Strikingly, YY1 also tethers Xist RNA to the inactive X nucleation center during X-chromosome inactivation.[132] How this relates to the role on YY1 in cancer biology is uncertain, but clearly YY1 can regulate large-scale chromosomal structures.

YY1 also physically interacts with the chromatin remodeling complex INO80, related to the yeast switch/sucrose nonfermentable complex.[133] As might be expected for a complex involved in chromatin remodeling, this interaction can result in access of YY1 to promoter sequences, leading to changes in gene expression.[133] However, this interaction also seems to be crucial for genomic stability because YY1-INO80 interactions seem to control homologous recombination-based repair.[134] Knockdown of YY1 leads to genomic instability and aneuploidy, and knockdown of INO80 subunits yields a similar phenotype.[134] The role of YY1 in genome and epigenetic functions is particularly intriguing. Mouse embryo fibroblasts isolated from $YY1^{f/f}$ mice are particularly sensitive to chromosomal aberrations after transfection with adenoviral-driven CRE recombinase to delete the endogenous *YY1* gene.[134] These cells also are highly sensitized to DNA damaging agents, suggesting that YY1 plays an important role in DNA repair and genomic integrity. Mouse embryo fibroblast knockout and knockdown studies indicate that YY1 and INO80 together are involved in homology-directed DNA repair, and YY1 can bind directly to recombination intermediates.[134] Therefore, YY1 loss or overexpression may disrupt genomic stability and predispose cells to acquiring mutations that eventually may lead to oncogenesis or to malignant progression. The ability of YY1 to interact with and stimulate Poly (adenosine diphosphate-ribose) function in DNA repair is consistent with this idea.[135]

Interestingly, we recently observed that YY1 can interact physically with activation-induced cytidine deaminase (AID).[136] Both Ig class switch recombination (CSR) and somatic hypermutation (SHM) require AID function,[137,138] and AID deficiency leads to loss of CSR and SHM. Both processes require that AID deaminate cytidine to uracil, followed by either mutagenic processing by error prone repair mechanisms (SHM) or double strand breaks leading to rearrangement (CSR).[139] AID function must be tightly regulated to avoid deleterious mutagenic activity because, in addition to diversifying the immune response, AID catalyzed cytidine deamination is believed to be involved in generation of lymphomagenic chromosome translocations, and overexpression of AID in transgenic animals leads to T-cell lymphomas and tumors in lung epithelium.[140–142] An increasing number of non-Ig genes also have been revealed to be hypermutated by AID in wild-type B cells in which efficient, error-free repair masks most AID mutations.[143]

AID expression levels directly correlate with the frequency of AID-dependent DNA remodeling events and incidence of c-Myc/IgH translocations.[141,144–147] Limiting AID levels in the nucleus protects the B-cell genome from mistargeted mutations and is regulated by multiple mechanisms. Upon stimulation of B cells, AID expression is dramatically upregulated in germinal center B cells.[138] However, most AID is retained in the cytoplasm and only a small fraction translocates to the nucleus to mediate CSR and SHM.[148–151]

Factors that control AID subcellular localization are only now being defined. However, we found that YY1 can interact physically with AID, leading to increased AID nuclear levels. This YY1-AID interaction and increased nuclear AID accumulation can regulate AID function in Ig CSR.[136] This suggests that if YY1 is overexpressed in B lymphoid or myeloid (chronic myelogenous leukemia) cancers that also express AID (diffuse large B-cell lymphoma, chronic myelogenous leukemia, acute lymphoblastic leukemia, Burkitt lymphoma, follicular lymphoma, chronic lymphoblastic leukemia), it would lead to increased levels of nuclear AID, increased mutagenic activity, and increased incidence of B-cell lymphomas or augmented disease progression. Indeed, patients with germinal center–derived diffuse large B-cell lymphoma show elevated YY1 expression.[52] In addition, AID expression seems to promote B lymphoid blast crisis and drug resistance in chronic myeloid leukemia.[152] Thus, high levels of YY1 could elevate nuclear AID levels, leading to accumulation of mutations that could contribute to disease progression from chronic to acute stages.

G. Yin Yang 1 and Fas-Induced Apoptosis

High levels of YY1 seem to contribute to the failure of therapies that induce apoptosis. CH11 is a monoclonal antibody against Fas/apoenzyme 1 that can induce apoptosis in Fas/apoenzyme 1–expressing cells.[153,154] Some tumors acquire resistance to CH-11-induced apoptosis apparently because of down-regulation of the Fas gene. The Bonavida group found that YY1 binds to a silencer in the Fas gene to mediate silencing.[155] Knockdown of YY1 causes elevated Fas expression, resulting in responsiveness to CH11-induced apoptosis.[155] Similar results are obtained by inhibiting YY1 DNA binding using the nitric oxide donor DETANONOate.[156] An additional approach is to down-regulate factors that control YY1 expression. Transcription factor NF-κB activates YY1 expression, and reduced levels of NF-κB results in reduced YY1 levels. In addition, the monoclonal antibody rituximab against cell surface protein CD20 can increase Fas expression.[156,157] Interestingly, rituximab reduces p38 signaling and constitutive NF-κB activity, leading to reduced YY1 expression and concomitant upregulation of Fas.[156,157] This increased Fas expression restores CH11-induced apoptosis in both non-Hodgkin lymphoma cells and prostate cancer cells.[156–158] Therefore, rituximab treatment of CH11-resistant cancers can be used to treat B lymphoid cancers that express CD20 on the cell surface. The general strategy of reducing YY1 expression can be used in other cancers via blocking tumor necrosis factor α activity that activates NF-κB and YY1, leading to reduced Fas expression.

VII. CONCLUSION

Despite the myriad functions performed by YY1 and its direct role in regulating growth control genes and protein functions, it is still unclear whether it directly acts as an oncoprotein. We propose that many of YY1's functions in oncogenesis and disease progression are "indirect" effects of its role in recruiting PcG proteins to DNA, regulating mutator protein accumulation (AID), controlling large-scale chromosomal dynamics (such as imprinting and X-inactivation), or controlling genomic integrity (DNA repair) (Fig. 4). Disruption of these functions may causally initiate cancer or may contribute to disease progression. In any event, YY1 provides some possible avenues for clinical intervention:

1. **PcG recruitment.** Substantial evidence indicates that PcG proteins are expressed at higher levels in various cancers and are intimately involved in the disease phenotype. Disruption of PcG recruitment to DNA by targeting YY1 REPO domain function is a promising potential therapy (Fig. 4A).
2. **Regulation of mutator proteins.** AID is a mutator enzyme expressed during antibody maturation phases of B-cell development. It is now clear that AID can contribute to a number of hematopoietic malignancies, and off target effects of AID can result in gene mutations and chromosomal translocations. Our observation that YY1 can control levels of AID in the nucleus suggest that disruption of AID-YY1 interactions, or reduction of YY1 levels, could be used to reduce AID nuclear accumulation, thus protecting against AID-induced mutations (Fig. 4B). This is a new area of investigation that will require more work to determine effectiveness as a therapy.
3. **Control of genome integrity.** It is now clear that reducing YY1 levels results in significant alterations in chromosomal integrity. The ability to maintain diploid status and to repair double stranded DNA breaks is greatly reduced. Modulation of this function of YY1 could be used to sensitize cancer cells to chemotherapeutic agents (Fig. 4C).
4. **Fas-induced apoptosis.** Overexpression of YY1 leads to loss of Fas gene expression and loss of CH11-induced apoptosis. On the contrary, reduction in YY1 results in elevated Fas expression and a restoration of CH11-induced apoptosis. Therefore, agents that regulate YY1 expression (such as rituximab) may be used in combination with agents that cause Fas-induced apoptosis (Fig. 4D). Although the precise role of YY1 in oncogenesis is not yet clear, our current knowledge enables us to develop therapies that may be useful in cancer treatment.

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ABBREVIATIONS

YY1	Yin Yang 1
YY2	Yin Yang 2
PHO	pleiohomeotic
HAT	histone acetyltransferase
HDAC	histone deacetylase
PcG	Polycomb Group
REPO	Recruitment of Polycomb
Ig	immunoglobulin
VDJ	variable diversity joining segments
NF-E1	nuclear factor E1
NF-κB	nuclear factor kappa B
UCRBP	upstream control region binding protein
AID	activation induced cytidine deaminase

CSR	class switch recombination
SHM	somatic hypermutation
MEF	mouse embryo fibroblasts
CTCF	CCCTC binding factor
Swi/Snf	Switch/Sucrose nonfermentable
DLBCL	diffuse large B cell lymphoma
CML	chronic myelogenous leukemia
ALL	acute lymphoblastic leukemia
TNFα	tumor necrosis factor alpha
Mdm2	mouse double minute 2
TBP	TATA binding protein
PRMT1	protein arginine N-methyltransferase
Rb	retinoblastoma protein
DZNep	3-Deazaneplanocin A
GST	glutathione S-transferase
CDC6	cell division cycle 6
SaOS2	sarcoma osteogenic 2
PRE	Polycome response element
Yaf2	YY1 associated factor 2
dRYBP	Drosophila Ring and YY1 binding protein

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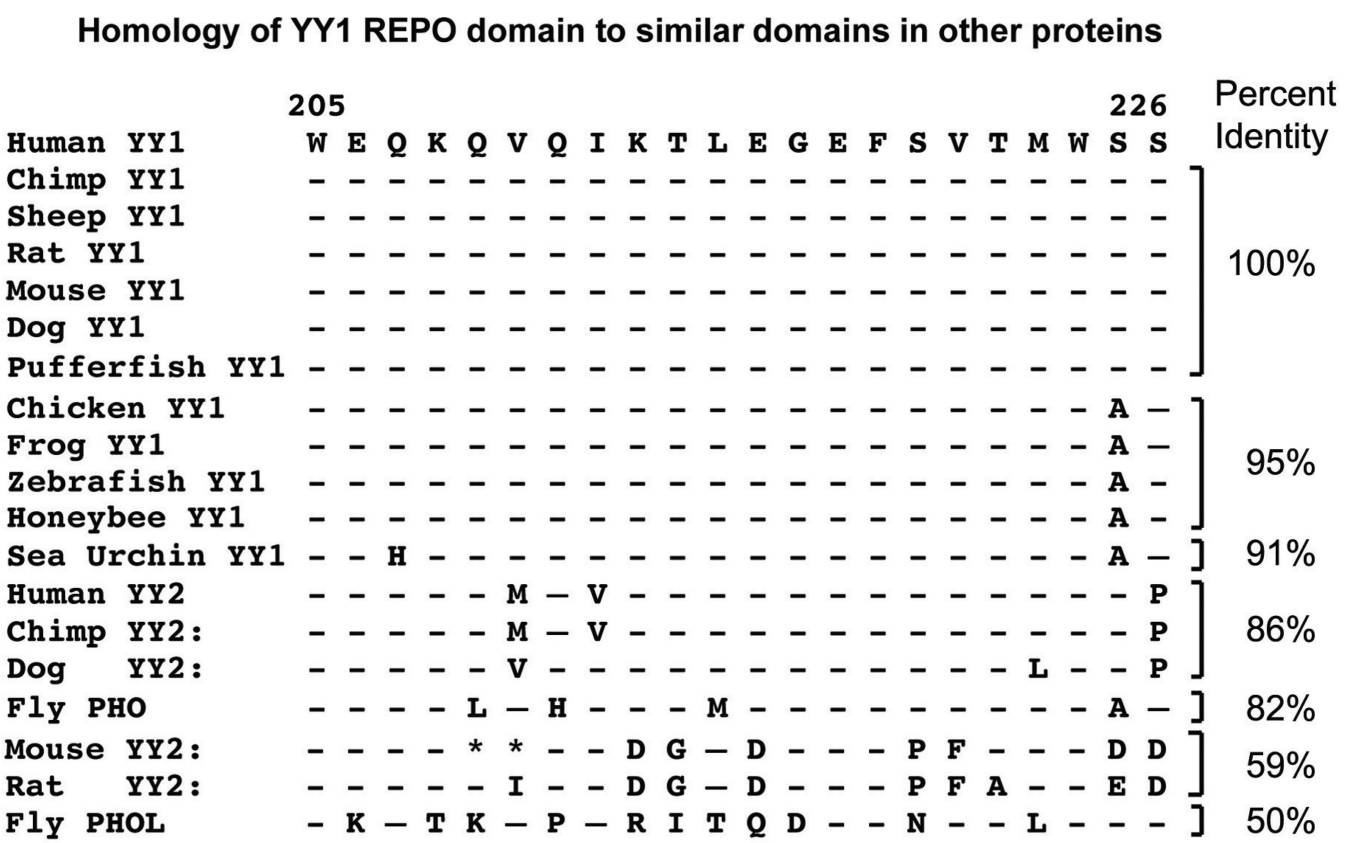

FIGURE 1.

The Yin Yang (YY) 1 recruitment of Polycomb (REPO) domain is highly conserved. Shown is the REPO domain from a variety of species. *Dashes* indicate identity. Amino acid replacements are shown and deletions are represented by *asterisks*. Accession numbers are as follows: human YY1 (AAA59926); chimpanzee YY1 (XP_510162); sheep YY1 (AAT74924); rat YY1 (AAR14688); mouse YY1 (AAH55899); dog YY1 (XP_854514); chicken YY1 (NP_510162); frog YY1 (CAA54777); zebra fish YY1 (AAH71351); puffer fish YY1 (CAG01508); sea urchin YY1 (XP_790188); honeybee YY1 (XP-397280); fly pleiohomeotic (AAL48765); fly PHOL (NP_648317); human YY2 (AAS68634); chimpanzee YY2 (XP_529235); dog YY2 (XP_868531); rat YY2 (AAZ38710). The mouse YY2 sequence was taken from Luo et al.[159]

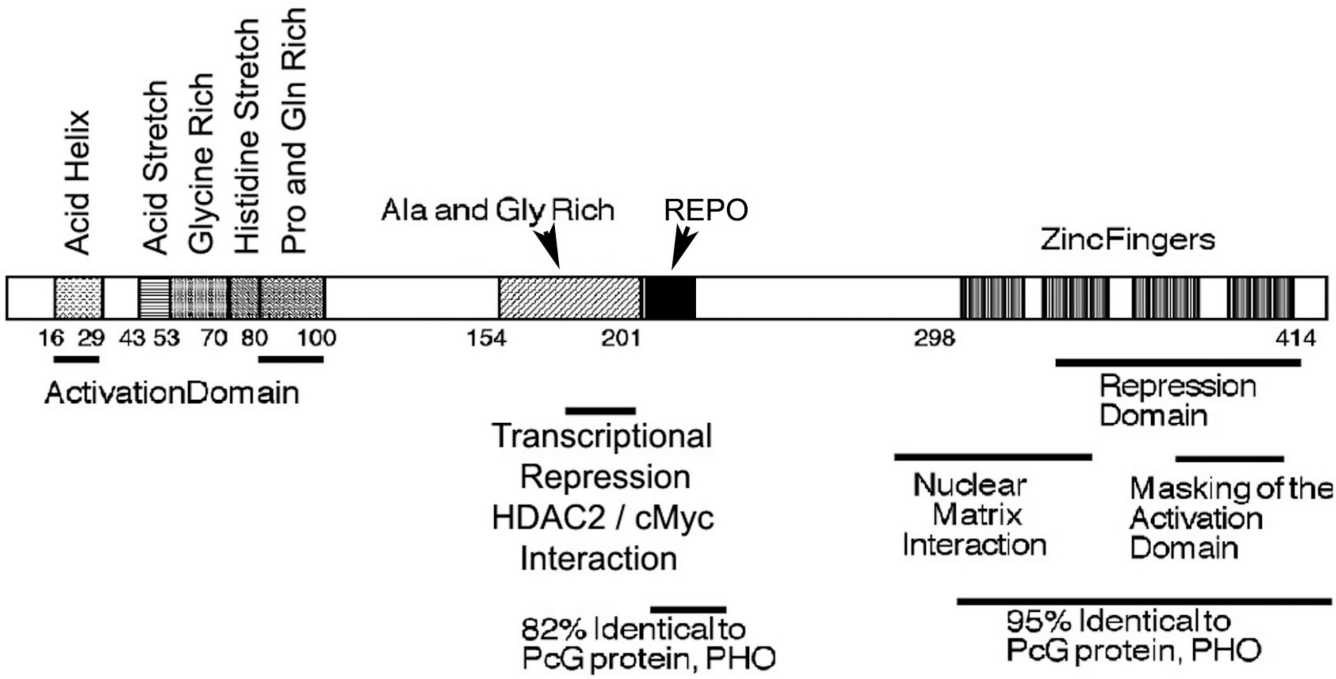

FIGURE 2.

Map of Yin Yang (YY) 1 functional domains and regions of similarity between YY1 and pleiohomeotic. Specific YY1 amino acid domains are listed above the map. Functional segments are shown below.

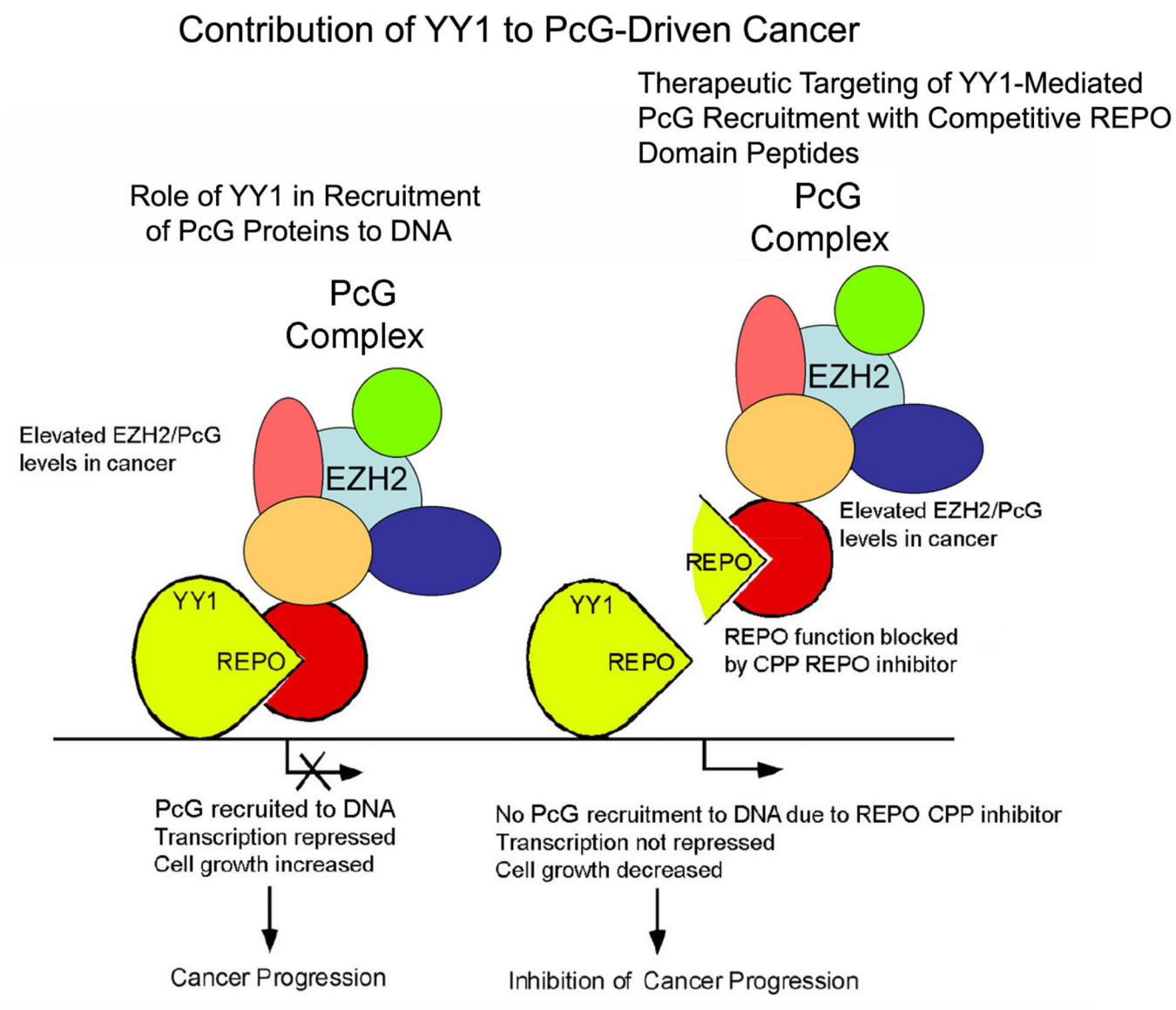

FIGURE 3.

Model of Polycomb group (PcG)–induced oncogenesis and the strategy of using recruitment of Polycomb (REPO) domain peptides as competitive inhibitors to reduce PcG DNA recruitment and to inhibit cancer growth. The *left panel* shows the Yin Yang (YY) 1 REPO domain recruiting PcG proteins to DNA, resulting in repression of gene expression. The *right panel* shows a REPO peptide acting as a competitive inhibitor to interfere with the ability of YY1 to recruit PcG proteins to DNA. Loss of PcG recruitment to DNA leads to de-repression of regulatory genes and inhibition of cancer cell growth. Adapted from Basu et al.[112]

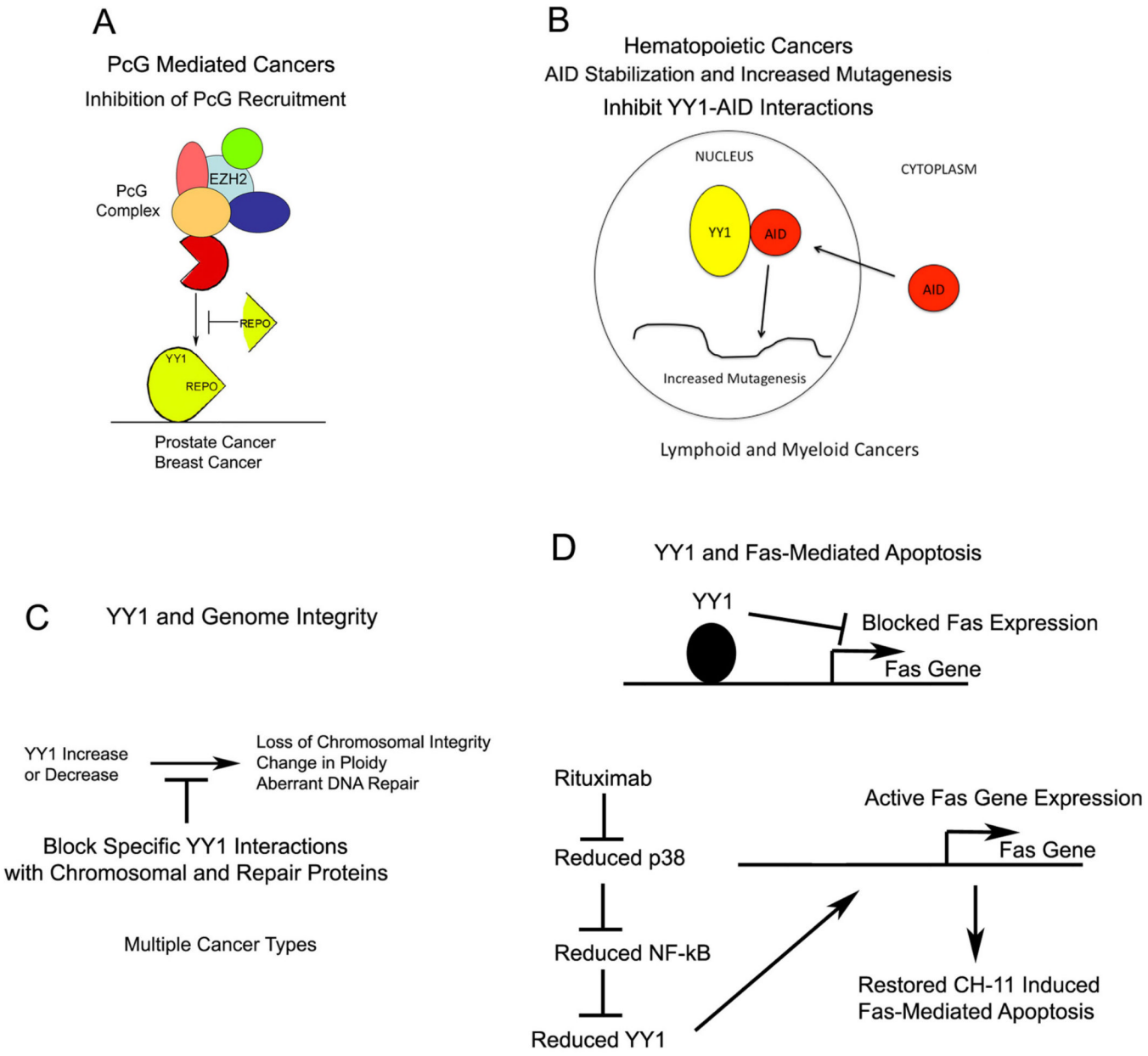

FIGURE 4.

Models of Yin Yang (YY) 1 function in cancer development and potential strategies for developing therapeutic agents to control YY1 function.