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The Yin and Yang of YY1 in the nervous system

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Abstract

The transcription factor Yin Yang 1 (YY1) is a multifunctional protein that can activate or repress gene expression depending on the cellular context. YY1 is ubiquitously expressed and highly conserved between species. However its role varies in diverse cell types and includes proliferation, differentiation and apoptosis. This review will focus on the function of YY1 in the nervous system including its role in neural development, neuronal function, developmental myelination and neurological disease. The multiple functions of YY1 in distinct cell types are reviewed and the possible mechanisms underlying the cell specificity for these functions are discussed.

Keywords

brain; neuron; oligodendrocyte; chromatin; HDAC

1. Introduction

Yin Yang 1 (YY1) is a multifunctional nuclear protein that can act as transcriptional repressor or activator. It was identified in 1991 as a protein that represses the activity of the adeno-associated viral (AAV) P5 promoter in the absence of the oncoprotein E1A, while it activates the promoter in the presence of E1A (Shi *et al*. 1991). Inspired by its dual transcriptional activity, Shi and colleagues named the protein "Yin Yang 1" from the Chinese "Yin", for repression and "Yang" for activation (Shi *et al*. 1997).

Human YY1 is a protein composed of 414 amino acids with a calculated molecular weight of 44kDa (Figure 1). YY1 contains four C2H2-type zinc fingers at the C-terminus (aa 295–414), which are responsible for sequence-specific binding to the consensus DNA recognition sequence: 5'-(C/g/a)(G/t)(C/t/a)CATN(T/a)(T/g/c)-3' (Hyde-DeRuyscher *et al*. 1995;Yant *et al*. 1995). The N-terminus contains a histidine-rich region (His) flanked by acidic aminoacids, and that serves as transcriptional activation domain (Fig.1). The center of the molecule is glycine and lysine-rich (aa 170–200), and corresponds to the interaction domain with HDAC and together with the C terminus, forms the transcriptional repression domain (Shi *et al*. 1997;Yao *et al*. 2001). An additional region within the central domain (PHR, aa 205–226) mediates the interaction with the homeobox Hox proteins (Brown *et al*. 1998;Wang *et al*. 2004; Luke *et al*. 2007). YY1 is highly conserved between species (aa identity: human vs. mouse 98.8%, human vs. Xenopus 90.3%) and is ubiquitously expressed in different tissues including brain, heart, limb and immune system (Pisaneschi *et al*. 1994;Shi *et al*. 1997;Donohoe *et al*. 1999;Affar *et al*. 2006;Liu *et al*. 2007b;He *et al*. 2007). The promoter of *yy1* does not contain a conventional TATA box, but has multiple Sp1

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binding sites and is GC rich, thereby resembling the promoter of a large subset of housekeeping and growth regulated genes (Safrany and Perry 1993;Yao *et al*. 1998). These features suggested that YY1 might have an important role in development. Consistent with this prediction, genetic ablation of *yy1* in mice resulted in lethality shortly after implantation (Donohoe *et al*. 1999).

2. Role of YY1 in cell proliferation, differentiation and survival

The role of YY1 in proliferation is quite controversial. Studies on lymphoid cell lines with genetic ablation of *yy1* suggested that this molecule might favor proliferation, since yy1 deficient cells were characterized by slow growth (Sui *et al*. 2004; Vega *et al*. 2005). This interpretation was supported by the detection of high levels of YY1 protein in human prostate cancer tissue (Seligson *et al*. 2005; Gordon *et al*. 2006). Very different conclusions were reached by studies in human breast cancer cells, where YY1 was identified as proliferation inhibitor due to its role as transcriptional repressor of cyclin D1, a critical factor for cell cycle entry (Cicatiello *et al*. 2004). To render the interpretation of YY1 function even more complex, recent studies conducted *in vivo*, in mice with conditional deletion of *yy1* in the oligodendrocyte lineage suggested that the role of YY1 in progenitor cells is independent of the cell cycle (He *et al*. 2007).

The role of YY1 in differentiation is also dependent on the specific cell type. In the C2C12 cells, a model system for myoblastic differentiation, down-regulation of YY1 is a prerequisite for the expression of muscle-specific genes such as skeletal alpha actin (Lee *et al*. 1994). Additional studies further confirmed the inhibitory role of YY1 in muscle differentiation, due to its effect on differentiation signaling pathways (Kurisaki *et al*. 2003). A similar role for YY1 was reported in keratinocytes, since YY1 negatively regulates differentiation by repressing the keratinocyte-specific gene *loricrin* (Xu *et al*. 2004). However, opposite role of YY1 in differentiation was proposed by *in vivo* studies in *yy1* conditional knockout mouse, in the lymphoid system (Liu *et al*. 2007a) and in the oligodendrocyte lineage (He *et al*. 2007). In both cases, ablation of *yy1* retained the cells at an immature stage, despite the dramatic diversity between the transcriptional program required for B cell differentiation and for oligodendrocyte differentiation. This raises the question of the exact role played by YY1 in cellular differentiation. It will also be interesting to determine whether the role of YY1 as pro-differentiation factor will also be detected in other lineages, by analyzing the phenotype of *yy1* conditional mutant mice in other systems.

A protective role of YY1 from apoptosis was suggested by studies using siRNA or genetic targeted mutation in lymphoid cells (Sui *et al*. 2004). It was suggested that YY1 exerts anti-apoptotic functions by negatively regulating Hdm2-mediated p53 degradation. However, knock-down experiments of *yy1* in embryonic carcinoma cell line did not induce apoptosis, despite increased p53 levels (Bain and Sinclair, 2005). In addition, studies in mouse embryonic fibroblasts (Affar el *et al*. 2006) or in oligodendrocyte lineage cells (He *et al*. 2007) indicated that decreased levels of YY1 did not affect p53 levels nor they increased apoptosis.

In addition to the described biological functions, new roles for YY1 include cancer biology (reviewed in Gordon *et al*. 2006) and DNA imprinting (Hendrich *et al*. 1997; Kim *et al*. 2006; Donohoe *et al*. 2007). A thorough discussion of these functions will not be included in this review due to space restriction. In contrast, we shall focus on the function of YY1 in the nervous system.

3. Role of YY1 in the nervous system

3.1 YY1 in the developing nervous system

The potential function of YY1 in the developing nervous system was first suggested by the phenotypic analysis of *yy1*$^{+/-}$ mice. Complete ablation of *yy1* in mice resulted in early embryonic lethality which precluded the analysis of later developmental stages. However, a small subset (16.7% – 24%) of *yy1* heterozygotes displayed growth retardation and neurulation defects. The brains of the abnormal embryos demonstrated exencephaly, asymmetric structure and the presence of pseudo-ventricles (Donohoe *et al*. 1999).

Studies in Xenopus after knock-down of the *Xenopus* homologue of YY1 (*XYY1*) using anti-sense morpholino oligonucleotides (MO) revealed similar neurulation defects (Morgan *et al*. 2004). While a dramatic reduction of XYY1 protein levels (below 20% of the controls) resulted in early embryonic lethality (Morgan *et al*.2004), a partial depletion of XYY1 resulted in antero-posterior patterning defects and reduction of head structures (Kwon and Chung 2003; Morgan *et al*. 2004). Together, these studies in mouse and Xenopus supported a pro-differentiative role of YY1 in the developing nervous system. Consistent with this concept, over-expression studies by injecting *XYY1* mRNA in *Xenopus* embryos, was sufficient to induce neural tissue, although it had no effect on the induction of mesodermal tissue (Satijn *et al*. 2001).

To begin elucidating the molecular mechanisms underlying the role of YY1 in nervous system development, gene expression profiling was conducted in *XYY1* depleted *Xenopus* embryos (Table 1). The genes whose expression was decreased upon *yy1* deletion could be grouped into two main categories: transcription factors involved in patterning (i.e. homeobox genes, *engrailed2*, *Otx2* and *Krox20*) and those involved in neural crest cell specification and migration (i.e. *slug*, *snail*).

The pattern of YY1 expression in the developing midbrain, hindbrain, and cerebellar primordia at midgestation further validates the importance of this molecule in neural development (Donohoe, et al., 1999). Indeed several YY1-dependent genes with decreased expression after XYY1 knockdown (i.e.*Otx2*, *engrailed 2* and *Krox20*) play an important role in the development of these brain regions (Kwon and Chung, 2003) and their concomitant decrease of expression may explain the defective anterior-posterior axial patterning and reduction of head structures observed in both mice and Xenopus with reduced YY1 expression. *Engrailed 2*, for instance marks the boundary between midbrain and hindbrain (Hemmati-Brivanlou *et al*. 1991), while *Krox20* regulates hindbrain patterning since *Krox20* null mice lack rhombomeres 3 and 5 (Schneider-Maunoury *et al*. 1993). *Otx2* is expressed in the anterior neuroectoderm, including forebrain and midbrain (Blitz and Cho, 1995), and this expression pattern is dependent on the presence of an enhancer containing YY1 consensus binding sequence (Takasaki *et al*. 2007). YY1 directly binds to two cis-sites in the promoter and the enhancer region of the *Otx2* gene (Takasaki *et al*. 2007) and mutations of this binding site within the enhancer region, abolished the expression of *Otx2* in the anterior neuroectoderm, suggesting a critical role of YY1 in determining the regional patterning of expression (Takasaki *et al*. 2007).

The additional group of genes with decreased expression upon deletion of Xyy1 included the neural marker *Nrp1* and the neural crest markers *slug* and *snail* (Morgan et al., 2004). Slug is a member of the Snail family of zinc finger proteins that directly bind to the DNA motif called E-box (Nieto *et al*. 1994). Both Slug and Snail are able to promote the epithelial to mesenchymal transition (Bolos *et al*. 2003). Inhibition of *slug* gene in *Xenopus* and chick embryos decreases the number and motility of neural crest (NC) cells, indicating its role in specification and migration of neural crest cells (Carl *et al*. 1999; LaBonne and Bronner-

Fraser, 2000). Additional evidence demonstrating YY1 direct regulation of *slug* expression include electrophoretic mobility shift assay, chromatin immunoprecipitation and slug promoter-driven GFP reporter assays (Morgan *et al* 2004). It is worth mentioning that the other YY1-regulated gene *Otx2*, similar to *slug* and *snail* is also expressed in neural crest cells at the migratory phase (Kimura *et al*. 1997). Together these data support an important role for YY1 in regulating anterior patterning in the central nervous system and possibly specification and migration of neural crest cells in the peripheral nervous system.

We have previously mentioned that YY1 has been shown to positively regulate the expression of the homeobox gene *Hoxb4* (Gilthorpe *et al*. 2002). This is a very interesting gene whose forced expression in hematopoietic stem cells has been correlated with trans-differentiation into oligodendrocytes (Miyake et al., 2006). The YY1-dependent regulation of homeobox genes is consistent with its function as Polycomb Group (PcG) protein during early development. PcG proteins are a group of chromatin modulators that were originally identified and characterized in *Drosophila* as critical factors to maintain the transcriptionally inactive state of homeobox genes in appropriate regions of the embryo (Pirrotta, 1998). Indeed, YY1 shows high degree of homology with the *Drosophila* PcG protein Pho (Brown *et al*. 1998&2003). Mutation of *pho* in *Drosophila* resulted in a typical homeotic transformation and abnormal development of the central nervous system, and the transient expression of human *yy1* was sufficient to rescue the phenotype (Atchison *et al*. 2003; Srinivasan *et al*. 2005). The mechanism of PcG repression has been related to the ability of specific enzymatic activities to catalyze repressive histone methylation. These enzymatic activities include EED (embryonic ectoderm development), a vertebrate homologue of the *Drosophila* PcG protein Extra Sex Combs (ESC) (Satijn *et al*. 2001; Atchison *et al*. 2003) and EZH2, related to *Drosophila* Enhancer of Zeste (E(Z)) (van Lohuizen *et al*. 1998). The $eed^{-/-}$ mice show defects in very early development, including gastrulation and neural defects (Schumacher *et al*. 1996). Over-expression of XEED (the *Xenopus* homologue of EED) and of XYY1, but not of any other PcG protein, induced an ectopic neural axis in *Xenopus* embryo without any effect on the induction of mesodermal tissue (Satijn *et al*. 2001).

3.2. YY1 in the neuronal differentiation and function

Neuronal differentiation is characterized by the expression of genes including SCG10, sodium channel type II, synapsin, glutamate receptor, and acetylcholine receptor. These differentiation genes are the main targets of the transcription factor called REST (i.e. repressor element 1 (RE1)-silencing transcription factor). REST plays essential roles in restricting the expression of neuronal genes to neurons by mediating active repression as well as long-term epigenetic silencing of neuronal genes in differentiated non-neuronal cells (Ballas *et al*. 2005). Interestingly, microarray analysis of *yy1* hypomorphic ($yy1^{flox/-}$) mouse embryonic fibroblasts revealed a significant decrease of REST expression levels (Affar *et al*. 2006). These results were further validated by the recent characterization of conserved YY1 binding sites in the promoter of the mouse *REST* gene and by the YY1-dependent positive regulation of the REST promoter in SH-SY5Y cells (Jiang *et al*. 2007). These results suggested that lack of YY1 might induce neuronal differentiation, a conclusion that is quite different from the one drawn from the studies in Xenopus and *yy1* heterozygotes, as discussed in the previous subchapter. *In vitro* differentiation studies of multipotential progenitors derived from the subventricular zone (SVZ) of $yy1^{flox/flox}$ mice and infected with adenovirus expressing Cre recombinase to delete *yy1 in vitro* indicated that the ability of these cells to differentiate into $Tuj1^{+}$ neurons was not affected in the absence of *yy1* (He *et al*. 2007). Yet, this single observation did not exclude an important role of YY1 in early embryonic development as reviewed above, or in the expression of late neuronal differentiation genes.

The role of YY1 in late neuronal differentiation has been suggested by the evidence that this molecule positively regulates the basal levels of expression of dopamine beta-hydroxylase (DBH) in noradrenergic neurons (which catalyzes dopamine to noradrenaline), by binding to specific sites in the promoter (Seo *et al*. 1996; Yang *et al*. 1998). YY1 has also been identified as negative regulator of *Dynamin I* (Yoo *et al*. 2001), a protein that is highly expressed in the brain and that plays a critical role in clathrin-mediated endocytosis and synaptic vesicle recycling (Kosaka and Ikeda 1983; Cook *et al*. 1996). The phenotypic characterization of *dynamin I* $^{-/-}$ mice revealed failure to thrive and death during the first two neonatal weeks. In the knockout mice synaptic vesicle endocytosis was severely impaired during strong exogenous stimulation but it efficiently resumed upon termination of the stimulus. These data suggested that indicating basal synaptic vesicle endocytosis is a dynamin I-independent mechanisms while recycling of vesicles during high levels of neuronal activity requires dynamin-1 function (Ferguson *et al*. 2007). It remains to be determined whether YY1 activity is differentially modulated by low or high levels of neuronal activity and is responsible for regulating synaptic vesicles recycling.

3.3. YY1 in astrocytes

YY1 function appears to be dispensable also for astrogliogenesis since deletion of *yy1* did not affect the generation of astrocytes from neurospheres generated from SVZ cells (He *et al*. 2007). In this lineage YY1 might play a different role by affecting the expression of molecules involved in glutamate transport. Glutamate is the major excitatory aminoacid neurotransmitter in the vertebrate brain and its extracellular levels are kept at physiologically low levels by transporter systems that are expressed in neurons and glial cells to prevent excitotoxic effects (Gegelashvili and Schousboe 1997). Among the identified glutamate transporters GLAST/EAAT1 is the major player and is expressed almost exclusively in astrocytes throughout the central nervous system, although it is significantly enriched in the Bergmann glial cells (BGC) of the cerebellum (Danbolt *et al*. 2001). In chick BGC, treatment with glutamate increases binding of YY1 to *glast* promoter and results in down-regulation of *glast* transcripts with consequent decreased glutamate re-uptake. Similar results can be obtained by over-expressing *yy1*. Together these data suggest a specific function of YY1 as transcriptional repressor for *glast* in cerebellar astrocytes (Rosas *et al*. 2007). It should be noted that in rat cortical astrocytes, glutamate has an opposite effect on *glast* by increasing rather than decreasing its expression (Gegelashvili *et al*. 1996), for this reason future studies will need to determine whether the function of YY1 in cortical astrocytes could be different from that defined in cerebellar BGCs.

3.4 Role of YY1 in myelination

In the central nervous system, myelination is carried out by oligodendrocytes. The function of YY1 in the oligodendrocyte lineage was first reported by Berndt and colleagues, who identified and characterized three YY1 binding elements in the myelin specific proteolipid protein (*plp*) promoter. Using CAT assay, they demonstrated that YY1 activates *plp* promoter and gene expression in rat oligodendrocyte CG4 cells (Berndt *et al*. 2001).

A more direct evidence for the role of YY1 in regulating myelination was provided by the analysis of *yy1* conditional knockout mice study in our laboratory (He *et al*. 2007). By crossing *yy1flox/flox* mice with mice expressing the recombinase Cre under the oligodendrocyte-specific *cnp1* promoter, the specific ablation of *yy1* in the oligodendrocytic lineage was achieved. These mice survived until 2 months of age, thereby allowing the detailed analysis of developmental myelination. The *yy1 cko* mice displayed tremor, ataxia and head wobbling from the second postnatal week and phenotypically resembled dysmyelination mutants. Ultrastructural studies confirmed the decreased number of myelinated axons in white matter tracks of the central nervous system, with the most severe

defects in the spinal cord. This phenotype was caused by the arrested development of oligodendrocytes at the progenitor stage, in the absence of changes in proliferation or apoptosis. At a molecular level, this block of differentiation was associated with high levels of expression of transcriptional inhibitors, including *Id4* and *Tcf4*, due to defective recruitment of repressive complexes containing YY1 and the histone deacetylase HDAC1 to their promoters (He *et al*. 2007). Together, the above mentioned experimental results identified YY1 as a critical player in developmental myelination of the central nervous system.

The function of YY1 in the peripheral nervous system has not been reported yet. However, it is likely that YY1 may also modulate this event since multiple YY1-target genes also regulate the activity or development of the myelinating cells of the PNS. Peripheral myelination is carried out by Schwann cells, which derive from neural crest cells (reviewed in Jessen and Mirsky, 2005). We have previously reviewed the evidence that YY1 regulates multiple genes (i.e. *slug, snail, Otx2*) that are important for neural crest specification and/or migration. We have also discussed the effect of YY1 on the zinc-finger protein *Krox20* a molecule that is directly involved in the maturation of myelinating Schwann cell (Topilko *et al*. 1994; Le *et al*. 2005). An additional evidence suggesting a potential role of YY1 in PNS myelination was suggested by the study of YY1 positively regulating *Bace1*. BACE1 is a type I trans-membrane aspartyl protease that has been recently defined as important for the cleavage of neuregulin-1 (NRG-1) into an active form (Willem *et al*. 2006). NRG-1 is an axonal membrane associated ligand and plays critical roles in the myelination of the peripheral nervous system (Michailov et al., 2004; Nave and Salzer 2006). As predicted, *Bace1* knockout mice revealed striking accumulation of full-length type III NRG-1 proteins in peripheral nerves and severe hypomyelination in peripheral nerves, resembling the phenotype of NRG-1 mutant mice (Willem *et al*. 2006; Hu *et al*. 2006). Since YY1 has been shown to be an activator for *Bace1* expression in neurons (Rosas *et al*. 2007), it is conceivable that it may indirectly modulate myelination of peripheral nerves.

4. Role of YY1 in neurodegeneration

In addition to its function in development, YY1 might also play a role in the neurological diseases such as Alzheimer disease (AD). One of the major hallmarks of AD is the brain deposition of the amyloid-beta peptide (Aβ). Aβ is proteolytically cleaved from amyloid precursor protein (APP) by β and γ-secretase and BACE1 (beta-site amyloid precursor protein-cleaving enzyme 1) is one of the major β-secretases (reviewed in Rossner *et al*. 2006). As mentioned before, YY1 acts as an activator of the BACE1 promoter in neurons and astrocytes, and mutations of the YY1 binding site in the *Bace1* promoter decrease its activity, while YY1 over-expression increases its transcriptional activity (Nowak *et al*. 2006). An alternative possibility is that YY1 might regulate the levels of Aβ indirectly, by modulating the expression of other molecules involved in APP processing, such as FE65. It has been reported that YY1 binds to the *FE65* minimal promoter and increases its transcription (Zambrano *et al*. 1997). FE65 is an adaptor protein with the ability to bind the C-terminal domain of APP (Ermekova *et al*. 1998). FE65 is highly expressed in neurons, it modulates APP processing and trafficking in several cell lines (Guenette *et al*. 1999; Santiard-Baron *et al*. 2005; Wiley *et al*. 2007) and its expression levels in AD patients' brain correlates with the severity of the disease and with the risk of developing late-onset AD (Lambert *et al*. 2000; Delatour *et al*. 2001). Together these studies suggest a potential role for YY1 in the pathogenesis of Alzheimer disease, although its actual function deserves further investigation.

A possible role for YY1 in neurodegeneration was suggested by the effect of glutamate treatment on YY1-containing protein complexes in cultured neurons (Korhonen *et al*. 2005).

Glutamate is the major excitatory aminoacid neurotransmitter in the vertebrate brain. However high levels of this aminoacid are toxic to neurons and will cause neuronal cell death (Ermak and Davies, 2002). Korhonen *et al*. discovered that treating cerebellar granule cells with glutamate induced the transition from a high molecular weight protein complex containing YY1 to a smaller protein complex (Korhonen *et al*. 2005). Treatment with other apoptotic stimuli, such as okadaic acid (inhibitor of serine/threonine protein phosphatase 2A), but not with etoposide (topoisomerase II inhibitor) or trichostatin A (HDAC inhibitor), caused a similar re-organization of YY1 protein complexes, although the biological significance of the high and low molecular weight complexes remains to be determined (Korhonen *et al*. 2005). An additional role of YY1 in modulating the levels of extracellular glutamate has been previously described and concerns the regulation of the astroglial glutamate transporter GLAST/EAAT1 (Danbolt *et al*. 2001; Rosas *et al*. 2007).

Finally, because YY1 is able to affect the expression of *engrailed 2* and recent human genetics studies have proposed the existence of a genetic linkage of *engrailed 2* with autism (Benayed *et al*. 2005; Brune *et al*. 2008), it would be interesting to define whether YY1 itself is involved in autism. In support of its new role, *engrailed 2* knockout mice displayed decreased social behavior and defective learning and memory tasks together with a cerebellar-specific increase in serotonin, al of which resembles autism spectrum disorder (Cheh *et al*. 2006)..

5. Regulation of YY1 activity

After more than a decade since its discovery, and an overwhelming literature on the opposing roles of YY1 in different cell types and at different developmental stages, it is imperative to ask the question: how can a ubiquitous protein, like YY1, be multifunctional? Generally, there are two ways to endow specificity of function. One possibility is that the protein itself is post-translationally modified in a cell-specific fashion. The other possibility is that the function of YY1 is dependent on the bioavailability of co-factors.

5.1. YY1 expression, subcellular localization and post-translational modifications

While several studies focused on YY1-dependent regulation of downstream target genes, very little is known about the mechanisms regulating YY1 expression itself. Although the levels of YY1 transcripts are relatively constant in the organism, there is some variation during development. For example, as previously mentioned, the *X*YY1 protein is localized in the anterior neural tube in embryonic Xenopus (Kwon and Chung 2003). For keratinocytes, higher levels of YY1 were detected in undifferentiated cells compared to differentiated cells (Xu *et al*. 2004). However, this was not the case for oligodendrocyte lineage cells, where the levels remain constant throughout development (He *et al*. 2007). Future studies on the characterization of YY1 promoter and its mechanisms of regulation will need to be addressed.

An additional modulation of YY1 function is determined by changes in the subcellular distribution. Nucleo-cytoplasmic shuttling of YY1, for instance was correlated with different phases of the cell cycle in Chinese hamster ovary and in HeLa cells (Palko *et al*. 2004). YY1 was mainly cytosolic during the G1 phase, nuclear in early S phase and cytosolic during late S phase (Palko *et al*. 2004). Also in Xenopus oocytes the subcellular localization of XYY1 changed at distinct developmental stages and correlated with the DNA binding activity, being nuclear in stage I oocytes, cytosolic in embryos until the early blastula stage and nuclear again after the mid-blastula transition (Ficzycz *et al*. 2001).

YY1 activity can also be modulated by multiple post-translational modifications, including phosphorylation, acetylation and caspase-dependent cleavage. YY1 contains several Ser/Thr

potential phosphorylation sites within the zinc finger DNA-binding domain. Since phosphatase treatment abolished binding of YY1 to the murine leukaemia virus LTR, it was suggested that phosphorylation decreased the ability of YY1 to modulate transcription (Becker *et al*. 1994). However the binding of YY1 to the AAV p5 promoter was not affected by phosphatase treatment (Shi *et al*. 1997). Acetylation of lysine residues located in the central region by p300 was also proposed to modulate its activity (Yao *et al*. 2001). Studies on YY1 dependent regulation of the mouse homeobox gene *Otx2* demonstrated that the deacetylated form is capable of bind to both the enhancer and promoter of *Otx2*, while the acetylated form can only bind to the enhancer (Takasaki *et al*. 2007). Finally, a recent study in Hela cells reported caspase-dependent cleavage of the first 119 amino acid of YY1 in response to apoptotic stimuli. The newly generated N-terminal truncated YY1 fragment is still able to bind to DNA although it is no longer able to stimulate transcription (Krippner-Heidenreich *et al*. 2005). It will be important for future studies to determine whether the truncated form of YY1 acts as dominant-negative that interferes with the normal function of YY1.

5.2. Co-factors

The cell-type specific function of YY1 in distinct cell types can be also affected by the availability of the co-factors and by the chromatin conformation of the promoters of its target genes that might be affected by the developmental stage and cell context. One of the most frequently adopted strategies for a ubiquitous protein to gain specificity is interacting with additional factors. The combined configuration would exponentially increase the specificity of the action. Indeed, the majority of the reports about YY1 also mention its binding partners (Figure 1). Some of the interacting factors have a restricted pattern of expression such as Smad, the downstream effector of BMP signaling pathway, Hoxa11 and the polycomb group protein EED, while others are also widely expressed, including HDACs, p300, INO80, PRMT1 and CTCF (Lee *et al*. 1995;Shi *et al*. 1997;Yao *et al*. 2001;Rezai-Zadeh *et al*. 2003;Satjin *et al*. 2001;Donohoe *et al*. 2007). The BMP-dependent recruitment of Smad by YY1 would justify its function in cardiac development where the two factors together result in the activation of the *Nkx2.5* promoter (Lee *et al*. 2004). However, the choice of the protein binding partner determines, at least in part, whether YY1 activates or represses a given promoter. INO80 is a chromatin remodeling complex that catalyzes ATP-dependent nucleosome sliding (Jin *et al*. 2005). The binding with INO80 is required for YY1-dependent activation of *CDC6* gene (Cai *et al*. 2007). Similarly, targeted recruitment of p300, histone acetyltransferase, and PRMT1, histone H4 (Arg3) methyltransferase, endows YY1 transcriptional activation ability, as reported in ER stress induced *Grp78* gene expression (Baumeister *et al*. 2005). In contrast, HDACs are histone deacetylase that are generally involved in transcriptional repression. A number of reports on YY1 as transcriptional repressor, including our work, indicated its association with HDAC1, 2 or 3 (Osborne *et al*. 2001;Luke *et al*. 2006;He *et al*. 2007;Liu *et al*. 2007b).

5. Concluding remarks

The complexity and cellular diversity of the nervous system requires a sequence of events that start with the formation of the neuro-ectoderm, is followed by the differentiation into multiple cell types (i.e. neurons, astrocytes and oligodendrocytes) and culminates with the organization of a complex network of interactions between different cell types. Each of these steps requires the temporal and spatial regulation of gene expression. Here we have reviewed evidence suggesting multiple roles for YY1 during development of the central and peripheral nervous system. As reviewed, its function is dependent on a multitude of parameters that include sub-cellular localization, post-translational modifications and binding with other proteins. It is anticipated that a more clear definition of YY1 function

will be gained from future conditional mutant mice generated in other lineages including the neuronal and astrocytic lineage.

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Abbreviations

AD	Alzheimer disease
APP	amyloid precursor protein
BACE1	beta-site amyloid precursor protein-cleaving enzyme 1
BGC	Bergmann glial cells
BMP	bone morphogenetic protein
DBH	dopamine beta-hydroxylase
EED	embryonic ectoderm development
HDAC	histone deacetylase
NRG	neuregulin
PcG	polycomb group
PHR	PHO homology region
REST	RE-1 silencing transcription factor
Shh	Sonic hedgehog
SVZ	subventricular zone
YY1	Yin Yang 1

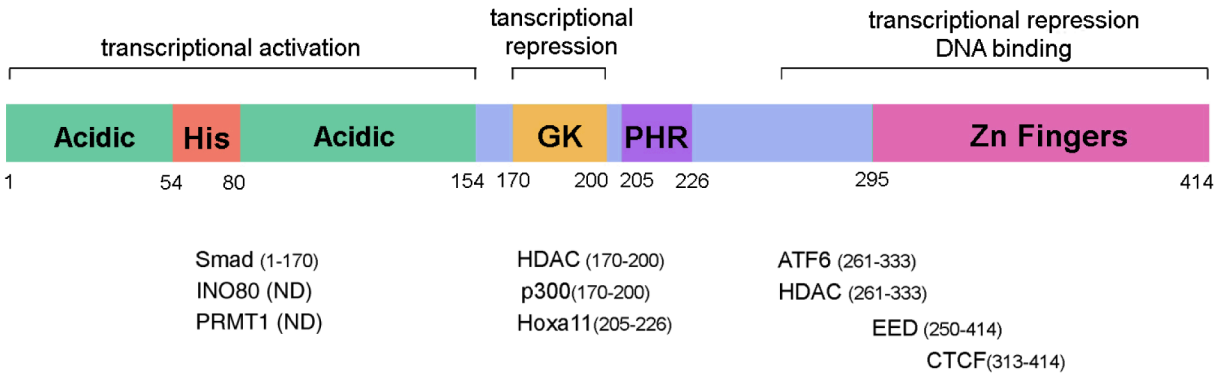

Figure 1.

Schematic diagram of human YY1 protein and its binding partners. The transcriptional activation and repression domains and the DNA binding domain are indicated. His, histidine-rich domain; GK, glycine-lysine-rich domain; PHR, PHO homology region. The protein/complex associated with YY1 are shown below each region of interaction. In parenthesis the aminoacid residues involved in binding are indicated. ND means not determined.

Table 1

List of genes regulated by YY1 in the nervous system

The function of YY1 (activation or repression of the target genes), is indicated. Note that the region or specific cell type of expression, the general function of the gene and the specific reference for each gene are also described

Gene	Function of YY1	Region or cell type	Function	System used	References
Bace1	activation	brain	β-secretase of APP and NRG-1	PC12 cell, rat neuron and astrocyte	Nowak *et al.* 2006
DBH	activation	neuron	Dopamine β-hydroxylase	Human neuroblastoma SK-N-BE(2)C	Seo *et al.* 1996
Dynamin I	repression	brain	Receptor-mediated endocytosis in neuron	Mouse neuroblastoma cell NS20Y	Yoo *et al*. 2000
Engrailed 2	activation	Midbrain-hindbrain junction	Midbrain-hindbrain patterning, autism	*Xenopus*	Kwon and Chung 2003
FE65	activation	neuron	APP interacting protein, Alzheimer disease	Rat brain extracts and Chinese hamster ovary cell	Zambrano *et al*. 1997
Glast	repression	astrocyte	Glutamate transporter	Chicken Bergmann glial cells	Rosas *et al.* 2007
Id4	Repression	oligodendrocyte	Myelination inhibitor	Mouse	He *et al*. 2007
Krox20	activation	Hindbrain, Schwann cell	Hindbrain development, Schwann cell myelination	*Xenopus*	Kwon and Chung 2003
Nrp1	activation	neuron	Neuronal marker	*Xenopus*	Satijn *et al.* 2001; Morgan *et al.* 2004
Otx2	activation	neural crest, forebrain and midbrain	Anterior neuroectoderm development, eye development	*Xenopus;* F9 embryonal carcinoma cells	Kwon and Chung 2003; Takasaki *et al*. 2007
plp	activation	oligodendrocyte	Myelin protein	Rat oligodendrocyte CG4 cell	Berndt *et al*. 2001
REST	activation	Non-neuronal cells	repress neuronal genes expression	mouse embryonic fibroblast; SH-SY5Y cells	Affar *et al*. 2006; Jiang *et al*. 2007
Slug	activation	neural crest	Neural crest migration	*Xenopus*	Morgan *et al*. 2004
Snail	activation	neural crest	Neural crest migration	*Xenopus*	Morgan *et al*. 2004
Tcf4	repression	brain	Wnt signal downstream effecter	Mouse	He *et al*. 2007