The biological implications of Yin Yang 1 in the hallmarks of cancer

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Abstract

Tumorigenesis is a multistep process characterized by the acquisition of genetic and epigenetic alterations. During the course of malignancy development, tumor cells acquire several features that allow them to survive and adapt to the stress-related conditions of the tumor microenvironment. These properties, which are known as hallmarks of cancer, include uncontrolled cell proliferation, metabolic reprogramming, tumor angiogenesis, metastasis, and immune system evasion. Zinc-finger protein Yin Yang 1 (YY1) regulates numerous genes involved in cell death, cell cycle, cellular metabolism, and inflammatory response. YY1 is highly expressed in many cancers, whereby it is associated with cell proliferation, survival, and metabolic reprogramming. Furthermore, recent studies also have demonstrated the important role of YY1-related non-coding RNAs in acquiring cancer-specific characteristics. Therefore, these YY1-related non-coding RNAs are also crucial for YY1-mediated tumorigenesis. Herein, we summarize recent progress with respect to YY1 and its biological implications in the context of hallmarks of cancer.

Key words: Yin Yang 1, hallmarks of cancer, tumorigenesis, transcriptional regulation, post-translational regulation.

Introduction

Yin Yang 1 (YY1) is a zinc-finger protein that belongs to the GLI-Krüppel family. It was first identified from a sequence originally isolated as a repressor of the P5 promoter of adeno-associated virus [1]. In humans, YY1 is encoded by the 23-kb YY1 gene located at the chromosomal locus 14q32, which contains five exons and is translated into a 45-kDa protein with 414 amino acids [1-4]. YY1, which is also known as NF-E1 in humans and DELTA or upstream conserved region-binding protein (UCRBP) in mice, is highly conserved in all vertebrates, as well as in some invertebrates (Figure 1A) [5].

The name YY1 stands for Yin Yang 1 or positive and negative in ancient Chinese philosophy, and is a reflection of the dual function played by the protein in gene regulation. Depending on the context, YY1 can function as a transcriptional activator or as an inhibitor [1, 6]. The dual function of YY1 in regulating gene transcription is due to the presence of an activation domain at the N-terminus, and a repression domain at the C-terminus (Figure 1B) [6]. YY1 might affect the transcriptional activity of approximately 7% of mammalian genes [7]. It traditionally binds to sites with the following consensus: GCCATnTT, CnCCATnTT, GnCGACATnTT, CCGCCATnTT,
taCGCCATTTg, CGCCATTTT, and GCCATTTT. While 5′-CCAT-3′ and 5′-ACAT-3′ are both conventional YY1 binding sites, YY1 appears to have higher affinity for 5′-CCAT-3′ [8, 9, 10].

YY1-mediated transcriptional repression can occur by direct and competitive binding between YY1 and an activator [11], interference with activator function [12] or by recruitment of a co-repressor involved in chromatin remodeling, such as the Ring1 and YY1 binding protein (RYBP) [13-15]. Examples of genes that are regulated by YY1 direct repression are death receptor 5 (DR5) [16] and peroxisome proliferator-activated receptor gamma coactivator-1β (PGC-1β) [17]. Genes that are regulated by co-repression are adenomatous polyposis coli (APC) [18] and CXC chemokine receptor type 4 (CXCR4) [19]. YY1 participates in transcriptional activation also via direct promoter binding and interaction with a general transcription factor involved in the formation of a complex with RNA polymerase II [20-22], by masking-unmasking of repression domain [6], or by recruitment of or acting as co-activators [23, 24]. Genes that are directly regulated by YY1 include epidermal growth factor receptor (EGFR) [25], glucose
transporter 3 (GLUT3) [21], and glucose-6-phosphate dehydrogenase (G6PD) [20]. Genes that are regulated by co-activation of YY1 and other transcription factors include erb-b2 receptor tyrosine kinase 2 (ERBB2) [26], vascular endothelial growth factor B (VEGFB) [27], and p73 [28]. Besides its role as a transcription factor, YY1 can regulate gene expression at the post-transcriptional stage by controlling the stability and activity of its target genes, including p53 and hypoxia-inducible factor 1-α (HIF-1α) [29, 30]. YY1 is also involved in epigenetic regulation of CDKN2A, DTDST, and ST6GalNAc6 through chromatin modification by polycomb-group proteins [31, 32], as well as in the post-translational epigenetic modification of histones through recruitment of histone deacetylases (HDACs) [33]. Furthermore, it is involved in epigenetic repression of human papilloma virus type 18, whereby it acts as an architectural protein that mediates the physical enhancer-promoter interaction through a chromatin looping-based mechanism [34, 35]. The ability of YY1 in forming protein-protein interaction with epigenetic modifiers such as EZH2, p300, and PRMT7 [36], is crucial in extending its capacity in regulating gene expression. The direct regulation of YY1 on various genes and its mechanism are shown in Table 1.

Considering that YY1 targets a wide range of genes, it is likely to exert critical roles in various biological and physiological functions, including development, proliferation and differentiation, DNA repair and recruitment, epigenetics, genetic imprinting, and oncogenic activity of the cell [37, 38]. YY1 mediates translational repression in Drosophila embryos during development [39], and is essential for organogenesis of intestinal villi and lung morphogenesis in mouse [40, 41]. In genetic imprinting, the difference in sequence motifs allows YY1 to bind both DNA and RNA, and thus act as an adaptor between regulatory RNA and chromatin targets in X-chromosome inactivation [42]. It is also involved in neointima formation through regulating p21WAF1/CIP1-cdk4-Cyclin D1 assembly [43]. Furthermore, homozygous deletion of YY1 resulted in embryonic lethality [44]; while overexpression of YY1 resulted in severe physiological consequences, such as cardiac hypertrophy and heart failure in transgenic hypertrophic cardiomyopathy (HCM) mice [45, 46].

Tumorigenesis subverts multiple characteristics of normal cells, which enables tumor cells to grow and survive without restraint. Tumor cells not only escape stringent cell cycle regulation—which in turn leads to their unlimited proliferation—but can also acquire resistance against apoptosis. To adapt to their microenvironment, which often lacks oxygen and nutrients supply, tumor cells alter their metabolism, and induce aberrant angiogenesis [47]. Critically, tumor cells can alter their characteristics from epithelial to mesenchymal (via epithelial-mesenchymal transition, EMT), and metastasize to other tissues [26]. They can also induce inflammation, as well as immune destruction [48]. YY1 has been shown to be highly expressed in various tumors. While for some tumors the overexpression of YY1 gives a favorable outcome, elevated YY1 expression is associated primarily with poor prognosis (Table 2). Its role in transcriptional as well as post-translational gene regulation is deemed crucial for acquiring tumor cell characteristics (Table 3) and, subsequently, for promoting tumorigenesis [36, 49]. Moreover, YY1 is also closely related to tumor progression, and its expression in various cancers reflects poor prognosis [36, 50, 51]. In this review, we will outline the involvement of YY1 in tumorigenesis, focusing on its role in regulating multiple hallmarks of cancer and the molecular mechanism(s) underlying them.

### YY1 and the hallmarks of cancer

Tumorigenesis is associated with several molecular and biochemical changes that trigger a variety of adaptive mechanisms and the acquisition of several tumor characteristics. These unique traits, which convert a normal cell into a malignant one, are considered the hallmarks of cancer [52, 53]. Over the past decade, studies have shed light on the role of YY1 in the acquisition of various cancer hallmarks in developing neoplasms, which will be detailed in the following sections.

#### Tumor cell proliferation

A stringent, fine-tuned control over proliferation is essential for maintaining the adequate number of cells in an organism. In contrast, a common feature of cellular transformation and tumor progression is escape from proliferative control. Tumor cells unlimited proliferation is supported by sustained proliferative signaling through oncogene activation, evading growth suppressors, and enabling replicative immortality [53]. YY1 controls cell proliferation by activating or repressing specific genes through its transcriptional or post-translational regulatory activity [29, 54]. YY1 activates the promoter of the c-Myc oncogene and increases its activity in fibroblast cells [55]. Moreover, YY1 interacts with protein kinase B (PKB) or AKT and promotes its phosphorylation and conformational change. This event leads to AKT activation by mTOR complex 2 in a phosphoinositide 3-kinase-independent manner and promotes oncogenic signaling [56].

Maintenance of cell homeostasis and proliferation involves interplay between oncogenes...
and tumor suppressors. The latter exert their function by maintaining cellular growth signal homeostasis, which needs to be disrupted by neoplastic cells. Malignant tumors can overcome the effect of tumor suppressor genes, such as retinoblastoma (Rb) and p53, whose task is to induce cell cycle arrest and apoptosis to avoid uncontrollable cell proliferation or proliferation of cells harboring unreparable DNA damage [57]. YY1 contributes to aberrant control of the cell cycle and apoptosis. YY1 overexpression induces progression into S phase by competitive binding to Rb, a nuclear phosphoprotein, and overcoming Rb-induced cell cycle arrest at the G1/S checkpoint [58]. YY1 can negatively regulate p53 expression by facilitating direct binding of p53 to its E3 ligase mouse double minute 2 (MDM2), thereby enhancing p53 ubiquitination and proteasomal degradation, and leading to decreased p53 expression by facilitating direct binding of p53 to its transcriptional factor 1 (E2F1) [28]. On the one hand, YY1 decreases the cell cycle and apoptosis. YY1 overexpression also contributes to cancer cell migration and proliferation of cells harboring unrepairable DNA damage [59]. YY1 overexpression also diminishes p53-dependent apoptosis [30]. YY1 can also positively regulate the p53 homologue p73 by inducing its transcriptional activity in a synergistic manner with E2F transcription factor 1 (E2F1) [28]. On the one hand, YY1 decreases the overall transcription activity of p53 by inhibiting the interaction between p53 and its co-activator p300 [59]. On the other hand, YY1 can maintain p53 transcriptional activity by forming a complex with BRCA2- and CDKN1A-interacting protein (BCCIP). The outcome of p53 transcriptional activity depends on the balance in the YY1/BCCIP/p53 complex, as YY1 inhibits p53RE-mediated p21 transcriptional activation, whereas BCCIP activates it [60].

### Table 1. Genes directly regulated by YY1.

| Gene | Regulation | Mechanism | Ref |
|------|------------|-----------|-----|
| AKT  | Upregulated | Protein stabilization | [56] |
| APC  | Downregulated | Epigenetic repression | [18] |
| Atg5 | Upregulated | Recruitment of / being co-activator | [83] |
| Beclin1 | Downregulated | Recruitment of / being co-activator | [83] |
| Bim  | Downregulated | Recruitment of / being co-repressor | [71] |
| CDKN2A | Downregulated | Epigenetic repression | [31, 64] |
| CDKN3 | Downregulated | Direct repression on promoter region | [11] |
| c-Myc | Uregulated | Direct activation on promoter region | [55] |
| COX2 | Uregulated | Direct activation on promoter region | [117, 118] |
| CXCR4 | Downregulated | Recruitment of / being co-activator | [19] |
| DEK  | Upregulated | Direct activation on promoter region | [100, 101] |
| DR5  | Downregulated | Direct repression on promoter region | [16] |
| DTDST | Downregulated | Epigenetic repression | [31, 32] |
| CDH1 | Downregulated | Epigenetic repression | [104] |
| EGRF | Upregulated | Direct activation on promoter region | [25] |
| ERBB2 | Upregulated | Recruitment of / being co-activator | [26] |
| Fat4 | Downregulated | Direct repression on promoter region | [69] |
| Gadd45α | Downregulated | Direct activation on promoter region | [20] |
| GLUT3 | Upregulated | Direct activation on promoter region | [21] |
| HIF-1α | Upregulated | Protein stabilization | [30] |
| hnRNPM | Downregulated | Direct activation on promoter region | [105] |
| HPV18 | Downregulated | Epigenetic repression | [34, 35] |
| IL6  | Upregulated | Direct activation on promoter region | [120] |
| KLF4 | Upregulated | Direct activation on promoter region | [63] |
| MAP1LC3B | Upregulated | Recruitment of / being co-activator | [83] |
| miR-125a | Downregulated | Recruitment of / being co-repressor | [116] |

### Table 2. YY1 expression in various cancers.

| Cancer types | YY1 expression level | Prognosis | Ref |
|--------------|----------------------|-----------|-----|
| Bladder      | Upregulated          | n/a       | [152] |
| Breast       | Downregulated        | Good      | [154] |
| Cervical     | Uregulated           | n/a       | [155] |
| Colon        | Uregulated           | Poor      | [127] |
| Glioma       | Uregulated           | n/a       | [159] |
| Hodgkin lymphoma | Uregulated | Poor      | [160] |
| Leukemia     | Uregulated           | n/a       | [161] |
| Liver        | Uregulated           | Poor      | [164] |
| Lung         | Uregulated           | Poor      | [163] |
| Melanoma     | Uregulated           | Poor      | [167] |
| Multiple myeloma | Uregulated | Poor      | [72] |
| Nasopharynx  | Downregulated        | Good      | [165] |
| Non-Hodgkin lymphoma | Uregulated | Poor      | [166] |
|                    |                      | n/a       | [167] |
| Non-Small cell lung cancer | Uregulated | Poor      | [168] |
| Osteosarcoma  | Uregulated           | Poor      | [50]  |
| Ovarian      | Uregulated           | n/a       | [169] |
| Pancreatic   | Uregulated           | Good      | [143] |
| Prostate     | Uregulated           | Good      | [170] |
| Renal        | Uregulated           | Poor      | [171] |
| Sarcoma      | Uregulated           | n/a       | [172] |
| Testicular seminoma | Uregulated | Poor      | [50]  |
| Thyroid      | Direct activated     | n/a       | [173] |

**Abbreviations:** n/a: not available

Cancer stem cells (CSCs) are defined as a subpopulation of cells with high self-renewal capability and pluripotency compared to other subpopulations in tumor tissues. CSCs are highly

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associated with metastasis, drug resistance, recurrence, as well as poor prognosis, which underlie the difficulty of completely eradicating tumors [61]. Proteomic tissue-based datasets have demonstrated an association between YY1 expression and CSC markers (Sox2, Oct4, Bmi1, and Nanog) in different tumors [62]. YY1 also directly activates a stem cell marker Krüppel-like factor 4 (KLF4) in non-Hodgkin B-cell lymphoma [63]. A specific association of YY1 with different CSC markers has been observed in different types of cancer and could serve as a potential therapeutic approach to suppress the expression of CSCs-related transcription factors.

One strategy used by tumor cells to maintain the proliferative signal is to avoid cellular senescence. CDKN2A is one of the most studied tumor suppressor genes associated with cellular senescence. CDKN2A encodes p16-INK4a, a cyclin-dependent kinase inhibitor that plays a critical role in cell cycle progression, differentiation, senescence, and apoptosis. YY1 is an epigenetic regulator that forms complexes with HDAC3 and HDAC4. By fine-tuning chromatin modifications, YY1 downregulates CDKN2A promoter activity, resulting in cellular escape from senescence [31, 64]. In addition to cell cycle regulation, YY1 mediates cellular escape from DNA-damage induced senescence [65] by facilitating DNA repair. YY1 forms a complex with INO80 complex ATPase subunit (INO80), an ATP-dependent chromatin remodeling complex essential in homologous recombination [66]. By binding to Holliday junctions, YY1 mediates homologous recombination DNA repair in double-strand breaks [66], which might otherwise lead to DNA damage-induced cell death or senescence.

Together, these studies show the prominent role of YY1 in tumor cell proliferation and reveal the multiple regulatory mechanisms employed by YY1 at transcriptional, post-translational (e.g., protein modification and protein stability), and epigenetic level. Altogether, activation of the proliferative signal, augmented by reduced tumor-suppressive activity, shifts cellular proliferation into overdrive. While reaping the benefits of sustained proliferative signaling requires the cell to be immortal, it is still unclear whether alteration of YY1 alone could give rise to tumor cells with replicative immortality, and thus, further investigation is needed.

### Table 3. Biological implications of YY1 on hallmarks of cancer.

| Related Genes | Implications on hallmarks of cancer | Effect | Mechanism | Ref |
|---------------|------------------------------------|--------|-----------|-----|
| CDKN2A        | Tumor cell proliferation           | Cellular escape from senescence     | Downregulates CDKN2A promoter activity | [31] |
| c-Myc         | Tumor cell proliferation           | Increased cell proliferation        | Activates the promoter of c-Myc | [55] |
| AKT           | Tumor cell proliferation           | Increased cell proliferation        | Promotes AKT phosphorylation and conformational change | [56] |
| p21           | Tumor cell proliferation           | Increased cell proliferation        | YY1/BCCIP complex regulates p53RE-mediated transcription of p21 | [60] |
| Rb            | Tumor cell proliferation           | Reduces Rb-induced cell cycle arrest at G1/S checkpoint | Direct competitive binding with Rb | [58] |
| p53           | Tumor cell proliferation           | Increased cell proliferation        | Induces proteosomal degradation of p53 | [29, 59] |
| DR5           | Resisting cell death               | Resistance to TRAIL-induced apoptosis | Negatively regulates DR5 transcription | [68] |
| FAS           | Resisting cell death               | Resistance to Fas-induced apoptosis | Represses FAS expression by binding to its silencer region | [69, 175] |
| NF-κB         | Resisting cell death               | Increased cell proliferation        | YY1-mediated epigenetic silencing of miR-9 leading to increased NF-κB expression | [70] |
| Bim           | Resisting cell death               | Reduced apoptosis                   | YY1 forms complex with RelA and directly represses the activity of Bim promoter | [71] |
| MCT1          | Resisting cell death, metabolic reprogramming | Tumor cell survival under oxidative stress | YY1 is targeted by MCT1 and mediates EGFR/Mes6OD (activation) and p53 (inhibition) gene expression | [76] |
| GLUT3         | Metabolic reprogramming            | Enhances the aerobic glucose metabolism in tumor cells | Activates GLUT3 transcription by direct binding on its promoter in p33-independent manner | [21] |
| G6PD          | Metabolic reprogramming            | Enhances the PPP pathway            | Activates G6PD transcription by direct binding on its promoter in p33-independent manner | [20] |
| VEGF          | Inducing angiogenesis              | Promote neoangiogenesis             | Forming complex with HIF-1α and activates VEGF expression | [27] |
| HIF-1α        | Inducing angiogenesis              | Expression of HIF-1α target genes and promotion of neoangiogenesis | YY1 has physical interaction with HIF-1α and regulates its expression in p53-independent manner. | [30] |
| MMP14         | Activating invasion and metastasis | Promotes metastasis                 | Promotes MMP14 transcription through direct binding on its promoter | [51] |
| CDH1          | Activating invasion and metastasis | Decreased cell-cell junction, induction of EMT | Represses E-cadherin expression by reducing histone trimethylation (H3K4me3) levels through recruitment of PRMT7-HDAC3 complex | [104] |
| INO80         | Genome instability and mutation    | Genome stabilization                | YY1 form complex with INO80 to regulate HDR in tumor cell | [66] |
| IL1R         | Tumor-promoting inflammation      | Induction of inflammatory response  | Interacts with RelB and p50, activating the transcription of IL1 proinflammatory cytokines | [112] |
| PD-L1         | Evading immune destruction         | Resistance to killing by immune cells | Regulates the expression of PD-L1 through various pathways | [120] |

**Abbreviations:** Bim: Bcl-2-interacting mediator of cell death; CDH1: Cadherin-1; CDKN2A: cyclin-dependent kinase inhibitor 2A; DR5: death receptor 5; G6PD: glucose-6-phosphate dehydrogenase; GLUT3: glucose transporter 3; HDR: homologous recombination DNA repair; HIF-1α: hypoxia-inducible factor 1 alpha; IL1R: interleukin 1β; INO80: INO80 complex ATPase subunit; MCT1: T-cell malignancy 1; MMP14: matrix metalloproteinase-14; NF-κB: nuclear factor-κB; PD-L1: programmed death ligand 1; Rb: retinoblastoma; VEGF: vascular endothelial growth factor.
Cell death resistance

Apoptosis is a self-protection mechanism that prevents the proliferation of cells with aberrant gene expression in response to severe, irreparable stress. Evasion from apoptosis, even after DNA damage, genome instability, and oncogene activation, is another important characteristic of malignant transformation. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a death ligand that triggers apoptosis in a p53-independent manner in various human cancer cell lines [67]. YY1 has been shown to mediate the TRAIL-resistant phenotype in a prostate carcinoma cell line by direct binding and inactivation of the promoter of DR5, also known as TRAIL receptor 2 (TRAILR2), and inhibit its transcription. Inhibition of YY1 increases DR5 expression and in turn sensitizes tumor cells to TRAIL-mediated apoptosis [68]. In addition to TRAIL resistance, YY1 induces also resistance to Fas ligand-induced apoptosis by directly repressing the activity of the FAS promoter [69]. Furthermore, YY1 affects the activity of enhancer of zeste homolog 2 (EZH2) in catalyzing histone H3 lysine 27 trimethylation (H3K27me3) and suppressing tumor suppressor miR-9 activity through DNA methylation. The resulting reduced activity of miR-9 by YY1 causes the activation of nuclear factor-κB (NF-κB), which consequently induces resistance to apoptosis and promotes tumor growth [70]. In multiple myeloma cells, YY1 also regulates cell survival by forming complex with RelA and directly repress the promoter of a pro-apoptotic gene, Bcl2-interacting mediator of cell death (Bim) [71], and promotes chemoresistance to cytotoxic chemotherapeutic drug bortezomib [72].

Cellular metabolic stress constitutes another type of cell death trigger that regulates survival. Tumor cells utilize a distinct metabolism, characterized by increased aerobic glycolysis and high levels of oxidative stress, to maintain redox homeostasis [73]. Though a low to moderate level of reactive oxygen species (ROS) benefits tumor metastasis, high ROS levels are lethal [74]. Tumor cells counteract the detrimental effect of oxidative stress by elevating antioxidant defense mechanisms [75]. T-cell malignancy 1 (MCT1) stabilizes YY1 mRNA and promotes its activity, which in turn transactivates EGFR expression and inhibits p53 expression. Enhanced EGFR activity leads to increased expression of manganese-dependent superoxide dismutase (MnSOD), a ROS scavenging enzyme, and benefits tumor development by suppressing excessive ROS in tumor cells [76]. Furthermore, as p53 serves as the transactivator of the ROS-generating enzymes, quinone oxidoreductase and proline oxidase, suppression of p53 might lead to further reduction of excessive ROS in tumor cells [77].

Autophagy is another type of cell death that, like apoptosis, involves a self-destructive process. Autophagic cell death is highly regulated. In tumors with a functional apoptotic pathway, autophagy promotes apoptotic tumor suppression in response to metabolic stress. However, in tumors with apoptosis defects, autophagy alleviates metabolic stress and promotes tumor cell survival [78]. This happens through catabolic degradation of organelles in response to metabolic stress, and results in sufficient nutrient reserves to sustain tumor cell homeostasis in a nutrient-deprived tumor microenvironment [78]. Autophagy has been shown to stimulate apoptosis-induced drug resistance in breast cancer treatment through aurora kinase A (AURKA) inhibition [79], confirming its role in tumorigenesis. During autophagy induction, YY1 co-localizes with transcription factor EB (TFEB) in the nucleus to activate the transcription of autophagy-related genes (MAP1LC3B, Beclin1, and Atg5). YY1 is also known to promote autophagy by stimulating the autophagy regulator SQSTM1 via epigenetic downregulation of its inhibitor miR-372 [80] or by suppressing miR-30a and dysregulating the NF-κB/SNAIL/YY1/RKIP/PTEN circuit [81, 82]. Upregulation of autophagy is known to be an adaptive response in BRAF-inhibitor resistant melanoma. A recent study demonstrated that YY1 knockdown resulted in the sensitization of melanoma cells resistant to vemurafenib, a BRAF-inhibitor [83].

Hence, YY1 aids tumor cells in resisting cell death by tipping the apoptosis-anti-apoptosis balance in favor of cell survival, thereby protecting the cells from damage, and by activating autophagy-mediated survival.

Deregulation of cellular energetics and metabolic reprogramming

Metabolism is a fundamental physiological process in living cells/organisms that provides them with energy and building blocks. Due to their elevated proliferation rate, tumor cells—especially those located in the center of a solid tumor—often face a severe microenvironment lacking oxygen and nutrients. To satisfy their demand for oxygen and nutrients, tumor cells secrete angiogenic factors to induce angiogenesis. However, the blood vessels formed in this way are usually immature and leaky. This results in a fluctuating and unstable oxygen supply to tumor tissues [84]. To meet their demand for large amounts of energy and macromolecules—required for the biosynthesis of organelles necessary
to form new cells—tumor cells reprogram their metabolism.

Tumor cell metabolic reprogramming was first observed by Otto Warburg, who noticed that the glucose uptake rate was significantly higher in tumor cells compared to that in normal cells [85]. Furthermore, he also found that even in the presence of sufficient oxygen, tumor cells preferred aerobic glycolysis to oxidative phosphorylation in the mitochondria. Recent studies have shown that YY1 is a critical regulator of tumor cell glucose metabolic reprogramming. YY1 induces a metabolic shift by binding directly to the GLUT3 promoter and activating its transcription [21]. This enhances not only the glucose uptake by tumor cells, but also lactate production, which could benefit tumor progression by promoting metastatic potential [86]. Furthermore, YY1 might be involved in tumor cell glucose metabolic reprogramming indirectly by promoting HIF-1α stability under hypoxia, which in turn enhances the expression of glucose transporters GLUT1 and GLUT3 [87]. HIF-1α also transactivates hexokinase-1 and hexokinase-2 in the first step of the glycolytic pathway [88]. Furthermore, YY1 enhances the activities of phosphoglycerate kinase 1 (PGK1), the first ATP-generating enzyme in the glycolytic pathway, and pyruvate kinase M2 (PKM2), which catalyzes the final step of glycolysis indirectly through HIF-1α [89]. Moreover, YY1 transcriptionally regulates genes associated with mitochondrial energy metabolism, such as those related to the Krebs cycle (ACO2, IDH2, OGDH, DLD, and FH) and electron transport chain (ATP5A1, ATP5B, ATP5F1, SDHA, SDHB, UQCRCC2, NDUFS1, COX2, COX5B, and COX4I1) [90]. YY1 also indirectly suppresses the Krebs cycle through HIF-1α stabilization by activating pyruvate dehydrogenase kinase 1 (PDK1), which subsequently inactivates pyruvate dehydrogenase (PDH), an important enzyme of the Krebs cycle [91, 92]. Finally, YY1 destabilizes p53, which is critical for maintaining the glucose metabolic balance as it activates the p53-induced glycolysis regulator TIGAR [93] and suppresses pyruvate dihydrogenase kinase 2 (PDK2) [94]. Hence, YY1 suppresses the level of TIGAR, which results in the increases of the fructose-2,6-bisphosphate level and PFK activity. Increases of PFK activity converts fructose-6-phosphate to fructose-1,6-bisphosphate and thus stimulates glycolysis. Moreover, YY1 positive regulation on the level of PDK2 subsequently suppresses Krebs cycle by inhibiting PDH. Further studies on YY1 regulation of these genes are required to reveal YY1-specific mechanisms that affect mitochondrial energy metabolism.

Anabolic biosynthesis constitutes an inherent and indispensable part of cellular replication, as it is necessary for a cell to replicate all of its contents during mitosis in order to produce two daughter cells. Our previous report showed that YY1 binds to the promoter of G6PD, the rate-limiting enzyme in the pentose phosphate pathway (PPP) [20]. YY1 promotes G6PD transcription and enhances the PPP in tumor cells. This leads to increased production of ribose-5-phosphate, the building block for de novo nucleotides biosynthesis, as well as NADPH, an intracellular reducing agent essential for lipid biogenesis. As a result, YY1 enhances PPP promotes tumorigenesis [20]. Furthermore, our recent study showed that YY1 could suppress expression of PGC-1β by binding directly to its promoter region. PGC-1β is an activator of medium- and long-chain acyl-CoA dehydrogenases (MCAD and LCAD, respectively), which are crucial for fatty acid β-oxidation. Hence, YY1 can enhance tumor cell lipid accumulation under both hypoxic and normoxic conditions by suppressing β-oxidation of fatty acids [17]. A previous study showed that under hypoxic conditions, HIF-1α suppressed PGC-1β expression, and thereby lipid accumulation in tumor cells [95]. Considering that YY1 stabilizes HIF-1α under hypoxia, regulation of PGC-1β-mediated fatty acid β-oxidation by YY1 likely occurs in both a direct and HIF-1α-dependent manner. This demonstrates the critical role of YY1 in lipid metabolism in tumor cells regardless of oxygen availability and tumorigenic stage, further supporting the role of YY1 as an important driver of tumorigenesis [17].

Overall, the role of YY1 in tumor metabolic reprogramming contributes to the adaptability of tumor cells to a changing environment. An altered glucose and lipid catabolism supports tumor cell survival during nutrient-depleted conditions by enabling the utilization of a wider range of carbon substrates (Figure 2). At the same time, an altered anabolism supports cell survival during nutrient-replete conditions by accelerating the rate of biosynthesis and reducing the damage incurred by ROS. As excessive intracellular ROS are lethal for tumor cells, various anti-tumor drugs including platinum complexes (cisplatin, carboplatin, and oxaliplatin) and anthracyclines (doxorubicin, epirubicin, and daunorubicin) aim to induce tumor cell death by increasing the intracellular ROS level [74]. Therefore, elevated YY1 expression in tumor cells might represent a hurdle during tumor treatment with DNA-damaging drugs. To overcome this problem, a combination treatment with YY1 inhibitor and DNA-damaging anti-tumor drugs might be an option.
Induction of angiogenesis

Stimulation of angiogenesis is another feature employed by tumor cells to overcome the lack of oxygen and nutrients. Angiogenesis is an intrinsic process stimulated by angiogenesis factors, such as VEGF-A, angiopoietin 1, EGF, fibroblast growth factor 2 (FGF2), platelet-derived growth factor B (PDGFB), and ephrin-B2 (EFNB2) [96]. These factors in turn affect the proliferation and migration of endothelial and smooth muscle cells, two major types of cells that form blood vessels, around the primary tumor [97].

The HIF family of transcriptional factors functions as a master gene regulator following exposure to hypoxia. HIF-1α is responsible for the acute hypoxic response. Under normoxic conditions, HIF-1α is hydroxylated at its Pro 402 and Pro 564 residues by prolyl hydroxylase domain (PHD)-containing proteins, utilizing oxygen as the substrate [98]. Hydroxylation of HIF-1α results in its ubiquitination and subsequent rapid degradation through the proteasomal pathway. In response to acute hypoxic stimuli, due to lack of oxygen as the substrate, HIF-1α is not hydroxylated, and instead gets accumulated in the nucleus [98], where it forms a heterodimer complex with HIF-1β, whose expression is ubiquitous under both normoxic and hypoxic conditions. The HIF-1 complex, in turn, activates genes promoting angiogenesis, such as VEGF, FGF2, and PDGFB. In addition, HIF-1α can activate genes involved in cell survival and metabolism, such as PGK, CA9, BNIP3, and GLUT1, all of which benefit tumor progression [30].

YY1 plays a crucial role in HIF-1α-induced tumor angiogenesis by regulating HIF-1α at post-translational level. Recently, we have shown that YY1 regulates HIF-1α at post-translational level by interacting physically with it and thus suppressing its proteasomal degradation in response to hypoxic conditions [30]. Accordingly, YY1 knockdown disrupts the stability of HIF-1α and reduces its accumulation, resulting in the suppression of VEGF and tumor growth factor alpha (TGF-α), and subsequent inhibition of tumor angiogenesis and tumorigenesis. Moreover, YY1 regulation of HIF-1α is independent of the status of p53, which is negatively regulated by YY1 as described above and could inhibit HIF-1α activity by interacting with p300 [29, 30]. This enables YY1 to induce tumor angiogenesis irrespective of the status of p53, which is frequently mutated and aberrantly downregulated in tumor cells.

Figure 2. YY1 and tumor metabolic reprogramming. YY1 is involved in the tumor metabolic reprogramming, as it regulates glycolysis, glucose uptake and lipid accumulation. YY1 elevates nutrient intake and enhances metabolic activity to meet the demand of biomolecules and maintain energy homeostasis in tumor cells, as well as to promote cell survival via ROS modulation. (Glu: glucose; G6P: glucose 6-phosphate; R5P: ribose 5-phosphate, F6P: fructose 6-phosphate, FBP: fructose 1,6-bisphosphate).
Besides regulating the stability of HIF-1α protein, YY1 also serves as a downstream effector of the CXCR4/SDF1 pathway and acts as a direct transcriptional activator of VEGF. Impairment of the CXCR4/SDF1/YY1 pathway alters the expression pattern of VEGF isoforms in osteosarcoma, and results in the downregulation of VEGF-A and upregulation of VEGF-B and VEGF-C. The two latter isoforms cannot activate the angiogenic VEGFR2 receptor, consequently reducing vessel formation and neoangiogenesis [27]. YY1 acts also as a co-transcription factor and upregulates the activity of the VEGF promoter by forming a complex with HIF-1α that binds to the hormone-response element in the VEGF promoter. The end result is increased VEGF expression and enhanced tumor neovascularization [27, 99].

Furthermore, YY1 could induce tumor angiogenesis in a HIF-1-independent manner. Together with the nuclear transcription factor-Y (NFY), YY1 binds to the promoter of DEK and activates its transcription. As a key regulator of VEGF expression, DEK upregulation enhances the expression of VEGF, stimulates new blood vessels formation, and promotes angiogenesis in vivo [100, 101].

Taken together, existing evidence suggests that YY1 regulation of tumor angiogenesis involves a complex, multi-pathway mechanism based on both direct and indirect activation of angiogenic genes, at the transcriptional as well as post-translational level.

**Activation of invasion and metastasis**

Malignant transformation is characterized by local invasion and distant metastases. Transformed cells acquire a motile-invasive phenotype, enabling them to spread via blood or lymph vessels. The induction of EMT is associated with the acquisition of invasive properties and is the first key limiting step in metastasis. Cells undergoing EMT exhibit a characteristic reduced expression of epithelial markers. Of particular importance is the loss of proteins involved in cell-cell contacts such as E-cadherin (CDH1). Downregulation of E-cadherin results in detachment from cell-cell junctions, thereby freeing the cells from physical confinement. Unconfined cells are free to invade the underlying basement membrane and enter circulation [102]. YY1 is highly expressed in metastatic tumor cells and is regarded as a bona fide inducer of cancer metastasis [103]. YY1 mediates the migratory and invasive potential of breast cancer cells by recruiting and interacting with the PRMT7-HDAC3 complex. This results in the reduction of histone trimethylation (H3K4me3) on the CDH1 promoter and, subsequently, the suppression of E-cadherin expression [104]. Moreover, YY1 can induce EMT by regulating twist-related protein 1 (Twist1), a key activator of EMT. YY1 binds directly to the upstream promoter sequence of heterogeneous nuclear ribonucleoprotein M (hnRNPM), an RNA-binding protein that participates in the processing of pre-mRNAs into mature RNAs, and inhibits its promoter activity. This, in turn, leads to the release of Twist1 from the suppressive effect of hnRNPM [105]. YY1 also induces the expression of snail through direct binding on its 3' enhancer region [106]. Furthermore, YY1 enhances the expression of vimentin, plausibly through direct binding with its promoter [106]. Both snail and vimentin are crucial EMT markers, thus YY1 regulation on them further convince close relation between YY1 and EMT.

Although EMT enables potentially invasive cancer cells to spread from the site of the primary tumor by entering the circulatory system, most of these cells will not survive. Only a small proportion manages to succeed in establishing metastasis in distant organs. Subcutaneous xenograft experiments with lung cancer and gastric cancer cell lines showed that YY1 overexpression enhanced lung metastatic potential, and resulted in a lower survival rate [30, 51]. Intravenous injection of YY1-knocked-down A549 cells resulted in decreased tumor cells colonization in lung compared to control cells [30].

The link between YY1 and metastasis has been further confirmed by clinical samples from melanoma and gastric cancer patients. Examination of samples from melanoma patient revealed that, compared to primary melanoma, the level of YY1 mRNA was higher in metastatic melanomas [107]. Immunohistochemistry on samples from gastric cancer patients showed that YY1 expression correlated positively with lymph node metastasis, distant metastasis, and advanced tumor-node-metastasis [51]. Collectively, this evidence supports the notion that elevated YY1 expression contributes to the acquisition of an EMT phenotype and tumor metastasis.

**Genome instability and mutation**

In the course of tumorigenesis, neoplastic lesions develop into malignant tumors accompanied by the accumulation of genomic mutations. The types of genomic alterations driving tumorigenesis vary in size from single point mutations to whole-chromosome gains and losses. Cancer genomes are generally dynamic owing to genome instability. Genome instability can be defined as the tendency of tumor cells to acquire mutations as a result of defective DNA maintenance. Failure to repair
extensive DNA damage can result in point mutations that activate an oncogene or inactivate a tumor suppressor gene, and hence acts as a driving force towards malignancy. Occasionally, further mutations involving genes required to maintain chromosome stability will result in a phenotype known as chromosomal instability, which favors the generation of additional mutations in oncogenes or tumor suppressor genes [108]. Notably, a constantly changing genome fuels intercellular heterogeneity and is a major driving force of tumor evolution and adaptation to challenges arising from the tumor microenvironment [109]. Intercellular heterogeneity within a tumor, resulting from genomic instability, provides abundant starting material for clonal selection, and a strong selective pressure eventually favors clones carrying factors essential for cell survival.

Although YY1 is not directly known to prompt the initiation of genomic instability, YY1 is a remarkable predictor of the outcome of breast cancer clonal selection, particularly in estrogen receptor (ER)-positive breast cancer patients undergoing hormone therapy. Through co-localization with ERα, YY1 assists the binding of ERα to the enhancer region, a specific active regulatory region associated with H3K27ac marks, on downstream genes and contributes to their transcription. In the background of hormone therapy aimed at inhibiting estrogen production in breast cancer, YY1 contributes to clonal selection by maintaining the binding of ERα-YY1 to the enhancer of SLC9A3R1, a hormone therapy-resistant gene. Thus, YY1 expression leads to the survival of tumor cells even under strong selective pressure, such as long-term estrogen deprivation by aromatase inhibitors, suggesting a role of YY1 in non-responder patients [23]. Aside from a report by Wu et al. that demonstrated the need for the YY1/INO80 complex to prevent the formation of polyploidy and chromatid aberrations [66], little is known about the role of YY1 in genome instability.

**Tumor-promoting inflammation and immunosuppression**

Chronic tissue inflammation in cancer is defined as an aberrantly prolonged form of protective tissue repair. Immune cells infiltrate the site of injury, mounting a lasting immune response to combat the intruding pathogen or molecule. In contrast to the anti-tumor activity of acute inflammation, chronic inflammation is a well-recognized tumor-promoting condition. Prolonged inflammation enables most of the core cellular and molecular adaptations required for tumorigenesis such as the release of DNA-damaging ROS, thus augmenting the risk of malignant transformation. Innate inflammatory immune cells recruited by tumor cells are found in the ROS-enriched microenvironment, where they secrete soluble growth factors and chemoattractants [48]. In contrast to a balanced inflammatory response that recruits leukocytes to eliminate foreign cells by ROS-mediated bacterial killing in the inflamed area [110], the unresolved inflammation cascade in tumor cells leads to a switch from tumor immune-surveillance to tumor-promoting inflammation, tumor initiation, and cancer progression [111]. Hence, instead of killing tumor cells, tumor-related inflammation promotes tumorigenesis.

YY1 was reported to interact with RelB and p50 in glioblastoma cells. This interaction “turns on” the RelB-dependent chronic inflammation switch, which then results in upregulation of proinflammatory cytokines IL1β, IL6, IL8, and oncostatin M. The proinflammatory signaling induced by these mediators enhances cell proliferation, invasiveness, tumor angiogenesis, as well as resistance to drugs and apoptosis. In addition, continuous secretion of these cytokines leads to the recruitment and activation of glioma-associated macrophages, a marker of immunosuppressive microenvironment resistant to immunotherapy [112]. Though it is unknown whether YY1 activates NF-κB, a major transcription factor for inflammatory gene expression, the reverse (i.e. regulation of YY1 by NF-κB) is known to occur. Activation of NF-κB stimulates YY1 transcription by direct binding of p65 to the NF-κB binding site on the YY1 promoter [113].

Chronic inflammation also allows tumors to recruit stromal cells and to form a microenvironment niche, which aids tumor cells in eventually escaping the immune system. This, in turn, makes it difficult to specifically identify and eliminate tumor cells by recognizing the expression of tumor-specific antigens before tumor cells can cause harm [114]. The cancer immune microenvironment is constituted of various stromal innate immune cells, including neutrophils, macrophages, mast cells, dendritic cells, and natural killer cells. Among them, a unique subset called tumor-associated macrophages (TAMs) is recognized for its characteristic plasticity, which enables the TAMs to acquire a number of distinct phenotypes and contribute in different ways to various stages of tumorigenesis. TAMs are characterized by a molecular signature reminiscent of alternatively activated M2 macrophages with immunosuppressive phenotype [115]. YY1 has been reported to downregulate miR-125a, thereby causing a shift from classically activated M1 macrophages to M2 macrophages. This impairs the immune system and its ability to prevent tumorigenesis [116]. YY1 can
bind to the cyclooxygenase COX2 promoter following macrophage activation. Overexpression of YY1 in macrophages increases the production of COX2, an activator of the pro-tumoral activity of macrophages, resulting in polarization towards M2 macrophages and in the ability of the tumor to evade the immune surveillance machinery [117, 118].

Adaptive immune response relies on the ability of cytotoxic T-cells to recognize foreign or mutated antigens displayed on transformed cells and to subsequently induce T-cell-mediated cell death. Tumor cells can evade immune destruction by either direct or indirect attenuation of the killing activity of infiltrating immune cells. Tumor cells directly create an immunosuppressive environment by secreting TGF-β and other immunosuppressive factors, such as IL10, HGF, IDO, and PGE2 [77]. Furthermore, YY1 might positively regulate the expression of programmed death ligand 1 (PD-L1), whose expression is correlated with poor clinical response to cell-mediated anti-tumor therapy, through crossstalk between YY1 and PD-L1 signaling pathways [119-121]. As a negative regulator of p53, YY1 might be able to suppress the expression of miR-34a, a downstream target of p53. The decrease of miR-34a in turn increases PD-L1 expression, as it could suppress PD-L1 expression by binding to its 3′ untranslated region (3′-UTR) [119]. YY1 could also directly activate c-Myc, and IL6, a positive regulator of signal transducer and activator of transcription 3 (STAT3), as well as stabilize HIF-1α protein, these factors subsequently increase PD-L1 transcription [120]. Collectively, YY1 is involved in ROS-mediated DNA mutagenesis, the generation of an immunosuppressive microenvironment, as well as the debilitation of the capability of the immune system to recognize nascent transformed cells. These findings indicate the possibility of combining cancer immunotherapy with YY1 inhibition to sensitize cancer cells to immunotherapeutic agents.

**YY1-related non-coding RNAs (ncRNAs) and the hallmarks of cancer**

Accumulating evidence demonstrates that a large portion of the human genome is transcribed into ncRNAs, such as microRNAs (miRNAs), long non-coding RNAs (lncRNAs), and circular RNAs (circRNAs), which play a crucial role in gene regulation at both transcriptional and post-transcriptional stages [122, 123]. With only 19–22 bp, miRNAs are important post-transcriptional regulators of gene expression that act via complementary base pairing to their target sites within the 3′-UTR of mRNAs. Depending on their complementarity, binding of miRNAs to mRNAs can induce either translational repression or mRNA degradation [124, 125]. Growing evidence points to reciprocal regulation between YY1 and miRNAs. On the one hand, YY1 is a negative regulator of let-7a, a tumor suppressor miRNA that inhibits the expression of anti-apoptotic protein B-cell lymphoma-extra-large (BCL-xL) in chemoresistance in acute myeloid leukemia [126]; YY1 is also a negative regulator of miR-29b, a suppressor of tumor proliferation in rhabdomyosarcoma [125]. On the other hand, miR-7 and miR-181 act as tumor suppressors by binding directly to the 3′-UTR of YY1 mRNA, thus inhibiting its translation and preventing YY1 protein accumulation [127, 128]. Known miRNAs regulated by YY1 and miRNAs that regulate YY1 are listed in Table 4 and Table 5, respectively.

As a large class of transcripts with <200 bp, IncRNAs indirectly modulate gene expression at the post-transcriptional level by functioning as a sponge of specific miRNAs. They can also interact with transcription factors or epigenetic proteins to regulate target gene expression, or promote mRNA translation of a specific target gene. Increasing evidence suggests the involvement of lncRNAs in a variety of biological processes, including cell proliferation, tumorigenesis, and invasiveness [129]. A recent report showed that the IncRNA nasopharyngeal carcinoma copy number amplified transcript-1 (NPCCAT1), whose expression increased in nasopharyngeal carcinoma, bound directly to the 5′-UTR of YY1 mRNA, causing the upregulation of YY1 translation and subsequently increased cell growth and migration [130].

Recently discovered, circRNAs are highly stable, circular (3′ and 5′ terminal joining) ncRNAs that regulate miRNAs. A circRNA binds to miRNAs, prevents their function, and terminates the suppression of target mRNAs [131, 132]. Dysregulated circRNAs have been identified in some types of cancers, suggesting the important role of circRNAs in tumorigenesis and in regulating hallmarks of cancer [133]. During EMT, the production of hundreds of circRNAs, including SMARCA5, POLE2, SHPRH, SMAD2, and ATXN2, is dynamically regulated by the alternative splicing factor quaking (QKI). QKI exerts pleiotropic effects, such as increased cell migration, invasion, and EMT [134]. Remarkably, YY1 binds to the super-enhancer and promoter of QKI and, together with the p65/p300 complex, activates the transcription of QKI. Thus, the fact that YY1 can regulate a pleiotropic factor such as QKI implies that the scale of YY1-mediated regulation of circRNAs and miRNAs might exceed beyond what is presently known [135].
**Table 4. Non-coding RNAs regulated by YY1.**

| Gene/promoter | Role in tumorigenesis | YY1 regulatory activity | Reported malignancy | Hallmarks | Ref |
|---------------|-----------------------|-------------------------|---------------------|-----------|-----|
| Let-7a        | Tumor-suppressor      | Repression              | AML                 | Cell death resistance | [126] |
| miR-1268b     | Oncogene              | Activation              | NSCLC               | Tumor cell proliferation, cell death resistance | [174] |
| miR-133b      | Oncogene              | Activation              | Pancreatic          | Tumor cell proliferation, cell death resistance | [170] |
| miR-140       | Tumor-suppressor      | Activation              | Breast              | Tumor cell proliferation, cell death resistance | [177] |
| miR-141       | Oncogene              | Repression              | Nasopharyngeal      | Tumor cell proliferation, cell death resistance | [165] |
| miR-29b       | Tumor-suppressor      | Repression              | Rhabdomyo-sarcoma   | Tumor cell proliferation | [125] |
| miR-320a      | Tumor-suppressor      | Activation              | Colorectal          | Tumor cell proliferation, cell death resistance | [178] |
| miR-361       | Tumor-suppressor      | Repression              | Endometrial         | Tumor cell proliferation, activation of invasion & metastasis | [179] |
| miR-489       | Tumor-suppressor      | Repression              | Pancreatic          | Activation of invasion & metastasis | [180] |
| miR-500a-5p   | Tumor-suppressor      | Repression              | Colorectal          | Tumor cell proliferation, cell death resistance, invasion & metastasis | [181] |
| miR-520c-3p   | Tumor-suppressor      | Activation              | Lung                | Tumor cell proliferation, cell death resistance | [182] |
| miR-526b-3p   | Tumor-suppressor      | Repression              | Colorectal          | Tumor cell proliferation | [183] |
| miR-5590-3p   | Oncogene              | Repression              | Breast              | Tumor cell proliferation, cell death resistance, invasion & metastasis | [184] |
| miR-9         | Tumor-suppressor      | Repression              | Melanoma            | Tumor cell proliferation, activation of invasion & metastasis | [107] |
| DDX11-AS1     | Oncogene              | Activation              | Colorectal          | Tumor cell proliferation, cell death resistance, invasion & metastasis | [185] |
| LINC00671     | Oncogene              | Activation              | Breast              | Tumor cell proliferation, cell death resistance | [186] |
| IncRNA-ARAPI-AS1 | Oncogene     | Activation              | Colorectal          | Invasion & metastasis | [187] |
| IncRNA-PVT1   | Oncogene              | Activation              | Lung                | Tumor cell proliferation | [188] |
| IncRNA-SOX2OT | Tumor-suppressor      | Repression              | Pancreatic          | Tumor cell proliferation | [189] |
| IncRNA-TUG1   | Oncogene              | Activation              | Glioma              | Tumor cell proliferation, cell death resistance | [190] |
| IncMER52A     | Oncogene              | Activation              | Liver               | Activation of invasion & metastasis | [191] |
| IncMCM3AP-AS1 | Oncogene              | Activation              | Lung                | Tumor cell proliferation, activation of invasion & metastasis, induction of angiogenesis | [192] |
| Multiple circRNAs | Oncogene and/or tumor-suppressor | Activation | Liver | Tumor cell proliferation, invasion & metastasis | [135] |

**Abbreviations:** AML: acute myeloid leukemia; ARAPI-AS1: ArfGAP with RhoGAP domain, ankyrin repeat and PH domain 1-antisense RNA 1; DDX11-AS1: DDX11-antisense RNA 1; Let-7a: lethal-7 a; LINC00671: long intergenic non-protein coding RNA 673; IncRNA: long non-coding RNA; MCM3AP-AS1: mini chromosome maintenance complex component 3 associated protein, ankyrin repeat and PH domain 1-antisense RNA 1; miR: microRNA; NSCLC: non-small-cell lung carcinoma; PVT1: plasmacytoma variant translocation 1; QKI: quaking; SOX2OT: SRY-Box 2 overlapping transcript; TUG1: taurine up-regulated 1.

**Table 5. Non-coding RNAs as YY1 regulators.**

| Gene/promoter | Role in tumorigenesis | Effect on YY1 activity | Reported malignancy | Hallmarks | Ref |
|---------------|-----------------------|------------------------|---------------------|-----------|-----|
| miR-101       | Tumor-suppressor      | Repression              | Gastric             | Tumor cell proliferation | [193] |
| miR-141-3p    | Tumor-suppressor      | Repression              | Thyroid             | Tumor cell proliferation, cell death resistance, invasion & metastasis | [194] |
| miR-181       | Tumor-suppressor      | Repression              | Cervical            | Tumor cell proliferation, cell death resistance | [128] |
| miR-186       | Tumor-suppressor      | Repression              | Colorectaloma, Lung | Cell death resistance, | [195] |
| miR-193a-5p   | Tumor-suppressor      | Repression              | Endometrial         | Tumor cell proliferation, invasion & metastasis | [18] |
| miR-215       | Tumor-suppressor      | Repression              | Colorectal          | Tumor cell proliferation, invasion & metastasis | [197] |
| miR-218       | Tumor-suppressor      | Repression              | Glioma              | Tumor cell proliferation, invasion & metastasis | [198] |
| miR-29a       | Tumor-suppressor      | Repression              | Lung                | Tumor cell proliferation, cell death resistance, invasion & metastasis | [199] |
| miR-34a       | Tumor-suppressor      | Repression              | Neuroblastoma, Esophageal, Gastric | Tumor cell proliferation, cell death resistance, invasion & metastasis | [200] |
| miR-381       | Tumor-suppressor      | Repression              | Ovarian             | Tumor cell proliferation, invasion & metastasis | [203] |
| miR-544       | Tumor-suppressor      | Repression              | Thyroid             | Tumor cell proliferation, invasion & metastasis | [204] |
| miR-5590-3p   | Tumor-suppressor      | Repression              | Breast              | Tumor cell proliferation, cell death resistance, invasion & metastasis | [184] |
| miR-635       | Tumor-suppressor      | Repression              | NSCLC               | Invasion & metastasis | [205] |
| miR-7         | Tumor-suppressor      | Repression              | Colorectal          | Tumor cell proliferation, cell death resistance | [127] |
| miR-7-5p      | Tumor-suppressor      | Repression              | Glioblastoma        | Cell death resistance | [206] |
| IncRNA-CASC15 | Oncogene              | Activation              | AML                 | Tumor cell proliferation, cell death resistance | [207] |
| IncRNA-NPCCAT1| Oncogene              | Activation              | Nasopharyngeal      | Tumor cell proliferation | [130] |
| circ-CTNNB1   | Oncogene              | Activation              | Gastric, prostate, colorectal | Tumor cell proliferation, invasion & metastasis | [208] |
| circ-HIPK3    | Oncogene              | Activation              | Colorectal          | Tumor cell proliferation, cell death resistance, invasion & metastasis | [209] |

**Abbreviations:** CASC15: cancer susceptibility candidate 15; circ: circular RNA; CTNNB1: catenin beta 1; HIPK3: homedomain interacting protein kinase 3; IncRNA: long non-coding RNA; miR: microRNA; NPCCAT1: nasopharyngeal carcinoma copy number amplified transcript-1; NSCLC: non-small-cell lung carcinoma.

**Conclusion**

Since its discovery, YY1 has emerged as an important factor in regulating the expression of a large number of genes, including ncRNAs. The studies discussed in this review emphasize the role of YY1 as a crucial regulator of target genes that influence the ‘hallmarks of cancer’ [52, 53]. YY1 both activates and suppresses the expression of a number of oncogenes and tumor suppressors involved in various cellular functions, including proliferation, redox homeostasis, DNA damage response, apoptosis, angiogenesis, metastasis, and immunosuppression (Figure 3). Considering that YY1 overexpression is observed in many cancers and has various biological implications with respect to the
hallmarks of cancer, it is an attractive approach to utilize YY1 as a novel target for therapeutic interventions. However, although most evidence supports oncogenic function of YY1, there are few reports about opposing roles of YY1 in tumorigenesis [49]. Furthermore, as shown in Table 2, while YY1 upregulation majorly related with poor prognosis, some cases showed the opposite. The mechanisms underlying this paradox, as well as whether it is related with the dual function of YY1 in regulating gene expression, remains to be solved. It is also crucial to reveal whether the role of YY1 as an oncogene or tumor suppressor is related with the cancer types, or even subtypes of cancers, especially when designing anti-tumor therapeutic strategy. Clearly, defining the molecular mechanism underlying the contrasting behavior of YY1 in cancer remains an interesting task.

Even in the absence of ongoing clinical trials with YY1 direct inhibitors, several YY1-inhibiting agents are under investigation for their potential use as anti-cancer therapies, either alone or in combination with other drugs. Previous studies showed that nitric oxide donors such as diethylenetriamine NONOate (DETA-NONOate) are encouraging for the development of YY1 inhibitors that can overcome immune and chemotherapy resistance [106, 136-140]. Several anti-tumor therapeutic agents that have been used clinically, including immunotherapeutic agent such as rituximab [16] and genotoxic agents such as cisplatin, etoposide, vincristine [68], can suppress YY1 expression; however, their molecular mechanism in regulating YY1, especially whether they can directly inhibit YY1, remains unclear. Furthermore, previous studies reported the tumor suppressive role of YY1 in some cancers [54, 141]. In some pancreatic cancers, YY1 could inhibit tumor proliferation, angiogenesis and metastasis by directly repressing tubulin polymerization-promoting protein (TPPP) and cyclin-dependent kinase inhibitor 3 (CDKN3) promoter activity [11, 141, 142], and high expression of YY1 is related with better prognosis [143]. These facts should also be considered for determining the suitability of YY1-targeted therapy.

Figure 3. YY1 and the hallmarks of cancer. Direct and indirect roles of YY1 in the hallmarks of cancer. YY1 is involved in tumorigenesis by regulating distinct hallmarks of cancer: growth suppressors evasion, sustaining proliferative signaling, cell death resistance, deregulation of cellular energetics and metabolic reprogramming, induction of angiogenesis, activation of invasion and metastasis, genome instability and mutation, tumor promoting inflammation, and avoiding immune destruction.
Another important issue to consider is the presence of Yin Yang 2 (YY2), which has only been discovered recently [144]. YY2 is a retroposed copy duplicated from YY1 mRNA located on chromosome X, and therefore is highly homologous to YY1 in terms of nucleotide and amino acid sequences (65% DNA sequence identity and 56% amino acid identity). As it had been retroposed from YY1 mRNA during the divergence of placental mammals from other vertebrates, YY2 does not possess any introns in its mRNA sequence [144, 145]. YY2 was recently reported to have a function distinct from that of YY1, and has been classified as an intrinsically disordered protein [146-148]. Due to the similarity with YY1 at the level of the zinc finger region, YY2 generally interacts with the same molecular partners as YY1 [148]. However, previous studies on YY2 have revealed an antagonist function to YY1 in regulating cells and cell proliferation [146, 149, 150]. Unlike YY1, YY2 expression is downregulated in tumor tissues, and might act as a tumor suppressor. The distinct function of YY2 could arise from a difference in the N-terminal domain [148]. Therefore, due to the high homology between YY1 and YY2, in the basic research, attention should be paid to the specificity of probes and antibodies used to detect them; while the specificity of any YY1 inhibitor is a crucial issue that needs to be considered when designing drugs for cancer therapy. This stresses the need for a better understanding of YY1/YY2 dynamics to shed light on the distinct roles of YY1 and YY2, as well as the interaction between them and the possibility of their competitive binding in the genomic DNA binding sites [151]. Therefore, novel tools for dissecting the dynamics of YY1/YY2 should be developed and used to direct the targeting of YY1, eventually leading to a significant addition to currently available cancer treatment regimens.

Overall, the fact that a single protein, YY1, regulates several hallmarks of cancer indicates the relevant role of YY1 in tumorigenesis. Furthermore, while there are still several crucial concerns need to be solved before its clinical application, these facts also emphasize the prognostic and therapeutic potential of YY1 for anti-tumor therapy.

**Abbreviations**

ACR: adenomatous polyposis coli; AURKA: aurora kinase A; BCL-xL: B-cell lymphoma-extra-large; Bim: Bcl2-interacting mediator of cell death; BCCIP: BRCA2- and CDKN1A-interacting protein; CDH1: Cadherin-1; CDKN2A: cyclin-dependent kinase inhibitor 2A; CDKN3: cyclin-dependent kinase inhibitor 3; circRNA: circular RNA; COX: cyclooxygenase; CSC: cancer stem cell; CXCR4: CXC chemokine receptor type 4; DR5: death receptor 5; DTDST: diastrophic dysplasia sulfate transporter; E2F1: E2F transcription factor 1; EGFR: epidermal growth factor receptor; EMT: epithelial-mesenchymal transition; EFNB2: ephrin-B2; ER: estrogen receptor; ERBB2: erb-b2 receptor tyrosine kinase 2; EZH2: enhancer of zeste homolog 2; FGFR: fibroblast growth factor 2; G6PD: glucose-6-phosphate dehydrogenase; GLUT: glucose transporter; HDAC: histone deacetylase; HIF-1α: hypoxia-inducible factor 1α; KLF4: Kruppel-like factor 4; LCAD: long-chain acyl-CoA dehydrogenase; IncRNA: long non-coding RNA; MCAD: medium-chain acyl-CoA dehydrogenase; MCT1: T-cell malignancy 1; MDM2: mouse double minute 2; miRNA: micro RNA; MnSOD: manganese-dependent superoxide dismutase; nncRNA: non-coding RNA; NF-κB: nuclear factor-κB; NFY: nuclear transcription factor-Y; NPCCAT1: nasopharyngeal carcinoma copy number amplified transcript-1; PD-L1: programmed death ligand 1; PDGFB: platelet-derived growth factor B; PDH: pyruvate dehydrogenase; PDK1: pyruvate dehydrogenase kinase 1; PDK2: pyruvate dehydrogenase kinase 2; PFK: phosphofructokinase; PGC-1β: peroxisome proliferator-activated receptor gamma coactivator-1β; PGK1: phosphoglycerate kinase 1; PHD: prolyl hydroxylase domain; PKM2: pyruvate kinase M2; PPP: pentose phosphate pathway; PRMT7: protein arginine methyltransferase 7; QKI: quaking; Rb: retinoblastoma; ROS: reactive oxygen species; SDF1: stromal cell-derived factor 1; ST6GalNAc6: N-acetylgalactosamine α2,6 sialyltransferase isoenzyme 6; STAT3: signal transducer and activator of transcription 3; TAM: tumor-associated macrophage; TFEB: transcription factor EB; TGF: tumor growth factor; TPPP: tubulin polymerization-promoting protein; TRAIL: tumor necrosis factor-related apoptosis-inducing ligand; Twist1: twist-related protein 1; UCRBP: upstream conserved region-binding protein; VEGF: vascular endothelial growth factor; YY1: Yin Yang 1; YY2: Yin Yang 2.

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Our intention is to summarize the state of art. However, due to space limitations, we would like to apologize to authors whose works are not cited here. Their contributions should not be considered less important than those that are cited.
Competing Interests

The authors have declared that no competing interest exists.

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