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Review Article

YY1 in four dimensions: From context-dependent transcription factor to spatiotemporal gene regulator☆

Silvia Vivarelli [a,*], Luca Falzone [b], Concettina Fenga [a], Massimo Libra [b]

[a] Department of Biomedical and Dental Sciences, Morphological and Functional Imaging, Section of Occupational Medicine, University of Messina, 98124 Messina, Italy
[b] Department of Biomedical and Biotechnological Sciences, University of Catania, 95123 Catania, Italy

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ABSTRACT

YY1 is a multifunctional transcription factor whose regulation spans transcriptional, post-transcriptional, and post-translational layers, conferring remarkable context-dependent plasticity. Several studies carried out in YY1-deficient mouse models highlight its essential roles in embryogenesis, organogenesis, and cellular homeostasis, while its deregulation in adulthood predisposes to multiple chronic diseases. In cancer, YY1 displays a bidirectional function, acting as either oncogene or tumor suppressor depending on cellular context and tumor type, and reshaping transcriptional and epigenetic networks. Emerging evidence further identifies YY1 as a clock-controlled gene and architectural regulator of circadian transcription, bridging together enhancer-promoter communication, chromatin state, and the temporal dimension of gene expression. In this context, its deregulation links circadian misalignment with oncogenic signaling, underscoring its key role as a diagnostic and prognostic biomarker, as well as a therapeutic target, thus highlighting its relevance in precision oncology.

1. Introduction

Yin Yang 1 (YY1) is a pleiotropic transcription factor (TF) belonging to the GLI-Krüppel family of zinc finger proteins [1]. YY1 is evolutionarily conserved, with high sequence and functional homology observed from Drosophila (namely Pho) to mammals, underscoring its fundamental role in gene regulation across species [2–4]. It is ubiquitously expressed in vertebrate cells and it plays essential roles in a number of biological processes, including development, cell proliferation, growth, differentiation, cell cycle progression, DNA repair, and apoptosis [5].

The pleiotropic nature of YY1 is largely attributable to its ability to act as a transcriptional activator, repressor, or DNA-binding protein, depending on its molecular context and interacting partners [6]. This functional versatility makes YY1 a crucial player not only in normal cellular physiology, but also in pathological processes such as tumorigenesis, underlining the necessity of understanding its diverse regulatory functions [7].

Animal studies have proven that mutations in YY1 disrupt its ability to regulate key genetic programs essential for proper embryonic and postnatal development. The seminal study by Donohoe and colleagues demonstrated that complete loss of YY1 in mice leads to early embryonic lethality [8]. More recently, in humans, YY1 was found to be directly involved in the etiology of a rare autosomal dominant neurodevelopmental disorder, known as Gabriele-de Vries syndrome (GADEVS), and firstly reported in 2017, which is caused by pathogenic variants within the YY1 gene sequence, with 29 affected individuals reported to date [9].

In GADEVS, YY1 mutations are predominantly de novo and typically cause haploinsufficiency through deletions or loss-of-function variants (including missense, nonsense, frameshift, small deletions, and initiation codon mutations) most often affecting exons 1, 4, and 5. These alterations reduce the amount of functional YY1 protein, leading to the characteristic clinical manifestations [9]. Several studies showed that loss of YY1 impairs global gene regulation by altering the epigenetic landscape [10]. These epigenetic disruptions may explain the broad phenotypic manifestations observed in GADEVS patients with YY1 mutations (Fig. 1) [11].

A recent study conducted by the group that originally identified GADEVS, undertaking a multi-modal approach using patient-derived 2D and 3D neuronal models, showed that YY1 mutations, caused by truncating or missense variants in its zinc-finger domain, impair neural progenitor competence and terminal neuronal differentiation, lead to

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* Corresponding author.
E-mail address: silvia.vivarelli@unime.it (S. Vivarelli).

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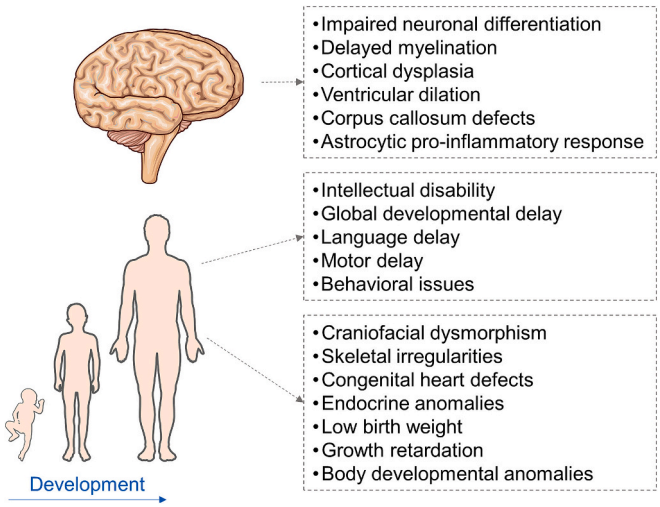

Fig. 1. Gabriele-de Vries Syndrome (GADEVS) features. Schematic illustrating congenital and developmental defects in individuals with GADEVS in the context of nervous system (pathological and behavioral), tissues and organs.

cytoarchitectural disorganization, and trigger a non-cell-autonomous pro-inflammatory response specifically within astrocytes [12]. These findings establish YY1 dosage as a key regulatory vulnerability in neurodevelopment and provide detailed mechanistic insights into the etiology of GADEVS, with future implication for therapeutic intervention [12].

Clinically, GADEVS presents with developmental anomalies such as intellectual disability, global delay, craniofacial dysmorphism, low birth weight, hypotonia, feeding issues, and congenital defects affecting multiple organ systems [13]. Neuroimaging often shows nonspecific abnormalities, including delayed myelination, cortical dysplasia, ventricular dilation, and corpus callosum defects [14]. Craniofacial features such as a broad forehead, micrognathia, generalized facial asymmetry, and external ear malformations are also common among affected individuals [15]. Language and motor delays are present in nearly all cases, and often the first signs, while about half of cases show behavioral issues such as autism, ADHD, or anxiety [16–19]. Additional features, such as endocrine anomalies, heart defects, and musculoskeletal irregularities, further increase phenotypic heterogeneity of the syndrome [18–20].

Diagnosis of GADEVS is established through molecular genetic testing. Management is symptomatic with early neurodevelopmental support. Most cases are de novo, although a 1 % recurrence risk remains due to possible mosaicism. Growing case numbers should improve genotype-phenotype insights and future therapies [10].

Owing to its central role in human development, this review seeks to elucidate the multifaceted contributions of YY1 to physiological processes, its dual and often paradoxical involvement in cancer initiation and progression, and its emerging significance in the temporal regulation of biological processes. Within the framework of chronobiology, YY1 occupies a critical nexus between cellular programs and circadian regulation, thereby providing novel avenues for deciphering disease mechanisms and developing novel targeted therapeutic strategies.

2. YY1 molecular features and multilayered regulation of its expression

YY1 gene was firstly cloned in 1991 by several research groups, each assigning it distinct names, such as NF-E1, Delta, and YY1, the latter named by Shi et al. in recognition of its dual regulatory role as either activator or repressor of the transcription [1,21,22]. The YY1 gene, on chromosome 14q32.2 near the telomere, spans over 40 kilobases with five exons. Its pre-mRNA is processed into a mature transcript of 3159 nucleotides, including a 5'-UTR of 480 nucleotides, a coding sequence of 1245 nucleotides, and a 3'-UTR of 1434 nucleotides [23]. YY1 is ubiquitously expressed in all cell types and tissues, regardless of cell cycle or differentiation, with a protein half-life of 3.5–4 h [24].

Transcriptional regulation of YY1 is primarily mediated through specificity protein 1 (Sp1), which binds to multiple sites within the proximal promoter [25]. Additional cis-regulatory elements such as a conserved CREB/ATF binding site and a series of tandem Myb-binding motifs contribute to its basal transcriptional control [26,27]. The minimal promoter, located near the transcription start site, is sufficient to drive basal gene expression [6]. YY1 transcription can also be activated by the NF-κB (p65/p50) protein complex, highlighting its responsiveness to pro-inflammatory signaling [28]. Moreover, YY1 exhibits autoregulatory ability via a negative feedback mechanism, as it can bind to its own intronic regulatory elements to suppress further transcription, thereby maintaining homeostatic levels [27].

Moreover, YY1 expression is influenced by epigenetic modifications as well as post-transcriptional and post-translational mechanisms. Epigenetic regulation of YY1 through promoter DNA methylation has been reported so far in animal models of hepatocarcinogenesis, such as thioacetamide-treated rats, but it has not yet been demonstrated in humans [29]. A recent book chapter summarizes a number of newly discovered post-transcriptional regulatory mechanisms involving YY1 [30]. For instance, the 3'-UTR. as well as the 5'-UTR of YY1 mRNA may serve as a binding platform for multiple microRNAs (miRNAs) that downregulate its translation. In contrast, several long non-coding RNAs (lncRNAs) enhance YY1 expression either directly, by stabilizing or promoting translation, or indirectly, by acting as competing endogenous RNAs (ceRNAs) that sequester miRNAs. Additionally, circular RNAs (circRNAs), also function as miRNA sponges to relieve post-transcriptional repression of YY1 [30].

YY1 protein sequence is 414 amino acids long with a theoretical molecular mass of approximately 45 kDa, and an apparent molecular weight of 50–65 kDa, due to several post-translational modifications [31]. YY1 possesses four C2H2-type zinc fingers localized at its C-terminal region (residues 296–407). These motifs are critical for DNA binding, enabling YY1 to recognize specific DNA binding sequences such as 5′- CCG(A/C)CATNTT -3′ [32]. In details, zinc finger domains align in tandem, fitting into the major groove of DNA to mediate sequence-specific interactions [33]. Beyond DNA binding, zinc finger motifs also mediate protein-protein interactions, enhancing its functional diversity in chromatin regulation [34].

The DNA-binding capability of YY1 is also tightly linked to its transcriptional regulatory domains. Transcriptional activation is primarily conferred by two regions within the N-terminal region (residues 16–29 and 80–100), both of which are embedded within acidic tracts [35]. Inside this region, is also located a histidine-rich sequence (residues 70–80) that directs YY1 to nuclear speckles, potentially linking it to RNA metabolism, and enables protein-protein interactions with co-activators for long-range gene activation at distal enhancers [36,37].

The central portion of YY1 harbors repression domains [38]. Notably, residues 154–201 are enriched in glycine-alanine and glycine-lysine repeats (namely GA- and GK-rich domain), contributing to transcriptional repression through potential interactions with histone deacetylases (HDACs) [35,39]. Adjacent to this region is the REPO domain (residues 201–226), later redefined as the Onco-Protein Binding (OPB) domain, essential for both Polycomb group (PcG) protein recruitment and YY1 oligomerization, serving as a platform for interaction with various oncoproteins [40]. Finally, nuclear localization is mediated by residues 257–341, overlapping zinc fingers 2 and 3, essential for nuclear import and subnuclear compartmentalization [41].

Since the first studies in the 1990s, it has become evident that YY1 exhibits context-dependent DNA-binding properties [42]. For instance, tandem YY1 binding sites alone can confer high-affinity binding, independent of cofactors [43]. Also, thanks to the capability to form dimers, YY1 is able to form DNA loops by bridging distant binding sites [44].

Additionally, YY1 has been shown to bind RNA molecules with high affinity, further expanding its functional repertoire beyond canonical transcriptional regulation [45].

The YY1 protein undergoes a diverse range of post-translational modifications, which critically regulate its subcellular localization, stability, protein-protein interactions, and transcriptional activity [31]. Among these, phosphorylation is the most extensively characterized. Depending on the specific residue and cellular context, phosphorylation regulates YY1 by controlling its localization, DNA-binding capacity, and protein interactions [46]. Key modifications, such as those mediated by Polo-like kinase 1, Aurora kinases, Src kinases, and Casein Kinase II α, affect transcriptional activity and apoptosis [47–53].

Beyond phosphorylation, lysine-targeted modifications, which include acetylation, ubiquitination, sumoylation, and methylation, further shape YY1 activity. Acetylation can either enhance promoter-enhancer bridging and transcription or reduce DNA binding while promoting HDAC association, depending on the modified domain [54,55]. Ubiquitination directs YY1 for proteasomal degradation, whereas sumoylation stabilizes the protein and modulates its gene regulatory effects [56–59]. Methylation at two key lysine residues may enhance DNA-binding affinity, adding another layer of functional control [60].

Additional post-translational modifications integrate cellular stress, metabolic, and redox signals. For instance, S-nitrosylation of zinc-coordinating cysteines abolishes DNA binding, while O-GlcNAcylation stabilizes YY1 while disrupting interactions with pRb in a cell cycle-dependent manner, and lactylation at lysine 183 fine-tunes gene expression in response to hypoxia and lactate accumulation [61–65]. Additionally, PARylation by PARP-1 following genotoxic stress reduces DNA-binding affinity while promoting DNA repair through transcriptional silencing [66]. Intriguingly, YY1 is both a target and a regulator of PARP1, this latter being a mechanism found involved in neuroblastoma progression [67]. Together, these diverse modifications underscore YY1 as a versatile transcriptional regulator, integrating multiple cellular cues to coordinate gene expressions in health and disease.

3. YY1 pleiotropic regulatory functions

As highlighted above, YY1 regulatory function is highly context-dependent, and it can be shaped by either post-translational modifications, cofactor availability, chromatin accessibility, or spatial genome configuration [42]. This adaptability underlies its versatility, which arises from a unique combination of sequence-specific DNA binding, dynamic protein interactions, recruitment of epigenetic machinery, and, finally, the ability to organize 3D genome architecture [31].

YY1 directly regulates a wide array of genes that span key cellular processes, underscoring its central role in transcriptional control. For instance, it drives cell cycle and proliferation by modulating CDC6, Cyclin D1, and c-Myc, influences oncogenic pathways through p53, ERBB2, and c-Fos, and shapes apoptotic balance via regulation of BCL2 and IAP family members [59,68–71]. Its impact on chromatin and epigenetic state is evident in its control of histone genes and DNMT3A, while its contribution to DNA damage response is reflected in the regulation of PARP1 and BRCA1 [72,73]. Also, YY1 coordinates transcriptional networks by regulating factors like E2F1 and YY2, controlling proliferation, survival, DNA repair, and chromatin dynamics [74–76].

As a transcriptional repressor, YY1 may directly compete with activating TFs for binding sites or indirectly block their activity through protein-protein interactions, as seen with Smad proteins in TGF-β and BMP signaling [77]. More broadly, YY1 enforces epigenetic silencing by recruiting PcG proteins, anchoring PRC1 and PRC2 to DNA via its REPO domain [78]. It also interacts with DNA methyltransferases, guiding DNMT1 for maintenance methylation and DNMT3A/3B for de novo methylation, thus extending repression to the level of DNA modification [72]. Collectively, these diverse mechanisms position YY1 as a multifaceted regulator capable of switching between activation and repression to achieve precise control of gene expression [31].

YY1 regulation extends beyond proximal promoter activity, encompassing chromatin remodeling and higher-order genome organization. For instance, by recruiting a wide spectrum of cofactors (i.e., adaptor proteins, chromatin remodelers, or bridging mediators), as well as chromatin-modifying enzymes, YY1 influences transcription through changes in chromatin state [79,80]. Beyond local chromatin regulation, YY1 plays a pivotal role in shaping 3D genome architecture. Its ability to homodimerize enables bridging of distal genomic elements and formation of enhancer-promoter loops, a mechanism essential for long-range gene regulation in contexts such as neuronal differentiation [81,82]. In detail, YY1-mediated looping has been shown to be indispensable for tissue-specific transcriptional programs, particularly in neural progenitors, where it coordinates dynamic chromatin interactions required for differentiation [44].

Deregulation of YY1 has been observed in several cancers, immune disorders, and neurodevelopmental syndromes [83]. Beyond these well-established roles, emerging evidence points also to its involvement in circadian and ultradian regulatory networks [84]. In fact, with its short half-life and dynamic chromatin recruitment, YY1 may link transcriptional programs to temporal regulation, and its disruption could contribute to chronopathologies like metabolic syndrome, cancer-related chronodisruption, and neuropsychiatric disorders [85].

4. YY1 deficiency in mouse models: From embryogenesis to disease

Human YY1 haploinsufficiency causes GADEVS, while in mice complete YY1 loss is embryonically lethal, establishing the essential and dosage-sensitive nature of this TF [8]. Early work showed that homozygous YY1-deficient embryos fail at peri-implantation due to defective egg cylinder formation, whereas partial loss results in growth restriction and neural tube defects [8]. Subsequent YY1 knockout (KO) and knockdown (KD) models revealed broad, context-dependent requirements for YY1 across embryogenesis, organogenesis, and adult tissue homeostasis.

Conditional YY1 deletion has revealed stage- and lineage-specific requirements across multiple systems. In early embryos and somatic tissues, YY1 deficiency causes mid-gestational to perinatal lethality, cytokinesis defects, and cell-cycle arrest, linking YY1 to fundamental mechanisms of cellular homeostasis [86,87]. During gastrulation and extraembryonic development, YY1 regulates Nodal-Lefty2 signaling, visceral endoderm integrity, and yolk sac vascular remodeling [88,89]. Endothelial and cardiac-specific YY1-deficient models further demonstrated critical functions in vascular stability, angiogenic balance, and cardiac morphogenesis [90,91].

YY1 is also essential for metabolic and mitochondrial regulation. Loss of YY1 in intestinal stem cells, adipocytes, β-cells, or skeletal muscle leads to defects in stem cell maintenance, nutrient metabolism, insulin secretion, and mitochondrial function, underscoring its role in systemic metabolic homeostasis [92–94]. Specifically, in skeletal muscle, YY1 interacts with PGC1α downstream of mTORC1 to drive mitochondrial biogenesis and metabolic adaptation, while repressing PcG/Ezh2 programs to maintain insulin sensitivity [95]. Loss of YY1 abolishes these repressive programs, preserving insulin responsiveness despite mTORC1 inhibition [96].

In hematopoiesis, YY1 maintains hematopoietic stem cell (HSC) self-renewal, enforces B- and T-cell lineage fidelity, by regulating c-Kit transcription and repressing alternative transcriptional states [97–101]. In B cells, YY1 integrates chromatin and metabolic cues to optimize antibody diversification through regulation of recombination, class-switch recombination, somatic hypermutation, and activation-induced cytidine deaminase (AID) stability [102–104]. In T cells, YY1 governs both early thymocyte survival and lineage specification. Thymocyte-specific deletion leads to hypocellularity, a block at the DN3-DN4 transition, and apoptosis via p53 hyperactivation. YY1 also directly

Table 1
Mouse models of YY1 genetic depletion.

Model	System / Tissue	YY1 Phenotype	Tissue	Condition	Stimulus	Techniques	YY1 Role/Outcome	Year	DOI
YY1+/−, −/− KO	Embryo	Lethality, growth/neural defects	Whole embryo	Development	No	KO, histology, ISH, IHC	Required for implantation, morphogenesis	1999	[8]
Cond. KO, MEFs	Embryo	Lethality, cytokinesis/ apoptosis defects	Embryo, MEFs	Development	DNA damage	Cre/loxP, WB, RT-PCR	Regulates cell cycle, apoptosis (p53-indep.)	2006	[86]
siRNA-YY1 KD	Embryo	Perinatal lethality, sex bias	Brain, multiple	Development, imprinting	No	siRNA mice, RT-PCR	Controls imprinted genes, X-inactivation	2008	[87]
Epiblast-YY1 KO	Embryo	Gastrulation block	Epiblast	Development	TGFβ inhibitor	ISH, ChIP	Activates Lefty2 for EMT	2012	[88]
Endodermal-YY1 KO	Embryo	Vascular/yolk sac defects	Yolk sac, endoderm	Vascular morphogenesis	VEGFA rescue/ inhibition	IHC, qPCR, EM	Regulates VEGFA, epithelial identity	2013	[89]
Endothelial-YY1 KO	Vascular	Vascular defects	Retina, vasculature	Angiogenesis	DAPT, tamoxifen	siRNA, RNA-seq	Represses Notch target Hey1	2020	[90]
Cardiac YY1 KO	Heart	Lethality, EMT/trabeculation defects	Cardiomyocytes	Heart morphogenesis	None	KO, histology	Activates cardiac/EMT genes	2015	[91]
YY1ˆf/f;Vil-CreERT2	Intestine	ISC loss, crypt degeneration	Intestinal epithelium	Mito function, ISC homeostasis	Tamoxifen, antioxidants	Organoids, ChIP-seq	Maintains ISC via mito genes	2014	[92]
Mx1-Cre, Vav-Cre, OE	Hematopoiesis	Pancytopenia, HSC depletion	HSCs	HSC quiescence	Irradiation, BMT	RNA-seq, ChIP-seq	Maintains HSC self-renewal via c-Kit	2018	[97]
Mb1-Cre	B cells	B → T fate shift	BM pro—B, thymus	Lineage commitment	Notch ligand OP9-DL4	RNA-seq, IgH/TCR assays	Enforces B-lineage fidelity	2024	[98]
TAT-CRE ex vivo KO	B cells	↓CSR, AID nuclear levels	Splenic B cells	CSR	None	Co-IP, qPCR	Regulates AID stability	2012	[102]
γ1-Cre KO	B cells	↓GCs, CSR, Ig affinity	GC B cells	GC formation	NP-CGG	Flow cytometry, ELISA	Drives early GC gene program	2016	[100]
Mb1-Cre KO	B cells	Block in IgH recomb.	Pro-B cells	V(*D*)J recomb.	None	ChIP, DNA-FISH	Coordinates IgH contraction	2007	[99]
Mb1-Cre KO, rescue	B cells	Arrest, restricted V_κ	BM, spleen B-lineage	V(*D*)J recomb.	None	Igκ rearrangement, ChIP	REPO domain essential for PcG binding	2013	[101]
TAT-CRE KO	B cells	↓CSR, SHM, AID levels	Splenic B cells	CSR, SHM	Cytokines/mitogens	ChIP, AID assays	YY1 prevents AID degradation	2018	[103]
TAT-CRE, CD20TamCre	B cells	↓mito genes, CSR	B cells	CSR, mito function	LPS + IL4, tamoxifen	OCR, ECAR, ChIP	Links mito genes to AID & CSR	2020	[104]
YY1ˆem1Cflox KO	TAMs (prostate CA)	↓Tumors, ↑CD8+ T cells	TAMs	TME hypoxia	PROTACs, tenapanor	Proteomics, IHC	Promotes immunosuppressive TAM phenotype	2025	[110]
Cd4-Cre KO	iNKT cells	Developmental arrest	Thymus, spleen	iNKT development	TCR stim.	ChIP, luciferase	Transactivates Plzf for iNKT identity	2018	[107]
PLZF-Cre, CD4-Cre KO	NKT cells	↓NKT dev. & function	NKT cells	NKT maturation	α-GalCer	Flow, cytokine assays	Controls NKT subset/cytokine programs	2019	[108]
shRNA KO via CD4-Cre	T cells (RA)	↓Th17, ↓IL-17, ↓arthritis	CD4+ T cells	Autoimmunity (RA)	CIA model	STAT3, ELISA	STAT3-dependent IL-17 activation	2018	[109]
CD2- & Lck-Cre KOs	T cells	DN block, apoptosis	Thymocytes	T dev., TCR recomb.	None	Flow, p53 rescue	p53 repression for thymocyte survival	2016	[105]
Mx1/Vav-Cre KO	T cells	DN3 block, ↓Notch1	Early thymocytes	Early T dev.	Poly(I:C)	Notch1 OE, OP9-DL1	Activates Notch1, ensures survival	2021	[106]
Adipoq-Cre KO	Adipose	↓Mito genes, ↑glucose tol.	WAT, BAT	Thermogenesis, obesity	Cold, spermidine inhibition	Metabolomics, GTT	Dual role: mito function + obesity resistance	2025	[93]
βYY1KO-Rip/Mip	Pancreas	β-cell death, diabetes	β-cells	Diabetes	None	GTT, mito assays	Supports β-cell mito health	2020	[94]
YY1mKO	Muscle	Myopathy, ↓mito	Oxidative muscle	Bioenergetics	Rapamycin	EM, mito respiration	Regulates mito genes via PGC1α	2012	[95]
Myogenin-Cre KO	Muscle	↓Insulin resistance	Muscle	Insulin resistance	Rapamycin	ChIP, glucose assays	Represses insulin/IGF genes via PcG	2012	[96]
Oligodendrocyte-lineage KO	CNS	Hypomyelination	Brain, spinal cord	Myelination	None	ChIP, IHC	Represses differentiation inhibitors	2007	[111]
Schwann cell KO	PNS	Hypomyelination, weakness	Sciatic nerve	Myelination	MEK inhibitor	WB, EM	Activates Egr2, integrates neuregulin	2011	[112]
En1Cre/+ KO	CNS	Midbrain/cerebellar defects	Neuroepithelial cells	CNS development	None	BrdU, TUNEL, ChIP	Promotes Wnt1, represses p53	2020	[113]
AAV5-GFAP-Cre KO	CNS	Neuroprotection vs Mn	Astrocytes	Neurotoxicity	Mn exposure	ICP-MS, behavior	Preserves Glu transporters under Mn	2020	[115]
GFAP-Cre KO	CNS	Severe neuro deficits	Astrocytes	Neurodev., inflammation	None	RNA-seq, proteomics	Maintains astrocyte homeostasis	2023	[116]
GFAP-Cre KO	CNS	Cerebellar degeneration	Astrocytes, cerebellum	Neurodegeneration	None	IHC, confocal	Preserves synapses, suppresses gliosis	2025	[117]

(*continued on next page*)

Table 1 (*continued*)

Model	System / Tissue	YY1 Phenotype	Tissue	Condition	Stimulus	Techniques	YY1 Role/Outcome	Year	DOI
CamKIIα-Cre KO	CNS/Behavior	↑Stress behavior	PFC neurons	Stress/depression	CUS, corticosterone	RNA-seq, ChIP	YY1 buffers stress-induced gene repression	2022	[118]
Emx1-Cre, iCreERT2	Cortex	Microcephaly, ↓NPCs	Cortical neurons	Neurogenesis	Tamoxifen	ChIP-seq, metabolomics	Controls NPC survival, metabolism	2019	[114]
Wnt1/Sox10/Tyr-Cre KOs	NCC/Skin	↓Melanocytes, ↓melanoma	NCC, melanoma	Dev., cancer	Tamoxifen	RNA-seq, siRNA	Regulates MITF–c-MYC, pigmentation	2019	[120]
TyrCre KO	Skin	Loss of pigmentation	Melanocytes	Pigmentation	None	ChIP, expression	YY1-MITF control melanocyte genes	2012	[119]
YY1 iΔEC KO	Tumor angiogenesis	↓Angiogenesis	ECs, tumors	Angiogenesis	Tamoxifen, VEGF	Matrigel assay	Promotes VEGF/BMP6 signals	2020	[121]
Zp3-Cre KO	Oocytes	Female infertility	Oocytes	Folliculogenesis	None	IHC, qPCR	Regulates oocyte/GC gene expression	2011	[122]
RNAi, KO	Testes	Meiotic arrest, infertility	Spermatocytes	Spermatogenesis	None	IHC, chromatin assays	Coordinates DNA repair, heterochromatin	2009	[123]

Table Abbreviations: Knockout, KO; Knockdown, KD; Overexpression, OE; In Situ Hybridization, ISH; Immunohistochemistry, IHC; Chromatin Immunoprecipitation, ChIP; Western Blot, WB; Glucose Tolerance Test, GTT; Tumor-Associated Macrophages, TAMs; Tumor Microenvironment, TME; Chronic Unpredictable Stress, CUS; Hematopoietic Stem Cell, HSC; Intestinal Stem Cell, ISC; Electron Microscopy, EM; Neural Progenitor Cell, NPC; Neural Crest Cell, NCC; Class Switch Recombination, CSR; Somatic Hypermutation, SHM; Germinal Center, GC; Activation-Induced Cytidine Deaminase, AID; Prefrontal Cortex, PFC; Promyelocytic Leukemia Zinc Finger, PLZF; Mouse Embryonic Fibroblasts, MEFs; Reverse Transcription Polymerase Chain Reaction, RT-PCR; Conditional Knockout, Cond. KO; Vascular Endothelial Growth Factor A, VEGFA; Quantitative PCR, qPCR; RNA Sequencing, RNA-seq; Bone Marrow Transplantation, BMT; Immunoglobulin Heavy Chain, IgH; T Cell Receptor, TCR; Co-Immunoprecipitation, Co-IP; Enzyme-Linked Immunosorbent Assay, ELISA; Fluorescence In Situ Hybridization, DNA-FISH; Oxidative Phosphorylation/Extracellular Acidification Rate, OCR/ECAR; Immunoglobulin Kappa, Igκ; Proteolysis Targeting Chimeras, PROTACs; Invariant Natural Killer T cells, iNKT; T Cell Receptor, TCR; Rheumatoid Arthritis, RA; Complete Freund's Adjuvant-Induced Arthritis, CIA; Cluster of Differentiation 2, CD2; Lymphocyte-Specific Protein Tyrosine Kinase, Lck; Double-Negative Thymocytes, DN; Polyinosinic:polycytidylic acid, Poly(I:C); Adiponectin-Cre, Adipoq-Cre; White Adipose Tissue, WAT; Brown Adipose Tissue, BAT; Reactive Oxygen Species, ROS; Glial Fibrillary Acidic Protein, GFAP; Inductively Coupled Plasma Mass Spectrometry, ICP-MS; Bromodeoxyuridine, BrdU; Terminal Deoxynucleotidyl Transferase dUTP Nick End Labeling, TUNEL; Calcium/Calmodulin-Dependent Protein Kinase II Alpha, CamKIIα; Ectodermal Lineage, iCreERT2; Microphthalmia-associated Transcription Factor, MITF; Bone Morphogenetic Protein 6, BMP6; Endothelial Cells, ECs; Zona Pellucida 3, Zp3.

activates Notch1 through enhancer binding, securing αβ T cell development [105,106].

NKT cell development is also YY1-dependent, as its NKT cell-specific depletion showed impaired maturation and cytokine production through a p53-independent mechanism [107,108]. In $CD4^+$ T cells, its downregulation attenuates Th17 differentiation. In these cells, YY1 cooperates with STAT3 to activate pro-inflammatory genes, delineating YY1 as a therapeutic target in autoimmune diseases driven by Th17 hyperactivity [109]. Finally, macrophage-specific deletion reprograms tumor-associated macrophages enhancing $CD8^+$ T cell infiltration and antitumor immunity via suppression of HIF-1α SUMOylation [110].

Within the nervous system, YY1 orchestrates neurodevelopment, myelination, astrocyte function, and stress-response programs. Oligodendrocyte progenitor-specific deletion recruits HDAC1/2 to repress inhibitors of myelination, while Schwann cell-specific KO impairs Egr2 activation downstream of neuregulin-MEK signaling [111,112]. Also, neural-specific deletion triggers p53-dependent apoptosis and Wnt1 reduction, causing microcephaly, cerebellar agenesis, and midbrain hypoplasia [113,114]. Astrocytic YY1 regulates anti-inflammatory programs, glutamate transport, and neuro-glial communication, and its deletion causes early lethality, neuroinflammation, oxidative stress, and behavioral deficits [115,116]. Cerebellar astrocyte-specific deletion disrupts Wnt/glutamate homeostasis, underscoring YY1 as a guardian of astrocytic integrity and neuro-glial communication [117]. YY1 also contributes to neurobehavioral regulation in adulthood. In excitatory cortical neurons, YY1 buffers chromatin accessibility to maintain stress-response and synaptic gene expression [118].

Intriguingly, tissue specific depletion models showed that YY1 regulates melanocytes, angiogenesis, and germline development. In melanocytes, it partners with MITF to control pigmentation, survival, and melanoma metabolic programs [119]. Mechanistically, YY1 remodels chromatin at the MITF-c-MYC axis to control metabolic and translational networks critical for melanocyte function and melanoma progression [120]. Endothelial YY1 governs angiogenesis by modulating BMP6- and VEGF-responsive cytoskeletal and transcriptional pathways underscoring its role in vascular remodeling and potential as an anti-angiogenic cancer target [121].

YY1 is essential for germline development and reproductive fitness. Female germline deletion disrupts oocyte-granulosa signaling, follicular maturation, and fertility, while male deletion impairs synaptonemal complex disassembly, DNA repair, and spermatogenesis [122,123].

Overall, murine YY1-deficient models reveal a ubiquitously expressed, dosage-sensitive regulator essential for embryonic viability and for sustaining metabolic, immune, neural, and reproductive functions (Table 1). The extensiveness of phenotypes associated with YY1 loss highlights its position as a central regulatory hub and a potential biomarker and therapeutic target.

5. The bidirectional role of YY1 in cancer

While YY1 depletion impairs lineage specification, organogenesis, and metabolism, its overexpression can also be harmful, driving abnormal cellular programs. This duality is particularly evident in cancer, where YY1 is frequently found deregulated [124]. Although most tumors display YY1 overexpression, instances of downregulation have been reported, suggesting a context-dependent role in oncogenesis [74]. Beyond its function in tumor cell-intrinsic programs, YY1 has also been found involved in regulating immune checkpoints, notably PD-L1, thereby linking it to therapeutic resistance and the efficacy of immune checkpoint blockade [125].

Animal studies show how YY1 shapes the tumor microenvironment. Macrophage-specific deletion in prostate cancer reprograms macrophages to an immunostimulatory state, boosts $CD8^+$ T cell infiltration, and inhibits tumor growth [110]. Whereas, in melanoma, YY1 controls the MITF-c-MYC axis to sustain melanocyte survival and tumor progression, while its deletion reduced melanocyte maintenance and

melanoma formation [119,120]. Endothelial-specific deletion revealed that YY1 promotes angiogenesis via VEGF- and BMP6-responsive genes, with its loss impairing vascularization and tumor perfusion [121]. Together, these findings establish YY1 as a regulator of both cancer cell biology and the tumor microenvironment in in vivo KO/KD models.

Human studies confirm these findings, showing YY1 upregulation across solid and hematological cancers, often correlating with poor prognosis [5]. For instance, elevated YY1 levels drive transcriptional programs that support proliferation, apoptosis resistance, metabolic reprogramming, EMT, and immune evasion [126]. In bladder cancer, elevated YY1 expression is associated with poor clinical outcomes, suggesting its role in driving tumor aggressiveness and therapy resistance [127,128]. Similarly, in breast cancer, YY1 overexpression correlates with unfavorable prognosis and appears to promote cancer cell survival, migration, and drug resistance through epigenetic and transcriptional reprogramming [129–132]. In cervical cancer, YY1 is markedly upregulated and contributes to malignancy by suppressing tumor suppressor networks while activating oncogenic programs [133–135].

In colorectal cancer, YY1 presents a paradoxical landscape [136]. Elevated expression is often associated with poor prognosis, supporting oncogenic functions [137,138]. Yet in certain molecular contexts, YY1 induces pro-apoptotic factors such as BCL2L15/Bfk, promoting cell death and tumor suppression [70,139].

In other gastrointestinal malignancies, including esophageal and gastric cancers, YY1 is consistently upregulated, facilitating EMT, chemoresistance, and immune evasion, correlating with poor survival [140–143]. Gliomas similarly show high YY1 expression, promoting glioma stem-like cell maintenance and therapeutic resistance [144,145]. In liver and lung cancers, elevated YY1 expression is strongly associated with poor prognosis, regulating genes involved in metabolic reprogramming, hypoxia responses, and immune checkpoint pathways, all contributing to aggressive tumor phenotypes [146–152].

In melanoma, YY1 overexpression correlates with poor outcomes and has been found involved in resistance to BRAF inhibitors and immune checkpoint blockade, highlighting its potential as both a prognostic marker and therapeutic target [153–155]. Osteosarcoma and other sarcomas also show high YY1 levels, which are associated with enhanced metastasis via modulation of extracellular matrix components and EMT-related genes [156–160].

In hematological malignancies, YY1 overexpression is linked to leukemia, non-Hodgkin lymphoma, and multiple myeloma, where it drives proliferation and suppresses apoptosis [161–164]. Notably, non-Hodgkin lymphomas exhibit subtype-specific YY1 patterns: most show upregulation linked to poor prognosis, while YY1 downregulation in some cases correlates with better outcomes [7,71]. YY1 upregulation is likewise reported in ovarian, pancreatic, renal, testicular seminoma, and thyroid cancers, correlating with poor patient outcomes. In ovarian cancer, YY1 regulates angiogenesis and DNA repair, whereas in pancreatic cancer it drives chemoresistance and tumor plasticity [165–171]. In renal cell carcinoma, YY1 promotes metastasis and immune escape, while in thyroid cancer, it drives dedifferentiation and therapy resistance [172–175].

An exception is the case of nasopharyngeal carcinoma, in which YY1 is downregulated, correlating with favorable prognosis. This suggests a tissue-specific, potentially tumor-suppressive role of YY1, reflecting its dual function as a transcriptional activator or repressor depending on cofactors and chromatin context [176,177].

Collectively, these studies highlight the context-dependent role of YY1 in cancer, either acting as an oncogene or tumor suppressor depending on tissue, subtype, and microenvironment [76]. Mechanistically, whether YY1 functions as an oncogene or tumor suppressor may be shaped by a combination of post-translational modifications, cofactor availability, and local chromatin context [124]. For instance, acetylation (e.g., mediated by p300/CBP) generally enhances YY1-mediated transcriptional activation of pro-proliferative genes, whereas deacetylation (e.g., via HDACs) promotes the assembly of YY1 into repressive complexes that can support differentiation or apoptosis [178,179]. Phosphorylation downstream of PI3K/AKT signaling increases YY1 stability and nuclear retention, thereby reinforcing oncogenic programs, while ubiquitination pathways can reduce YY1 abundance and unmask tumor-suppressive activities [50,137]. Interactions with context-specific cofactors (including p53, NF-κB, MYC, EZH2/PRC2, BRD proteins, and SWI/SNF chromatin remodelers) may further determine whether YY1 binds enhancers and promoters as an activator or recruits repressive machinery [31]. Although incompletely understood, these regulatory layers likely underlie the divergent cancer phenotypes associated with YY1 deregulation.

This duality underscores the need for precision in therapeutic targeting. Indeed, the fine-tuning of YY1 levels holds promise for counteracting tumor progression, overcoming drug resistance, and enhancing immunotherapy efficacy, but it must be tailored to the specific cancer context to avoid unintended consequences.

6. YY1 and chronobiology

The multilayered regulatory mechanisms described above underscore the complexity of YY1 expression control, extending beyond its classical classification as a constitutive TF [31]. Ongoing research continues to explore the dynamic regulation of YY1, particularly in pathological conditions such as cancer, where its expression is frequently deregulated, as well as in novel emerging contexts such as circadian biology, where YY1 may integrate with rhythmic gene expression networks to modulate time-dependent transcriptional programs [180]. Beyond spatial genome architecture and classical transcriptional control, time emerges as the compelling fourth dimension of gene regulation, positioning YY1 at the intersection of these regulatory layers [181].

Although YY1 is not a core component of the circadian clock, accumulating evidence suggests it participates in dynamic regulatory networks that include circadian rhythms. It has been associated with the modulation of clock-controlled genes and the synchronization of peripheral oscillators [182]. Also, YY1 interacts with key elements of the circadian machinery, and its promoter contains binding motifs responsive to circadian-regulated factors [84]. Furthermore, YY1 itself may undergo subtle rhythmic modulation in certain tissues, potentially affecting rhythmic chromatin accessibility, metabolic cycling, and DNA repair timing, all processes tightly linked to cancer biology [104].

The circadian clock is a conserved biological timing system that orchestrates daily rhythms in physiology and behavior, aligning them with the 24-h environmental cycle [183]. At its core are transcription-translation feedback loops (TTFLs) composed of clock genes and their protein products, which drive rhythmic gene expression in a tissue-specific manner to anticipate and adapt to predictable environmental changes [184].

The circadian system comprises a central pacemaker in the suprachiasmatic nucleus (SCN) and peripheral clocks in nearly all tissues [185–187]. These clocks operate through TTFLs in which CLOCK-BMAL1 activate PER and CRY, whose protein products feedback to inhibit CLOCK-BMAL1. Additional stabilizing loops mediated by REV-ERB and ROR nuclear receptors refine oscillation phase and amplitude [188,189]. Light entrains SCN rhythms, whereas non-photic cues such as feeding, temperature, and hormonal oscillations synchronize peripheral clocks [190]. All tissues and organs, including liver, muscle, pancreas, and adipose tissue, respond strongly to these cues, making them potential sites where the metabolic and mitochondrial regulatory functions mediated by YY1 can intersect with circadian timing [191–193].

Disruption of circadian coordination through shift work, irregular sleep, diet, stress, or molecular defects, decouples central and peripheral oscillators and perturbs rhythmic control of metabolism, immunity, hormone secretion, and cell-cycle progression [194]. Such chrononodisruption is increasingly linked to chronic disease, including metabolic syndrome, neurodegeneration, cardiovascular disease, and cancer

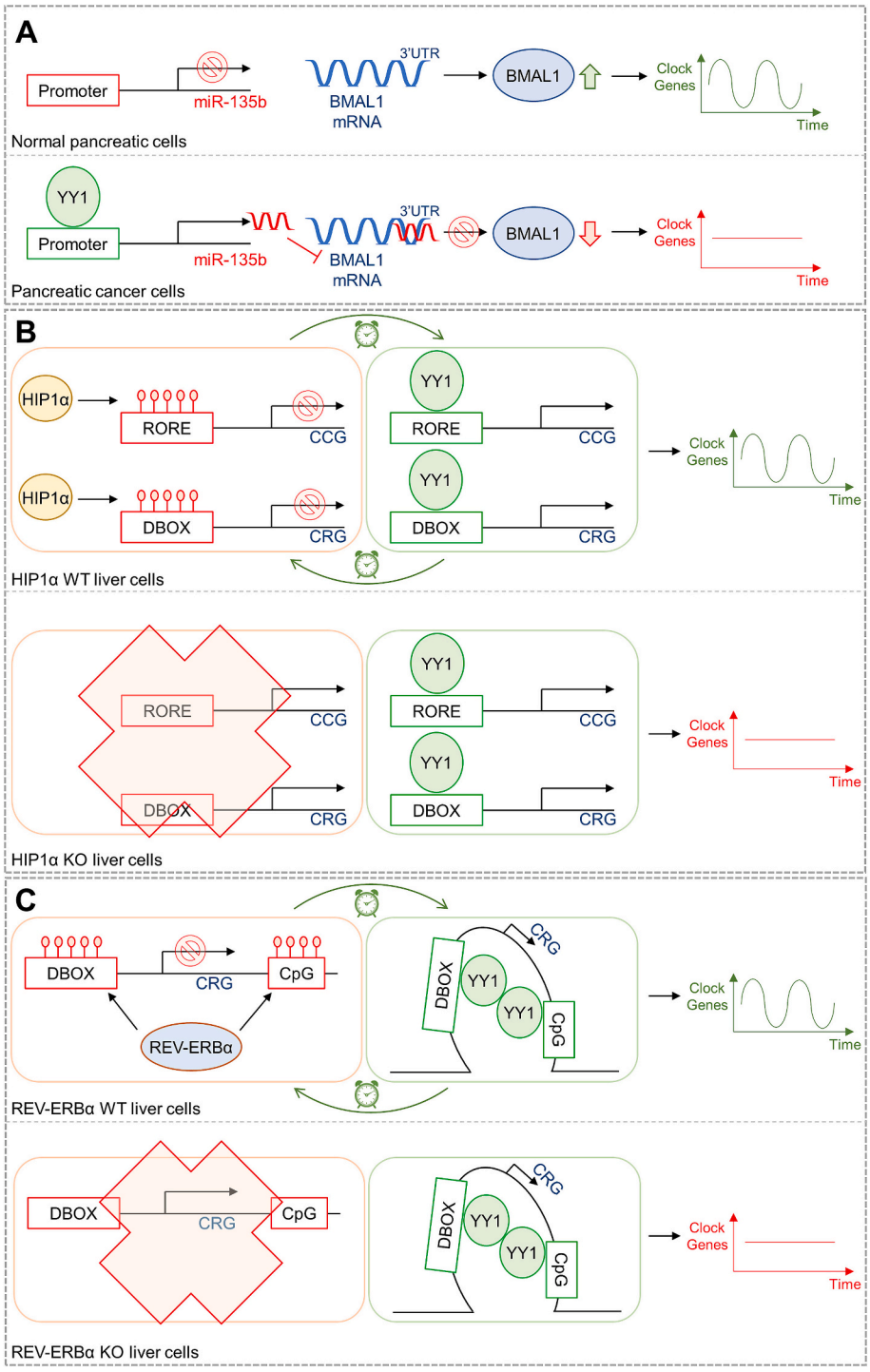

Fig. 2. YY1 as the key regulator of circadian clock gene expression. (A) Normal pancreatic cells (top) versus pancreatic cancer cells (bottom). Each schematic depicts the miR-135b promoter, BMAL1 mRNA (negatively regulated by miR-135b), BMAL1 protein, and downstream clock gene expression. In normal cells, the absence of miR-135b permits circadian oscillation of BMAL1 and rhythmic expression of clock genes (green waveform). In cancer cells, YY1 activates miR-135b, which represses BMAL1, eliminating BMAL1 protein and abolishing circadian oscillations of clock gene expression (red flat line). (B) HIP1α wild-type (WT) (top) versus HIP1α knockout (KO) liver cells (bottom). HIP1α regulates core clock genes (CCG) and clock-regulated genes (CRG) by promoting epigenetic silencing through activation of DNA methyltransferases and histone methyltransferases at enhancer elements (RORE/DBOX) upstream of CCG/CRG loci. These elements support YY1-mediated circadian transcription in HIP1α WT cells, resulting in circadian expression of clock genes (green waveform). In HIP1α KO cells, loss of HIP1α disrupts this alternating circadian regulation, leading to arrhythmic transcription and constitutive YY1 binding at these elements (red flat line). (C) REV-ERBα WT (top) versus REV-ERBα KO liver cells (bottom). YY1 dimerization–mediated chromatin looping at CRG promoters (DBOX regions and CpG islands downstream to the TSS) is shown. In REV-ERBα WT cells, alternating DNA methylation and YY1 binding drive circadian CRG expression (green waveform). In REV-ERBα KO cells, this alternation is lost, YY1 remains constitutively bound, and circadian CRG expression is abolished (red flat line). (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

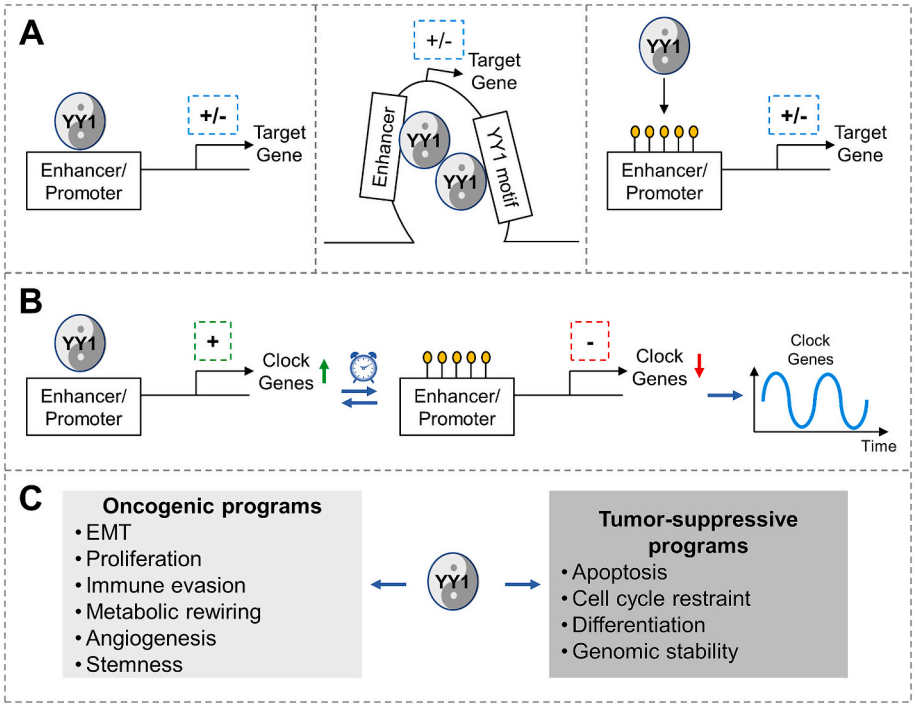

Fig. 3. YY1 as a spatiotemporal integrator of gene regulation. (A) Spatial regulation: YY1 binds (directly or indirectly) to enhancers and promoters to activate or repress target genes (left), stabilizes enhancer-promoter loops while recruiting activating or repressive complexes (middle), and modulates the expression of epigenetic enzymes, indirectly affecting downstream gene expression (right). (B) Temporal regulation: circadian cues control YY1 expression and activity at enhancers and promoters of clock genes, modulating clock gene expression over time. (C) Spatiotemporal integration: the combination of spatial and temporal inputs by YY1 determines cellular phenotypes in cancer, driving either oncogenic or tumor-suppressive programs. EMT, Epithelial to mesenchymal transition.

[195].

In this context, YY1 may serve as a key modulator of circadian resilience, regulating genes involved in hypoxia, inflammation, and metabolic adaptation that intersect with circadian pathways [196,197]. It modulates NF-κB signaling and cytokine expression in inflammation, and nutrient-sensing pathways like mTOR and AMPK in metabolic tissues [83]. In cancer, YY1 overexpression with circadian disruption may promote tumor progression by uncoupling cell cycle checkpoints, while in metabolic syndrome, aberrant YY1 impairs rhythmic metabolic gene expression, worsening insulin resistance and dyslipidemia [198,199]. Its ability to reprogram chromatin accessibility may also disrupt peripheral clock coherence, contributing to disease [200].

In a seminal 2013 study, YY1 was recognized as a TF with potential circadian relevance through genome-wide expression and binding site analyses. Its context-dependent and multifaceted regulation precluded integration into core quantitative circadian models, yet it was positioned within the broader transcriptional landscape as a possible temporal regulator, highlighting the need to study its rhythmic binding, post-translational regulation, and interactions with core clock components [201].

Subsequent studies have expanded the functional scope of YY1 by demonstrating its role in circadian disruption in pancreatic cancer. Using pancreatic ductal epithelial cell lines, xenograft models, and human tissue samples, YY1 was shown to transcriptionally activate miR-135b through direct promoter binding, establishing a miR-135b-BMAL1-YY1 feedback loop. In this circuit, miR-135b represses BMAL1 by targeting its 3'-UTR, leading to desynchronization of local rhythmic gene expression. Normally, YY1 exhibits oscillatory expression antiphasic to BMAL1, but this rhythmicity is attenuated in pancreatic cancer cells. Functionally, YY1 overexpression promotes oncogenic drivers such as Snail and VEGF, reinforcing its dual role as a mediator of circadian misalignment and a contributor to tumor progression [85].

More recently, mechanistic insights have linked YY1 to circadian chromatin remodeling. In hepatocyte-specific HP1α KO mice, HP1α normally coordinates recruitment of histone methyltransferases and DNA methylation machinery (DNMT3a, MeCP2, MBD4) at intronic CpG islands containing D-box and RORE elements in core clock genes. Loss of HP1α caused chromatin decompaction and inappropriate transcription. In these livers, YY1 bound constitutively near intronic CpG islands and promoters of circadian genes, unlike the temporally restricted binding in wild-type mice. This indicates that HP1α-mediated chromatin compaction constrains YY1, and its deregulated binding disrupts temporal transcriptional control, positioning YY1 as a permissive factor normally restrained by HP1α-dependent epigenetic repression [202].

A complementary study established YY1 as an architectural regulator of circadian transcription. Experimental data demonstrated that YY1 binds rhythmically to sites upstream of D-box and RORE enhancers and downstream of intronic CpG islands in output genes. Enhancer-proximal binding precedes promoter occupancy, suggesting that YY1 dimerization facilitates dynamic enhancer-promoter communication. Rhythmic recruitment requires RORα and BMAL1, while binding becomes constitutive in E4BP4 or Rev-Erbα KO livers, highlighting regulation by core clock activators and repressors. Bisulfite sequencing further showed YY1-bound regions undergo rhythmic DNA methylation, linking TF-mediated looping to circadian epigenetic dynamics [84].

Altogether, these studies position YY1 as a central architectural regulator, integrating transcriptional timing with chromatin state (Fig. 2). By coordinating enhancer-promoter interactions, epigenetic modifications, and feedback loops, YY1 links core clock components to broader transcriptional and oncogenic programs. Its rhythmic and plastic activity illustrates how circadian regulation spans both genomic space and the temporal dimension, with dysregulation contributing to the development of chronic pathologies such as cancer [124].

7. Conclusions and perspectives

Collectively, the findings disclosed in this review elevate YY1 from a context-dependent transcription factor to a paradigm for how regulatory

proteins integrate spatial and temporal dimensions of gene control. At the molecular level, the multilayered regulation of this multifaceted TF, spanning transcriptional, post-transcriptional, and post-translational mechanisms, awards it with exceptional plasticity, enabling context-specific functions in development, tissue homeostasis, and disease.

Furthermore, insights from YY1-deficient mouse models highlight its essential role in embryogenesis and organogenesis, while also revealing how its loss or deregulation disrupts fundamental cellular processes and predisposes to pathological states. In particular, in cancer, YY1 assumes a bimodal role, acting as either oncogene or tumor suppressor depending on cellular context, where its capability to rewire transcriptional and epigenetic networks becomes a critical determinant of disease trajectory.

In chronobiology, YY1 is emerging as both a clock-controlled gene and an architectural regulator of rhythmic transcription, integrating chromatin state, enhancer-promoter communication, and temporal dynamics.

In conclusion, circadian transcription can be descripted as a dynamic four-dimensional process, with YY1 working as structural organizer, temporal gatekeeper, and disease modifier. In this context, its deregulation in cancer links circadian misalignment to oncogenic signaling (Fig. 3). In the future, a deeper understanding on how YY1 coordinated activity over time might be able to shape transcriptional and epigenetic networks will uncover novel therapeutic strategies to restore proper gene regulation in cancer.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

No data was used for the research described in the article.

References

[1] Y. Shi, E. Seto, L.S. Chang, T. Shenk, Transcriptional repression by YY1, a human GLI-Krüppel-related protein, and relief of repression by adenovirus E1A protein, Cell 67 (1991) 377–388, https://doi.org/10.1016/0092-8674(91)90189-6.

[2] L. Atchison, Transcription factor YY1 functions as a PcG protein in vivo, EMBO J. 22 (2003) 1347–1358, https://doi.org/10.1093/emboj/cdg124.

[3] Z.R. Belak, N. Ovsenek, C.H. Eskiw, Conserved RNA binding activity of a Yin-Yang 1 homologue in the ova of the purple sea urchin Strongylocentrotus purpuratus, Sci. Rep. 8 (2018) 8061, https://doi.org/10.1038/s41598-018-26264-0.

[4] X. Zheng, M. Cheng, L. Xiang, J. Su, Y. Zhou, L. Xie, R. Zhang, Cloning and identification of a YY-1 homolog as a potential transcription factor from Pinctada fucata, Gene 572 (2015) 108–115, https://doi.org/10.1016/j.gene.2015.07.003.

[5] L.M. Khachigian, The Yin and Yang of YY1 in tumor growth and suppression, Int. J. Cancer 143 (2018) 460–465, https://doi.org/10.1002/ijc.31255.

[6] R.P. Hyde-DeRuyscher, E. Jennings, T. Shenk, DNA binding sites for the transcriptional activator/repressor YY1, Nucleic Acids Res. 23 (1995) 4457–4465, https://doi.org/10.1093/nar/23.21.4457.

[7] M. Jung, I. Bui, B. Bonavida, Role of YY1 in the regulation of anti-apoptotic gene products in drug-resistant cancer cells, Cancers (Basel) 15 (2023) 4267, https://doi.org/10.3390/cancers15174267.

[8] M.E. Donohoe, X. Zhang, L. McGinnis, J. Biggers, E. Li, Y. Shi, Targeted disruption of mouse Yin Yang 1 transcription factor results in Peri-implantation lethality, Mol. Cell. Biol. 19 (1999) 7237–7244, https://doi.org/10.1128/MCB.19.10.7237.

[9] M. Gabriele, A.T. Vulto-van Silfhout, P.L. Germain, A. Vitriolo, R. Kumar, E. Douglas, E. Haan, K. Kosaki, T. Takenouchi, A. Rauch, K. Steindl, E. Frengen, D. Misceo, C.R.J. Pedurupillay, P. Stromme, J.A. Rosenfeld, Y. Shao, W. J. Craigen, C.P. Schaaf, D. Rodriguez-Buritica, L. Farach, J. Friedman, P. Thulin, S.D. McLean, K.M. Nugent, J. Morton, J. Nicholl, J. Andrieux, A. Stray-Pedersen, P. Chambon, S. Patrier, S.A. Lynch, S. Kjaergaard, P.M. Tørring, C. Brasch-Andersen, A. Ronan, A. van Haeringen, P.J. Anderson, Z. Powis, H.G. Brunner, R. Pfundt, J.H.M. Schuurs-Hoeijmakers, B.W.M. van Bon, S. Lelieveld, C. Gilissen, W.M. Nillesen, L.E.L.M. Vissers, J. Gecz, D.A. Koolen, G. Testa, B.B.A. de Vries, YY1 haploinsufficiency causes an intellectual disability syndrome featuring transcriptional and chromatin dysfunction, Am. J. Hum. Genet. 100 (2017) 907–925, https://doi.org/10.1016/j.ajhg.2017.05.006.

[10] J. Yang, C. Yu, N. Lyn, L. Liu, D. Li, Q. Shang, Clinical analysis of Gabriele-de Vries caused by YY1 mutations and literature review, Mol. Genet. Genomic Med. 12 (2024), https://doi.org/10.1002/mgg3.2281.

[11] F. Cherik, J. Reilly, J. Kerkhof, M. Levy, H. McConkey, M. Barat-Houari, K. M. Butler, C. Coubes, J.A. Lee, G. Le Guyader, R.J. Louie, W.G. Patterson, M. L. Tedder, M. Bak, T.B. Hammer, W. Craigen, F. Démurger, C. Dubourg, M. Fradin, R. Franciskovich, E. Frengen, J. Friedman, N.R. Palares, M. Iascone, D. Misceo, P. Monin, S. Odent, C. Philippe, F. Rouxel, V. Saletti, P. Strømme, P. C. Thulin, B. Sadikovic, D. Genevieve, DNA methylation episignature in Gabriele-de Vries syndrome, Genet. Med. 24 (2022) 905–914, https://doi.org/10.1016/j.gim.2021.12.003.

[12] M.F. Pereira, V. Finazzi, L. Rizzuti, D. Aprile, V. Aiello, L. Mollica, M. Riva, C. Soriani, F. Dossena, R. Shyti, D. Castaldi, E. Tenderini, M.T. Carminho-Rodrigues, J.F. Bally, B.B.A. de Vries, M. Gabriele, A. Vitriolo, G. Testa, YY1 mutations disrupt corticogenesis through a cell type specific rewiring of cell-autonomous and non-cell-autonomous transcriptional programs, Mol. Psychiatry 30 (2025) 3413–3429, https://doi.org/10.1038/s41380-025-02929-x.

[13] J.A. Morales-Rosado, C. Kaiwar, B.E. Smith, E.W. Klee, R. Dhamija, A case of YY1 -associated syndromic learning disability or Gabriele-de Vries syndrome with myasthenia gravis, Am. J. Med. Genet. A 176 (2018) 2846–2849, https://doi.org/10.1002/ajmg.a.40626.

[14] L.E.L.M. Vissers, J. de Ligt, C. Gilissen, I. Janssen, M. Steehouwer, P. de Vries, B. van Lier, P. Arts, N. Wieskamp, M. del Rosario, B.W.M. van Bon, A. Hoischen, B.B.A. de Vries, H.G. Brunner, J.A. Veltman, A de novo paradigm for mental retardation, Nat. Genet. 42 (2010) 1109–1112, https://doi.org/10.1038/ng.712.

[15] N. Koruga, S. Pušeljić, M. Babić, M. Ćuk, A. Cvitković Roić, V. Vrtarić, A. Soldo Koruga, A. Rončević, V. Tomac, T. Rotim, T. Turk, D. Kretić, N. Pušeljić, R. Nađ, I. Serdarušić, First reported case of Gabriele-de Vries syndrome with spinal dysraphism, Children 10 (2023) 623, https://doi.org/10.3390/children10040623.

[16] H.J. Khamirani, S. Zoghi, Z.M. Namdar, N. Kamal, M. Dianatpour, S.M.B. Tabei, S. Mohammadi, F. Dehghanian, Z. Farbod, S.A. Dastgheib, Clinical features of patients with Yin Yang 1 deficiency causing Gabriele-de Vries syndrome: a new case and review of the literature, Ann. Hum. Genet. 86 (2022) 52–62, https://doi.org/10.1111/ahg.12448.

[17] S. Balakrishnan, P. Ranganath, Report of an unusual association of hydrosyringomyelia with Gabriele-de Vries syndrome in an Asian-Indian patient, Clin. Dysmorphol. 30 (2021) 204–206, https://doi.org/10.1097/MCD.0000000000000385.

[18] M.T. Carminho-Rodrigues, D. Steel, S.B. Sousa, G. Brandt, M. Guipponi, S. Laurent, S. Fokstuen, A. Moren, A. Zacharia, E. Dirren, R. Oliveira, M. A. Kurian, P.R. Burkhard, J.F. Bally, Complex movement disorder in a patient with heterozygous YY1 mutation (Gabriele-de Vries syndrome), Am. J. Med. Genet. A 182 (2020) 2129–2132, https://doi.org/10.1002/ajmg.a.61731.

[19] S.R. dos Santos, R.M. Piergiorge, J. Rocha, B.B. Abdala, A.P. Gonçalves, M.M. G. Pimentel, C.B. Santos-Rebouças, A de novo YY1 missense variant expanding the Gabriele-de Vries syndrome phenotype and affecting X-chromosome inactivation, Metab. Brain Dis. 37 (2022) 2431–2440, https://doi.org/10.1007/s11011-022-01024-2.

[20] H. Huang, D. Zhang, Y. Yang, L. Yang, Y. Chai, Hashimoto's thyroiditis and nanophthalmos in Gabriele-de Vries syndrome: a case report, Front. Endocrinol. (Lausanne) 16 (2025), https://doi.org/10.3389/fendo.2025.1583190.

[21] K. Park, M.L. Atchison, Isolation of a candidate repressor/activator, NF-E1 (YY-1, delta), that binds to the immunoglobulin kappa 3′ enhancer and the immunoglobulin heavy-chain mu E1 site, Proc. Natl. Acad. Sci. USA 88 (1991) 9804–9808, https://doi.org/10.1073/pnas.88.21.9804.

[22] N. Hariharan, D.E. Kelley, R.P. Perry, Delta, a transcription factor that binds to downstream elements in several polymerase II promoters, is a functionally versatile zinc finger protein, Proc. Natl. Acad. Sci. USA 88 (1991) 9799–9803, https://doi.org/10.1073/pnas.88.21.9799.

[23] Y.L. Yao, B.R. Dupont, S. Ghosh, Y. Fang, R.J. Leach, E. Seto, Cloning, chromosomal localization and promoter analysis of the human transcription factor YY1, Nucleic Acids Res. 26 (1998) 3776–3783, https://doi.org/10.1093/nar/26.16.3776.

[24] M. Austen, B. Lüscher, J.M. Lüscher-Firzlaff, Characterization of the transcriptional regulator YY1, J. Biol. Chem. 272 (1997) 1709–1717, https://doi.org/10.1074/jbc.272.3.1709.

[25] H. Li, H. Liu, Z. Wang, X. Liu, L. Guo, L. Huang, L. Gao, M.A. McNutt, G. Li, The role of transcription factors Sp1 and YY1 in proximal promoter region in initiation of transcription of the mu opioid receptor gene in human lymphocytes, J. Cell. Biochem. 104 (2008) 237–250, https://doi.org/10.1002/jcb.21616.

[26] Q. Zhou, R.W. Gedrich, D.A. Engel, Transcriptional repression of the c-fos gene by YY1 is mediated by a direct interaction with ATF/CREB, J. Virol. 69 (1995) 4323–4330, https://doi.org/10.1128/jvi.69.7.4323-4330.1995.

[27] J.D. Kim, S. Yu, J.D. Kim, YY1 is autoregulated through its own DNA-binding sites, BMC Mol. Biol. 10 (2009) 85, https://doi.org/10.1186/1471-2199-10-85.

[28] H. Wang, E. Hertlein, N. Bakkar, H. Sun, S. Acharyya, J. Wang, M. Carathers, R. Davuluri, D.C. Guttridge, NF-kappaB regulation of YY1 inhibits skeletal myogenesis through transcriptional silencing of myofibrillar genes, Mol. Cell. Biol. 27 (2007) 4374–4387, https://doi.org/10.1128/MCB.02020-06.

[29] H. Abe, T. Ogawa, L. Wang, M. Kimura, T. Tanaka, R. Morita, T. Yoshida, M. Shibutani, Promoter-region hypermethylation and expression downregulation of Yy1 (Yin yang 1) in preneoplastic liver lesions in a thioacetamide rat hepatocarcinogenesis model, Toxicol. Appl. Pharmacol. 280 (2014) 467–474, https://doi.org/10.1016/j.taap.2014.08.013.

[30] S. Vivarelli, L. Falzone, M. Libra, YY1 and noncoding RNAs: A two-way relationship, in: YY1 Control Pathog. Drug Resist. Cancer, Elsevier, 2021, pp. 19–38, https://doi.org/10.1016/B978-0-12-821909-6.00012-2.
[31] T.C.J. Verheul, L. van Hijfte, E. Perenthaler, T.S. Barakat, The why of YY1: mechanisms of transcriptional regulation by Yin Yang 1, Front. Cell Dev. Biol. 8 (2020), https://doi.org/10.3389/fcell.2020.592164.
[32] H.B. Houbaviy, A. Usheva, T. Shenk, S.K. Burley, Cocrystal structure of YY1 bound to the adeno-associated virus P5 initiator, Proc. Natl. Acad. Sci. USA 93 (1996) 13577–13582, https://doi.org/10.1073/pnas.93.24.13577.
[33] K. Chen, Y. Lu, K. Shi, D.B. Stovall, D. Li, G. Sui, Functional analysis of YY1 zinc fingers through cysteine mutagenesis, FEBS Lett. 593 (2019) 1392–1402, https://doi.org/10.1002/1873-3468.13431.
[34] M. Figiel, F. Szubert, E. Luchinat, P. Bonarek, A. Baranowska, K. Wajda-Nikiel, M. Wilamowski, P. Miłek, M. Dziedzicka-Wasylewska, L. Banci, A. Górecki, Zinc controls operator affinity of human transcription factor YY1 by mediating dimerization via its N-terminal region, Biochim. Biophys. Acta Gene Regul. Mech. 1866 (2023) 194905, https://doi.org/10.1016/j.bbagrm.2022.194905.
[35] S. Bushmeyer, K. Park, M.L. Atchison, Characterization of functional domains within the multifunctional transcription factor, YY1, J. Biol. Chem. 270 (1995) 30213–30220, https://doi.org/10.1074/jbc.270.50.30213.
[36] E. Salichs, A. Ledda, L. Mularoni, M.M. Albà, S. de la Luna, Genome-wide analysis of histidine repeats reveals their role in the localization of human proteins to the nuclear speckles compartment, PLoS Genet. 5 (2009) e1000397, https://doi.org/10.1371/journal.pgen.1000397.
[37] W. Wang, S. Qiao, G. Li, J. Cheng, C. Yang, C. Zhong, D.B. Stovall, J. Shi, C. Teng, D. Li, G. Sui, A histidine cluster determines YY1-compartmentalized coactivators and chromatin elements in phase-separated enhancer clusters, Nucleic Acids Res. 50 (2022) 4917–4937, https://doi.org/10.1093/nar/gkac233.
[38] M.L. Atchison, Function of YY1 in long-distance DNA interactions, Front. Immunol. 5 (2014) 45, https://doi.org/10.3389/fimmu.2014.00045.
[39] Y.L. Yao, W.M. Yang, E. Seto, Regulation of transcription factor YY1 by acetylation and deacetylation, Mol. Cell. Biol. 21 (2001) 5979–5991, https://doi.org/10.1128/mcb.21.17.5979-5991.2001.
[40] S. Qiao, W. Wang, C. Yi, Q. Xu, W. Wang, J. Shi, D.B. Stovall, D. Li, G. Sui, YY1 oligomerization is regulated by its OPB domain and competes with its regulation of oncoproteins, Cancers (Basel) 14 (2022) 1611, https://doi.org/10.3390/cancers14071611.
[41] S. McNeil, B. Guo, J.L. Stein, J.B. Lian, S. Bushmeyer, E. Seto, M.L. Atchison, S. Penman, A.J. van Wijnen, G.S. Stein, Targeting of the YY1 transcription factor to the nucleolus and the nuclear matrix in situ: the C-terminus is a principal determinant for nuclear trafficking, J. Cell. Biochem. 68 (1998) 500–510. http://www.ncbi.nlm.nih.gov/pubmed/9493912.
[42] C.J. Fry, P.J. Farnham, Context-dependent transcriptional regulation, J. Biol. Chem. 274 (1999) 29583–29586, https://doi.org/10.1074/jbc.274.42.29583.
[43] J. Do Kim, A.K. Hinz, A. Bergmann, J.M. Huang, I. Ovcharenko, L. Stubbs, J. Kim, Identification of clustered YY1 binding sites in imprinting control regions, Genome Res. 16 (2006) 901–911, https://doi.org/10.1101/gr.5091406.
[44] A.S. Weintraub, C.H. Li, A.V. Zamudio, A.A. Sigova, N.M. Hannett, D.S. Day, B. J. Abraham, M.A. Cohen, B. Nabet, D.L. Buckley, Y.E. Guo, D. Hnisz, R. Jaenisch, J.E. Bradner, N.S. Gray, R.A. Young, YY1 is a structural regulator of enhancer-promoter loops, Cell 171 (2017) 1573–1588.e28, https://doi.org/10.1016/j.cell.2017.11.008.
[45] D.C.C. Wai, M. Shihab, J.K.K. Low, J.P. Mackay, The zinc fingers of YY1 bind single-stranded RNA with low sequence specificity, Nucleic Acids Res. (2016) gkw590, https://doi.org/10.1093/nar/gkw590.
[46] G.Z. Wang, S.P. Goff, Regulation of Yin Yang 1 by tyrosine phosphorylation, J. Biol. Chem. 290 (2015) 21890–21900, https://doi.org/10.1074/jbc.M115.660621.
[47] R. Rizkallah, K.E. Alexander, A. Kassardjian, B. Lüscher, M.M. Hurt, The transcription factor YY1 is a substrate for polo-like kinase 1 at the G2/M transition of the cell cycle, PLoS One 6 (2011) e15928, https://doi.org/10.1371/journal.pone.0015928.
[48] A. Kassardjian, R. Rizkallah, S. Riman, S.H. Renfro, K.E. Alexander, M.M. Hurt, The transcription factor YY1 is a novel substrate for Aurora B kinase at G2/M transition of the cell cycle, PLoS One 7 (2012) e50645, https://doi.org/10.1371/journal.pone.0050645.
[49] K.E. Alexander, R. Rizkallah, Aurora a phosphorylation of YY1 during mitosis inactivates its DNA binding activity, Sci. Rep. 7 (2017) 10084, https://doi.org/10.1038/s41598-017-10935-5.
[50] S. Riman, R. Rizkallah, A. Kassardjian, K.E. Alexander, B. Luscher, M.M. Hurt, Phosphorylation of the transcription factor YY1 by CK2 prevents cleavage by caspase 7 during apoptosis, Mol. Cell. Biol. 32 (2012) 797–807, https://doi.org/10.1128/MCB.06466-11.
[51] H. Zheng, J. Chu, Y. Zeng, H.H. Loh, P.-Y. Law, Yin Yang 1 phosphorylation contributes to the differential effects of μ-opioid receptor agonists on MicroRNA-190 expression, J. Biol. Chem. 285 (2010) 21994–22002, https://doi.org/10.1074/jbc.M110.112607.
[52] A. Rizor, E. Pajarillo, D.-S. Son, M. Aschner, E. Lee, Manganese phosphorylates Yin Yang 1 at serine residues to repress EAAT2 in human H4 astrocytes, Toxicol. Lett. 355 (2022) 41–46, https://doi.org/10.1016/j.toxlet.2021.11.007.
[53] S.-Y. Wei, Y.-T. Shih, H.-Y. Wu, W.-L. Wang, P.-L. Lee, C.-I. Lee, C.-Y. Lin, Y.-J. Chen, S. Chien, J.-J. Chiu, Endothelial Yin Yang 1 phosphorylation at S118 induces atherosclerosis under flow, Circ. Res. 129 (2021) 1158–1174, https://doi.org/10.1161/CIRCRESAHA.121.319296.
[54] N. Takasaki, D. Kurokawa, R. Nakayama, J. Nakayama, S. Aizawa, Acetylated YY1 regulates Otx2 expression in anterior neuroectoderm at two cis-sites 90 kb apart, EMBO J. 26 (2007) 1649–1659, https://doi.org/10.1038/sj.emboj.7601619.
[55] M.J. Barrero, Targeting YY1 in cancer through histone acetylation, in: YY1 Control Pathog. Drug Resist. Cancer, Elsevier, 2021, pp. 211–223, https://doi.org/10.1016/B978-0-12-821909-6.00008-0.
[56] H.M. Jeong, S.H. Lee, J. Yum, C.-Y. Yeo, K.Y. Lee, Smurf2 regulates the degradation of YY1, Biochim. Biophys. Acta, Mol. Cell Res. 2014 (1843) 2005–2011, https://doi.org/10.1016/j.bbamcr.2014.04.023.
[57] J. Jin, K. Wang, C. Lu, C. Yao, F. Xie, NEDD4L inhibits the proliferation and migration of keloid fibroblasts by regulating YY1 ubiquitination-mediated glycolytic metabolic reprogramming, Exp. Dermatol. 33 (2024), https://doi.org/10.1111/exd.70008.
[58] L. Chen, Q. Sun, R. Yue, H. Yan, X. Huang, H. Yu, Y. Yang, Involvement of E3 ubiquitin ligase NEDD4-mediated YY1 ubiquitination in alleviating idiopathic pulmonary fibrosis, Int. J. Biol. Macromol. 269 (2024) 131976, https://doi.org/10.1016/j.ijbiomac.2024.131976.
[59] Z. Deng, M. Wan, G. Sui, PIASy-mediated sumoylation of Yin Yang 1 depends on their interaction but not the RING finger, Mol. Cell. Biol. 27 (2007) 3780–3792, https://doi.org/10.1128/MCB.01761-06.
[60] W.J. Zhang, X.N. Wu, T.T. Shi, H.T. Xu, J. Yi, H.F. Shen, M.F. Huang, X.Y. Shu, F. F. Wang, B.L. Peng, R.Q. Xiao, W.W. Gao, J.C. Ding, W. Liu, Regulation of transcription factor Yin Yang 1 by SET7/9-mediated lysine methylation, Sci. Rep. 6 (2016) 21718, https://doi.org/10.1038/srep21718.
[61] H.J. Garbán, B. Bonavida, Nitric oxide inhibits the transcription repressor Yin-Yang 1 binding activity at the silencer region of the Fas promoter: a pivotal role for nitric oxide in the up-regulation of Fas gene expression in human tumor cells, J. Immunol. 167 (2001) 75–81, https://doi.org/10.4049/jimmunol.167.1.75.
[62] F. Hongo, H. Garban, S. Huerta-Yepez, M. Vega, A.R. Jazirehi, Y. Mizutani, T. Miki, B. Bonavida, Inhibition of the transcription factor Yin Yang 1 activity by S-nitrosation, Biochem. Biophys. Res. Commun. 336 (2005) 692–701, https://doi.org/10.1016/j.bbrc.2005.08.150.
[63] M. Hiromura, C.H. Choi, N.A. Sabourin, H. Jones, D. Bachvarov, A. Usheva, YY1 is regulated by O-linked N-acetylglucosaminylation (O-glcNAcylation), J. Biol. Chem. 278 (2003) 14046–14052, https://doi.org/10.1074/jbc.M300789200.
[64] G. Zhu, M. Qian, L. Lu, Y. Chen, X. Zhang, Q. Wu, Y. Liu, Z. Bian, Y. Yang, S. Guo, J. Wang, Q. Pan, F. Sun, O -GlcNAcylation of YY1 stimulates tumorigenesis in colorectal cancer cells by targeting SLC22A15 and AANAT, Carcinogenesis (2019), https://doi.org/10.1093/carcin/bgz010.
[65] X. Wang, W. Fan, N. Li, Y. Ma, M. Yao, G. Wang, S. He, W. Li, J. Tan, Q. Lu, S. Hou, YY1 lactylation in microglia promotes angiogenesis through transcription activation-mediated upregulation of FGF2, Genome Biol. 24 (2023) 87, https://doi.org/10.1186/s13059-023-02931-y.
[66] W. Chen, Q. E, B. Sun, P. Zhang, N. Li, S. Fei, Y. Wang, S. Liu, X. Liu, X. Zhang, PARP1-catalyzed PARylation of YY1 mediates endoplasmic reticulum stress in granulosa cells to determine primordial follicle activation, Cell Death Dis. 14 (2023) 524, https://doi.org/10.1038/s41419-023-05984-w.
[67] C. Yang, J. Qu, Y. Cheng, M. Tian, Z. Wang, X. Wang, X. Li, S. Zhou, B. Zhao, Y. Guo, L. Zheng, Q. Tong, YY1 drives PARP1 expression essential for PARylation of NONO in mRNA maturation during neuroblastoma progression, J. Transl. Med. 22 (2024) 1153, https://doi.org/10.1186/s12967-024-05956-4.
[68] Q. Zhang, D.B. Stovall, K. Inoue, G. Sui, The oncogenic role of Yin Yang 1, Crit. Rev. Oncog. 16 (2011) 163–197, https://doi.org/10.1615/critrevoncog.v16.i3-4.30.
[69] S. Gordon, G. Akopyan, H. Garban, B. Bonavida, Transcription factor YY1: structure, function, and therapeutic implications in cancer biology, Oncogene 25 (2006) 1125–1142, https://doi.org/10.1038/sj.onc.1209080.
[70] S. Vivarelli, L. Falzone, S. Candido, B. Bonavida, M. Libra, YY1 silencing induces 5-fluorouracil-resistance and BCL2L15 downregulation in colorectal Cancer cells: diagnostic and prognostic relevance, Int. J. Mol. Sci. 22 (2021) 8481, https://doi.org/10.3390/ijms22168481.
[71] S. Vivarelli, L. Falzone, G. Ligresti, S. Candido, A. Garozzo, G.G. Magro, B. Bonavida, M. Libra, Role of the transcription factor Yin Yang 1 and its selectively identified target survivin in high-grade B-cells non-Hodgkin lymphomas: potential diagnostic and therapeutic targets, Int. J. Mol. Sci. 21 (2020) 6446, https://doi.org/10.3390/ijms21176446.
[72] X. Dong, R. Guo, T. Ji, J. Zhang, J. Xu, Y. Li, Y. Sheng, Y. Wang, K. Fang, Y. Wen, B. Liu, G. Hu, H. Deng, H. Yao, YY1 safeguard multidimensional epigenetic landscape associated with extended pluripotency, Nucleic Acids Res. 50 (2022) 12019–12038, https://doi.org/10.1093/nar/gkac230.
[73] M.H. Lee, T. Lahusen, R.H. Wang, C. Xiao, X. Xu, Y.S. Hwang, W.W. He, Y. Shi, C. X. Deng, Yin Yang 1 positively regulates BRCA1 and inhibits mammary cancer formation, Oncogene 31 (2012) 116–127, https://doi.org/10.1038/onc.2011.217.
[74] S. Sarvagalla, S.P. Kolapalli, S. Vallabhapurapu, The two sides of YY1 in Cancer: a friend and a foe, Front. Oncol. 9 (2019) 1230, https://doi.org/10.3389/fonc.2019.01230.
[75] L. Li, Y. Li, I. Timothy Sembiring Meliala, V. Kasim, S. Wu, Biological roles of Yin Yang 2: its implications in physiological and pathological events, J. Cell. Mol. Med. 24 (2020) 12886–12899, https://doi.org/10.1111/jcmm.15919.
[76] I.T.S. Meliala, R. Hosea, V. Kasim, S. Wu, The biological implications of Yin Yang 1 in the hallmarks of cancer, Theranostics 4 (2020) 4183–4200, https://doi.org/10.7150/thno.43481.
[77] K. Kurisaki, A. Kurisaki, U. Valcourt, A.A. Terentiev, K. Pardali, P. ten Dijke, C.-H. Heldin, J. Ericsson, A. Moustakas, Nuclear factor YY1 inhibits transforming growth factor β- and bone morphogenetic protein-induced cell differentiation,

Mol. Cell. Biol. 23 (2003) 4494–4510, https://doi.org/10.1128/MCB.23.13.4494-4510.2003.
[78] F.H. Wilkinson, K. Park, M.L. Atchison, Polycomb recruitment to DNA in vivo by the YY1 REPO domain, Proc. Natl. Acad. Sci. 103 (2006) 19296–19301, https://doi.org/10.1073/pnas.0603564103.
[79] Z. Gao, M. Wang, A. Smith, J. Boyes, YY1 binding to regulatory elements that lack enhancer activity promotes locus folding and gene activation, J. Mol. Biol. 435 (2023) 168315, https://doi.org/10.1016/j.jmb.2023.168315.
[80] Z. Zhang, F. Li, J. Zhao, C. Zheng, CapsNetYY1: identifying YY1-mediated chromatin loops based on a capsule network architecture, BMC Genomics 24 (2023) 448, https://doi.org/10.1186/s12864-023-09217-4.
[81] G.R. Lee, Role of YY1 in long-range chromosomal interactions regulating Th2 cytokine expression, Transcription 5 (2014) e27976, https://doi.org/10.4161/trns.27976.
[82] A.A. Perreault, J.D. Brown, B.J. Venters, Erythropoietin regulates transcription and YY1 dynamics in a pre-established chromatin architecture, IScience 23 (2020) 101583, https://doi.org/10.1016/j.isci.2020.101583.
[83] Y. Tan, D. Ye, C. Qian, J. Shan, J. Li, Yin yang 1: a potential regulator of immune related diseases and cancer immunity, Biochim. Biophys. Acta Rev. Cancer 1880 (2025) 189389, https://doi.org/10.1016/j.bbcan.2025.189389.
[84] N. Misra, M. Damara, T. Ye, P. Chambon, The circadian demethylation of a unique intronic deoxymethylCpG-rich island boosts the transcription of its cognate circadian clock output gene, Proc. Natl. Acad. Sci. 120 (2023), https://doi.org/10.1073/pnas.2214062120.
[85] W. Jiang, S. Zhao, J. Shen, L. Guo, Y. Sun, Y. Zhu, Z. Ma, X. Zhang, Y. Hu, W. Xiao, K. Li, S. Li, L. Zhou, L. Huang, Z. Lu, Y. Feng, J. Xiao, E.E. Zhang, L. Yang, R. Wan, The MiR-135b–BMAL1–YY1 loop disturbs pancreatic clockwork to promote tumourigenesis and chemoresistance, Cell Death Dis. 9 (2018) 149, https://doi.org/10.1038/s41419-017-0233-y.
[86] El B. Affar, F. Gay, Y. Shi, H. Liu, M. Huarte, S. Wu, T. Collins, E. Li, Essential dosage-dependent functions of the transcription factor yin yang 1 in late embryonic development and cell cycle progression, Mol. Cell. Biol. 26 (2006) 3565–3581, https://doi.org/10.1128/MCB.26.9.3565-3581.2006.
[87] J. Kim, J. Do Kim, In vivo YY1 knockdown effects on genomic imprinting, Hum. Mol. Genet. 17 (2008) 391–401, https://doi.org/10.1093/hmg/ddm316.
[88] M.C. Trask, K.D. Tremblay, J. Mager, Yin-Yang1 is required for epithelial-to-mesenchymal transition and regulation of nodal signaling during mammalian gastrulation, Dev. Biol. 368 (2012) 273–282, https://doi.org/10.1016/j.ydbio.2012.05.031.
[89] S. Rhee, M.-I. Guerrero-Zayas, M.C. Wallingford, P. Ortiz-Pineda, J. Mager, K. D. Tremblay, Visceral endoderm expression of Yin-Yang1 (YY1) is required for VEGFA maintenance and yolk sac development, PLoS One 8 (2013) e58828, https://doi.org/10.1371/journal.pone.0058828.
[90] S. Zhang, J.Y. Kim, S. Xu, H. Liu, M. Yin, M. Koroleva, J. Guo, X. Pei, Z.G. Jin, Endothelial-specific YY1 governs sprouting angiogenesis through directly interacting with RBPJ, Proc. Natl. Acad. Sci. 117 (2020) 4792–4801, https://doi.org/10.1073/pnas.1916198117.
[91] I. Beketaev, Y. Zhang, E.Y. Kim, W. Yu, L. Qian, J. Wang, Critical role of YY1 in cardiac morphogenesis, Dev. Dyn. 244 (2015) 669–680, https://doi.org/10.1002/dvdy.24263.
[92] A.O. Perekatt, M.J. Valdez, M. Davila, A. Hoffman, E.M. Bonder, N. Gao, M. P. Verzi, YY1 is indispensable for Lgr5+ intestinal stem cell renewal, Proc. Natl. Acad. Sci. USA 111 (2014) 7695–7700, https://doi.org/10.1073/pnas.1400128111.
[93] C. Qiu, Y. Lu, S. Wu, W. Guo, J. Ni, J. Song, Z. Liu, X. Chang, K. Wang, P. Sun, Q. Zhang, S. Yang, K. Li, Blocking adipocyte YY1 decouples thermogenesis from beneficial metabolism by promoting spermidine production, Diabetes 74 (2025) 295–307, https://doi.org/10.2337/db24-0501.
[94] D. Song, Q. Yang, X. Jiang, A. Shan, J. Nan, Y. Lei, H. Ji, W. Di, T. Yang, T. Wang, W. Wang, G. Ning, Y. Cao, YY1 deficiency in β-cells leads to mitochondrial dysfunction and diabetes in mice, Metabolism 112 (2020) 154353, https://doi.org/10.1016/j.metabol.2020.154353.
[95] S.M. Blättler, F. Verdeguer, M. Liesa, J.T. Cunningham, R.O. Vogel, H. Chim, H. Liu, K. Romanino, O.S. Shirihai, F. Vazquez, M.A. Rüegg, Y. Shi, P. Puigserver, Defective mitochondrial morphology and bioenergetic function in mice lacking the transcription factor Yin Yang 1 in skeletal muscle, Mol. Cell. Biol. 32 (2012) 3333–3346, https://doi.org/10.1128/MCB.00337-12.
[96] S.M. Blättler, J.T. Cunningham, F. Verdeguer, H. Chim, W. Haas, H. Liu, K. Romanino, M.A. Rüegg, S.P. Gygi, Y. Shi, P. Puigserver, Yin Yang 1 deficiency in skeletal muscle protects against rapamycin-induced diabetic-like symptoms through activation of insulin/IGF signaling, Cell Metab. 15 (2012) 505–517, https://doi.org/10.1016/j.cmet.2012.03.008.
[97] Z. Lu, C.C. Hong, G. Kong, A.L.F.V. Assumpção, I.M. Ong, E.H. Bresnick, J. Zhang, X. Pan, Polycomb group protein YY1 is an essential regulator of hematopoietic stem cell quiescence, Cell Rep. 22 (2018) 1545–1559, https://doi.org/10.1016/j.celrep.2018.01.026.
[98] S. Banerjee, S. Sanyal, S. Hodawadekar, S. Naiyer, N. Bano, A. Banerjee, J. Rhoades, D. Dong, D. Allman, M.L. Atchison, YY1 knockout in pro-B cells impairs lineage commitment, enabling unusual hematopoietic lineage plasticity, Genes Dev. 38 (2024) 887–914, https://doi.org/10.1101/gad.351734.124.
[99] H. Liu, M. Schmidt-Supprian, Y. Shi, E. Hobeika, N. Barteneva, H. Jumaa, R. Pelanda, M. Reth, J. Skok, K. Rajewsky, Y. Shi, Yin Yang 1 is a critical regulator of B-cell development, Genes Dev. 21 (2007) 1179–1189, https://doi.org/10.1101/gad.1529307.
[100] A. Banerjee, V. Sindhava, R. Vuyyuru, V. Jha, S. Hodewadekar, T. Manser, M. L. Atchison, YY1 is required for germinal center B cell development, PLoS One 11 (2016) e0155311, https://doi.org/10.1371/journal.pone.0155311.
[101] X. Pan, M. Papasani, Y. Hao, M. Calamito, F. Wei, W.J. Quinn III, A. Basu, J. Wang, S. Hodawadekar, K. Zaprazna, H. Liu, Y. Shi, D. Allman, M. Cancro, M. L. Atchison, YY1 controls Igκ repertoire and B-cell development, and localizes with condensin on the Igκ locus, EMBO J. 32 (2013) 1168–1182, https://doi.org/10.1038/emboj.2013.66.
[102] K. Zaprazna, M.L. Atchison, YY1 controls immunoglobulin class switch recombination and nuclear activation-induced deaminase levels, Mol. Cell. Biol. 32 (2012) 1542–1554, https://doi.org/10.1128/MCB.05989-11.
[103] K. Zaprazna, A. Basu, N. Tom, V. Jha, S. Hodawadekar, L. Radova, J. Malcikova, B. Tichy, S. Pospisilova, M.L. Atchison, Transcription factor YY1 can control AID-mediated mutagenesis in mice, Eur. J. Immunol. 48 (2018) 273–282, https://doi.org/10.1002/eji.201747065.
[104] S. Nandi, G. Liang, V. Sindhava, R. Angireddy, A. Basu, S. Banerjee, S. Hodawadekar, Y. Zhang, N.G. Avadhani, R. Sen, M.L. Atchison, YY1 control of mitochondrial-related genes does not account for regulation of immunoglobulin class switch recombination in mice, Eur. J. Immunol. 50 (2020) 822–838, https://doi.org/10.1002/eji.201948385.
[105] L. Chen, D.P. Foreman, D.B. Sant'Angelo, M.S. Krangel, Yin Yang 1 promotes Thymocyte survival by downregulating p53, J. Immunol. 196 (2016) 2572–2582, https://doi.org/10.4049/jimmunol.1501916.
[106] A.L.F.V. Assumpção, G. Fu, D.K. Singh, Z. Lu, A.M. Kuehnl, R. Welch, I.M. Ong, R. Wen, X. Pan, A lineage-specific requirement for YY1 polycomb group protein function in early T cell development, Development 148 (2021), https://doi.org/10.1242/dev.197319.
[107] X. Ou, J. Huo, Y. Huang, Y.-F. Li, S. Xu, K.-P. Lam, Transcription factor YY1 is essential for iNKT cell development, Cell. Mol. Immunol. 16 (2019) 547–556, https://doi.org/10.1038/s41423-018-0002-6.
[108] P.W. Darcy, K. Jin, L. Osorio, L.K. Denzin, D.B. Sant'Angelo, Coexpression of YY1 is required to elaborate the effector functions controlled by PLZF in NKT cells, J. Immunol. 203 (2019) 627–638, https://doi.org/10.4049/jimmunol.1900055.
[109] J. Kwon, S.-Y. Lee, H.-B. Seo, Y.-M. Moon, J.-G. Ryu, K.-A. Jung, J.-Y. Jhun, J.-S. Park, S.-S. Hwang, J.-M. Kim, G.R. Lee, S.-H. Park, M.-L. Cho, YinYang1 deficiency ameliorates joint inflammation in a murine model of rheumatoid arthritis by modulating Th17 cell activation, Immunol. Lett. 197 (2018) 63–69, https://doi.org/10.1016/j.imlet.2018.03.003.
[110] W. Li, S. Chen, J. Lu, W. Mao, S. Zheng, M. Zhang, T. Wu, Y. Chen, K. Lu, C. Chu, C. Shu, Y. Hou, X. Yang, N. Shi, Z. Chen, L. Zhang, L. Zhang, R. Na, M. Chen, S. Ju, D. Zhang, Y. Ma, B. Xu, YY1 enhances HIF-1α stability in tumor-associated macrophages to suppress anti-tumor immunity of prostate cancer in mice, Nat. Commun. 16 (2025) 6261, https://doi.org/10.1038/s41467-025-61560-0.
[111] Y. He, J. Dupree, J. Wang, J. Sandoval, J. Li, H. Liu, Y. Shi, K.A. Nave, P. Casaccia-Bonnefil, The transcription factor Yin Yang 1 is essential for oligodendrocyte progenitor differentiation, Neuron 55 (2007) 217–230, https://doi.org/10.1016/j.neuron.2007.06.029.
[112] Y. He, J.Y. Kim, J. Dupree, A. Tewari, C. Melendez-Vasquez, J. Svaren, P. Casaccia, Yy1 as a molecular link between neuregulin and transcriptional modulation of peripheral myelination, Nat. Neurosci. 13 (2010) 1472–1480, https://doi.org/10.1038/nn.2686.
[113] X. Dong, K.M. Kwan, Yin Yang 1 is critical for mid-hindbrain neuroepithelium development and involved in cerebellar agenesis, Mol. Brain 13 (2020) 104, https://doi.org/10.1186/s13041-020-00643-z.
[114] L. Zurkirchen, S. Varum, S. Giger, A. Klug, J. Häusel, R. Bossart, M. Zemke, C. Cantù, Z.K. Atak, N. Zamboni, K. Basler, L. Sommer, Yin Yang 1 sustains biosynthetic demands during brain development in a stage-specific manner, Nat. Commun. 10 (2019) 2192, https://doi.org/10.1038/s41467-019-09823-5.
[115] E. Pajarillo, J. Johnson, A. Rizor, I. Nyarko-Danquah, G. Adinew, J. Bornhorst, M. Stiboller, T. Schwerdtle, D.-S. Son, M. Aschner, E. Lee, Astrocyte-specific deletion of the transcription factor Yin Yang 1 in murine substantia nigra mitigates manganese-induced dopaminergic neurotoxicity, J. Biol. Chem. 295 (2020) 15662–15676, https://doi.org/10.1074/jbc.RA120.015552.
[116] E. Pajarillo, I. Nyarko-Danquah, A. Digman, C. Vied, D. Son, J. Lee, M. Aschner, E. Lee, Astrocytic Yin Yang 1 is critical for murine brain development and protection against apoptosis, oxidative stress, and inflammation, Glia 71 (2023) 450–466, https://doi.org/10.1002/glia.24286.
[117] K. Mockenhaupt, M. Zarei-Kheirabadi, A.K. Gonsiewski, A. Hariprashad, L. Dain, J. Verheijen, S.K. Singh, T. Kordula, Defective astrocyte maturation drives cerebellar neuroinflammation and degeneration, FASEB J. 39 (2025), https://doi.org/10.1096/fj.202501225RR.
[118] D.Y. Kwon, B. Xu, P. Hu, Y.-T. Zhao, J.A. Beagan, J.H. Nofziger, Y. Cui, J. E. Phillips-Cremins, J.A. Blendy, H. Wu, Z. Zhou, Neuronal Yin Yang1 in the prefrontal cortex regulates transcriptional and behavioral responses to chronic stress in mice, Nat. Commun. 13 (2022) 55, https://doi.org/10.1038/s41467-021-27571-3.
[119] J. Li, J.S. Song, R.J.A. Bell, T.-N.T. Tran, R. Haq, H. Liu, K.T. Love, R. Langer, D. G. Anderson, L. Larue, D.E. Fisher, YY1 regulates melanocyte development and function by cooperating with MITF, PLoS Genet. 8 (2012) e1002688, https://doi.org/10.1371/journal.pgen.1002688.
[120] S. Varum, A. Baggiolini, L. Zurkirchen, Z.K. Atak, C. Cantù, E. Marzorati, R. Bossart, J. Wouters, J. Häusel, E. Tuncer, D. Zingg, D. Veen, N. John, M. Balz, M.P. Levesque, K. Basler, S. Aerts, N. Zamboni, R. Dummer, L. Sommer, Yin Yang 1 orchestrates a metabolic program required for both neural crest development and melanoma formation, Cell Stem Cell 24 (2019), https://doi.org/10.1016/j.stem.2019.03.011, 637–653.e9.

[121] H. Liu, Y. Qiu, X. Pei, R. Chitteti, R. Steiner, S. Zhang, Z.G. Jin, Endothelial specific YY1 deletion restricts tumor angiogenesis and tumor growth, Sci. Rep. 10 (2020) 20493, https://doi.org/10.1038/s41598-020-77568-z.
[122] G.J. Griffith, M.C. Trask, J. Hiller, M. Walentuk, J.B. Pawlak, K.D. Tremblay, J. Mager, Yin-Yang1 is required in the mammalian oocyte for follicle expansion, Biol. Reprod. 84 (2011) 654–663, https://doi.org/10.1095/biolreprod.110.087213.
[123] S. Wu, Y.-C. Hu, H. Liu, Y. Shi, Loss of YY1 impacts the heterochromatic state and meiotic double-strand breaks during mouse spermatogenesis, Mol. Cell. Biol. 29 (2009) 6245–6256, https://doi.org/10.1128/MCB.00679-09.
[124] N. Agarwal, D. Theodorescu, The role of transcription factor YY1 in the biology of cancer, Crit. Rev. Oncog. 22 (2017) 13–21, https://doi.org/10.1615/CritRevOncog.2017021071.
[125] A. Dillen, I. Bui, M. Jung, S. Agioti, A. Zaravinos, B. Bonavida, Regulation of PD-L1 expression by YY1 in Cancer: therapeutic efficacy of targeting YY1, Cancers (Basel) 16 (2024) 1237, https://doi.org/10.3390/cancers16061237.
[126] Z. Li, X. Jia, I.T.S. Meliala, Y. Li, V. Kasim, Yin Yang 1 (YY1) as a central node in drug resistance pathways: potential for combination strategies in cancer therapy, Biomolecules 15 (2025) 1069, https://doi.org/10.3390/biom15081069.
[127] W. Xia, Y. Li, Z. Wu, Y. Wang, N. Xing, W. Yang, S. Wu, Transcription factor YY1 mediates epithelial–mesenchymal transition through the TGFβ signaling pathway in bladder cancer, Med. Oncol. 37 (2020) 93, https://doi.org/10.1007/s12032-020-01414-5.
[128] G. Zhang, W. Wei, S. Li, J. Yang, Transcription factor yin-Yang 1 augments nucleoporin 93 oncogene activity and modulates bladder cancer malignancy, Toxicol. in Vitro 99 (2024) 105875, https://doi.org/10.1016/j.tiv.2024.105875.
[129] M. Wan, W. Huang, T.E. Kute, L.D. Miller, Q. Zhang, H. Hatcher, J. Wang, D. B. Stovall, G.B. Russell, P.D. Cao, Z. Deng, W. Wang, M. Lei, S.V. Torti, S. A. Akman, G. Sui, Yin Yang 1 plays an essential role in breast cancer and negatively regulates p27, Am. J. Pathol. 180 (2012) 2120–2133, https://doi.org/10.1016/j.ajpath.2012.01.037.
[130] J. Xu, Y. Zhou, S. He, Y. Wang, J. Ma, C. Li, Z. Liu, X. Zhou, Activation of the YY1-UGT2B7 axis promotes mammary estrogen homeostasis dysregulation and exacerbates breast tumor metastasis, Drug Metab. Dispos. 52 (2024) 408–421, https://doi.org/10.1124/dmd.124.001640.
[131] C.D. Cha, S.H. Son, C.G. Kim, H. Park, M.S. Chung, Prognostic implication of YY1 and CP2c expression in patients with primary breast cancer, Cancers (Basel) 15 (2023) 3495, https://doi.org/10.3390/cancers15133495.
[132] C. Zhang, S. Chen, W. Wang, Y. Gao, YY1 regulates the proliferation and invasion of triple-negative breast cancer via activating PLAUR, Funct. Integr. Genom. 23 (2023) 269, https://doi.org/10.1007/s10142-023-01193-y.
[133] A. Warowicka, J. Broniarczyk, M. Węglewska, W. Kwaśniewski, A. Goździcka-Józefiak, Dual role of YY1 in HPV life cycle and cervical cancer development, Int. J. Mol. Sci. 23 (2022) 3453, https://doi.org/10.3390/ijms23073453.
[134] J. Wibisono, M.G. Wibisono, M.H. Wibisono, MO52-2 YinYang 1 (YY1) and P53 gene expression analysis in cervical cancer and its relationship with cancer staging, Ann. Oncol. 35 (2024) S1357, https://doi.org/10.1016/j.annonc.2024.07.612.
[135] W. Wang, Z. Yue, Z. Tian, Y. Xie, J. Zhang, Y. She, B. Yang, Y. Ye, Y. Yang, Expression of Yin Yang 1 in cervical cancer and its correlation with E-cadherin expression and HPV16 E6, PLoS One 13 (2018) e0193340, https://doi.org/10.1371/journal.pone.0193340.
[136] Z. Shao, W. Yang, X. Meng, M. Li, P. Hou, Z. Li, S. Chu, J. Zheng, J. Bai, The role of transcription factor Yin Yang-1 in colorectal cancer, Cancer Med. 12 (2023) 11177–11190, https://doi.org/10.1002/cam4.5745.
[137] L. Wu, Z. Zhou, Y. Yu, C. Cheng, S. Zhou, Y. Yan, B. Yu, Y. Zhang, Z. Liu, Phosphorylation-dependent deubiquitinase OTUD3 regulates YY1 stability and promotes colorectal cancer progression, Cell Death Dis. 15 (2024) 137, https://doi.org/10.1038/s41419-024-06526-8.
[138] Z.-Y. Shao, W.-D. Yang, H. Qiu, Z.-H. He, M.-R. Lu, Q. Shen, J. Ding, J.-N. Zheng, J. Bai, The role of USP7-YY1 interaction in promoting colorectal cancer growth and metastasis, Cell Death Dis. 15 (2024) 347, https://doi.org/10.1038/s41419-024-06740-4.
[139] A. Lonare, K. Raychaudhuri, S. Shah, G. Madhu, A. Sachdeva, S. Basu, R. Thorat, S. Gupta, S.N. Dalal, 14-3-3σ restricts YY1 to the cytoplasm, promoting therapy resistance, and tumor progression in colorectal cancer, Int. J. Cancer 156 (2025) 623–637, https://doi.org/10.1002/ijc.35176.
[140] C. Luo, X. Chen, Y. Bai, L. Xu, S. Wang, L. Yao, X. Guo, D. Wang, X. Zhong, Upregulation of Yin-Yang-1 associates with proliferation and glutamine metabolism in esophageal carcinoma, Int. J. Genom. 2022 (2022) 1–27, https://doi.org/10.1155/2022/9305081.
[141] D. Bhaskar Rao, P. Panneerpandian, K. Balakrishnan, K. Ganesan, YY1 regulated transcription-based stratification of gastric tumors and identification of potential therapeutic candidates, J. Cell Commun. Signal 15 (2021) 251–267, https://doi.org/10.1007/s12079-021-00608-4.
[142] P. Panneerpandian, H.J. Devanandan, A. Marimuthu, C. Karthikeyan, K. Ganesan, Abacavir induces the transcriptional activity of YY1 and other oncogenic transcription factors in gastric cancer cells, Antivir. Res. 174 (2019) 104695, https://doi.org/10.1016/j.antiviral.2019.104695.
[143] W. Chen, H. Wang, N. Achi, J. Hao, R. Gong, Q. Zhao, Bioinformatics analysis of the expression and prognostic significance of transcription factor YY1 in gastric cancer, Cancer Rep. 8 (2025), https://doi.org/10.1002/cnr2.70181.
[144] J. You, B. Tao, L. Peng, T. Peng, H. He, S. Zeng, J. Han, L. Chen, X. Xia, X. Yang, C. Zhong, Transcription factor YY1 mediates self-renewal of glioblastoma stem cells through regulation of the SENP1/METTL3/MYC axis, Cancer Gene Ther. 30 (2023) 683–693, https://doi.org/10.1038/s41417-022-00580-0.
[145] S. Liang, L. Zhu, F. Yang, H. Dong, Transcription factor YY1-activated GNG5 facilitates glioblastoma cell growth, invasion, stemness and glycolysis through Wnt/β-catenin pathway, Sci. Rep. 14 (2024) 25234, https://doi.org/10.1038/s41598-024-76019-3.
[146] M. Zhang, Y. Zhang, S. Yang, J. Zhou, W. Gao, X. Yang, D. Yang, Z. Tian, Y. Wu, B. Ni, Multifunctional YY1 in liver diseases, Semin. Liver Dis. 37 (2017) 363–376, https://doi.org/10.1055/s-0037-1607451.
[147] Q. Zhu, Z. Yuan, Q. Huo, Q. Lu, Q. Wu, J. Guo, W. Fu, Y. Lu, L. Zhong, W. Shang, D. Cui, S. Li, X. Liu, K. Tu, D. Huang, Q. Xu, X. Hu, YY1 induced USP13 transcriptional activation drives the malignant progression of hepatocellular carcinoma by deubiquitinating WWP1, Cell. Mol. Biol. Lett. 30 (2025) 56, https://doi.org/10.1186/s11658-025-00733-7.
[148] Y. Zhi, Y. Guo, S. Li, X. He, H. Wei, K. Laster, Q. Wu, D. Zhao, J. Xie, S. Ruan, N. R. Lemoine, H. Li, Z. Dong, K. Liu, FBL promotes hepatocellular carcinoma tumorigenesis and progression by recruiting YY1 to enhance CAD gene expression, Cell Death Dis. 16 (2025) 348, https://doi.org/10.1038/s41419-025-07684-z.
[149] S. Vivarelli, L. Falzone, C.M. Grillo, B. Bonavida, C. Crimi, I. La Mantia, M. Libra, Computational analyses of YY1 and its target RKIP reveal their diagnostic and prognostic roles in lung cancer, Cancers (Basel) 14 (2022) 922, https://doi.org/10.3390/cancers14040922.
[150] P. Xu, H. Xiao, Q. Yang, R. Hu, L. Jiang, R. Bi, X. Jiang, L. Wang, J. Mei, F. Ding, J. Huang, The USP21/YY1/SNHG16 axis contributes to tumor proliferation, migration, and invasion of non-small-cell lung cancer, Exp. Mol. Med. 52 (2020) 41–55, https://doi.org/10.1038/s12276-019-0356-6.
[151] X. Huang, W. Zhou, Y. Zhang, Transcription factor YY1 enhances the stemness of lung cancer cells by stabilizing hypoxia factor HIF-1α under a hypoxic microenvironment, Environ. Toxicol. 36 (2021) 114–122, https://doi.org/10.1002/tox.23017.
[152] C.-C. Lin, I.-Y. Kuo, L.-T. Wu, W.-H. Kuan, S.-Y. Liao, J. Jen, Y.-E. Yang, C.-W. Tang, Y.-R. Chen, Y.-C. Wang, Dysregulated Kras/YY1/ZNF322A/Shh transcriptional axis enhances neo-angiogenesis to promote lung cancer progression, Theranostics 10 (2020) 10001–10015, https://doi.org/10.7150/thno.47491.
[153] S. Zhou, P. Li, L. Qin, S. Huang, N. Dang, Transcription factor YY1 contributes to human melanoma cell growth through modulating the p53 signalling pathway, Exp. Dermatol. 31 (2022) 1563–1578, https://doi.org/10.1111/exd.14628.
[154] D. Kwiatkowska, A. Reich, YY1 is a potential key player in the pathogenesis of malignant melanoma, in: YY1 Control Pathog. Drug Resist. Cancer, Elsevier, 2021, pp. 163–169, https://doi.org/10.1016/B978-0-12-821909-6.00009-2.
[155] D. Kwiatkowska, E. Mazur, A. Reich, YY1 is a key player in melanoma immunotherapy/targeted treatment resistance, Front. Oncol. 12 (2022), https://doi.org/10.3389/fonc.2022.856963.
[156] F. de Nigris, L. Zanella, F. Cacciatore, A. De Chiara, F. Fazioli, G. Chiappetta, G. Apice, T. Infante, M. Monaco, R. Rossiello, G. De Rosa, M. Alberghini, C. Napoli, YY1 overexpression is associated with poor prognosis and metastasis-free survival in patients suffering osteosarcoma, BMC Cancer 11 (2011) 472, https://doi.org/10.1186/1471-2407-11-472.
[157] D. Jing, W. Wu, X. Huang, Z. Zhang, X. Chen, F. Huang, J. Liu, Z. Zhang, Z. Shao, F. Pu, Transketolase promotes osteosarcoma progression through the YY1-PAK4 axis, FEBS J. 292 (2025) 1798–1812, https://doi.org/10.1111/febs.17375.
[158] F. de Nigris, R. Rossiello, C. Schiano, C. Arra, S. Williams-Ignarro, A. Barbieri, A. Lanza, A. Balestrieri, M.T. Giuliano, L.J. Ignarro, C. Napoli, Deletion of Yin Yang 1 protein in osteosarcoma cells on cell invasion and CXCR4/angiogenesis and metastasis, Cancer Res. 68 (2008) 1797–1808, https://doi.org/10.1158/0008-5472.CAN-07-5582.
[159] W. Yao, Q. Yan, X. Du, J. Hou, TNK2-AS1 upregulated by YY1 boosts the course of osteosarcoma through targeting miR-4319/WDR1, Cancer Sci. 112 (2021) 893–905, https://doi.org/10.1111/cas.14727.
[160] B. Wu, P. Li, E. Qiu, J. Chen, Metformin alleviates adriamycin resistance of osteosarcoma by declining YY1 to inhibit MDR1 transcriptional activity, BMC Pharmacol. Toxicol. 24 (2023) 50, https://doi.org/10.1186/s40360-023-00685-8.
[161] S. Kaufhold, S. Wottrich, H. Garban, M. Libra, B. Bonavida, Yin Yang 1 (YY1) acting primarily as an oncogene and rarely as a tumor suppressor in distinct hematological malignancies: prognostic and therapeutic implications, Blood 128 (2016) 5122, https://doi.org/10.1182/blood.V128.22.5122.5122.
[162] S. Kaufhold, H. Garban, B. Bonavida, In silico tissue-based expression analysis of YY1 and Cancer stem cell (CSC) transcription factors in hematological malignancies: unraveling new therapeutic targets, Blood 126 (2015) 4814, https://doi.org/10.1182/blood.V126.23.4814.4814.
[163] N.I. Noguera, S. Travaglini, S. Scalea, C. Catalanotto, A. Reale, M. Zampieri, A. Zaza, M.R. Ricciardi, D.F. Angelini, A. Tafuri, T. Ottone, M.T. Voso, G. Zardo, YY1 knockdown relieves the differentiation block and restores apoptosis in AML cells, Cancers (Basel) 15 (2023) 4010, https://doi.org/10.3390/cancers15154010.
[164] T. Shimizu, T. Shindo, H. Ogawa, K. Teranaka, A. Watanabe, A. Takaori-Kondo, Upregulation of YY1 EZH2 and MLH1 as therapeutic targets for adult T-cell leukemia/lymphoma, Cancer Sci. 116 (2025) 2163–2175, https://doi.org/10.1111/cas.70095.
[165] T. Zhao, X. Chen, J. Wu, S. Chen, Y. Gan, C. Liu, X. Ha, Y. Wu, X. Zhou, Y. Wu, X. Wu, YY1-induced USP43 drives ferroptosis suppression by FASN stabilization and subsequent activation of SLC7A11 in ovarian cancer, Cell Death Dis. 16 (2025) 589, https://doi.org/10.1038/s41419-025-07886-5.
[166] S. Qian, W. Wang, M. Li, Transcriptional factor Yin Yang 1 facilitates the stemness of ovarian cancer via suppressing miR-99a activity through enhancing its

deacetylation level, Biomed. Pharmacother. 126 (2020) 110085, https://doi.org/10.1016/j.biopha.2020.110085.
[167] H. Wu, L. Xia, L. Sun, D. Li, X. Liu, H. Song, J. Sheng, K. Wang, Q. Feng, RPL35A drives ovarian cancer progression by promoting the binding of YY1 to CTCF promoter, J. Cell. Mol. Med. 28 (2024), https://doi.org/10.1111/jcmm.18115.
[168] P. Pellakuru, R. Guenter, N. Hariharan, G.P. Nagaraju, Role of YY1 in pancreatic ductal adenocarcinoma: mechanisms and therapeutic perspectives, Biochim. Biophys. Acta Rev. Cancer 1880 (2025) 189415, https://doi.org/10.1016/j.bbcan.2025.189415.
[169] B. Li, J. Wang, J. Liao, M. Wu, X. Yuan, H. Fang, L. Shen, M. Jiang, YY1 promotes pancreatic cancer cell proliferation by enhancing mitochondrial respiration, Cancer Cell Int. 22 (2022) 287, https://doi.org/10.1186/s12935-022-02712-w.
[170] Q. Chen, C. Yang, L. Chen, J.-J. Zhang, W.-L. Ge, H. Yuan, L.-D. Meng, X.-M. Huang, P. Shen, Y. Miao, K.-R. Jiang, YY1 targets tubulin polymerisation-promoting protein to inhibit migration, invasion and angiogenesis in pancreatic cancer via p38/MAPK and PI3K/AKT pathways, Br. J. Cancer 121 (2019) 912–921, https://doi.org/10.1038/s41416-019-0604-5.
[171] Q. Chen, J.J. Zhang, W.L. Ge, L. Chen, H. Yuan, L.D. Meng, X.M. Huang, P. Shen, Y. Miao, K.R. Jiang, YY1 inhibits the migration and invasion of pancreatic ductal adenocarcinoma by downregulating the FER/STAT3/MMP2 signaling pathway, Cancer Lett. 463 (2019) 37–49, https://doi.org/10.1016/j.canlet.2019.07.019.
[172] W. Weng, M. Wang, S. Xie, Y. Long, F. Li, F. Sun, Y. Yu, Z. Li, YY1-C/EBPα-miR34a regulatory circuitry is involved in renal cell carcinoma progression, Oncol. Rep. 31 (2014) 1921–1927, https://doi.org/10.3892/or.2014.3005.
[173] W. Li, K. Ye, X. Li, X. Liu, M. Peng, F. Chen, W. Xiong, Y. Wang, L. Zhu, YTHDC1 is downregulated by the YY1/HDAC2 complex and controls the sensitivity of ccRCC to sunitinib by targeting the ANXA1-MAPK pathway, J. Exp. Clin. Cancer Res. 41 (2022) 250, https://doi.org/10.1186/s13046-022-02460-9.
[174] S. Li, Z. Zhang, H. Peng, X. Xiao, YY1-induced up-regulation of FOXE1 is negatively regulated by miR-129-5p and contributes to the progression of papillary thyroid microcarcinoma, Pathol. Res. Pract. 221 (2021) 153337, https://doi.org/10.1016/j.prp.2020.153337.
[175] X. Fu, F. Ji, Q. He, X. Qiu, A systematic Pan-Cancer analysis of YY1 aberrations and their relationship with clinical outcome, tumor microenvironment, and therapeutic targets, J Immunol Res 2022 (2022) 1–23, https://doi.org/10.1155/2022/5826741.
[176] M. Li, Y. Duan, J. Wei, S. Chen, C. Xue, L. Zheng, H. Deng, S. Fan, W. Xiong, G. Li, M. Tan, F. Tang, K. She, M. Zhou, Yin Yang 1 suppresses tumor invasion and metastasis in nasopharyngeal carcinoma by negatively regulating eIF4E transcriptional activity and expression, Am. J. Cancer Res. 13 (2023) 3763–3780. http://www.ncbi.nlm.nih.gov/pubmed/37693135.
[177] M. Li, Y. Liu, Y. Wei, C. Wu, H. Meng, W. Niu, Y. Zhou, H. Wang, Q. Wen, S. Fan, Z. Li, X.X. Li, J. Zhou, K. Cao, W. Xiong, Z. Zeng, Y. Qiu, G. Li, M. Zhou, X.X. Li, Y. Qiu, G. Li, M. Zhou, Zinc-finger protein YY1 suppresses tumor growth of human nasopharyngeal carcinoma by inactivating c-Myc-mediated, J. Biol. Chem. 294 (2019) 6172–6187, https://doi.org/10.1074/jbc.RA118.006281.
[178] W. Tang, W. Zhou, L. Xiang, X. Wu, P. Zhang, J.J.J.J. Wang, G. Liu, W. Zhang, Y. Peng, X. Huang, J. Cai, Y. Bai, L. Bai, W. Zhu, H. Gu, J. Xiong, C. Ye, A. Li, S. Liu, J.J.J.J. Wang, The p300/YY1/miR-500a-5p/HDAC2 signalling axis regulates cell proliferation in human colorectal cancer, Nat. Commun. 10 (2019) 663, https://doi.org/10.1038/s41467-018-08225-3.
[179] M. Li, M. Li, Y. Xia, G. Li, X. Su, D. Wang, J. Ye, F. Lu, T. Sun, C. Ji, HDAC1/3-dependent moderate liquid–liquid phase separation of YY1 promotes METTL3 expression and AML cell proliferation, Cell Death Dis. 13 (2022) 992, https://doi.org/10.1038/s41419-022-05435-y.
[180] R. Hosea, S. Hillary, S. Wu, V. Kasim, Targeting transcription factor YY1 for Cancer treatment: current strategies and future directions, Cancers (Basel) 15 (2023) 3506, https://doi.org/10.3390/cancers15133506.
[181] Z.S. Ameen, A.S. Mubarak, M. Hamad, R. Hamoudi, S. Jemimah, D.U. Ozsahin, M. Hamad, Incorporating time as a third dimension in transcriptomic analysis using machine learning and explainable AI, Comput. Biol. Chem. 117 (2025) 108432, https://doi.org/10.1016/j.compbiolchem.2025.108432.
[182] G. Yoon, J. Roh, W. Jang, W. Kim, Circadian genes and non-coding RNAs: interactions and implications in cancer, Anim. Cells Syst. (Seoul). 29 (2025) 135–148, https://doi.org/10.1080/19768354.2025.2459622.
[183] A. Thakur, R. Kishore, Neurobiology of the circadian clock and its role in cardiovascular disease: mechanisms, biomarkers, and chronotherapy, Neurobiol. Sleep Circadian Rhythm. 19 (2025) 100131, https://doi.org/10.1016/j.nbscr.2025.100131.
[184] F. Fagiani, D. Di Marino, A. Romagnoli, C. Travelli, D. Voltan, L. Di Cesare Mannelli, M. Racchi, S. Govoni, C. Lanni, Molecular regulations of circadian rhythm and implications for physiology and diseases, Signal Transduct. Target. Ther. 7 (2022) 41, https://doi.org/10.1038/s41392-022-00899-y.
[185] A.H. Cheng, H.-Y.M. Cheng, Genesis of the master circadian pacemaker in mice, Front. Neurosci. 15 (2021), https://doi.org/10.3389/fnins.2021.659974.
[186] C. Harding, D.A. Bechtold, T.M. Brown, Suprachiasmatic nucleus-dependent and independent outputs driving rhythmic activity in hypothalamic and thalamic neurons, BMC Biol. 18 (2020) 134, https://doi.org/10.1186/s12915-020-00871-8.
[187] A.-M. Finger, A. Kramer, Peripheral clocks tick independently of their master, Genes Dev. 35 (2021) 304–306, https://doi.org/10.1101/gad.348305.121.
[188] Y. Huang, Y. Zhang, R. Braun, A minimal model of peripheral clocks reveals differential circadian re-entrainment in aging, Chaos An Interdiscip. J. Nonlinear Sci. 33 (2023), https://doi.org/10.1063/5.0157524.
[189] J. Bautista, S. Ojeda-Mosquera, D. Ordóñez-Lozada, A. López-Cortés, Peripheral clocks and systemic zeitgeber interactions: from molecular mechanisms to circadian precision medicine, Front. Endocrinol. (Lausanne) 16 (2025), https://doi.org/10.3389/fendo.2025.1606242.
[190] S. Vivarelli, A. Marconi, S. Matera, L. Falzone, C. Fenga, Night shift work, circadian disruption, and gut microbiome: implications for human health, Crit. Rev. Oncog. (2025), https://doi.org/10.1615/CritRevOncog.2025059579.
[191] C.M. Greco, P. Sassone–Corsi, Circadian blueprint of metabolic pathways in the brain, Nat. Rev. Neurosci. 20 (2019) 71–82, https://doi.org/10.1038/s41583-018-0096-y.
[192] Y. Zeng, Z. Guo, M. Wu, F. Chen, L. Chen, Circadian rhythm regulates the function of immune cells and participates in the development of tumors, Cell Death Discov. 10 (2024) 199, https://doi.org/10.1038/s41420-024-01960-1.
[193] E. Yildirim, R. Curtis, D. Hwangbo, Roles of peripheral clocks: lessons from the fly, FEBS Lett. 596 (2022) 263–293, https://doi.org/10.1002/1873-3468.14251.
[194] R.W. Logan, C.A. McClung, Rhythms of life: circadian disruption and brain disorders across the lifespan, Nat. Rev. Neurosci. 20 (2019) 49–65, https://doi.org/10.1038/s41583-018-0088-y.
[195] C.J. Morris, T.E. Purvis, J. Mistretta, F.A.J.L. Scheer, Effects of the internal circadian system and circadian misalignment on glucose tolerance in chronic shift workers, J. Clin. Endocrinol. Metab. 101 (2016) 1066–1074, https://doi.org/10.1210/jc.2015-3924.
[196] J. Lu, K. Jin, J. Jiao, R. Liu, T. Mou, B. Chen, Z. Zhang, C. Jiang, H. Zhao, Z. Wang, R. Zhou, M. Huang, YY1 (Yin-Yang 1), a transcription factor regulating systemic inflammation, is involved in cognitive impairment of depression, Psychiatry Clin. Neurosci. 77 (2023) 149–159, https://doi.org/10.1111/pcn.13510.
[197] C.M. Bartman, T. Eckle, Circadian-hypoxia link and its potential for treatment of cardiovascular disease, Curr. Pharm. Des. 25 (2019) 1075–1090, https://doi.org/10.2174/1381612825666190516081612.
[198] F.L. Martins Peçanha, R. Jaafar, J.P. Werneck-de-Castro, C.-C. Apostolopolou, A. Bhushan, E. Bernal-Mizrachi, The transcription factor YY1 is essential for normal DNA repair and cell cycle in human and mouse β-cells, Diabetes 71 (2022) 1694–1705, https://doi.org/10.2337/db21-0908.
[199] G. Pan, K. Diamanti, M. Cavalli, A. Lara Gutiérrez, J. Komorowski, C. Wadelius, Multifaceted regulation of hepatic lipid metabolism by YY1, Life Sci. Alliance. 4 (2021) e202000928, https://doi.org/10.26508/lsa.202000928.
[200] J. Wang, X. Wu, C. Wei, X. Huang, Q. Ma, X. Huang, F. Faiola, D. Guallar, M. Fidalgo, T. Huang, D. Peng, L. Chen, H. Yu, X. Li, J. Sun, X. Liu, X. Cai, X. Chen, L. Wang, J. Ren, J. Wang, J. Ding, YY1 positively regulates transcription by targeting promoters and super-enhancers through the BAF complex in embryonic stem cells, Stem Cell Rep. 10 (2018) 1324–1339, https://doi.org/10.1016/j.stemcr.2018.02.004.
[201] P.O. Westermark, H. Herzel, Mechanism for 12 Hr rhythm generation by the circadian clock, Cell Rep. 3 (2013) 1228–1238, https://doi.org/10.1016/j.celrep.2013.03.013.
[202] N. Misra, M. Damara, P. Chambon, The HP1α protein is mandatory to repress the circadian clock and its output genes during the 12 h period of transcriptional repression, Proc. Natl. Acad. Sci. 120 (2023), https://doi.org/10.1073/pnas.2213075120.