Abstract. Numerous miRNAs have been found to be involved in the regulation of the p53 signaling pathway. Conversely, p53 regulates the transcription or processing of microRNAs (miRNAs). Given that complexities in the association between p53 and miRNAs exist, and due to the rapidly increasing amount of literature regarding the interactions between p53 and miRNAs, the present study systematically analyzed the associations between miRNAs and p53 in breast cancer using a literature-based discovery approach, natural language processing. A total of 22 miRNAs were found to be associated with p53. Next, three popular online tools (PicTar, miRanda and TargetScan) were used to predict the targets of each miRNA, and certain targets were validated by experiments. Gene Ontology annotation and network analysis demonstrated that the majority of the targets of the p53-related miRNAs were enriched in the cell cycle process. These results suggest that, in addition to regulating the transcription of cell cycle-related genes, p53 also indirectly modulates the cell cycle via miRNAs.

Introduction
Tumor suppressor p53 plays a central role in protecting cells against carcinogenesis, mainly functioning as a transcription factor. In response to stress signals, such as DNA damage, oncogenic stimuli and hypoxia, the p53 protein regulates the transcription of numerous different genes, leading to cell cycle arrest, apoptosis, DNA repair or senescence (1). The inactivation of p53 by mutation is a frequent event in carcinogenesis. Mutations in the TP53 gene, which encodes the p53 protein, occur in around half of all tumor specimens, but the overall frequency of p53 mutations in breast cancer is only 20-30% (2,3). It is believed that, in breast cancer harboring the wild-type p53 gene, p53 function is compromised by other genetic or epigenetic alterations (4,5). A number of studies have demonstrated that changes in interactome components or the target genes of p53 could contribute to reduce the roles of p53 during stress [reviewed in (4,5)].

Recently, a number of microRNAs (miRNAs) have been found to be involved in the p53 signaling pathway and breast carcinogenesis (6). Certain miRNAs directly target the mRNA of p53 and negatively regulate p53 expression, such as miR-125b (7), miR-375 (8) and miR-504 (9). A study in murine models of postmenopausal breast cancer suggested that miR-504 expression induced by obesity contributes to the reduced p53 protein expression and mammary tumor progression (9). Another class of miRNAs indirectly affected p53 signaling through regulating genes associated with p53. For example, miR-21 antagonizes the p53 pathway in breast cancer by inhibiting the expression of p53-regulated genes (10); oncomiRs miR-221/222 promoted proliferation in breast cancer by inhibiting p53 upregulated modulator of apoptosis expression (10). Conversely, p53 can regulate miRNA transcription, for example, that of miR-10b (11), miR-22 (12), miR-26a (13), miR-34a (14), miR-148a (15), miR-200b (16), miR-200c (16) and miR-205 (17), or miRNA processing, such as that of miR-16 (13,18), miR-145 (18,19) and miR-203 (20).

Given the rapidly increasing amount of literature regarding the interaction between p53 and miRNAs, and as complexities in the association between p53 and miRNAs exist, the present study systematically analyzed p53-related miRNAs and their targets in breast cancer using a literature-based discovery approach, natural language processing (NLP).

Materials and methods
NLP analysis of miRNAs associated with p53 and breast cancer. NLP analysis was performed as described by Gao et al (21) and Tang et al (22). Briefly, a PubMed search was conducted with the following combination of query terms:
Identification of miRNAs associated with p53 and breast cancer by NLP analysis. NLP has been successfully used to identify molecular interactions. To find the miRNA interacting with p53 in breast cancer, the present study searched PubMed with the following combination of query terms: ('mammary cancer' OR 'mammary tumour' OR 'mammary tumor' OR 'mammary neoplasm' OR 'mammary carcinoma' OR 'breast cancer' OR 'breast tumour' OR 'breast neoplasm' OR 'breast carcinoma') AND ('p53' OR 'TP53' OR 'TRP53'). Among these miRNAs, the three most frequently cited were miR-34a, miR-21 and miR-200c, which were cited by 8, 6 and 5 studies, respectively.

Computational prediction and experimental investigation of miRNA targets. To make a reliable prediction, three popular online tools (PicTar, miRanda and TargetScan) were used to predict the targets of each p53- and breast cancer-related miRNA. These tools make predictions based on different features of miRNA-mRNA interactions (31). Therefore, for a certain miRNA, the three tools provide different lists of predicted targets. The common targets predicted by these tools were selected for further experimental validation.

(continued)
three prediction tools were chosen for further analysis in the present study. With the exception of miR-342, miR-497 and miR-504, each miRNA exhibited a different number of predicted targets. The miRNA with the most targets was miR-9, with 59 targets, while miR-200b and miR-210 only had one target. A total of 320 genes were predicted to be targeted.

| miRNA     | PubMed count | Predicted targets                                                                 |
|-----------|--------------|-----------------------------------------------------------------------------------|
| miR-34a   | 8            | ZNF281, RPS6KA4, PNOC, SYVN1, MYRIP, CRHR1, TAF5, MPP2, CACNB3, DPYSL4, EVISL, STRN3, UHRF2, AXL, COPS7B, ACXL, ASB1, SNX15, ALDOA |
| miR-21    | 6            | WWP1, NFI1, CCL1, C17orf39, NTF3, ASPN, CNTFR, PEL1, SOX2, JAG1, RECK, TGFBI, MAT2, SPRY2 |
| miR-200c  | 5            | DGA, BAP1, NDST1                                                                   |
| miR-200b  | 4            | HSST1                                                                             |
| miR-200a  | 3            | SPAG9, DIIXDC1, GATA6, TCERG1, HMG20A, TP53NP1, SOX5, PCDH9                       |
| miR-203   | 3            | COPS7B, PHLD3A, CCNG1, DGL5, DKG2, CITLED, GLI3, DUSP5, DLX5, ACO2, ARNTL, FOXL2, CUL1, C18orf34, CSN2, QVOL1, ZNF281, GABRB2 |
| miR-205   | 3            | DLG2, E2F1, C21orf63, LRP1, HSST1, ERBB3, MATN2, SPRY2                           |
| miR-145   | 2            | GLI5, Sema3A, FBKP3, NEDD9, ATXN2, C11orf9, CCNL1, ZBTB10, PLCL2, RGS7, RIKN, CTNNB1, LEPRE1, LEPRE1, ZFYVE9, NMYA, BCL9L, MAT2A |
| miR-155   | 2            | SALL1, IKBKE, SDSCP, HIVEP2, BOC, H3F3A, FBXO11, ACTA1, BRD1, LRP1B, CARHSP1, SOCS1, TP53NP1, WEE1, RNF123, MYO10, DNAJ8, AICDA, ASTN2, CKN1G2, CHD7, MAPK10, CSF1R, HBP1, CEBPB |
| miR-10b   | 1            | DOCK11, HSST2, CECR6, NCOB2, FXR2, ARIH2, DAZAP1                                  |
| miR-133a  | 1            | SOLH, PTHR1, CTBP2, ATP6AP2, RAPH1, CSNK1G3, RCE1, CLTA, EVI1, ELF2, TAFAP2D, MLLT3, VPS54, NRP3, PTPTD, LLR7, NDRG1, ABCA2, G2D2 |
| miR-148a  | 1            | ATP6AP2, ITS2, ROBO1, GTF2H1, YPEL3, USP47, KLIF4, AKA1, ABCB7, RAB34, CNTNR, WNT10B, ALS2CR2, SFRS11, NOG, PRKAG2, MTF1, GAP3, CCKBR, SYN1, MA1, GPR116, C1GALT1, GADD45A, DYRK1B, TRPS1, DNMT1, PLLA, SFRS21P, UCP3, MILRT10, USP48, LBR, CHD7, COL2A1, RNF38 |
| miR-16    | 1            | CHRNA, CCNE1, WBP11, LPHN2, SHGIL2, ZSWIM3, RBSN1, CCNT2, KCTD8, DLL4, ATXN2, ADRB2, OMG, COPS2, SCOC, ADAMTS18, YWHAQ, TGFBR3, SEMA6D, TAF15, EPHA1, KIF21A, CHEK1, STXBP3, GOS2 |
| miR-191   | 1            | RNF139, GAP43, PLCB1, NDST1                                                       |
| miR-210   | 1            | EFNA3                                                                              |
| miR-22    | 1            | JMJD1A, PURB, ERBB3, DOF1, CSF1R, MAX, EMLIN3, SATB2, IP07, PRR6, RXFANK, SV2A, EPC1, STAG2, TRUB1, FAM49B, MTHFD2, IL13RA1, DNAJ8B, TAGLN, AVM, CKN1A, MEC2P, ZFYVE9, NMYA, BCL9L, MAT2A |
| miR-222   | 1            | RBM24, CDK11C, GNA2, IRX5, KHDDB32, RSNB1L, CDKN1B, MESCDC1                       |
| miR-26a   | 1            | RC2N, NFE2L3, USP15, ABHD2, ZDHHC18, ADM, DEPDC1B, EPHA2, PTPNC1, UL1K, CDK2AP1, HOXAX, COXAX, RL, PRKCD, ASPN, MTX2, SAL1, HAO1, DGL5, SMAD1, PTTP13, HIPK1, PRKAG2, ZNF283, CAMSAP1, PTER, ZDHHC6, PDHX, NAP1L5, PAPD4, COL1A2, KCNQ4, ALS2CR2, SENP5, RPS6KA6, EPC2, PAN3, SACS, MGAT4A |
| miR-9     | 1            | CCNE2, ENTPDF5, FOXP4, NOX4, NOCE1, RNF11, RBM9, RPS6KA4, DYRK1B, ITPKC, CNTFR, PYGO2, GAD1, RAB34, ARCPA1, SCL35B3, ODZ1, PARG, SACS, FBXW2, FN1, AHH, ARMCX2, LEPR2, PLSCR3, LRC4H, MUM1L1, KIF21A, ERBB2P, CALB2, TNFRSF21, CTHRC1, TBPI1, EVISL, NCO2, TESK2, SLC30A3, HDAC5, ARID1A, SLC31A2, RANBP2, SLC27A4, DIPX4, AP2M1, PCK6, LAMP1, PALMD, NID2, CSDA, DBNL, DIAPH1, SCL10A3, SNX7, LMNA, TGOLN2, P4HA2, TRIM2, AP3B1, LHFPI |
| miR-342   | 1            | -                                                                                  |
| miR-497   | 1            | -                                                                                  |
| miR-504   | 1            | -                                                                                  |

Common targets of two or more miRNAs are shown in bold. The underlined genes belong to GO term ‘cell cycle and proliferation’. GO, Gene Ontology; miRNA, microRNA.
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Table II. Top 5 significantly enriched Gene Ontology terms in the microRNA targets.

| Category | Term                                | n  | P-value   |
|----------|-------------------------------------|----|-----------|
| CC       | Nucleus                             | 108| 1.67x10^-7 |
|          | Extracellular matrix                | 14 | 2.98x10^-4 |
|          | ER/golgi                           | 23 | 0.347901  |
|          | Plasma membrane                    | 47 | 0.351261  |
|          | Cytosol                             | 6  | 0.530201  |
| MF       | Transcription regulatory activity   | 40 | 9.53x10^-7 |
|          | Kinase activity                    | 30 | 3.15x10^-5 |
|          | Extracellular structural activity   | 3  | 0.007524  |
|          | Enzyme regulator activity          | 19 | 0.009502  |
|          | Nucleic acid binding activity      | 56 | 0.010738  |
| BP       | Cell cycle and proliferation       | 42 | 5.36x10^-6 |
|          | RNA metabolism                     | 70 | 3.13x10^-5 |
|          | Cell organization and biogenesis   | 50 | 4.74x10^-4 |
|          | Protein metabolism                 | 57 | 0.027053  |
|          | Cell death                         | 21 | 0.031232  |

MF, molecular function; CC, cellular component; BP, biological process.

Table III. Kyoto Encyclopedia of Genes and Genomes pathways overrepresented in the lists of microRNA targets.

| Pathway                                | n  | P-value   |
|----------------------------------------|----|-----------|
| Cell cycle                             | 11 | 3.83x10^-5 |
| Axon guidance                          | 9  | 0.002147584|
| p53 signaling pathway                  | 6  | 0.003804563|
| Notch signaling pathway                | 4  | 0.019950756|
| Phosphatidylinositol signaling system  | 5  | 0.026477865|
| Hedgehog signaling pathway             | 4  | 0.037347722|
| TGF-β signaling pathway                | 5  | 0.041980514|
| Basal transcription factors            | 3  | 0.042039395|

and SPRY2 (38)]. These results suggested that the present miRNA target prediction is reliable.

GO annotation analysis of miRNA targets. These 320 miRNA target genes were subjected to GO enrichment analysis. All these genes were categorized based on BP, MF and CC (Table II). In the CC category, the nucleus term was the most significant term (with the lowest P-value) and contained the largest number of genes. In the MF category, the term with the lowest P-value was transcription regulatory activity. In the BP category, the most significantly enriched genes belonged to the cell cycle and proliferation process, and a total of 42 genes were categorized to this process. These 42 genes belonged to the targets of 16 miRNAs (Table I). KEGG pathway analysis also showed similar results, with the number of genes involved in the cell cycle being the largest (Table III). This suggested that the targets of p53-related miRNAs mainly play roles in the cell cycle and proliferation process.

Network analysis of miRNA targets. To understand the association between these miRNA targets, the KEGG dataset, PPI and Pubmed datasets were integrated to construct a network...
of miRNA targets (Fig. 2A). The resulting network was composed of nodes (genes) and edges (interactions). Fig. 2B shows the degree (i.e., the number of edges emanating from a node) of each node. In the present network, the nodes with degree >10 were defined as hubs, including CDKN1A, SOX2, CDKN1B, CUL1 and TGFBI. According to the aforementioned GO annotation, these hub genes, with the exception of TGFBI, were annotated to the term 'cell cycle and proliferation' (Table I). In a molecular interaction network, hubs are more essential for the global network structure than non-hubs (39). Therefore, it indicates the roles of targets of p53-related miRNAs in the cell cycle and proliferation, in accordance with the aforementioned pathway analysis.

Discussion

In the present study, for the first time, the interactions of miRNAs and p53 were systematically analyzed in breast
cancer using NLP analysis, and 22 miRNAs associated with p53 in breast cancer were identified. Among these miRNAs, 11 are transcriptionally or post-transcriptionally upregulated by p53 [miR-10b (11), miR-16 (13,18), miR-22 (12), miR-26a (13), miR-34a (14), miR-145(18,19), miR-148a (15), miR-200b (16), miR-200c (16), miR-205 (20) and miR-205 (17)], one directly targets p53 [miR-504 (9)], and others do not directly interact with p53, but indirectly play roles in the p53 signaling pathway [e.g., miR-9 (40), miR-21 (41) and miR-222 (10)]. Bioinformatics analysis identified 320 targets of p53-related miRNAs.

Although these 22 p53-related miRNAs have different sets of targets, GO annotation revealed that the majority of the miRNA targets were significantly enriched in the cell cycle and proliferation process. In the network of miRNA targets, the five hub genes, with the exception of TGFBI, were annotated to cell cycle processes. TGFBI has been recently reported to affect the cell cycle via the regulation of p21 and p53 expression (42). Cyclin-dependent kinase inhibitor 1A (CDKN1A; also known as p21, Cip1 or WAF1) was identified as the most highly connected hub gene. CDKN1A has been proven to be a direct target of the p53 tumor suppressor and to play key roles in mediating p53-dependent cell cycle arrest in response to DNA damage. In a molecular interaction network, hubs are more essential for the global network structure than non-hubs (39). The results suggest that p53-related miRNAs play roles in the cell cycle. A number of studies have demonstrated that p53 acts as a key regulator of the cell cycle, mainly by transcriptional regulation of certain key genes in the cell cycle, such as CDKN1A. The present study suggested that, in addition to transcriptionally regulating cell cycle-related genes, p53 also indirectly regulates them through miRNAs. These results also suggest a previously unknown mechanism for p53 function, and thus provide an important contribution to our knowledge of p53. Furthermore, the results of the present study were consistent with those of Otsuka et al (43) which revealed that p53-induced miRNAs control the cell cycle and cell survival via the repression of cell-cycle regulators and/or antiapoptotic proteins. Additionally, Rokavec et al (44) summarized previously published data regarding the interaction between p53 and miRNAs in gastrointestinal cancer, and found that a total of 32 p53-related miRNAs exhibit differential expression between normal and tumor tissue and are associated with clinical and pathological parameters of gastrointestinal cancer. Among the 32 miRNAs, only 9 miRNAs (miR-34a, miR-200a, miR-200b, miR-200c, miR-205, miR-145, miR-16, miR-22, miR-504) are common in both gastrointestinal cancer and breast cancer (Table I). Thus, we hypothesize that p53 regulates different sets of miRNAs in various types of cancer.

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