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Yin yang 1 expression in human tumors

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The Yin Yang 1 (YY1) transcription factor has been identified to target a plethora of potential target genes, the products of which are important for proliferation and differentiation. The mechanisms of YY1 action are related to its ability to initiate, activate or repress transcription depending on the context in which it binds. This article sheds a light on the role that YY1 plays in different human types of cancer, through the context of its expression levels. Moreover, we concentrate on the most relevant studies that have focused on YY1 regulation. We performed computational analysis on thirty-six publicly available Gene Expression Omnibus (GEO) datasets, to further understand whether differences in YY1 transcript levels occur in different cancer types when compared with relative normal tissue, benign tumor or its metastatic counterpart. Our results suggest a dual role of YY1 in cancer development, either through overexpression or under-expression, depending on the tumor type.

Introduction

Yin Yang 1 (YY1), also known as δ, NF-E1, UCRBP and CF1, is a ubiquitous and multifunctional zinc-finger transcription factor that can act as a transcriptional repressor, activator or initiator element binding protein.[1,2] Studies have repeatedly shown the association and modulation of YY1 by the adenovirus-derived E1A, an oncoprotein that activates the AAV P5 promoter.[3] The presence of the oncoprotein E1A induces YY1-mediated activation of transcription. In its absence, the role of YY1 is reversed, converting to a transcriptional repressor;[1] hence the name Yin Yang 1. To clarify the process by which activation is favored in the presence of E1A, but switched to repression in its absence, studies were designed to test its functional status by masking and/or exposing the binding sites of YY1. In the absence of E1A, the AAV virus fails to undergo transcription, most likely due to YY1 binding to the P5 promoter.[4] Mechanisms that have been proposed to explain this phenomenon include the possibility of a conformational change in YY1 through covalent modification, or a direct interaction between YY1 and an E1A-type accessory protein.

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YY1 Structure

The structure of YY1 has been reviewed in the past.[5] The human YY1 gene produces eight different transcripts (a, b, c, d, e, f, g and h) generated by alternative splicing, encoding eight different putative protein isoforms (three complete, three COOH-complete and two partial). The functional significance of these isoforms remains elusive. There are two alternative promoters. Different transcripts differ by truncation of the 5' end, truncation of the 3' end, presence or absence of four cassette exons, and different boundaries on common exons due to variable splicing of an internal intron.

The Role of YY1/Molecular Interactions

YY1 is involved in the transcriptional control of a large number of mammalian genes, approximately 10% of the total mammalian gene set.[6] Consequently, YY1 plays important roles in a number of biological processes, including cell cycle control, embryogenesis, viral infection, programmed cell death, oncogenesis, Polycomb Group (PcG) function and B-cell development.[7] Since it is a general transcription factor involved in many pathways, the expression levels of YY1 must be tightly monitored for the survival of cells and organisms.[8] Accordingly, abnormal YY1 protein levels have been shown to cause defects in cell proliferation and differentiation, neural development and the repression mediated by the PcG complex. There are several types of the YY1-related diseases, such as viral infection and cancers, which are also linked to abnormal YY1 protein levels.[5]

Previous studies identified a plethora of potential YY1 target genes, the products of which are important for proliferation and differentiation.[1,2] The putative role of YY1 in tumorigenesis has been supported by its interaction with cell cycle regulation (**Fig. 1**). Specifically, Cicatiello et al.[9] noted that cyclin D1 gene promoter activation in estrogen-responsive human breast cancer is marked by release of the YY1 transcriptional repressor complex including HDAC-1. Moreover, cyclin D1 gene promoter activation is sufficient to induce the assembly of the basal transcription machinery on the promoter and to lead to initial cyclin D1 accumulation in the cell. Upon estrogen stimulation, the cyclin D1/CDK4 holoenzyme associates with the cyclin D1 promoter, where E2F and pRb also occur, and contributes to the long-lasting gene enhancement required to drive G_1-phase completion.

Moreover, YY1 has been found to be associated with the tumor suppressor p53. Yakovleva et al.[10] showed that YY1 inhibits p53-activated transcription from the p53-binding site that contains the ACAT sequence. Furthermore, YY1 and p53 were noted to

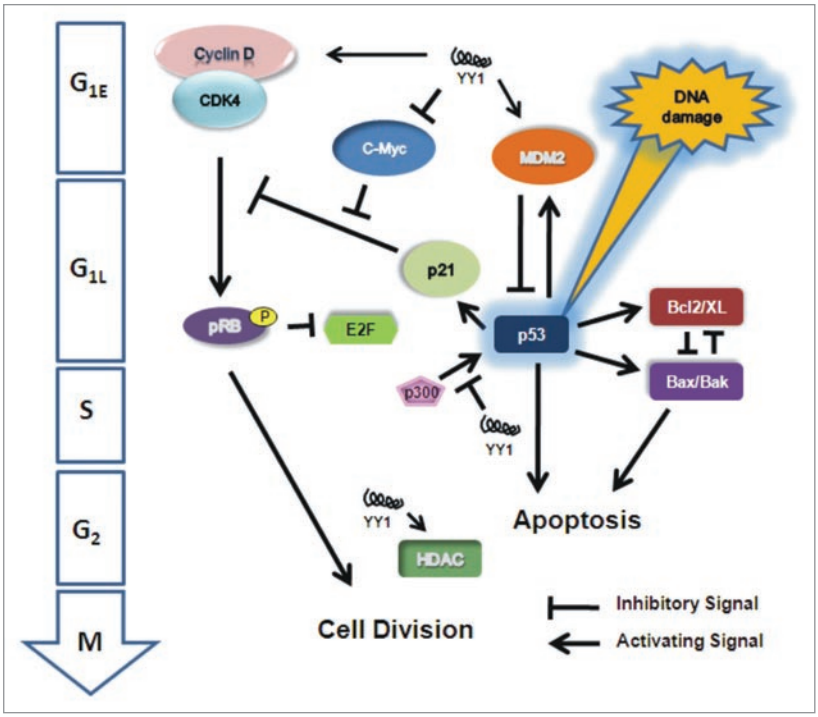

Figure 1. Interaction of YY1 with key cell cycle regulator genes. Specific interactions in detail are described in the text (The Role of YY1 Molecular Interactions).

be colocalized around the nucleoli, as well as in discrete nuclear domains in an in vitro model of apoptosis in PC-12 rat adrenal tumor cells. YY1 may attenuate p53-dependent transcription from a subset of p53 target genes, a hypothesis that is relevant for defining the role of YY1 in directing cells either to growth arrest or apoptosis upon p53 binding.

Sui et al.[11] demonstrated that YY1 interacts with p53 and inhibits its transcriptional activity by disrupting the interaction between p53 and its coactivator p300, thereby blocking p300-dependent p53 acetylation and stabilization, and disabling this checkpoint mechanism. It was shown that ablation of endogenous YY1 results in p53 accumulation due to a reduction in p53 ubiquitination and an increased expression of p53 target genes in response to genotoxic stress in vivo. Conversely, YY1 overexpression stimulates p53 ubiquitination and degradation, thereby supporting the hypothesis that an increased YY1 expression and activity inhibits the accumulation of p53.

Alternatively, YY1 has been shown to promote the assembly of the p53-mdm2 complex, enhancing the mdm2-mediated ubiquitination and subsequent inactivation of p53.[12] Similarly, studies demonstrating the direct physical interaction between Hdm2 (the human homologue of Mdm2) and p53 show that the basis for YY1 regulation of p53 ubiquitination is its ability to facilitate Hdm2/p53 interaction.[11] Moreover, YY1 has been shown to bind p53 at the neurofibromatosis 1 (NF1)/YY1 promoter binding site.[13]

Riggs et al.[14] and Shrivastava et al.[15] independently demonstrated in murine and human tumor models that YY1 can activate both endogenous and exogenous c-myc promoters when overexpressed. In turn c-myc overexpression appears to alter the constitutive repressive role of YY1 by interfering with the association between YY1 and basal transcription proteins such as TATA-binding protein and the transcription factor IIF, with altered transcription of target genes.[16]

More recently, Kim et al.[17] identified a very unusual cluster of YY1 binding sites within its own gene locus, prompting a potential auto-regulation mechanism for YY1 transcription.

Overexpression of Yin Yang 1 in Different Cancer Types

It has been recently shown that YY1 overexpression may affect the clinical behavior of several cancer types.[78,79] In the present study, computational analysis was performed to further understand whether differences in YY1 transcript levels occur in different cancer types when compared with the relative normal tissue, benign tumor or its metastatic counterpart. Thirty-six publicly available Gene Expression Omnibus (GEO) datasets were analyzed.[18-59] Gene expression patterns of YY1 in 19 different primary tumor types, benign and/or metastatic, as well as the corresponding normal counterparts were extracted from the normalized datasets (**Table 1**). The results were expressed as mean levels of the $\log_2$ intensity and were statistically compared by the Mann-Whitney U test (**Fig. 2**).

This analysis showed that in the majority of the tumors studied, YY1 transcript levels are significantly higher than in the relative normal counterparts for each cancer type analyzed. Moreover, in many human cancer types YY1 expression levels are significantly elevated in the metastatic tumor compared to its primary counterpart. In the cases of prostate, colon and liver cancer, the benign tumors always exhibited significantly higher relative expression rates compared to the normal tissues. However, these rates were lower than the corresponding rates in their metastatic counterparts. In contrast, in the reviewed Datasets, melanomas expressed significantly decreased YY1 relative expression rates, versus both benign nevi and normal tissues. Moreover, metastatic malignant melanomas exhibited significantly lower expression rates compared to malignant melanomas. Similarly, YY1 transcription levels decreased in pediatric osteosarcomas, versus normal human osteoblasts. These results suggest a dual role of YY1 in cancer development, either through overexpression or underexpression, depending on the tumor type.

Previous studies reported that YY1 is overexpressed and affects the clinical behavior of several tumor types.[78] In the present study, we performed computational analysis to further understand whether differences in YY1 transcript levels occur in different cancer types when compared with the relative normal tissue, benign tumor or its metastatic counterpart.

Prostate cancer. Pilarsky et al.[60] performed microarray analysis and identified the overexpression of YY1 among a group of

Table 1. Gene expression analysis of the transcription factor YY1 in different tumor types

Tumor type	N. of samples				Log. mean expression of YY1				P †	Gene expression omnibus (GEO) data set or database URL		
	Metastatic tumor	Primary tumor	Benign tumor	Normal tissue	Metastatic tumor	Primary tumor	Benign tumor	Normal tissue		Author (Ref.)	Year	Ref. series
Testicular seminoma		22 pT1 14 pT2 4 pT3		3		0.78 pT1 0.78 pT2 0.76 pT3		0.55	0.006 pT1-n 0.008 pT2-n 0.157 pT3-n	Gashaw et al. (18)	2005	GSE8607
Testicular germ cell tumors	3 MM	12 TS 6 NSM 6 T			1.22 MM	1.18 TS 1.26 NSM 1.31 T			0.039 TS-T	Monzon et al. (19)	2009	GSE12630
Testicular germ cell tumors		5 EmC 4 YST 3 T 3 TS 3 TIG		3		0.59 EC 0.40 YST 0.85 T 1.12 TS 0.59 TIG		0.31	0.180 EmC-n 0.480 YST-n 0.050 T-n 0.050 TS-n 0.127 TIG-n	Skotheim et al. (20)	2005	GSE1818
Pediatric malignant germ cell tumors		9 S 18 YST		3 ‡		0.31 S 0.30 YST		0.31	0.237 S-YST 0.405 S-n 0.366 YST-n	Palmer et al. (43)	2008	GSE10615
Prostate		26		2		0.97		0.91	0.174	Nanni et al. (22)	2006	GSE3868
Prostate	6	7	6		1.32	1.27	1.26		0.199 PP-BP 0.109 MP-BP 0.022 PP-MP	Varambally et al. (23)	2005	GSE3325
Prostate		52		50		-1.06		-2.15	0.007	Singh et al. (24)	2002	http://www.genome.wi.mit.edu/MPR/prostate
Prostate	5	23		12		1.50		1.09	0.007	Vanaja et al. (25)	2003	-
Prostate	6	6			1.16	1.10			0.409	Monzon et al. (19)	2009	GSE12630
Ovarian		27		3		0.98		0.92	0.049	Welsh et al. (26)	2000	http://www.gnf.org/cancer/ovary
Ovarian		99 37 EC 41 SC 13 MC 8 CC		4		1,93 EC 1.91 MC 1.92 CC 1.94 SC		1.83	0.001 EC-n 0.003 MC-n 0.007 CC-n 0.001 SC-n	Hendrix et al. (27)	2006	GSE6008
Ovarian		10 LGSOC 10 HGSOC		3		-0.87 LGSOC -0.89 HGSOC		-0.94	0.011 LGSOC-n 0.043 HGSOC-n	Tung et al. (41)	2009	GSE14001
Ovarian		35 ASOC 8 ESOC		10		1.02 ASOC 1.00 ESOC		0.93	<0.0001 ASOC-n 0.003 ESOC-n	Yoshihara et al. (42)	2009	GSE12470
Ovarian	3 M	1 CC 2 P 5 SC 1 HGSO			0.86 M	1.17 CC 1.21 P 1.23 SC 1.34 HGSO			0.025 SC-M	Monzon et al. (19)	2009	GSE12630
Urinary bladder		13 mTCC 15 sTCC without CIS 13 sTCC with CIS		9 N 10 CS		0.84 mTCC 0.79 sTCC without CIS 0.87 sTCC with CIS		0.73 N 0.79 CS	<0.0001 * 0.010 ** 0.956 ‡ 0.245 ‡‡ 0.011 mTCC-CS 0.030 mTCC-N 0.165 CS-N	Dyrskjøt et al. (46)	2004	GSE3167
Urinary bladder	8	13			1.10	1.27			0.025	Monzon et al. (19)	2009	GSE12630
Breast		40 BLC		7		0.34		0.34	0.045	Richardson et al. (28)	2006	GSE3744

Table 1. Gene expression analysis of the transcription factor YY1 in different tumor types (continued)

Breast		5 IDC 5 ILC		10 IDC normal 10 ILC normal		0.99 IDC 1.02 ILC		0.99 IDC 0.98 ILC	0.221 $^{ILC-n}$ 0.903 $^{IDC-n}$	Turashvili et al. (29)	2007	GSE5764
Breast	4	7			1.09	1.19			0.450	Monzon et al. (19)	2009	GSE12630
Colon		12 nCRC		10		1.26		1.28	0.075	Hong et al. (44)	2007	GSE4107
Colon	3 SW620	3 SW480			0.83	0.68			0.275	Provenzani et al. (45)	2006	GSE1323
Colon		18	4 Ad	18 4 N(Ad)		0.56	0.58	0.55 N(Ad) 0.52 N	0.386 $^{ad-n}$ 0.011 $^{c-n}$	Notterman et al. (30)	2001	http://microarray.princeton.edu/oncology
Colon	2	7			1.11	1.06			0.77	Monzon et al. (19)	2009	GSE12630
Liver	10	102 HCC 10 HCCcl	7	74	0.18	-0.33 HCC 0.58 HCCcl	0.19	-0.22	0.686 $^{m-HCC}$ 0.120 $^{HCC-n}$ 0.446 $^{b-n}$ 0.145 $^{HCC-cl-n}$	Chen X et al. (31)	2002	GSE3500
Liver		17 dn 13 ci 18 eHCC 17 aHCC		10		1.10 dn 1.11 ci 1.11 eHCC 1.12 aHCC		1.12	0.256 $^{m-HCC}$ 0.079 $^{dn-c}$ 0.420 $^{ci-c}$ 0.774 $^{eHCC-c}$ 0.725 $^{eHCC-c}$	Wurmbach et al. (48)	2007	GSE6764
Liver	6 mHC	19 HCC			1.12 mHC	1.28 HCC			0.036	Monzon et al. (19)	2009	GSE12630
Kidney	4 M	9 CK			0.88 M	0.98 CK			0.355	Monzon et al. (19)	2009	GSE12630
Pancreas	6 MAP	18 AP			1.33	1.12			0.014	Monzon et al. (19)	2009	GSE12630
Lung		5		5		0.86		0.81	0.009	Wachi et al. (49)	2005	GSE3268
Lung		48 SCC 9 AD		30		-0.03 SCC 0.26 AD		-0.17	0.081 $^{SCC-n}$ 0.002 $^{AD-n}$	Jones et al. (50)	2004	GSE2088
Lung		16 AD		3		1.27		1.19	0.19	Wrage et al. (51)	2009	GSE10799
Lung		94 AD 35 SCC 9 SCLC 20 LCC		5		-0.24 AD -0.05 SCC 0.03 SCLC -0.27 LCC		-0.31	0.462 $^{AD-n}$ 0.024 $^{SCC-n}$ 0.083 $^{SCLC-n}$ 1.00 $^{LCC-n}$	Takeuchi et al. (52)	2006	GSE11969
Lung		20 AD		19 AdjN		0.43		0.42	0.899	Stearman et al. (34)	2005	GSE2514
Lung	4	11			1.02	1.11			0.29	Monzon et al. (19)	2009	GSE12630
Melanoma		18 BN 45 M		7		1.08 BN 1.04 M		1.11	0.005 $^{M-BN}$ <0.001 $^{M-N}$ 0.18 $^{BN-N}$	Talantov et al. (54)	2005	GSE3189
Melanoma	11 MM	11 M			1.06	1.18			0.039	Monzon et al. (19)	2009	GSE12630
NMSC		4 AK 5 SCC		6		1.33 AK 1.36 SCC		1.33	0.068 $^{SCC-n}$ 0.670 $^{AK-n}$	Nindl et al. (53)	2006	GSE2503
Leukemia		87 B-lineage ALL 11 T-cell ALL 23 AML		6		-0.001 B-lineage ALL 0.29 T-cell ALL 0.008 AML		-0.62	0.006 $^{B-lineage ALL-N}$ 0.004 $^{T-cell ALL-N}$ 0.002 $^{AML-N}$	Andersson et al. (36)	2007	GSE7186
Leukemia		6 T-PLL		8		1.29		1.25	0.093	Dürig et al. (37)	2007	GSE5788
Leukemia		9 CML		8		0.30		0.29	0.001	Diaz-Blanco et al. (38)	2007	GSE5550
Leukemia		26 AML		18 N1 10 N2 10N3		1.05		1.07 N1 1.05 N2 1.06 N3	0.189 $^{AML-N1}$ 0.437 $^{AML-N2}$ 0.805 $^{AML-N3}$	Stirewalt et al. (55)	2008	GSE9476
Lymph node		16 L 5 ML				1.21 L 1.02 ML			0.058	Monzon et al. (19)	2009	GSE12630

Table 1. Gene expression analysis of the transcription factor YY1 in different tumor types (continued)

Thyroid		10 TC 15 PC				1.07 TC 1.29 PC			0.015	Monzon et al. (19)	2009	GSE12630
Gastric	5 M	17 AS			1.19 M	1.22 AS			0.557	Monzon et al. (19)	2009	GSE12630
Cervical cancer		24		8		0.16		0.19	0.632	Wong et al. (56)	2003	GSE527
Cervical cancer		33 9 cl		24		0.98 0.98 cl		0.96	0.006 $^{C\text{-}n}$ 0.017 $^{cl\text{-}n}$	Scotto et al. (57)	2008	GSE9750
Cervical cancer	19 C2	21 C1		5	0.13 C2	-0.04 C1		-0.31	0.002 $^{C1\text{-}n}$ 0.003 $^{C2\text{-}n}$ 0.001 $^{C1\text{-}C2}$	Biewenga et al. (58)	2008	GSE7410
Osteosarcoma		12		2		0.31		0.32	0.028	Sadikovic et al. (59)	2009	GSE12865
Hodgkin Lymphoma		64 cHL 3 Lcl 3 Ad		3 H/TCRBCL		0.89 cHL 0.92 Lcl 0.85 Ad		0.85 H/TCRBCL	0.060 ‡ 0.050 ‡‡ 0.049 ‡‡‡	Chetaille et al. (73)	2009	GSE13996
B-cell Non-Hodgkin Lymphoma		38 MCL 9 BL 6 NMZL 33 FL 38 CLL 36 DLBL		8 RLN 5 SC		0.06 MCL 0.38 BL -0.56 NMZL -0.96 FL 0.04 CLL -0.19 DLBL		-0.29 RLN -0.12 SC	0.039 $^{MCL\text{-}RLN}$ 0.007 $^{BL\text{-}RLN}$ <0.001 $^{FL\text{-}RLN}$ 0.023 $^{CLL\text{-}RLN}$ <0.001 $^{DLBL\text{-}FL}$	Ruiz-Vela et al. (74)	2008	GSE9327

Note: Gene expression patterns of YY1 in different types of tumors and the relative normal counterpart were extracted from the normalized dataset. Results are expressed as mean levels of the $\log_2$ intensity and statistically compared by the Mann-Whitney U test (p-values are reported for each comparison between expression levels in tumor and normal cases). †Mann-Whitney U test. ‡Normal samples acquired from Data Set with Ref. Series GSE1818 (Skotheim et al. 2005). **Testicular germ cell tumors:** EmC, Embryonal carcinoma; YST, Yolk sac tumor; T, Teratoma; TS, Testicular seminoma; TIG, Testicular intratubular germ cell neoplasia; S, Seminomas (ovarian dysgerminomas and extragonadal germinomas); MM, Metastatic malignant germ cell neoplasm; $^{EmC\text{-}n}$, correlation between EmC and normal testis; $^{YST\text{-}n}$, correlation between YST and normal testis; $^{T\text{-}n}$, correlation between T and normal testis; $^{TS\text{-}n}$, correlation between TS and normal testis; $^{TIG\text{-}n}$, correlation between TIG and normal testis; $^{pT1\text{-}n}$, correlation between TS (pT1) and normal testis; $^{pT2\text{-}n}$, correlation between TS (pT2) and normal testis; $^{pT3\text{-}n}$, correlation between TS (pT3) and normal testis; $^{s\text{-}YST}$, correlation between S and YST; $^{S\text{-}n}$, correlation between S and normal testis; $^{YST\text{-}n}$, correlation between YST and normal testis; $^{TS\text{-}T}$, correlation between Testicular seminoma and normal Teratoma. **Prostate:** BP, Benign prostate tissues; PP, Clinically localized primary prostate cancers; MP, Metastatic prostate cancers; NPADJ, Normal prostate tissues adjacent to tumor; $^{PP\text{-}BP}$, correlation between primary prostate and benign prostate cancer; $^{MP\text{-}BP}$, correlation between metastatic prostate and benign prostate cancer; $^{PP\text{-}MP}$, correlation between primary prostate and metastatic prostate cancer. **Ovary:** EC, Endometrioid carcinoma; SC, Serous carcinoma; MC, mucinous carcinoma; CC, clear cell carcinoma; $^{EC\text{-}n}$, correlation between EC and normal; $^{MC\text{-}n}$, correlation between MC and normal; $^{CC\text{-}n}$, correlation between CC and normal; $^{SC\text{-}n}$, correlation between SC and normal; LGSOC, Low-grade ovarian serous carcinoma; HGSOC, High-grade ovarian serous carcinoma; $^{LGSOC\text{-}n}$, correlation between LGSOC and normal; $^{HGSOC\text{-}n}$, correlation between HGSOC and normal; ASOC, Advanced serous ovarian cancer; ESOC, Early serous ovarian cancer; $^{ASOC\text{-}N}$, correlation between ASOC and normal; $^{ESOC\text{-}n}$, correlation between ESOC and normal; P, Papillary; M, Metastatic carcinoma. **Urinary Bladder:** mTCC, muscle invasive carcinomas (mTCC); sTCC without CIS, superficial transitional cell carcinoma (sTCC) without surrounding carcinoma in situ; sTCC with CIS, superficial transitional cell carcinoma (sTCC) with surrounding carcinoma in situ; N, normal bladder mucosa from patients without bladder cancer history; CS, cystectomy specimens; *correlation between sTCC with CIS and CS; **correlation between sTCC with CIS and N; ‡correlation between sTCC without CIS and CS; ‡‡correlation between sTCC without CIS and N; $^{mTCC\text{-}CS}$, correlation between mTCC and CS; $^{mTCC\text{-}N}$, correlation between mTCC and N; $^{CS\text{-}N}$, correlation between CS and N. **Breast:** IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; ⁱcorrelation between ILC tumor and normal; ʲcorrelation between IDC tumor and normal; BLC, Basal-like tumor. **Colon:** CRC, Colorectal cancer; nCRC, Normal-appearing colonic mucosa of early onset CRC patients without a prior family history of CRC; Ad, Adenoma; N(Ad), Normal tissue, adjacent to adenoma; $^{Ad\text{-}N(Ad)}$, correlation between adenoma and normal tissue, adjacent to adenoma; $^{c\text{-}n}$, correlation between adenocarcinoma and normal. **Liver:** HCC, Hepatocellular carcinoma; dn, dysplasia; ci, cirrhosis; eHCC, early hepatocellular carcinoma; aHCC, advanced hepatocellular carcinoma; $^{dn\text{-}c}$, correlation between dysplasia and normal tissue; $^{ci\text{-}c}$, correlation between cirrhosis and normal tissue; $^{eHCC\text{-}c}$, correlation between early hepatocellular carcinoma and normal tissue; $^{aHCC\text{-}c}$, correlation between advanced hepatocellular carcinoma and normal tissue; HCC-cl, Hepatocellular carcinoma cell lines; $^{m\text{-}HCC}$, correlation between metastatic cancer and HCC; $^{HCC\text{-}n}$, correlation between HCC and normal; $^{b\text{-}n}$, correlation between benign tumor and normal; $^{HCC\text{-}cl\text{-}n}$, correlation between Hepatocellular carcinoma cell lines and normal; mHC, Metastatic hepatocellular carcinoma. **Kidney:** M, Metastatic renal cell carcinoma; CK, Carcinoma of kidney. **Pancreas:** AP, Adenocarcinoma of pancreas; MAP, Metastatic Adenocarcinoma of Pancreas. **Lung:** SCC, squamous cell lung carcinoma; NSCLC, non-small cell lung cancer; AD, Adenocarcinoma; SCLC, small cell lung cancer; LCC, large cell carcinoma; AdjN, Adjacent normal tissue; $^{SCC\text{-}n}$, correlation between SCC and normal; $^{AD\text{-}n}$, correlation between AD and normal; $^{SCC\text{-}AD}$, correlation between SCC and AD; $^{SCLC\text{-}n}$, correlation between SCLC and normal; $^{LCC\text{-}n}$, correlation between LCC and normal. **Leukemia:** B-lineage ALL, B-lineage acute lymphoblastic leukemia; AML, acute myeloid leukemia; T-PLL, T-cell prolymphocytic leukemia; CML, chronic myelogenous leukemia; PML, promyelocytic leukemia with t(15;17); ML, monocytic leukemia; NML, non-monocytic leukemia; N1, Normal hematopoietic samples included $CD34^+$ selected cells; N2, unselected bone marrows; N3, unselected peripheral bloods; $^{B\text{-}lineage\ ALL\text{-}N}$, correlation between B-lineage ALL and normal Bone Marrow; $^{T\text{-}cell\ ALL\text{-}N}$, correlation between T-cell ALL and normal Bone Marrow; $^{AML\text{-}N}$, correlation between AML and normal Bone Marrow. **NMSC, Non-melanoma skin cancers:** AK, Actinic keratosis; SCC, Squamous cell carcinoma. **Melanoma:** M, Melanoma; BN, Benign nevi; N, normal; MM, Metastatic Malignant Melanoma. **Lymph node:** L, lymphoma; ML, malignant lymphoma. **Thyroid:** TC, Carcinoma of the Thyroid; PC, Papillary Carcinoma of the Thyroid. **Cervical Cancer:** cl, Cervical cancer cell lines; $^{C\text{-}n}$, correlation between Cervical cancer and normal cervix; $^{cl\text{-}n}$, correlation between Cervical cancer cell lines and normal cervix; C1, Early stage cervical tumour without lymph node metastasis; C2, Early stage cervical tumour with lymph node metastasis; $^{C1\text{-}n}$, correlation between C1 and normal cervix; $^{C2\text{-}n}$, correlation between C2 and normal cervix. **Hodgkin's Lymphoma:** cHL, classical Hodgkin lymphoma; H/TCRBCL, histiocyte T cell-rich B-cell lymphoma; Lcl, Lymphoma cell line; Ad, adenite; ‡correlation between cHL and H/TCRBCL;

‡‡correlation between H/TCRBCL and Lcl; ‡‡‡correlation between cHL and Ad. **B-cell Non-Hodgkins Lymphoma:** RLN, Reactive Lymph Node; MCL, Mantle Cell Lymphoma; BL, Burkitt Lymphoma; NMZL, Nodal Marginal Zone Lymphoma; FL, Follicular Lymphoma; CLL, Chronic Lymphocytic Lymphoma; DLBL, Diffuse Large B-cell Lymphoma; SMZL, Splenic Marginal Zone Lymphoma; SC, Spleen Control; $^{MCL\text{-}RLN}$, correlation between MCL and RLN; $^{BL\text{-}RLN}$, correlation between BL and RLN; $^{FL\text{-}RLN}$, correlation between FL and RLN; $^{CLL\text{-}RLN}$, correlation between CLL and RLN; $^{DLBL\text{-}FL}$, correlation between DLBL and FL.

several other genes in prostate cancer. Supporting data came from Seligson et al.[61] who detected YY1 overexpression by immunohistocheminstry (IHC) in a large series of prostate cancer and prostatic intraepithelial neoplasia (PIN) compared to normal or benign prostatic hypertrophy (BPH) tissues. The authors reported that in non-malignant prostatic epithelium YY1 was observed mostly in the nucleus of glandular epithelium and basal cells, consistent with its activity in transcription regulation. Interestingly, 95% of the malignant samples analyzed also displayed a significant cytoplasmic staining. Similarly, YY1 was overexpressed in metastatic prostate cancer tissues from patients that had relapsed following prostatectomy.[61] However, when van Leenders et al.[62] identified YY1 immunohistochemically in tissue microarrays of prostate cancer patients and scored the protein expression levels semi-quantitatively, YY1 was ubiquitously present (>75% of cells) in prostate adenocarcinoma, but generally at a moderate level of intensity (2+).

We performed a computational analysis for the expression of YY1 in prostate cancer, based on data extracted from 5 different normalized Datasets.[19,22-25] Our results showed that YY1 transcription levels were significantly higher in prostate cancers versus the normal tissues (mean level of the $\log_2$ intensity: -1.06 vs. -2.15, p = 0.007, Mann-Whitney U test). Similarly, the analysis of the Dataset provided by Vanaja et al.[25] exhibited matching results (mean level of the $\log_2$ intensity: 1.50 vs. 1.09, p = 0.007, Mann-Whitney U test). The Dataset provided by Monzon et al.[19] comprised of a small sample number (6 metastatic tumors and 6 primary tumors). However, the difference was not statistically significant. According to these authors, YY1 presented higher YY1 expression levels in the first group compared to the latter (mean level of the $\log_2$ intensity: 1.16 vs. 1.10). Similarly, an analysis of the Dataset provided by Nanni et al. failed to show a statistically significant difference in the YY1 transcription levels between primary prostate cancers and normal tissues (mean level of the $\log_2$ intensity: 0.97 vs. 0.91), possibly due to the small number of control tissues (n = 3). Of note is that the analysis of the Dataset by Varambally et al.[23] showed that YY1 was significantly higher in primary prostate cancers than in metastatic prostate cancers (p = 0.022, Mann-Whitney U test), thereby arguing the concept that YY1 expression levels are higher in metastatic than primary prostate cancer.

Colon cancer. Chinnappan et al.[40] examined the expression of YY1 in a wide range of human cancer cell lines and in human colon cancer samples. Their results showed that YY1 was overexpressed in colon cancer in the absence of gene amplification and chromosomal translocation. We performed a computational analysis for the expression of YY1 in colon cancer, based on data extracted from the normalized Dataset provided by Notterman et al.[30] and found that YY1 expression levels were significantly higher in colon adenocarcinoma than normal specimens (mean level of the $\log_2$ intensity: 0.56 vs. 0.52, p = 0.011, Mann-Whitney U test).

Ovarian cancer. Previous studies conducted in 65 and 88 ovarian cancer tissues by microarray analysis showed that YY1 overexpression is positively correlated with long-term survival.[63,64] These observations may be explained by the fact that YY1 overexpression improves sensitivity to microtubule-stabilizing agents, such as taxanes. Moreover, YY1 knockdown in ovarian cancer cell lines resulted in the inhibition of cell growth, proliferation and increased resistance to taxanes.[64]

We analyzed the normalized data of five distinct Datasets[19,27,41,42] and concluded that YY1 transcription levels were significantly elevated in ovarian carcinomas, compared to the normal tissue (**Table 1**).

Breast cancer. In contrast, in breast cancer patients, YY1 overexpression appears to be associated with a poor prognosis as YY1 protein expression levels are positively correlated with Human Epidermal growth factor Receptor 2 (ERBB2).[65] Lieberthal et al.[66] studied the invasive breast cancer cell line HS578T and demonstrated that YY1 overexpression suppresses HS578T cell migration in vitro. Moreover, they concluded that a decreased YY1 expression may contribute to the invasive phenotype of metastatic breast cancer cells. The role of YY1 in metastatic breast cancer has recently been verified by meta-analysis.[67]

Notably, analysis of the Dataset GSE3744,[28] showed that YY1 exhibited significantly elevated mRNA levels in basal-like breast cancers versus normal tissue (mean level of the $\log_2$ intensity: 0.346 vs. 0.340; p = 0.045, Mann-Whitney U test).

Cervical cancer. Accordingly, elevated transcription levels of YY1 were found in other female neoplasms such as cancer intraepithelial neoplasm (CIN) and cervical cancer compared to controls suggesting its important prognostic value. YY1 was also overexpressed at the protein level in high-grade squamous intraepithelial lesion (HG-SIL) and in cancer tissues compared to low-grade squamous intraepithelial lesion (LG-SIL). In addition, the authors showed that the increase of YY1 at both transcript and protein levels was associated with the presence of Human Papilloma Virus (HPV) infection indicating that YY1 may play an important role in malignant transformation.[68]

Our computational analysis performed on the Datasets GSE9750,[57] and GSE7410,[58] showed that YY1 levels are significantly increased in cervical cancer versus normal tissue (mean level of the $\log_2$ intensity: 0.98 vs. 0.96; p = 0.006, Mann-Whitney U test). This difference was also verified between cervical carcinoma cell lines and normal tissue (mean level of the $\log_2$ intensity: 0.98 vs. 0.96; p = 0.017, Mann-Whitney U test), verifying the above-stated indication. Stronger verification came from our computational analysis on the Dataset GSE7410, which showed that YY1 transcription levels are significantly elevated in early stage cervical tumor with lymph node metastasis, compared to early stage cervical tumor without lymph node metastasis (mean level of the $\log_2$ intensity: 0.13 vs. -0.04; p = 0.001, Mann-Whitney U test). Furthermore, YY1 levels were significantly higher in each of the above-mentioned tumors, compared

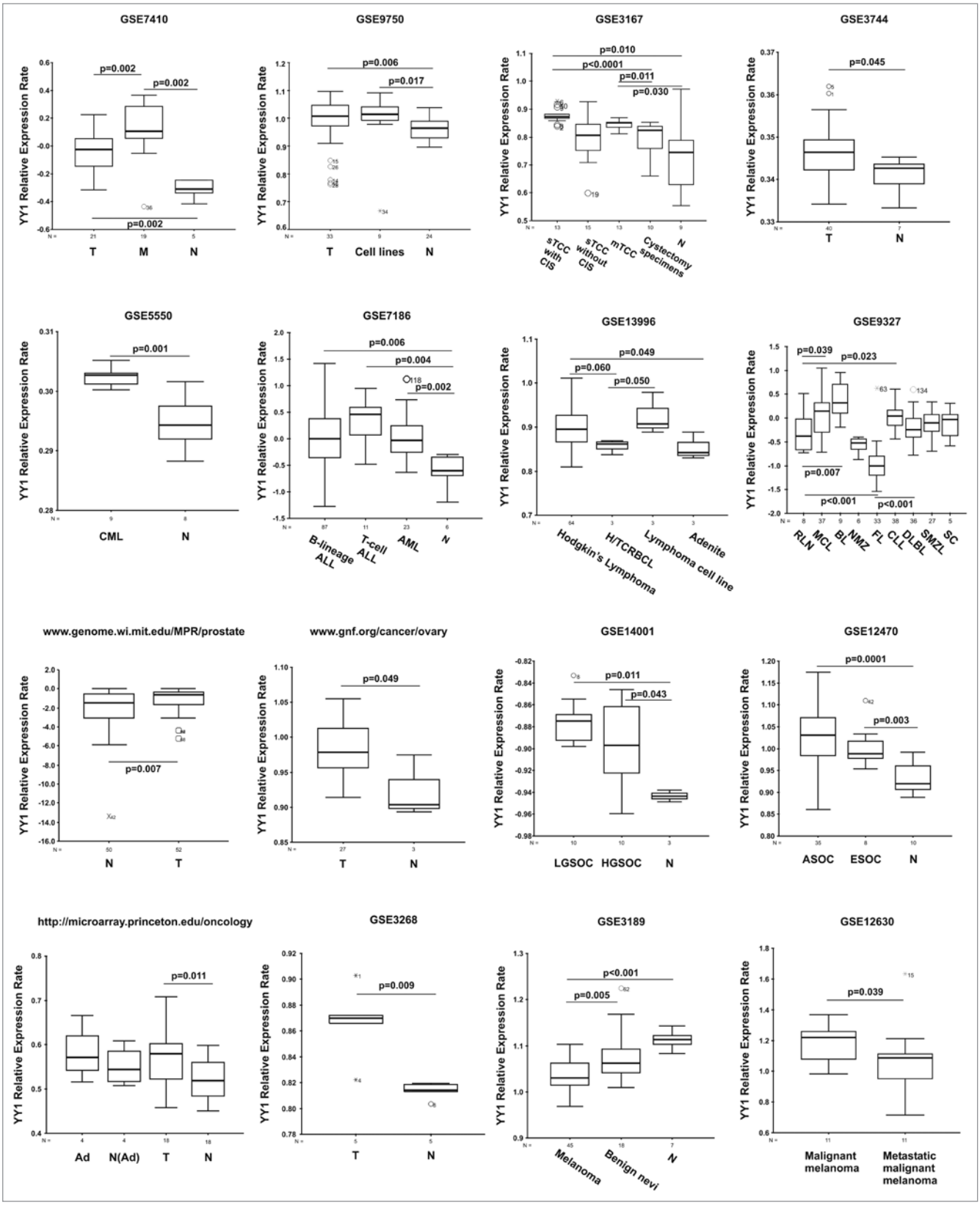

Figure 2. For figure legend, see p. 519.

Figure 2 (see opposite page). YY1 gene expression analysis was performed on data extracted from the following publicly available datasets: GSE7410 and GSE9750, Cervical cancer; GSE3167 Urinary bladder cancer; GSE3744, Breast cancer; GSE5550 and GSE7186 Leukemia; GSE13996, Hodgkin Lymphoma; GSE9327, B-cell Non-Hodgkin Lymphoma; www.genome.wi.mit.edu/MPR/prostate, Prostate cancer; www.gnf.org/cancer/ovary, GSE14001 and GSE12470, Ovarian cancer; http://microarray.princeton.edu/oncology, Colon cancer; GSE3268, Lung cancer; GSE3189, GSE12630, Melanoma. Results are expressed as mean levels of the log2 intensity and statistically compared by the Mann-Whitney U test. The majority of the tumors studied, exhibited significantly higher YY1 expression levels compared to the relative normal counterparts. Moreover, the metastatic tumors presented significantly higher YY1 relative expression rates in comparison to the primary tumors. In contrast, melanomas expressed significantly decreased YY1 relative expression rates, compared to both benign nevi and normal tissues. Moreover, metastatic malignant melanomas exhibited significantly lower expression rates compared to malignant melanomas. Boxplots show the 25th, 50th (median), and 75th percentile values. Whiskers show the minimum and maximum values. T, tumor; M, metastasis, N, normal tissue; sTCC with CIS, superficial transitional cell carcinoma (sTCC) with surrounding carcinoma in situ (CIS); sTCC without CIS, superficial transitional cell carcinoma (sTCC) without surrounding carcinoma in situ (CIS); mTCC, muscle invasive carcinomas (mTCC); CML, chronic myelogenous leukemia; B-lineage ALL, B-lineage acute lymphoblastic leukemia; T-cell ALL, T-cell acute lymphoblastic leukemia; AML, acute myeloid leukemia; H/TCRBCL, histiocyte T cell-rich B-cell lymphoma; RLN, Reactive Lymph Node; MCL, Mantle Cell Lymphoma; BL, Burkitt Lymphoma; NMZL, Nodal Marginal Zone Lymphoma; FL, Follicular Lymphoma; CLL, Chronic Lymphocytic Lymphoma; DLBL, Diffuse Large B-cell Lymphoma; SMZL, Splenic Marginal Zone Lymphoma; SC, Spleen Control; LGSOC, Low grade ovarian serous carcinoma; HGSOC, High grade ovarian serous carcinoma; ASOC, Advanced serous ovarian cancer; ESOC, Early serous ovarian cancer.

to the normal tissue (mean level of the $\log_2$ intensity: 0.13 vs. -0.31; p = 0.003 and -0.04 vs. -0.31; p = 0.002, respectively; Mann-Whitney U test).

Osteosarcoma. YY1 overexpression has been documented in human osteosarcoma. De Nigris et al.[69] demonstrated that YY1 is overexpressed in osteosarcoma cell lines and tissues compared to normal osteoblastic cells with a predominant localization in the nucleus. Based on their results, they considered that YY1 activation is an early event in the process of osteoblastic transformation and its detection may represent a useful diagnostic tool in human osteosarcomas.

However, an analysis of the Dataset GSE12865,[59] showed that YY1 presented lower expression levels in pediatric osteosarcomas, compared to normal human osteoblasts (mean level of the $\log_2$ intensity: 0.31 vs. 0.32; p = 0.028, Mann-Whitney U test).

Other solid tumors. The microarray analysis performed by Pilarsky et al.[60] in a wide range of solid tumors showed YY1 overexpression not only in colon cancer, but also in liver, lung, bladder, prostate, testicular as well as ovarian cancer.

We analyzed three normalized Datasets provided by Chen et al.[31] Wurmbach et al.[48] and Monzon et al.[19] in order to compare YY1 expression levels among hepatocellular carcinoma, dysplasia, cirrhosis and normal tissue. An analysis of the first two Datasets did not reveal any significant difference in the YY1 expression pattern. However, analysis of the third, showed that YY1 transcription levels decreased in metastatic compared to hepatocellular carcinoma (mean level of the $\log_2$ intensity: 1.12 vs. 1.28, p = 0.036, Mann-Whitney U test).

We also analyzed six normalized Datasets to compare YY1 transcription levels among squamous cell carcinoma (SCC), adenocarcinoma (Ad), small cell and non-small cell lung carcinoma (SCLC/NSCLC) and normal tissue.[19,34,49-52] YY1 mRNA levels were significantly higher in SCC compared to normal tissue (mean level of the $\log_2$ intensity: 0.86 vs. 0.81, p = 0.009, Mann-Whitney U test) in data extracted from the Dataset with Reference number GSE3268.[49] The corresponding $\log_2$ intensities (between SCC and normal) for Dataset GSE2088,[50] were not significantly different (-0.03 vs. -0.17, p = 0.081). However, in the same Dataset, Ad samples significantly expressed elevated YY1 levels compared to the normal tissue carcinoma (mean level of the $\log_2$ intensity: 0.26 vs. -0.17, p = 0.002, Mann-Whitney U test). A computational analysis of the Dataset GSE11969,[52] also revealed significantly higher YY1 levels in SCC compared to normal tissue (mean level of the $\log_2$ intensity: -0.05 vs. -0.31, p = 0.024, Mann-Whitney U test).

YY1 transcription levels were also significantly higher in urinary bladder cancer compared to normal tissue. Specifically, following the analysis of Dataset GSE3167,[46] we detected significant differences between superficial transitional cell carcinoma (*s*TCC) with carcinoma in situ, and normal specimens (mean level of the $\log_2$ intensity: 0.87 vs. 0.79; p < 0.010, Mann-Whitney U test), as well as between muscle invasive carcinoma (mTCC) and normal tissue (mean level of the $\log_2$ intensity: 0.84 vs. 0.79; p = 0.030, Mann-Whitney U test). Notably, the analysis of the Dataset GSE12630,[19] showed that YY1 RNA levels were lower in metastatic urothelial carcinoma versus transitional cell carcinoma (mean level of the $\log_2$ intensity: 1.10 vs. 1.27; p = 0.025, Mann-Whitney U test).

We analyzed the expression of YY1 in various testicular germ cell tumors.[18-20,43] Our results indicate that pT1 and pT2 testicular seminomas expressed significantly higher YY1 versus the normal tissue (mean levels of the $\log_2$ intensity: 0.78 vs. 0.55; p = 0.006 and p = 0.008, respectively; Mann-Whitney U test). Moreover, an analysis of the Dataset GSE12630,[19] showed that YY1 expression levels are significantly elevated in teratomas versus testicular seminomas (mean level of the $\log_2$ intensity: 1.31 vs. 1.18; p = 0.039, Mann-Whitney U test). Notably, analysis of the Dataset GSE1818,[20] showed that YY1 levels were significantly higher in teratomas and testicular seminomas, compared to normal testis (mean level of the $\log_2$ intensity: 0.85 vs. 0.31; and 1.12 vs. 0.31, respectively; p = 0.050, Mann-Whitney U test).

Contrary to the results from the above-mentioned tumors, analysis of the Datasets GSE3189,[54] and GSE12630,[19] in melanomas, showed that YY1 had a significant decrease compared to both benign nevi and normal tissues (mean level of the $\log_2$ intensity: 1.04 vs. 1.08, p = 0.005; and 1.04 vs. 1.11, p < 0.001, respectively; Mann-Whitney U test). Moreover, metastatic malignant melanomas exhibited significantly lower expression rates versus malignant melanomas (mean level of the $\log_2$ intensity: 1.06 vs. 1.18, p = 0.039; Mann-Whitney U test).

Acute myeloid leukemia (AML). Elevated YY1 levels have also been observed in non-solid tumors. Grubach et al.[70] analyzed the expression levels of Polycomb group (PcG) genes, including

YY1, in bone marrow samples from 126 acute myeloid leukemia (AML) patients and compared them to 20 healthy donors. Their results showed an overexpression of YY1 and the rest of the PcG genes in the AML patients, compared to the controls. Moreover, Erkeland et al.[71] detected increased YY1 expression in human AML. Their results implied a possible role of perturbed YY1 expression in the development of AML, through interference with the myeloid differentiation program in the leukemic progenitor cells.

Our computational analysis on the Dataset GSE7186,[36] verified that YY1 transcription levels are higher in acute myeloid leukemia (AML) (mean level of the $\log_2$ intensity: 0.008 vs. -0.62, p = 0.02, Mann-Whitney U test), as well as in both B-lineage acute lymphoblastic leukemia (B-lineage ALL) and T-cell acute lymphoblastic leukemia (T-cell ALL), compared to the normal counterpart (mean level of the $\log_2$ intensity: -0.001 vs. -0.62, p = 0.006, and 0.29 vs. -0.62, p = 0.004; Mann-Whitney U test). Moreover, the data analysis of the Dataset GSE5550,[38] showed that YY1 is significantly elevated in chronic myelogenous leukemia (CML) versus the normal counterpart (mean level of the $\log_2$ intensity: 0.30 vs. 0.29, p = 0.001, Mann-Whitney U test).

Hodgkin lymphoma (HD). As regards Hodgkin lymphoma (HD), Dukers et al.[72] reported that immunohistochemical staining for YY1 showed a strong nuclear expression in the nuclei of virtually all the neoplastic Reed-Sternberg cells (RS cells) and their mononuclear variants, the Hodgkin cells (H cells).

We analyzed the Dataset GSE13996 provided by Chetaille et al.[73] that comprised a set of 63 classical Hodgkin lymphoma (cHL) tissue samples and was profiled using DNA microarrays. YY1 gene expression profile differed from that of histiocyte T cell-rich B-cell lymphoma (H/TCRBCL) samples, which were used as controls (mean level of the $\log_2$ intensity: 0.89 vs. 0.85, p = 0.06, Mann-Whitney U test). YY1 overexpression was also verified in a lymphoma cell line compared to H/TCRBCL samples (mean level of the $\log_2$ intensity: 0.92 vs. 0.85, p = 0.05, Mann-Whitney U test). Similarly, YY1 expression was significantly higher in classical Hodgkin lymphoma versus adenite samples (mean level of the $\log_2$ intensity: 0.89 vs. 0.85, p = 0.049, Mann-Whitney U test).

Non-hodgkin lymphoma (NHL). Similarly, increased YY1 expression levels have also been reported for Non-Hodgkin lymphoma (NHL).[77] We analyzed the YY1 transcriptional profile from the Dataset GSE9327 provided by Ruiz-Vella et al.[74] Our analysis included major types of B-cell NHL clinical samples, the YY1 expression of which was compared against reactive lymph nodes (RLN), apart from Splenic Marginal Zone Lymphomas (SMZL), the expression of which was compared against normal splenic cells. Interestingly, YY1 transcription levels of Mantle-cell (MCL), Burkitt (BL) and Chronic Lymphocytic lymphomas (CLL), were significantly higher compared to the corresponding controls/RLN (mean level of the $\log_2$ intensity: MCL vs. RLN, 0.06 vs. -0.29, p = 0.039; BL vs. RLN, 0.38 vs. -0.29, p = 0.007; CLL vs. RLN, 0.04 vs. -0.29, p = 0.023; Mann-Whitney U test).

Follicular lymphoma (FL) and in diffuse large B-cell lymphoma (DLBCL). Furthermore, Sakhinia et al.[75] showed that YY1 was upregulated in follicular lymphoma (FL) and in diffuse large B-cell lymphoma (DLBCL), using RT-PCR. The elevated YY1 levels were associated with a shorter survival interval in both FL and DLBCL. Finally, it has recently been demonstrated that YY1 is overexpressed in FL resistant to rituximab suggesting its implication in drug resistance.[76]

However, our computational analysis performed on the Dataset GSE9327,[74] showed reduced YY1 transcript levels in FL compared to reactive lymph nodes (mean level of the $\log_2$ intensity: FL vs. RLN, -0.96 vs. -0.29, p < 0.001; Mann-Whitney U test). Hence, YY1 expression levels were significantly higher in DLBCL compared to FL (mean level of the $\log_2$ intensity: DLBCL vs. FL, -0.19 vs. -0.96, p < 0.001; Mann-Whitney U test).

Conclusion

YY1 is a transcription factor with complex biological functions, including apoptosis, tumorigenesis, development and differentiation. Overexpression of YY1 in tumor tissues exerts different clinical behavior in different tumor types. Higher transcript levels of YY1 were observed in many different cancer tissues when compared to the relative normal counterparts. Moreover, in many human cancer types, YY1 expression levels were found to be significantly elevated in the metastatic tumor compared to its primary counterpart, supporting the potential role of YY1 in cancer development. The unusually high levels of YY1 expression levels observed in cancer cells may be an outcome of deregulated YY1 transcription. One interesting possibility would be that some epigenetic changes, such as DNA methylation or histone modification, and subsequent malfunction of the cluster of YY1 binding sites may be responsible for this deregulation. In that regard, it would be interesting to test the epigenetic modification of this region in cancer cells in the future.

However, in some tumor types, such as melanoma and adenocarcinoma, YY1 transcription rates significantly decreased versus both the benign and normal counterparts. These results support a dual role of YY1 in cancer development, either through overexpression or under-expression, depending on the tumor type.

In general, our observations corroborate that YY1 is an important prognostic marker for several human tumors. Therefore, its regulation in cancer along with the development of new therapeutic targets of YY1 may represent promising tools against cancer therapy.

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