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Report

The involvement of the transcription factor Yin Yang 1 in cancer development and progression

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The Yin Yang 1 (YY1) transcription factor has a pivotal role in normal biological processes such as development, differentiation, replication and cell proliferation exerting its effects on a huge number of genes involved in these processes. Mechanisms of YY1 action are related to its ability to initiate, activate, or repress transcription depending upon the context in which it binds. The role of YY1 played in cancer has been recently explored. This article summarizes the most relevant studies focused on YY1 regulation and dwells on the way how its overexpression may affect the clinical behavior of several cancer types. Furthermore, the contribution of the upregulation of YY1 exerted in response to therapeutic-induced apoptosis is discussed.

Introduction

Cancer is the second leading cause of death in the Western world. The most common leading causes of cancer deaths are lung cancer, breast cancer, prostate cancer, ovarian cancer, colon-rectum cancer, pancreatic cancer and hematologic malignancies.[1] When detected at locally advanced or metastatic stages, no consistently curative treatment regimen exists. It has been demonstrated that new cancer therapies can improve outcome, however, many patients relapse after treatment. The mechanism responsible for the anti-apoptotic phenotype, if identified, may be useful as a prognostic and/or diagnostic indicator and target for therapeutic strategies. Recently, it has been reported that the transcription factor Yin Yang 1 (YY1) inhibits Fas expression and renders cells resistant to Fas ligand-mediated apoptosis and its inhibition results in upregulation of Fas expression and sensitization to Fas-mediated apoptosis.[2] Moreover, the numerous evidences that YY1 overexpression may promote p53 degradation or inhibit its transcriptional activity may give further insight into YY1's role in cancer development.[3] In this study, the clinical relevance of YY1 overexpression in different cancer types was explored to better understand the diagnostic/prognostic significance of YY1. Finally, implication of YY1 in tumor development and drug resistance was examined.

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Yin Yang 1: Gene and Protein Structure

YY1 is a member of the Polycomb Group protein family, a group of homeobox gene receptors that play critical roles in hematopoiesis and cell cycle control. YY1 was initially cloned and characterized simultaneously in 1991 by two independent groups, Shi et al.[4] and Park and Atchison.[5] The gene is highly conserved among different species. The human YY1 gene is located on the telomere region of human chromosome 14 at the segment q32.2.[6] It consists of five highly conserved exons encoding a protein of 414 amino acids in length, and an estimated molecular weight of 44 kDa. Rat YY1 is composed of 411 amino acid residues and its amino acid sequences is 97.6% identical to that of mouse YY1 and 97.8% identical to that of human YY1.[7] 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.

The YY1 protein contains four C2H2-type zinc-finger motifs with two specific domains that characterize its function as an activator or repressor. YY1 is a phosphoprotein with a half-life of 3.5 hours. Post-traslational modification of YY1 could potentially change the way YY1 functions in transcription by altering protein stability and binding affinity to DNA and switching protein partners. Acetylation and deacetylation have intriguing influences on the sequence-specific DNA binding and transcriptional activities of YY1.[8]

Yin Yang 1 Function

YY1 is ubiquitously expressed and may play an important role in the regulation of many cellular and viral genes through the consensus cis recognition sequence CGCCATNTT. When the YY1 consensus sequence was used to search the Eukaryotic Promoter Database, a total of 1,664 potential YY1 sites were

Table 1 **Clinical significance of YY1 overexpression in cancer**

Tumor type (n. cases)	Methods	Clinical relevance of YY1 overexpression	References
Prostate cancer (190)	IHC	Positive correlation with metastasis and inverse correlation with poorer outcome	18
Ovarian Cancer (65)	Microarray	Positive correlation with long-term survival	19
Ovarian Cancer (88)	Microarray, RT-PCR, IHC	Positive correlation with survival and response to taxane	20
Breast cancer (55)	IHC	Positive correlation with ERBB2 overexpression	21
Cervical Neoplasms (22)	RT-PCR	Positive correlation with disease progression	22
Osteosarcoma (19)	RT-PCR, IHC, WB	Positive correlation with more malignant histological phenotypes	23
Myeloid Leukaemia (126)	RT-PCR	Positive correlation with t(8;21)	24
Hodgkin Lymphoma (54)	IHC	N.A.	25
Non-Hodgkin Lymphoma (96)	RT-PCR	Positive correlation with poor outcome	26
Non-Hodgkin Lymphoma (796)*	Computational analysis	Positive correlation with more malignant phenotype and poorer outcome	27
Non-Hodgkin Lymphoma (104)	WB, IHC	Positive correlation with more malignant phenotype and poorer outcome	27

*Non-Hodgkin Lymphoma samples derived from 3 different datasets of publicly available microarray data, see refs. 28–30; NA, Not applicable.

found in the promoter of 2,540 vertebrate genes and 93 sites in the promoter of 129 viral genes.[9]

YY1 can activate or repress the expression of many cellular and viral genes depending on its relative concentration.[7] YY1 has been described as an initiator-binding protein. This result has been supported by the finding that in the absence of TATA-binding protein (TBP), YY1 together with TFIIB and RNA polymerase II were sufficient to correctly initiate transcription from a supercoiled DNA template in vitro.[10] The authors suggested that under the appropriate conditions, YY1 could function like TBP, as a factor that binds to the initiation complex. Other studies have repeatedly shown the association and modulation of YY1 by adenovirus-derived E1A, a protein that activates the AAV P5 promoter.[11] The presence of E1A induced YY1-mediated activation of transcription in contrast with the absence of E1A, a repression of transcription was induced; hence the name Yin-Yang 1.[7]

Several mechanisms have been implicated as determinants of YY1-mediated transcriptional activation or repression and a wide list of human promoters/gene products has been reported (reviewed in ref. 12). Overall these findings demonstrated that the function of YY1 in transcription is context-specific and requires interactions with many cellular factors. As a result, YY1 develops intracellular networks that allow it to induce multiple functions in transcriptional initiation, activation and repression, ultimately leading to the regulation of normal cell growth and survival.[13]

Yin Yang 1 and Tumorigenesis

p53. The putative role of YY1 in tumorigenesis is supported by its known interaction with the cell cycle regulation.[3] Uncontrolled cell cycle progression is a main player in tumorigenesis. Several molecules that act to prevent uncontrolled cell division are involved in cancer development and *p53* is one of them. It is a tumor suppressor protein and a transcriptional regulator that plays an important role in cellular responses to various stress signals, like a DNA damage or an oncogenic insult.[14] The importance of *p53* as a tumor suppressor is highlighted by the fact that over 50% of all tumors carry inactivating mutations in *p53* gene.[15] The loss of YY1 results in a significant increase in *p53* levels. In fact YY1, *MDM-2* and *p53* can form a ternary complex and YY1 is essential for optimal *MDM2-p53* physical interactions in vivo, which is a prerequisite for *MDM-2* to be able to ubiquinate *p53*. Ubiquitination induces the translocation of *p53* to the proteasome which leads to its degradation.[16] Therefore overexpression of YY1 significantly decrease endogenous *p53* level.[3]

FAS. YY1 can also interferes with apoptosis process favoring an uncontrolled cell growth. Previous studies demonstrate that YY1 confers resistance to *Fas*-induced apoptosis through binding to silencer regions of the *Fas* promoter.[2] Therefore, inhibition of YY1 activity results in upregulation of *Fas* expression and sensitization of tumor cells to *Fas*-induced apoptosis. Thus, downregulation of YY1 activity expression in tumor cells may provide a new therapeutic strategy to potentiate tumor-directed immunotherapy. It has been demonstrated that NO causes S-nitrosothiol modification of critical cysteine residues in the zinc-finger domains of YY1 with consequent disruption of the structural conformation of YY1 binding to its cognate responsive element. Inhibition of YY1 DNA-binding activity through S-nitrosation consequently resulted in upregulation of *Fas* expression and tumor cell sensitization to *Fas*-induced apoptosis.[17]

Overexpression of Yin Yang 1 in Different Cancer Types

Previous studies reported that YY1 is overexpressed and affects the clinical behavior of several tumor types (Table 1). YY1 overexpression has been detected by immunohistocheminstry (IHC) in a large series of prostate cancer and prostatic intraepithelial neoplasia (PIN) compared to normal or benign prostatic hypertrophy (BPH) tissues histological diagnosed.[18] 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 displayed also a significant cytoplasmic staining. Similarly, YY1 was overexpressed in metastatic prostate cancer tissues from patients relapsed after prostatectomy.[18] These data are in agreement with our observations by analyzing the publicly available gene expression dataset by Yu et al.[31] considering 64 primary and 25 hormone-refractory metastatic prostate carcinoma tissues. This analysis revealed that YY1 transcription levels were significantly higher in metastatic samples than in primary tumors (Mean level of the $\log_2$ intensity: 1.78 vs. 2.25, $p < 0.0001$, Mann-Whitney test) (Our unpublished data). Although Seligson et al.[18] reported that YY1 protein levels are higher in prostate metastatic tissues than primary tumors, intriguingly, low YY1 levels correlated with a poorer outcome. The authors suggested that decreased YY1 expression may enhance the survival of metastatic prostate cancer cells.[18]

Previous studies conducted, respectively, in 65 and 88 ovarian cancer tissues by microarray analysis showed that YY1 overexpression is positively correlated with a long-term survival.[19,20] 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 inhibition of cell growth, proliferation and increase resistance to taxanes.[20]

In contrast, in breast cancer patients, YY1 overexpression seams to be associated with a poor prognosis as YY1 protein expression levels are positively correlated with Human Epidermal growth factor Receptor 2 (ERBB2).[21] It has been described that ERBB2 gene is amplified in 20–30% of breast cancers. ERBB2 overexpression is common among estrogen receptors-negative tumors and linked to a worse prognosis in breast cancer patients.[32]

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 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 were associated with the presence of Human Papilloma Virus (HPV) infection indicating that YY1 may play an important role in the malignant transformation.[22]

YY1 overexpression has been documented also in human osteosarcoma.[23] The authors, using different approaches, demonstrated that YY1 is overexpressed in osteosarcoma cell lines and tissues compared to normal osteoblastic cells with a predominant localization in the nucleus.[23]

High levels of YY1 were observed in non-solid tumors, including myeloid leukemia (AML),[24] Hodgkin lymphoma (HD)[25] and Non-Hodgkin lymphoma (NHL),[26,27] when compared to normal samples. Sakhinia et al.[26] showed that YY1 was upregulated in follicular lymphoma (FL) and in diffuse large B-cell lymphoma (DLBCL). While, our preliminary studies, analyzing the microarray data publicly available by Basso et al.[28] showed that YY1 transcript levels were significantly higher in high-grade lymphomas (DLBCL and Burkitt's lymphoma) compared with low-grade lymphomas (FL) and normal B-cells.[27] The association of YY1 expression levels with the available main clinical and biological parameters was analyzed using the expression data from two high-grade lymphoma studies[29,30] with a total of approximately 400 samples. In agreement with the previous studies,[26] survival analysis in both datasets revealed that higher levels of YY1 gene transcription were associated with poor outcome.[27]

The correlation between all the genes present in the dataset by Hummel et al.[30] and YY1 gene expression profile was previously evaluated by our group of research.[27] Using the proprietary Ingenuity Pathway Analysis software, the analysis showed 29 biological networks significantly associated to YY1. Several of the genes modulated coordinatively with YY1 are related to cellular movement, cell morphology, cell cycle, carbohydrate metabolism and cell-to-cell adhesion. Ingenuity Pathway analysis predicts that 19 and 4 of the 23 genes involved in the cell cycle and significantly associated to YY1 are directly and inversely co-regulated (Fig. 1). Overall these data indicate that YY1 may be involved in the B cells transformation given rise to high-grade lymphomas and may be implicated in the regulation of cell cycle. These observations are also supported by previous studies demonstrating that YY1 is involved in controlling multiple stages of early B-cell development especially the pro-B-to-pre-B-cell transition.[33] Finally, it has been recently demonstrated that YY1 is overexpressed in FL resistant to rituximab suggesting its implication in drug resistance.[34]

In the present study computational analysis was performed to further understand if differences in YY1 transcript levels occur in different cancer types when compared with the relative normal tissue. Fifteen publicly available gene expression datasets were analyzed.[28,35-48] Gene expression patterns of YY1 in nine different types of tumor and the relative normal counterpart were extracted from the normalized datasets (Table 2). This analysis reveals that YY1 transcript levels are significantly higher in cancer tissues than in the relative normal counterparts for each cancer type analyzed. These results support the potential role of YY1 in cancer development.

Implication of Yin Yang 1 in Response to Therapeutic-Induced Apoptosis

Cancer patients cured with conventional therapies may relapse after initially response. Therefore, new therapeutic strategies are currently being explored. Targeted anti-cancer therapies are becoming the new choice in the treatment of resistant tumors. Monoclonal antibodies targeting TRAIL-death receptors have been developed and currently used in clinical trials as targeted therapy (reviewed in ref. 49). Unfortunately many cancers, like breast, prostate, ovarian, lung carcinoma, multiple myeloma and leukemia, show resistance to TRAIL-mediated apoptosis.[49] Recently, it has been demonstrated that YY1 may be a potential therapeutic target to reverse resistance to TRAIL-induced apoptosis.[50,51] The authors show that chemotherapeutic drugs may sensitize tumor cells to TRAIL-mediated apoptosis through inhibition of the transcription repressor YY1 and upregulation of DR5 expression.[52,53] Our recent findings show the capacity of GIT-27 nitric-oxide (NO) to induce p53-mediated apoptosis along with inhibition of YY1 in

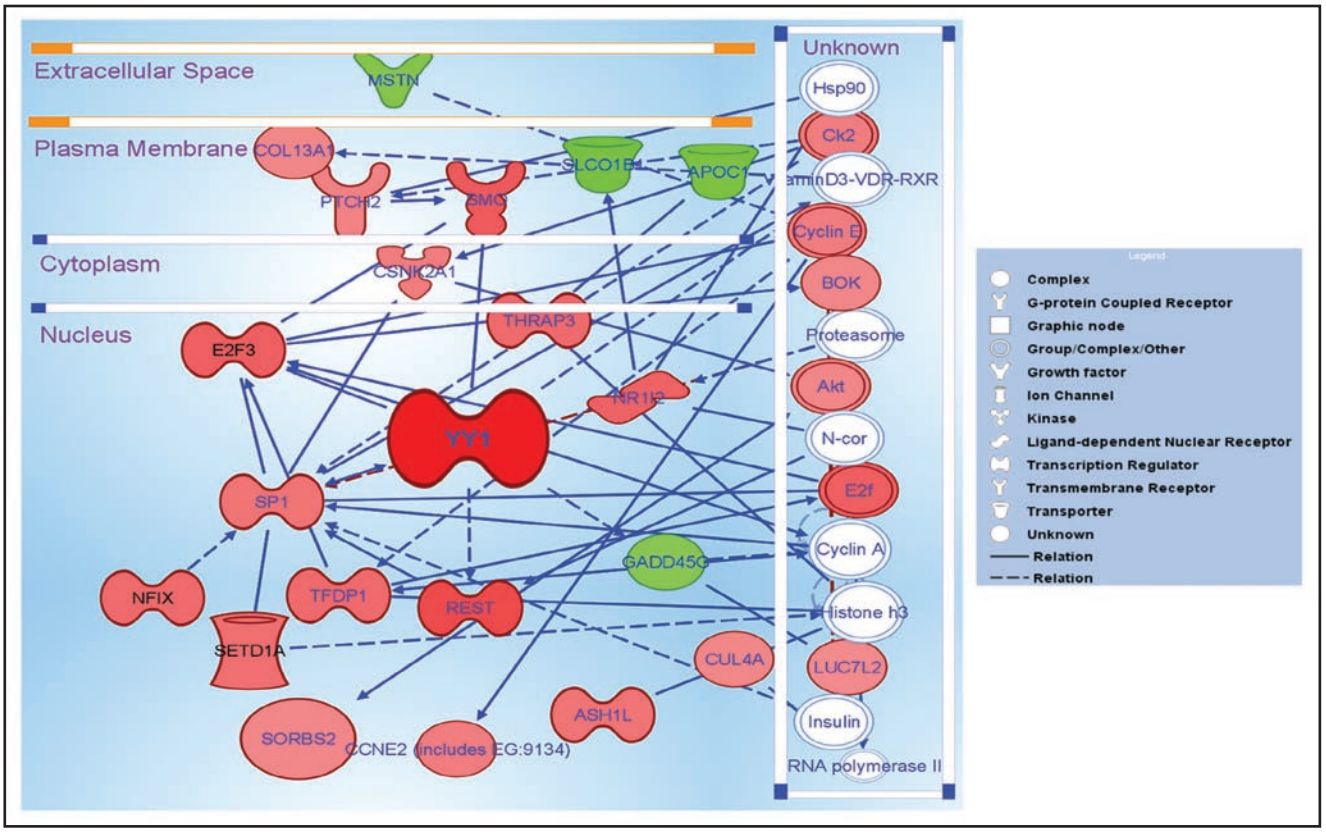

Figure 1. Scheme of the association among genes belonging to the cell cycle and the YY1 transcription factor as predicted by the Ingenuity Pathway Analysis. A publicly available dataset of gene expression data from B cell lymphoma samples containing a total of 166 samples,[30] was used to evaluate the correlation between all the genes in the platform and YY1 gene expression profile. Ingenuity Pathway analysis predicts that 19 and 4 of the 23 genes involved in the cell cycle and significantly associated to YY1 are directly (red fill) and inversely (green fill) co-regulated. The genes, whose shape refer to their function, are reported in the scheme in relation to their cellular location. The direct and indirect associations between the genes are indicated by continuous and dotted lines, respectively.

Table 2 **Gene expression analysis of the transcription factor YY1 in different tumor types**

Tumor type	N. of samples		Log. mean expression of YY1		p	Data set	
	Primary tumor	Normal tissue	Primary tumor	Normal tissue		Author (ref.)	Year
Prostate	52	50	-1.19	-1.86	0.0012	Singh et al. (35)	2002
Prostate	27	8	1.50	1.09	0.0007	Vanaja et al. (36)	2003
Ovarian	28	4	1.07	0.69	0.0004	Welsh et al. (37)	2001
Ovarian	41	4	0.05	-0.23	0.0192	Hendrix et al. (38)	2006
Breast	40	7	1.95	1.79	0.0003	Richardson et al. (39)	2006
Breast	5	5	1.59	1.23	0.0039	Turashvili et al. (40)	2007
Colon	18	18	0.56	0.29	0.0062	Notterman et al. (41)	2001
Colon	53	28	0.30	-0.03	0.0072	Ki et al. (42)	2007
Liver	100	72	-030	-0.48	0.01529	Chen et al. (43)	2002
Liver	35	10	2.31	2.10	0.0196	Wurmbach et al. (44)	2007
Lung	31	17	0.64	0.14	0.0000	Bhattacharjee et al. (45)	2001
Lung	20	19	0.98	0.76	0.0000	Stearman et al. (46)	2005
Melanoma	24	3	-0.36	-1.01	0.0048	Hoek et al. (47)	2006
Leukemia	87	6	1.18	-0.67	0.0002	Andersson et al. (48)	2007
Lymphoma	31	25	1.51	1.29	0.0000	Basso et al. (28)	2005

Note: Gene expression patterns of YY1 in 9 different type of tumors and the relative normal counterpart were extracted from the normalized dataset. Results are expressed as mean level of the $\log_2$ intensity and statistically compared by Mann-Whitney test (p-values are reported for each comparison between expression levels in tumor and normal cases).

A375 melanoma cells indicating its important anti-cancer pharmacological profile.[54] Altogether, these data indicate that YY1 may represent a novel target of antitumor therapy.

Conclusions

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. Our analyses on NHL show that YY1 may be involved in the B cells transformation given rise to high-grade lymphomas and may be implicated in the regulation of cell cycle. Furthermore, higher transcript levels of YY1 were observed in different cancer tissues when compared to the relative normal counterparts supporting the potential role of YY1 in cancer development. The relationship between inhibition of YY1 by drugs and reverse resistance to TRAIL-induced apoptosis through DR5 upregulation, suggest to use YY1 as a target for antitumor therapy. Overall these observations indicate that YY1 may be an important prognostic marker for several tumors and its regulation in cancer along with the development of new therapeutics targets of YY1 may represent new tools against cancer therapy.

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References

1. Coleman MP, Quaresma M, Berrino F, Lutz JM, De Angelis R, Capocaccia, et al. Cancer survival in five continents: a worldwide population-based study (CONCORD). Lancet Oncol 2008; 9:730-56.
2. Garban NJ, Bonavida B. Nitric oxide inhibits the transcription repressor Yin-Yang 1 binding activity at the silencer region of Fas promoter: a pivotal role for nitric oxide in the upregulation of Fas gene expression in human tumor cells. J Immunol 2001; 167:75-81.
3. Sui G, Affar E, Shi Y, Brignone C, Wall NR, Yin P, et al. Yin Yang 1 is a negative regulator of p53. Cell 2004; 117:859-72.
4. Shi Y, Seto E, Chang LS, Shenk T. Transcriptional repression by YY1, a human GLI-Kruppel-related protein, and relief of repression by adenovirus E1A protein. Cell 1991; 67:377-88.
5. Park K, Atchison ML. Isolation of a candidate repressor/activator, NF-E1 (YY-1, delta), that binds to the immunoglobulin kappa 3' enhancer and the immunoglobulin heavy-chain mu E1 site. Proc Natl Acad Sci USA 1991; 88:9804-8.
6. Yao YL, Dupont BR, Ghosh S, Fang Y, Leach RJ, Seto E. Cloning, chromosomal localization and promoter analysis of the human transcription factor YY1. Nucleic Acids Res 1998; 26:3776-83.
7. Shi Y, Lee JS, Galvin KM. Everything you have ever wanted to know about Yin-Yang 1. Biochim Biophys Acta 1997; 1332:49-66.
8. Hiromura M, Choi CH, Sabourin NA, Jones H, Bachvarov D, Usheva A. YY1 is regulated by O-linked N-acetylglucosaminylayion. J Biol Chem 2003; 278:14046-52.
9. Hyde-Deruyscher RP, Jennings E, Shenk T. DNA binding sites for the transcriptional activator/repressor YY1. Nucleic Acids Res 1995; 23:4457-65.
10. Uscheva A, Shenk T. TATA binding protein-indipendent initiation: YY1, TFIIB and RNA polymerase II direct basal transcription on supercoiled template DNA. Cell 1994; 76:1115-21.
11. Chang LS, Shi Y, Shenk T. Adeno-associated virus P5 promoter contains an adenovirus E1A-inducible element and a binding site for the major late transcription factor. J Virol 1989; 63:3479-88.
12. Gordon S, Akopyan G, Garban H, Bonavida B. Transcription factor YY1: structure, function and therapeutic implications in cancer biology. Oncogene 2006; 25:1125-42.
13. Palko L, Bass HW, Beyrouthy MJ, Hurt MM. The Yin Yang-1 (YY1) protein undergoes a DNA-replication-associated switch in localization from the cytoplasm to the nucleus at the onset of S phase. J Cell Sci 2004; 117:465-76.
14. Blattner C. Regulation of p53: the next generation. Cell Cycle 2008; 7:3149-53.
15. Lane DP. p53 and human cancers. Br Med Bull 1994; 50:582-99.
16. Naski N, Gajjar M, Bourougaa K, Malbert-Colas L, Fåhraeus R, Candeias MM. The p53 mRNA-Mdm2 interaction. Cell Cycle 2009; 8:31-4.
17. Hongo F, Garban H, Huerta-Yepez S, Vega M, Jazirehi AR, Mizutani Y, et al. Inhibition of the transcription factor Yin Yang 1 activity by S-nitrosatio. Biochem Biophys Res Commun 2005; 336:692-701.
18. Seligson D, Horvath S, Huerta-Yepez S, Hanna S, Garban H, Roberts A, et al. Expression of transcription factor Yin Yang 1 in prostate cancer. Int J Oncol 2005; 27:131-41.
19. Berchuck A, Iversen ES, Lancaster JM, Pittman J, Luo J, Lee P, et al. Patterns of gene expression that characterize long-term survival in advanced stage serous ovarian cancers. Clin Cancer Res 2005; 11:3686-96.
20. Matsumura N, Huang Z, Baba T, Lee PS, Barnett JC, Mori S, et al. Yin Yang 1 modulates taxane response in epithelial ovarian cancer. Mol Cancer Res 2009; 7:210-20.
21. Allouche A, Nolens G, Tancredi A, Delacroix L, Mardaga J, Fridman V, et al. The combined immunodetection of AP-2alpha and YY1 transcription factors is associated with ERBB2 gene overexpression in primary breast tumors. Breast Cancer Res 2008; 10:9.
22. Baritaki S, Sifakis S, Huerta-Yepez S, Neonakis IK, Soufla G, Bonavida B, et al. Overexpression of VEGF and TGFβ1 mRNA in Pap smears correlates with progression of cervical intraepithelial neoplasia to cancer: implication of YY1 in cervical tumorigenesis and HPV infection. Int J Oncol 2007; 31:69-79.
23. De Nigris F, Botti C, de Chiara A, Rossiello R, Apice G, Fazioli F, et al. Expression of transcription factor Yin Yang 1 in human osteosarcomas. Eur J Cancer 2006; 42:2420-4.
24. Grubach L, Juhl-Christensen C, Rethmeier A, Olesen LH, Aggerholm A, Hokland P, et al. Gene expression profiling of Polycomb, Hox and Meis genes in patients with acute myeloid leukaemia. Eur J Haematol 2008; 8:112-22.
25. Dukers DF, van Galen JC, Giroth C, Jansen P, Sewalt RG, Otte AP, et al. Unique polycomb gene expression pattern in Hodgkin's lymphoma and Hodgkin's lymphoma-derived cell lines. Am J Pathol 2004; 164:873-81.
26. Sakhinia E, Glennie C, Hoyland JA, Menasce LP, Brady G, Miller C, et al. Clinical quantitation of diagnostic and predictive gene expression levels in follicular and diffuse large B-cell lymphoma by RT-PCR gene expression profiling. Blood 2007; 109:3922-8.
27. Libra M, Castellano G, Baritaki S, Huerta-Yepez S, Ligresti G, Militello L, et al. Expression, role in transformation and prognostic significance of the transcription factor Yin Yang 1 (YY1) in non-Hodgkin's lymphoma: analyses in NHL tissues by experimental and bioinformatic approaches. Blood (ASH Annual Meeting Abstracts) 2008; 112:2827.
28. Basso K, Margolin AA, Stolovitzky G, Klein U, Dalla-Favera R, Califano A. Reverse engineering of regulatory networks in human B cells. Nat Genet 2005; 37:382-90.
29. Rosenwald A, Wright G, Chan WC, Connors JM, Campo E, Fisher RI, et al. The use of molecular profiling to predict survival after chemotherapy for diffuse large-B-cell lymphoma. N Eng J Med 2002; 346:1937-47.
30. Hummel M, Bentink S, Berger H, Klapper W, Wessendorf S, Barth TF, et al. A biologic definition of Burkitt's lymphoma from transcriptional and genomic profiling. N Engl J Med 2006; 354:2419-30.
31. Yu YP, Landsittel D, Jing L, Nelson J, Ren B, Liu L, et al. Gene expression alterations in prostate cancer predicting tumor aggression and preceding development of malignancy. J Clin Oncol 2004; 22:2790-9.
32. Révillion F, Bonneterre J, Peyrat JP. ERBB2 oncogene in human breast cancer and its clinical significance. Eur J Cancer 1998; 34:791-808.
33. Liu H, Schmidt-Supprian M, Shi Y, Hobeika E, Barteneva N, Jumaa H, et al. Yin Yang 1 is a critical regulator of B-cell development. Genes & Dev 2007; 21:1179-89.
34. Dalle S, Dupire S, Brunet-Manquat S, Reslan L, Plesa A, Dumontet C. In vivo model of follicular lymphoma resistant to rituximab. Clin Cancer Res 2009; 15:851-7.
35. Singh D, Febbo PG, Ross K, Jackson DG, Manola J, Ladd C, et al. Gene expression correlates of clinical prostate cancer behavior. Cancer Cell 2002; 1:203-9.
36. Vanaja DK, Cheville JC, Iturria SJ, Young CY. Transcriptional silencing of zinc finger protein 185 identified by expression profiling is associated with prostate cancer progression. Cancer Res 2003; 63:3877-82.
37. Welsh JB, Zarrinkar PP, Sapinoso LM, Kern SG, Behling CA, Monk BJ, et al. Analysis of gene expression profiles in normal and neoplastic ovarian tissue samples identifies candidate molecular markers of epithelial ovarian cancer. Proc Natl Acad Sci USA 2001; 98:1176-81.
38. Hendrix ND, Wu R, Kuick R, Schwartz DR, Fearon ER, Cho KR. Fibroblast growth factor 9 has oncogenic activity and is a downstream target of Wnt signaling in ovarian endometrioid adenocarcinomas. Cancer Res 2006; 66:1354-62.
39. Richardson AL, Wang ZC, De Nicolo A, Lu X, Brown M, Miron A, et al. X chromosomal abnormalities in basal-like human breast cancer. Cancer Cell 2006; 9:121-32.
40. Turashvili G, Bouchal J, Baumforth K, Wei W, Dziechciarkova M, Ehrmann J, et al. Novel markers for differentiation of lobular and ductal invasive breast carcinomas by laser microdissection and microarray analysis. BMC Cancer 2007; 7:55.
41. Notterman DA, Alon U, Sierk AJ, Levine AJ. Transcriptional gene expression profiles of colorectal adenoma, adenocarcinoma and normal tissue examined by oligonucleotide arrays. Cancer Res 2001; 61:3124-30.
42. Ki DH, Jeung HC, Park CH, Kang SH, Lee GY, Lee WS, et al. Whole genome analysis for liver metastasis gene signatures in colorectal cancer. Int J Cancer 2007; 121:2005-12.
43. Chen X, Cheung ST, So S, Fan ST, Barry C, Higgins J, et al. Gene expression patterns in human liver cancers. Mol Biol Cell 2002; 13:1929-39.

44. Wurmbach E, Chen YB, Khitrov G, Zhang W, Roayaie S, Schwartz M, et al. Genome-wide molecular profiles of HCV-induced dysplasia and hepatocellular carcinoma. Hepatology 2007; 45:938-47.
45. Bhattacharjee A, Richards WG, Staunton J, Li C, Monti S, Vasa P, et al. Classification of human lung carcinomas by mRNA expression profiling reveals distinct adenocarcinoma subclasses. Proc Natl Acad Sci USA 2001; 98:13790-5.
46. Stearman RS, Dwyer-Nield L, Zerbe L, Blaine SA, Chan Z, Bunn PA Jr, et al. Analysis of orthologous gene expression between human pulmonary adenocarcinoma and a carcinogen-induced murine model. Am J Pathol 2005; 167:1763-75.
47. Hoek KS, Schlegel NC, Brafford P, Sucker A, Ugurel S, Kumar R, et al. Metastatic potential of melanomas defined by specific gene expression profiles with no BRAF signature. Pigment Cell Res 2006; 19:290-302.
48. Andersson A, Ritz C, Lindgren D, Edén P, Lassen C, Heldrup J, et al. Microarray-based classification of a consecutive series of 121 childhood acute leukemias: prediction of leukemic and genetic subtype as well as of minimal residual disease status. Leukemia 2007; 21:1198-203.
49. Johnstone RW, Frew AJ, Smyth MJ. The TRAIL apoptotic pathway in cancer onset, progression and therapy. Nat Rev Cancer 2008; 8:782-98.
50. Baritaki S, Katsman A, Chatterjee D, Yeung KC, Spandidos D, Bonavida B. Regulation of tumor cell sensitivity to TRAIL-induced apoptosis by metastatic suppressor Raf kinase inhibitor protein via Yin Yang 1 inhibition and death receptor 5 upregulation. J Immunol 2007; 179:5441-53.
51. Baritaki S, Suzuki E, Umezawa K, Spandidos D, Berenson J, Daniels TR, et al. Inhibition of Yin Yang 1-dependent repressor activity of DR5 transcription and expression by the novel proteasome inhibitor NPI-0052 contributes to its TRAIL-enhanced apoptosis in cancer cells. J Immunol 2008; 180:6199-210.
52. Baritaki S, Huerta-Yepez S, Toshiyuki S, Spandidos D, Bonavida B. Chemoterapeutic drugs sensitize cancer cells to TRAIL-mediated apoptosis: upregulation of DR5 and inhibition of Yin Yang 1. Mol Cancer Ther 2007; 6:1387-99.
53. Lee JY, Huerta-Yepez S, Vega M, Baritaki S, Spandidos DA, Bonavida B. The NO TRAIL to YES TRAIL in cancer therapy (review). Int J Oncol 2007; 31:685-91.
54. Mijatovic S, Maksimovic-Ivanic D, Mojic M, Malaponte G, Libra M, Cardile V, et al. Novel nitric oxide-donating compound (S,R)-3-phenyl-4,5-dihydro-5-isoxazole acetic acid-nitric oxide (GIT-27NO) induces p53 mediated apoptosis in human A375 melanoma cells. Nitric Oxide 2008; 19:177-83.