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The transcription factor p53: Not a repressor, solely an activator

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Abbreviations: CDE, cell cycle-dependent element; CHR, cell cycle genes homology region; DREAM, DP, RB-like, E2F4, and MuvB complex; ChIP, chromatin immunoprecipitation; NF-Y, Nuclear factor Y; cdk, cyclin-dependent kinase; HPV, human papilloma virus.

The predominant function of the tumor suppressor p53 is transcriptional regulation. It is generally accepted that p53-dependent transcriptional activation occurs by binding to a specific recognition site in promoters of target genes. Additionally, several models for p53-dependent transcriptional repression have been postulated. Here, we evaluate these models based on a computational meta-analysis of genome-wide data. Surprisingly, several major models of p53-dependent gene regulation are implausible. Meta-analysis of large-scale data is unable to confirm reports on directly repressed p53 target genes and falsifies models of direct repression. This notion is supported by experimental re-analysis of representative genes reported as directly repressed by p53. Therefore, p53 is not a direct repressor of transcription, but solely activates its target genes. Moreover, models based on interference of p53 with activating transcription factors as well as models based on the function of ncRNAs are also not supported by the meta-analysis. As an alternative to models of direct repression, the meta-analysis leads to the conclusion that p53 represses transcription indirectly by activation of the p53-p21-DREAM/RB pathway.

Introduction

Initially, p53 was falsely described as an oncogene. About a decade after its discovery, p53 was found to be a tumor suppressor.[1,2] Despite 35 years of research and an ever growing number of publications, currently over 70,000 listed in PubMed, the central function of p53 as a transcriptional regulator still holds a major contradiction. It remains unresolved how p53 binding results in activation of one target gene and repression of another.

Following the discovery of p53's first transcriptional targets, many more genes were claimed to harbor p53 binding sites and thus to be potential targets resulting in an "expanding universe of p53 targets".[3,4] In recent years, genome-wide analyses led to the discovery of novel p53 target genes by combining p53 chromatin occupancy data with gene expression analyses.[5-9] Hundreds of genes were identified as novel direct p53 targets. For a long time the search for direct p53 target genes often was undertaken without distinguishing significant regulation from experimental noise, similar to the assignment of function to large parts of the genome despite the substantial lack of conservation in these genomic regions by the ENCODE Consortium.[10]

While reproducibility is a hallmark of scientific discovery, results from a substantial fraction of published work remain irreproducible.[11] A general problem appears to be that today's science is strongly biased for significant positive findings encouraging researchers to overinterpret small effects and inflate associations.[12] One method to clarify contradictions is meta-analysis of data from independent experiments.[11]

In this study, we employ a meta-analysis on p53's transcriptional network employing data on 19,736 known protein-coding genes from several independent genome-wide studies to evaluate models of transcriptional regulation by p53. Six major mechanisms of p53-dependent transcriptional regulation are currently accepted in the literature:[13-17]

- direct activation of target genes following p53 binding to a p53 response element (RE)

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- direct repression of target genes after p53 binding to p53 REs, including variations such as head-to-tail elements or p53 REs with inverted dinucleotide cores
- direct repression of target genes through p53 binding via adaptor proteins, in particular NF-Y
- indirect repression via direct activation of p21 by p53 and subsequent formation of pocket protein/E2F complexes such as RB/E2F and DREAM
- indirect repression through interference with transcriptional activators, in particular NF-Y, Sp1 and TBP
- indirect repression of target genes via non-coding RNAs (ncRNAs), with *mir34a*, *lincRNA-p21* and *PANDA* as prominent examples

We provide a comprehensive overview on original research findings and compare them to results from the meta-analysis. With this comparison we test the previously proposed models on p53-dependent transcriptional regulation. Important findings from the meta-analysis are supported by experimental validation. In general, our analysis resolves major contradictions and leads to a paradigm shift.

Results and Discussion

Computational meta-analysis on binding and regulation by p53

To evaluate the function of p53 as a transcription factor we have performed a computational meta-analysis from several independent experiments to minimize the influence of laboratory-specific effects and bias in study design.[11,18] Data from 6 genome-wide analyses of p53-dependent gene expression were extracted.[7,19-23] In each study a gene can be identified as activated (positive score; +1) or repressed (negative score; −1) by p53. By calculating the sum over all analyses, *Expression Scores* ranging from −6 to +6 were assigned to genes, forming 13 gene groups (**Table S1**). Thus, the *Expression Score* represents direction of regulation as well as confidence of classification. By matching these data with transcription factor binding analyses, it is possible to evaluate whether activated or repressed genes are enriched for binding of a transcription factor such as p53. In case that the transcription factor is a repressor, its binding is expected to be substantially enriched at genes in negative *Expression Score* groups compared to genes in *Expression Score* group 0. We used 6 genome-wide p53 binding studies[6-9,24,25] and observed that 13.4% of all known protein-coding genes were identified as bound by p53.

Next, we compared the distribution of p53-bound genes across *Expression Score* groups to a theoretical uniform distribution of 13.4% (**Fig. 1A**). A uniform distribution would be expected if there is no correlation between p53 binding and p53-dependent regulation.

In contrast to most current models[13-17] but in agreement with observations made in recent genome-wide studies,[9,26-28] solely genes activated by p53 are found enriched for p53 binding (**Fig. 1A**; **Fig. S1**). Thus, these data strongly suggest that p53 does not act as a direct transcriptional repressor.

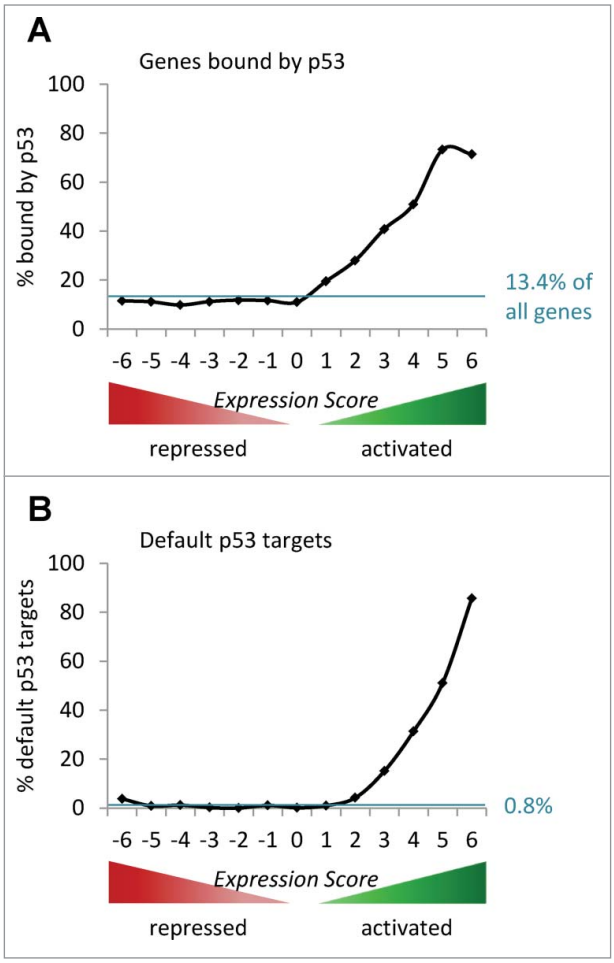


Figure 1. Solely genes activated by p53 are found enriched for p53 binding. A regulation score, named *Expression Score,* ranging from −6 to +6 was assigned to 19,736 known protein-coding genes from 6 genome-wide p53-dependent gene expression analyses.[7,19-23] (**A**) All ChIP-peaks from 6 genome-wide p53 binding studies, that were identified in at least 2 studies, were allocated to the nearest gene.[6-9,24,25] Out of the 19,736 genes, 13.4% were assigned at least one such p53 ChIP-peak. The percentage of genes with a p53 ChIP-peak in a specific *Expression Score* group is displayed by the black line. The blue line indicates a theoretical uniform distribution of ChIP-peak-containing genes across the 13 *Expression Score* groups. (**B**) The percentage of default p53 targets (**Table S2**) in each *Expression Score* group is given by the black line. The theoretical uniform distribution of default p53 targets (n = 171 or 0.8% of 19,736 genes) across the 13 *Expression Score* groups is indicated by the blue line.

Default p53 target genes

The authors of 2 recent genome-wide studies argue that a "default program" of p53 targets can be found that is shared regardless of cell type or treatment.[7,9] Based on the criteria that a target gene is bound and regulated by p53, we collated information describing individual p53 targets from about 300 reports (**Table S2**).[19,20,23,29-324] This compilation was then complemented with data from 5 genome-wide studies on target genes bound and also regulated by p53.[5-9] Furthermore, we have correlated 2 genome-wide p53 binding studies[24,25] with the 6 genome-wide gene expression studies[7,19-23] identifying additional

target genes. This meta-analysis yielded potential direct p53 targets of which 892 are assigned as activated, 384 repressed, and 10 ambiguously regulated genes (**Table S3**). However, most genes in this compilation were observed in one study but were not confirmed in any other report. Many p53 target genes that were described in the literature earlier could not be confirmed in genome-wide approaches.

With this data collection, we included essentially all targets that might have been missed by single studies (false negatives). Yet, combining data sets in order to limit false negatives, inflates detection of false positives. One has to consider that each study can contain false positives and false negatives because of imperfect experimental conditions.[18] Therefore, after extending the data set on direct p53 targets, we defined limits to identify "default" targets. Genes detected in only one study have a high potential of being false positive hits and are most likely not part of the default program. Thus, from the published studies we derived weighted data sets to assign *Default Target Scores* to each direct p53 target gene. We considered a gene as a default target that was reported in at least 3 data sets, which corresponds to a *Default Target Score* > 2. We found 157 (17.6%) of all activated direct p53 target genes to meet these criteria (**Table S3**). Highest *Default Target Scores* were reached by many well established p53 target genes, all of which are activated by p53 (**Table S3**), such as *CDKN1A* (p21),[72] *BTG2*,[54] *GADD45A*,[112] *BAX*,[45] and *MDM2*.[122-124] In contrast, only 15 (3.9%) of the direct p53 target genes which have been described as repressed by p53 were assigned a *Default Target Score* > 2 (**Table S3**). Thus, the average *Default Target Score* of potentially repressed p53 targets is much lower compared to the score of activated target genes. Additionally, we evaluated the distribution of all default p53 target genes across the *Expression Score* groups (**Fig. 1B**). Only genes activated by p53 were found enriched for default p53 targets. Taken together, in addition to looking solely at p53 binding as described above (**Fig. 1A**), also data on default p53 targets substantiates the view that p53 does not directly repress its targets (**Fig. 1B**).

Concordantly, recent genome-wide studies on p53 targets acknowledged a low abundance of p53-bound targets among repressed genes and entertained the possibility that repression by p53 may be largely indirect.[9,26-28] Nevertheless, 90 reports describe 91 genes in detail as transcriptionally downregulated by direct binding of p53 (**Table S2**). The observations reported in these articles require further consideration.

Experimental validation of meta-analysis data

The meta-analysis data stand in contrast to the mechanisms of direct transcriptional repression by p53 and the regulation reported for many potential p53 targets (**Table S2**). Thus, we retested 18 genes for binding and regulation by p53 that were described to be directly repressed by p53, namely *ABCB1* (*MDR1*),[325] *BCL2*,[245,326] *BNIP3*,[251] *CCNB1*,[254,327] *CD44*,[262] *CDC20*,[328] *CDK1* (*CDC2*),[258] *CRYZ*,[260] *HSPA8*,[260] *ID2*,[275] *LASP1*,[281] *MAD1L1* (*MAD1*),[260,329] *ME1*, *ME2*, *ME3*,[285] *NEK2*,[289] *PTK2* (*FAK*),[306] and *TPT1* (*TCTP*).[320]

We tested p53 binding in chromatin immunoprecipitation assays (ChIP) followed by real-time PCR. Gene regulation by p53 was assayed by reverse transcriptase reaction followed by real-time PCR. If available, we used the published primers for PCR (**Fig. 2**; **Fig. S2**). No p53 binding was observed at the *GAPDHS* gene which served as a negative control. Binding of p53 was observed at the positive controls of *CDKN1A* (*p21*) and *MDM2* (**Fig. 2A**). Most importantly, at all other regions tested no significant p53 binding was observed (**Fig. 2A**). Thus, the p53 response elements (RE) reported for the genes listed above can neither be confirmed by genome-wide studies nor by direct experimental re-analysis.

Although *ABCB1*, *CD44*, *CDK1*, *MAD1L1*, *ME2*, and *PTK2* were found in genome-wide studies to bind p53 within 25 kb of their transcriptional start sites (TSS), the regions detected in genome-wide studies do not overlap with reported p53 REs (**Table S1**).[258,260,262,285,306,325,329] Therefore, all our results confirm data from the genome-wide studies and the meta-analysis. We asked how the discrepancies could arise between genome-wide data with the confirmatory results presented here and the observations from the reports mentioned above. Most discrepancies are explained by the use of real-time PCR instead of traditional PCR to evaluate binding of p53 in ChIP assays. Relative quantification is necessary to evaluate binding of a protein to one locus compared to non-bound regions. However, traditional PCR hardly allows relative quantifications often leading to erroneous results.

Expression of mRNA from these 18 genes depending on p53 was examined in doxorubicin- or nutlin3a-treated HCT116 cells compared to DMSO treatment. *GAPDH* mRNA, *L7* mRNA, and *U6* RNA served as negative controls not regulated by p53. The positive controls *CDKN1A* (*p21*), *MDM2*, and *PPM1D* were significantly upregulated upon treatment with doxorubicin or nutlin3a (**Fig. 2B**). In contrast, only *CCNB1*, *CDC20*, *CDK1*, and *NEK2* were significantly repressed after treatment with doxorubicin and nutlin3a, while *ABCB1*, *BCL2*, *BNIP3*, *CRYZ*, *HSPA8*, *ID2*, *LASP1*, *MAD1L1*, *ME1*, *ME2*, *ME3*, *PTK2*, and *TPT1* were not significantly regulated by both treatments (**Fig. 2B**). Again, these results confirm data from genome-wide studies and the meta-analysis, but do not support observations from the reports on direct transcriptional repression (**Fig. 2B**; **Tables S1** and **S2**). These discrepancies might largely stem from insufficient controls and overinterpretation of small effects.[11] In most reports criteria for p53 target genes were not met that were formulated 2 decades ago.[3] In addition to the p53 targets that were not confirmed by our re-analysis (**Fig. 2**), reports of directly repressed p53 targets in mouse such as *NANOG*,[288] *PPARGC1A* (*PGC1a*), and *PPARGC1B* (*PGC1b*)[300] are also not supported by human genome-wide data (**Table S2**).

Since *CCNB1*, *CDC20*, *CDK1*, and *NEK2* are repressed but not bound by p53 (**Fig. 2**), we asked whether mechanisms other than direct repression have been postulated for the p53-dependent regulation of these genes. All 4 genes were shown to be repressed by the p53 target and CDK-inhibitor p21.[330-334] Furthermore, p53-dependent repression of *CCNB1*, *CDC20*, and *CDK1* was shown to depend on the pocket proteins p107 and p130,[335] which also contrasts direct transcriptional repression by

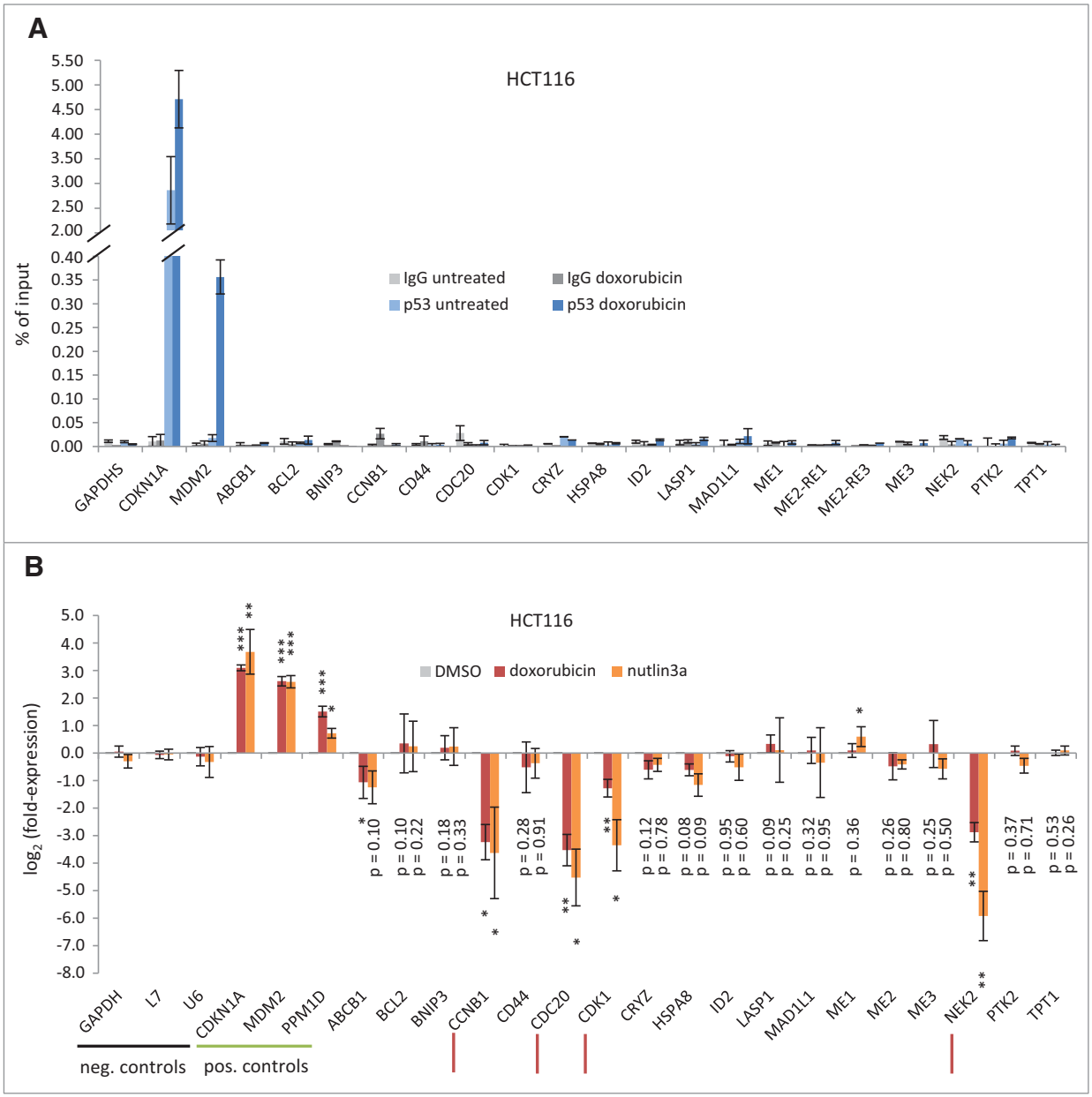


Figure 2. Experimental validation of data from the meta-analysis. (**A**) p53 protein binding to reported p53 response regions in untreated and doxorubicin-treated HCT116 cells was tested by ChIP. A fragment of the *GAPDHS* promoter served as a negative control while *CDKN1A* and *MDM2* served as positive controls. (**B**) mRNA expression in HCT116 cells treated with doxorubicin or nutlin3a for 24 h. Cells treated with DMSO served as a control. The $\log_2$ fold-expression from doxorubicin- or nutlin3a-treated cells compared to DMSO control cells is displayed as. *GAPDH*, *L7*, and *U6* served as negative controls, while *CDKN1A*, *MDM2*, and *PPM1D* were employed as positive controls. Significance of expression was tested against *U6* expression levels using paired Student's t-test. Experiments were performed with 2 biological replicates and 2 technical replicates each (n = 4). $^{*}P \leq 0.05$; $^{**}P \leq 0.01$; $^{***}P \leq 0.001$.

p53. In agreement with the reported p53-dependent repression via p21, we found that doxorubicin-induced repression of *CCNB1*, *CDC20*, *CDK1*, and *NEK2*, but not activation of *MDM2* and *PPM1D,* is essentially lost in HCT116 $p21^{-/-}$ cells (**Fig. S3**).

Taken together, in most cases binding of p53 as well as p53-dependent regulation were not confirmed. Therefore, the reported mechanisms of direct transcriptional repression by p53 are unlikely of importance.

Challenging models of direct repression

Early in the history of p53 research, numerous genes were found to be repressed upon p53 induction.[336] For a long time the question remained open how binding of a transcription factor

such as p53 can result in activation of one target gene and repression of another.

One of the proposed models is based on a head-to-tail p53 RE that had been described as a repressive element in the *ABCB1* (*MDR1*) promoter.[325] Later, related elements were found to bind p53 and mediate downregulation of genes such as *NANOG*, *CD44* and *TPT1* (*TCTP*).[262,288,320] However, these results were never confirmed in any genome-wide study.[5-9] Moreover, *NANOG*, *ABCB1*, *CD44* and *TPT1* were actually found not to be repressed by p53 (*Expression Scores* ≥ 0) (**Fig. 2B**; **Table S1** and **S2**). Therefore, investigating their regulation could not yield a mechanism for p53-dependent transcriptional repression in the first place. Additionally, retesting the proposed p53 REs of *ABCB1*, *CD44*, and *TPT1* provided evidence that these loci are not detected as bound by p53 when using ChIP followed by real-time PCR.

The authors of one report claimed to have found a dinucleotide core code underlying the p53 RE that determines whether a target gene is activated or repressed by p53 binding.[337] Based on their finding, the authors re-analyzed 162 published p53 REs and described 20 of them to be falsely assigned as either activators or repressors. However, the discrepancies included re-assignment of well established p53 targets such as *BTG2* and *PLK2*.[54,163,337] One explanation of this discrepancy could be that in the experiments p53 REs were tested in an artificial promoter context. Importantly, a recent genome-wide search for a preference of the dinucleotide core in repressed versus activated genes did not yield data to support this model.[8] Thus, the dinucleotide core model was disproved, and we refrained from including these results in our analysis.

The third model of direct repression proposes p53 binding to its target promoter via proteins that are general activators of the gene. The transcription factor NF-Y is the most prominent example serving as an adaptor for p53 binding to repressed target promoters.[243,255,338] Fourteen genes were described as being controlled by this mechanism (**Table S2**). Searching in the genome-wide p53 target studies,[5-9] only one gene was confirmed in a single study, although the locus of p53 binding does not overlap with the CCAAT-box.[6] Furthermore, NF-Y-binding CCAAT-boxes were not found to be enriched at loci bound by p53.[8] One might argue that ChIP studies are less efficient if the target protein does not directly bind to the DNA, although the method has been used successfully with other indirectly bound transcription factors such as FoxM1, p130, RB, and LIN9.[339-342] However, arguing against indirect ChIPs similarly questions the initial findings that are all based on the same method. Thus, adaptor function of NF-Y recruiting p53 to repress target genes cannot be considered a general mechanism.

Similarly, examining genome-wide data from all 91 p53 targets published as directly repressed, only 5 (5.5%) could be confirmed by at least one genome-wide p53 target study, which resembles the typical false discovery rate of genome-wide studies (**Table S2**). Yet, 21 (23.1%) were actually observed to be activated instead of being repressed (*Expression Score* > 0) (**Table S2**).

Taken together, results from the meta-analysis falsify the models involving direct transcriptional repression through p53. Target genes that were reported to be directly repressed by p53 are either not repressed by p53 after all, not bound by p53 at the proposed p53 RE, or both. This inevitably leads to the conclusion that p53 is not a direct repressor of transcription.

Indirect repression through p53-p21-DREAM or -RB/E2F pathways

Many genes downregulated by p53 are cell cycle genes (**Table S1**). Researchers argued for a long time whether p53-dependent transcriptional regulation of cell cycle genes requires direct binding of p53 or occurs indirectly. One well known example is the p53-dependent regulation of the *CDC25C* phosphatase gene. Initially, *CDC25C* was published to be activated as a direct target of p53.[343] Later, the gene was shown to be actually repressed by p53 signaling [344] and that p21 is required for indirect downregulation.[333] Then, *CDC25C* was claimed to be both, downregulated by the p53-p21 pathway and by direct interaction of p53 with the promoter.[257] Another study supported the model of direct repression by p53,[258] while two other reports described indirect downregulation of *CDC25C* via p107/p130/E2F4.[335,345] Thus, over a period of 15 y the proposed mechanism for p53-dependent regulation of *CDC25C* changed from direct activation of transcription over direct repression to indirect downregulation.

The history of *CDC25C* regulation shows that in addition to direct also indirect repression of p53 target genes has been suggested. Even prior to these reports, p53-dependent downregulation of many cell cycle genes, including *CCNB1*, *CDC20*, *CDK1*, and *NEK2* (**Fig. 2**; **Fig. S3**), was shown to depend on p21 (WAF1, CIP1, CDKN1A).[330-333,346-350] Similar to p21, RB was suggested to be involved in p53-dependent transcriptional repression of genes such as *CCNA2*, *CCNB1*, *CDK1*, *CHEK1*, *FOXM1*, *MAD2L1*, *PCNA*, *PLK1*, and *TERT*.[332,335,348,350-353]

Recently, attention has shifted to the p53-p21-DREAM pathway.[354-357] The mammalian DREAM complex consists of the pocket proteins p107 or p130, the transcription factors E2F4 or E2F5 and the dimerization partner DP1, as well as the MuvB core composed of RBBP4 and the LIN proteins LIN9, LIN37, LIN52 and LIN54.[341,358,359] The DREAM components E2F4 and p107/p130 have repeatedly been reported to participate in p53-dependent downregulation of cell cycle genes.[335,345,346,350,352,360,361]

In order to evaluate the proposed indirect repression mechanism involving p21, DREAM, or RB/E2F, we searched the literature and found 88 genes that were described to be indirectly regulated by p53 through this mechanism (**Table S4**).[9,98,248,257,330-335,345-357,360-371] Impressively, 83 (94.3%) genes were confirmed as repressed (*Expression Score* $\leqq -1$) (**Table S4**). Therefore, in contrast to the direct repression models, the mechanism of indirect repression employing p21, DREAM, or RB/E2F is supported by the genome-wide expression studies.

Next, we evaluated whether genome-wide protein binding to these 88 genes is in agreement with this mechanism. To this end, ChIP-Chip data on DREAM binding [341] and ChIP-Seq data on p130 and RB binding [340] were used. We found that 79 (89.8%)

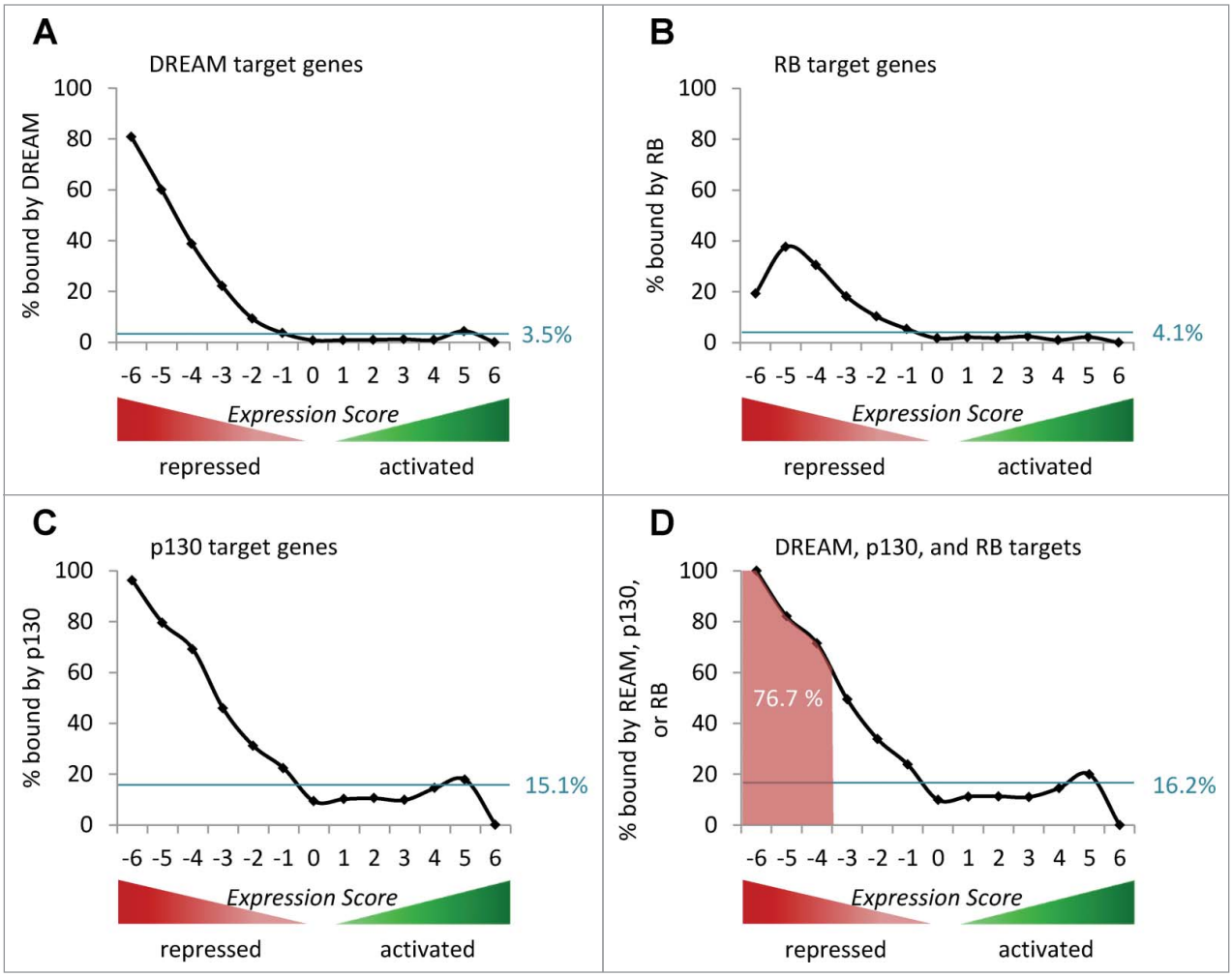


Figure 3. Indirect repression through p53-p21-DREAM or -RB/E2F pathways. (**A**) The percentage of genes bound by DREAM in proximity to their transcriptional start site (TSS) in each *Expression Score* group is displayed.[341,408] The theoretical uniform distribution across the 13 *Expression Score* groups of genes bound by DREAM is indicated by the blue line (3.5% of 19,736 genes). (**B**) Displayed for each *Expression Score* group is the percentage of genes bound by RB in proximity to their TSS.[340] The blue line indicates a theoretical uniform distribution of genes bound by RB (4.1% of 19,736 genes) across the 13 *Expression Score* groups. (**C**) The percentage of genes bound by p130 in proximity to their TSS is shown for each *Expression Score* group.[340] A theoretical uniform distribution of genes bound by p130 (15.2% of 19,736 genes) across the 13 *Expression Score* groups is indicated. (**D**) Compilation of targets displayed in (**A**-**C**). The blue line indicates a theoretical uniform distribution of genes bound by DREAM, p130, or RB (16.1% of 19,736 genes) across the 13 *Expression Score* groups. The red area marks the fraction of genes bound by DREAM, p130, or RB in *Expression Score* groups −6, −5 and −4 (76.7 % of 399 genes).

of the 88 genes were indeed shown to bind DREAM, p130, or RB (**Table S4**). Furthermore, we evaluated the distribution of DREAM-, p130-, or RB-bound genes across the *Expression Score* groups (**Fig. 3**; **Table S1**). In fact, we find DREAM, p130, or RB binding to be highly enriched at p53-repressed target genes. As an example, 306 (76.7%) of 399 genes that are found to be repressed by p53 in at least 4 expression studies (*Expression Score* $\leqq$-4) are found to bind DREAM, p130, or RB in proximity of their transcription start site (**Fig. 3D**; **Table S1**). Interestingly, binding of DREAM or p130 appears to correlate stronger with repression by p53 than binding of RB (**Fig. 3A-C**). With *CCNB2* as an example for cell cycle genes, the complete pathway from induction of DNA damage over activation of p21 through p53 and finally to downregulation of the target was presented as a mechanism that involves binding of DREAM including its component p130 to specific elements in the promoter.[355,372] In summary, these data strongly support the notion that DREAM, p130, or RB mediates p53-dependent repression.

Lately, E2F7 attracted much attention as another possible factor in mediating p53-dependent transcriptional repression of cell cycle genes.[98] This report described that G_1/S genes such as *E2F1*, *DHFR*, *RRM2*, and *E2F8* require E2F7 for p53-dependent downregulation. While the initial study suggested that downregulation of all targets also requires p21,[98] it was observed in another study that repression of *GBJ2* and *E2F8* depends on E2F7 but not on p21.[9] However, a more recent study concluded that a contribution of E2F7 to p53-dependent downregulation of target genes such as *E2F1* is unlikely.[345]

Unfortunately, the authors did not discuss these contradictory results although there is an overlap in authorship with the initial study.[98,345] Thus, it is difficult to conclude whether E2F7 contributes to p53-dependent gene regulation. Nevertheless, we included E2F7 ChIP-Seq data [373] to investigate whether E2F7 target genes are repressed by p53. In general, our data support the possibility that E2F7 participates in p53-dependent transcriptional repression (**Fig. S4**). However, essentially all E2F7 target genes are also bound by DREAM, p130, or RB (**Table S1**). This suggests that a p53-dependent repression via E2F7 occurs, if at all, only in conjunction with DREAM, p130, or RB. In conclusion, the results uncover a dominant role of the p53-p21-DREAM/RB pathway in p53-dependent transcriptional repression.

Lessons learned from network perturbations by viral oncoproteins

Oncogenic viruses often interfere with the p53 pathway.[21] In addition to targeting p53, many viruses interfere with pocket protein/E2F complexes such as RB/E2F and DREAM. Human papilloma virus (HPV) employs E6 and E7 oncoproteins to selectively target p53 and pocket protein complexes, respectively.[374] Importantly, RB/E2F and DREAM are disrupted by HPV E7.[357,375,376] Thus, one would expect that the expression of genes directly targeted by p53 is impaired by HPV E6 but not by E7 expression. In contrast, genes targeted by RB/E2F or DREAM downstream of the p53 pathway are expected to be deregulated similarly by HPV E6 and E7. Therefore, we investigated genome-wide expression data after induction of HPV16/18 E6 and HPV16/18 E7 [21] (**Table S1**). Indeed, we find prominent p53 targets such as *CDKN1A*, *MDM2*, *BAX*, *FAS*, *BTG2*, and *PLK2* to be downregulated upon induction of HPV E6, while they show no regulation or a slight upregulation after induction of HPV E7 (**Table S1**). Thus, their p53-dependent regulation is not impaired by HPV E7. In contrast, established targets of the p53-p21-DREAM-CDE/CHR pathway such as *CCNB2*, *KIF23*, and *PLK4* are upregulated upon induction of HPV E6 and are also upregulated by HPV E7 (**Table S1**). Next, we investigated whether this is a general phenomenon of genes directly activated by p53 in contrast to genes indirectly repressed via the p53-p21-DREAM/RB pathway. We find 469 genes that are upregulated by HPV E6, which display an *Expression Score* $\leqq$-2, and bind DREAM, p130, or RB (**Table S1**). Interestingly, solely 14 (3.0%) of these genes display a significantly divergent expression (>2.5-fold or negative ratio) after HPV E6 compared to E7 expression. In contrast, 119 genes are downregulated by HPV E6, which show an *Expression Score* $\geqq$2, and bind p53. Most interestingly, 50 (42.0%) of these genes display a significantly divergent expression (>2.5-fold or negative ratio) by HPV E6 compared to E7 (**Table S1**). This 14-fold increase of gene numbers regulated by HPV E7 in addition to E6 among pocket protein target genes is highly significant ($P < 10^{-27}$) and thus substantiates the model that p53 can directly activate its target genes while p53-dependent repression largely occurs via the p53-p21-DREAM/RB pathway.

Evaluating alternative models of indirect repression

Among the first models trying to explain p53-dependent transcriptional repression, interference of p53 with the TATA-box binding protein (TBP) and its associated factors was proposed.[377,378] Another model involves displacement of NF-Y (CBF) binding to CCAAT-boxes by p53, which was observed at the *HSPA4* (*hsp70*) promoter.[379] The model was supported by the finding that the NF-Y subunit C interacts with p53 *in vitro* and *in vivo*.[255] Furthermore, this model was extended toward a possible direct p53-NF-Y-CCAAT repression model with the observation that p53 binds to several CCAAT-box-containing cell cycle genes.[255,338] However, as outlined in the chapters above, direct p53 binding to target promoters most likely does not lead to repression but solely to activation. Consistent with this notion, a genome-wide motif search at p53 binding regions did not find TATA-, CCAAT- or GC-boxes to be enriched.[8]

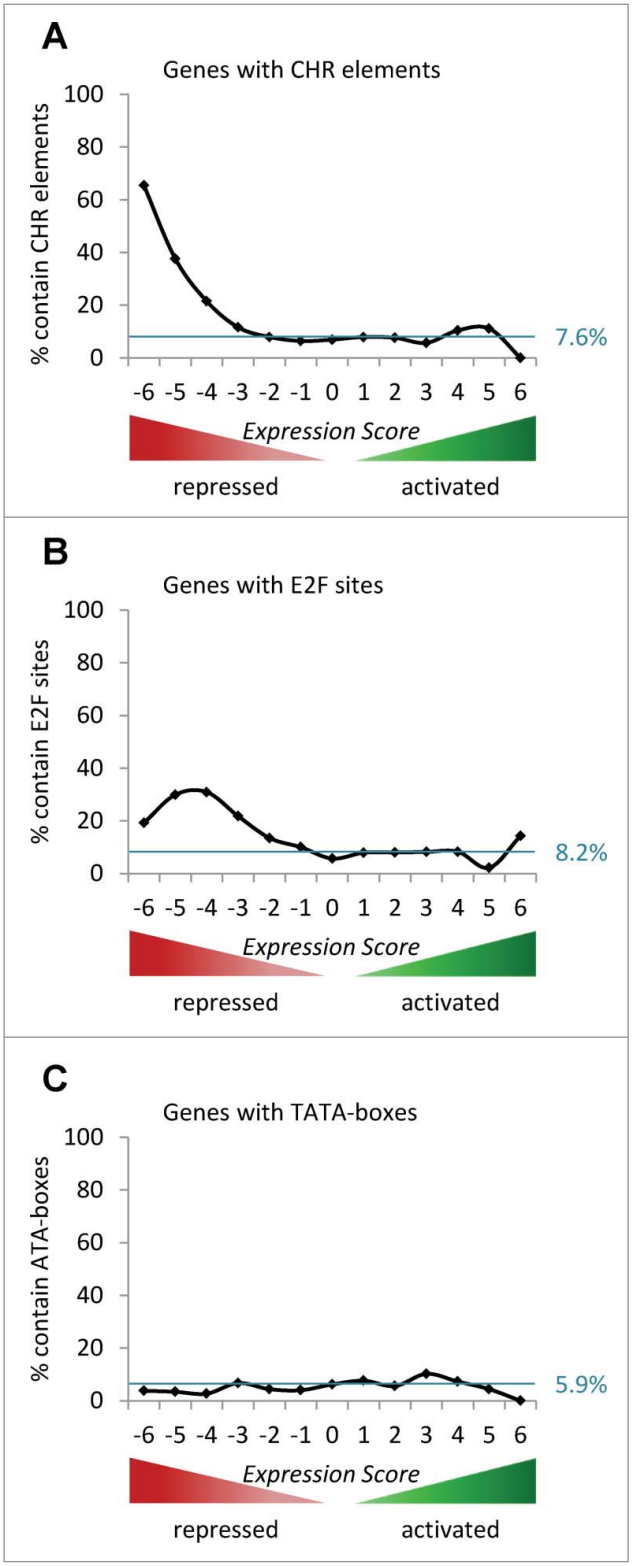
Yet, several reports describe that transcriptional repression of target genes by p53 is lost upon mutation of CCAAT-boxes. Thus, we searched the literature for reports of indirect repression involving interference of p53 with activating transcription factors such as NF-Y (**Table S5**).[191,309,333,377,379-402] We asked whether target genes are possibly repressed through NF-Y-bound CCAAT-boxes after p53 activation. It was observed that downregulation by p53 is lost after CCAAT elements were destroyed in the promoters of genes such as *CCNB2*,[255,384] *CDK1* (*CDC2*),[403] *CDC20*,[334] and *TOP2A*.[397] We and others observed a loss of p53-dependent repression and falsely interpreted that CCAAT-boxes bound by NF-Y are involved. In these reports it was not considered that mutation of CCAAT-boxes essentially inactivates promoters. Thus, the inactive promoters could not be repressed any further. In support of this interpretation, it is well established that NF-Y-bound CCAAT-boxes are essential for activity of the respective genes.[404,405] This is further supported by the observation that recruitment of RNA polymerase II depends on intact CCAAT-boxes.[406]

Many of the cell cycle genes activated through CCAAT-boxes also carry phylogenetically conserved cell cycle-dependent elements (CDE) and cell cycle genes homology regions (CHR) in their promoters which are responsible for cell cycle-dependent transcriptional regulation.[405,407] It has been shown that DREAM binds to CDE and CHR elements.[408] Importantly, p53-dependent repression of these genes is controlled by DREAM binding to CDE and CHR sites.[355-357] Consistently, instead of losing activity by altering the CCAAT-boxes, destruction of CDE and CHR elements leads to derepression of genes such as *CCNB2*,[355] *CDK1* (*CDC2*),[349,360] *CDC20*,[363] and *TOP2A*.[349]

In addition to NF-Y, Sp1 has also repeatedly been implicated in mediating p53-dependent repression (**Table S5**). Similar to the observations on NF-Y-mediated regulation, it was described that repression by p53 can depend on Sp1 binding sites, namely GC-boxes. The *Survivin* (*BIRC5*) gene served as an example where promoter activity is lost upon GC-box mutation.[381,382] As shown for promoters regulated by CCAAT-boxes, also *Survivin* possesses a phylogenetically conserved CHR downstream of its Sp1 sites.[408,409] Considering DREAM-mediated repression via CHRs,[355-357] it is likely that also in the case of *Survivin* the

CHR mediates p53-depedent repression. Concordantly, binding of DREAM components was shown to mediate repression of *Survivin* upon induction of p53.[354]

In order to evaluate a possible general function of CCAAT-, GC-, TATA-boxes, CHRs, and E2F sites in p53-dependent transcriptional control, we investigated the distribution of genes harboring such phylogenetically conserved elements across the *Expression Score* groups. CHR elements which bind DREAM [408] and E2F sites that recruit RB/E2F complexes [410-412] are also enriched at genes repressed by p53 (**Fig. 4A** and **B**). Consistent with this notion, DREAM, p130, and RB binding are strongly enriched at genes downregulated by p53 (**Fig. 3**). In contrast, TATA-box-containing genes are not accumulated in groups of genes activated or repressed by p53 (**Fig. 4C**).



It is established that NF-Y and Sp1 often activate E2F and DREAM/CHR target genes.[334,357,405,413-415] Thus, it is not surprising that CCAAT- and GC-boxes are overrepresented at target genes repressed by p53 (**Fig. 5A** and **B**). However, when removing all DREAM-, p130-, and RB-bound genes from the analysis, we observe that CCAAT- and GC-box enrichment is essentially lost in the group of genes downregulated compared to genes activated by p53 (**Fig. 5C–E**). These results lead to the conclusion that CCAAT- and GC-boxes do not mediate repression by p53 independently of DREAM, p130, or RB. Still, it is unknown why the transcription factors NF-Y and Sp1 particularly often activate genes that are regulated by pocket protein complexes such as DREAM.

Taken together, gene regulation by interference of p53 with activating transcription factors is, if at all, an exception.

ncRNAs in p53's transcriptional network: major players or minor influence?

The most prominent examples of ncRNAs in p53's transcriptional network are *mir34a*,[416] *lincRNA-p21*,[417] and *PANDA*.[418] The original studies on *mir34a* and *lincRNA-p21* were performed in mouse cells.[416,417] Here, we are limited to draw conclusions for p53's transcriptional network in human by comparing results of the meta-analysis with major findings from the initial ncRNA studies.

The original study on *mir34a* explicitly described *mir34a*-dependent downregulation of *Cdk4*, *Ccne2*, and *Met* via their 3′UTR.[416] Indeed, *CDK4* and *CCNE2* are found to be repressed by p53. However, both genes are also targeted by pocket proteins making it difficult to distinguish the influence of *mir34a* from that of the pocket proteins (**Table S1**). In contrast, *Met* does not bind pocket proteins and even showed the strongest repression by *mir34a* in the initial study.[416] This observation was confirmed

Figure 4. Genes repressed by p53 are enriched for CHRs which bind DREAM and E2F sites which recruit RB/E2F complexes. (**A**) The percentage of genes possessing a phylogenetically conserved CHR element in proximity to their TSS in each *Expression Score* group is displayed. The theoretical uniform distribution across the 13 *Expression Score* groups of genes with a phylogenetically conserved CHR element is indicated by the blue line (12.1% of 19,736 genes). (**B**) The percentage of genes harboring a phylogenetically conserved E2F site in proximity to their TSS in each *Expression Score* group is displayed. The theoretical uniform distribution across the 13 *Expression Score* groups of genes possessing a phylogenetically conserved E2F sites is indicated by the blue line (8.2% of 19,736 genes). (**C**) The percentage of genes with a phylogenetically conserved TATA-box in proximity to their TSS in each *Expression Score* group is displayed. The theoretical uniform distribution across the 13 *Expression Score* groups of genes holding a phylogenetically conserved TATA-box is indicated by the blue line (5.9% of 19,736 genes).

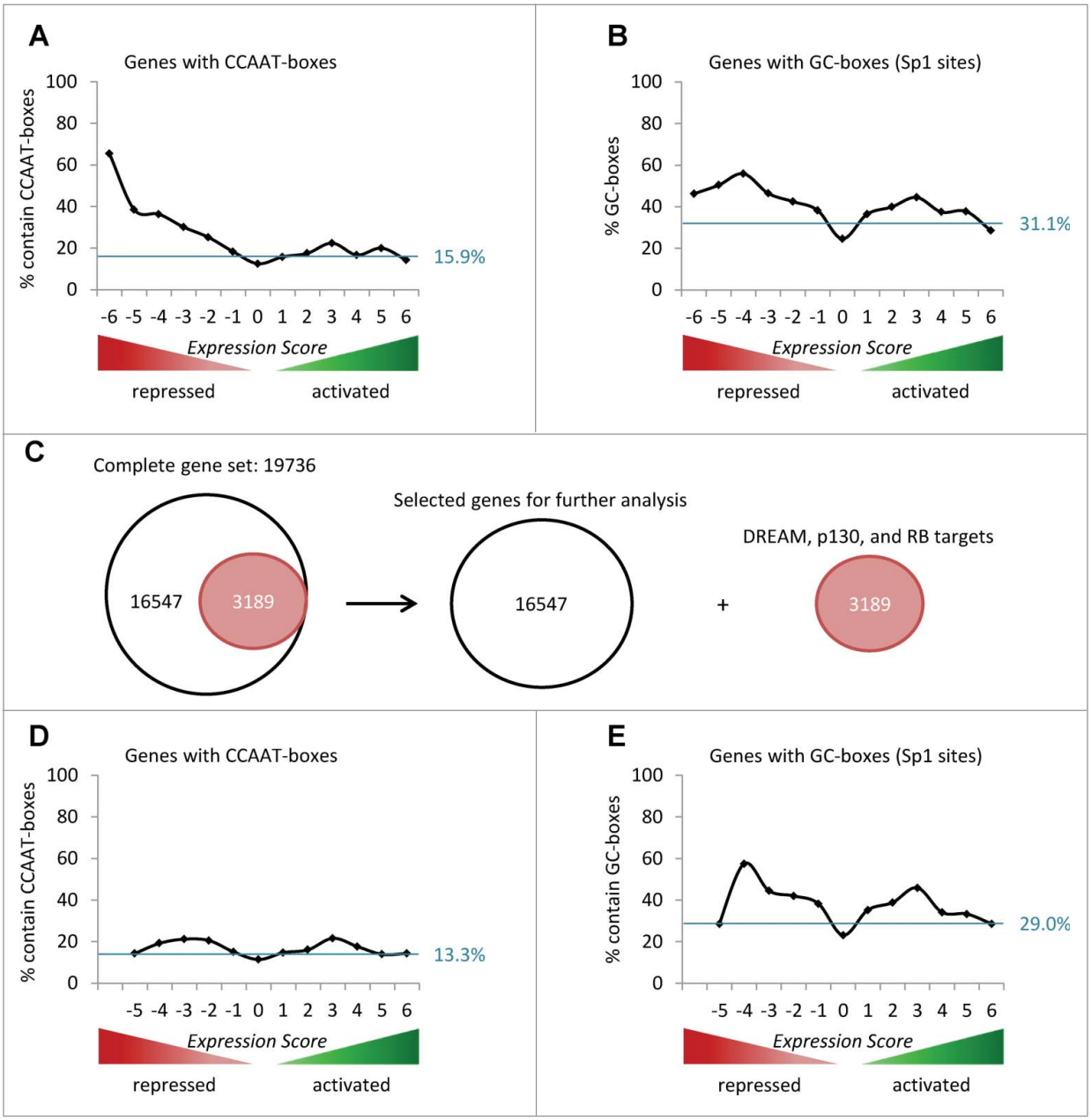


Figure 5. CCAAT- and GC-boxes do not mediate repression by p53 independent of DREAM, p130, or RB. (**A**) The percentage of genes harboring a phylogenetically conserved CCAAT-box in proximity to their TSS in each *Expression Score* group is displayed. The theoretical uniform distribution across the 13 *Expression Score* groups of genes with a phylogenetically conserved CCAAT-box is indicated by the blue line (15.9% of 19,736 genes). (**B**) The percentage of genes holding a phylogenetically conserved GC-box (Sp1 site) in proximity to their TSS in each *Expression Score* group is displayed. The theoretical uniform distribution across the 13 *Expression Score* groups of genes possessing a phylogenetically conserved GC-box (Sp1 site) is indicated by the blue line (31.1% of 19,736 genes). (**C**) All genes bound by DREAM, p130, or RB (n = 3,189) are removed from the total set of 19,736 genes for further analyses. (**D**) The percentage of genes harboring a phylogenetically conserved CCAAT-box in proximity to their TSS in each *Expression Score* group is displayed. The theoretical uniform distribution across the 13 *Expression Score* groups of genes with a phylogenetically conserved CCAAT-box is indicated by the blue line (13.3% of 16,547 genes). (**E**) The percentage of genes possessing a phylogenetically conserved GC-box (Sp1 site) in proximity to their TSS in each *Expression Score* group is displayed. The theoretical uniform distribution across the 13 *Expression Score* groups of genes holding a phylogenetically conserved GC-box (Sp1 site) is indicated by the blue line (29.0% of 16,547 genes).

by another report.[419] Interestingly, human *MET* appears not to be repressed by p53 (*Expression Score* = 2) (**Table S1**). Thus, the influence of *mir34a* on p53's transcriptional program is not the same between mouse and human. Importantly, experiments on *mir34a-c* triple knockout mice showed that the *mir34* family is not necessary for p53 function.[420] Considering these observations, the mir34 family appears to have only a minor influence on p53-dependent transcription.

The initial study on *lincRNA-p21* explicitly reported *Vcan*, *Cxcr6*, *Hus1*, *Kdm6b* (*Jmjd3*), *Zbtb20*, *Atf2*, *Rb1*, *Lpp*, *Pdlim2*, and *Usp25* to be repressed by *lincRNA-p21* and hnRNP-K in response to p53.[417] However, solely *ATF2* and *USP25* show a slightly negative *Expression Score* of -1, while *VCAN*, *CXCR6*, *HUS1*, *KDM6B*, *ZBTB20*, *RB1*, *LPP*, and *PDLIM2* are not found to be repressed by p53 in human (*Expression Scores* $\geqq 0$) (**Table S1**). Considering these large discrepancies between mouse and human, it appears unlikely that p53-dependent repression via *lincRNA-p21* and hnRNP-K plays a major role in human. Concordantly, the authors of a very recent study investigating *lincRNA-p21* knockout mice concluded that *lincRNA-p21* unlikely has genome-wide regulatory functions.[421]

In addition to *mir34a* and *lincRNA-p21*, the *PANDA* ncRNA was observed to be p53-dependently induced.[418] *PANDA* was described to interfere with NF-YA upon induction of p53. However, as outlined above, genes regulated by NF-Y/CCAAT-boxes are not generally repressed by p53 (**Fig. 5**). Consistently, the authors observed only 224 genes to be induced upon *PANDA* knockdown,[418] although 1412 genes are downregulated after NF-YA was targeted directly by shRNA.[422] Moreover, *FAS*, *PIDD* (*LRDD*), *APAF1*, and *BIK* were explicitly reported to be downregulated by the p53-*PANDA*-NF-YA pathway.[418] In contrast, expression of *FAS*, *PIDD* (*LRDD*), and *APAF1* was not found to be deregulated upon depletion of NF-YA by shRNA, while *BIK* even was observed to be activated.[422] Thus, one can conclude that the p53-*PANDA*-NF-YA pathway does not generally influence gene transcription, but regulates, if at all, only a few promoters in certain cell types. In the initial study, *PANDA* was shown to fine-tune the p53-dependent transcription of pro-apoptotic target genes in human fetal fibroblasts.[418]

Taken together, a major contribution of well known ncRNAs to p53's transcriptional program is not evident. The transcriptional influence of the ncRNAs discussed above appears to be, if at all, limited to fine-tuning expression of a few genes in certain cell types.

Conclusions and Perspective

Our results resolve the longstanding question on how p53 binding can activate one target gene and repress another. Most surprisingly, results from the computational meta-analysis do not support models involving direct transcriptional repression through p53. Experimental validation supports the conclusions from the meta-analysis. Thus, the previously reported regulation of several target genes appear questionable (**Table S2**). Generally, binding and regulation are not necessarily cause and consequence, considering that not every binding event leads to regulation and that regulation can be indirect.

As an alternative to direct repression, the results show that p53-dependent repression occurs indirectly and is largely mediated by activation of the p53-p21-DREAM/RB pathway (**Fig. 6**). Other reported indirect pathways such as ncRNAs appear to be, if at all, either an exception or to merely mediate fine-tuning of p53's transcriptional program.

In summary, with direct activation and indirect downregulation via the p53-p21-DREAM/RB pathway only 2 out of the previously reported 6 major mechanisms of p53-dependent regulation are supported by the meta-analysis (**Fig. 6**). Future research will have to show whether there are still other mechanisms that are of general importance mediating p53-dependent transcription.

Materials and Methods

Computational meta-analysis on binding and regulation by p53

Expression data on known protein-coding genes were extracted from 6 studies on p53-dependent regulation.[7,19-23] The expression values of the analyzed genes were compiled and classified into repressed (−1), induced (+1), and not-regulated (0) by p53. For every gene the *Expression Score* was calculated as the sum of the classifications of the individual studies. *Expression Scores* range from −6 to 6, where "6" means found as induced by p53 in all studies and "−6" means classified as repressed by p53 in all 6 studies. Thus, the *Expression Score* describes the direction of regulation as well as the confidence of the classification (**Table S1**).

Due to the fact that the data originate from different sources, all studies must be evaluated and filtered with individual thresholds for log-fold change and/or p-values. We aimed not to alter criteria that were used in the original studies. However, if a study yielded many more regulated genes compared to a related study, we slightly adjusted thresholds in p-values and expression fold-changes to yield data sets of similar size. The following thresholds were used for the 6 studies: For the data from the study by Böhlig et al. (kindly provided by Levin Böhlig) the p-value must not exceed 0.05, the log-fold change has to exceed 1 to be classified as "induced" and undercut −1 for classification "repressed".[19] For the data from the Nikulenkov et al. study (kindly provided by Galina Selivanova) 0.5 and -0.5 are used as thresholds of the log-fold change and 0.05 of the p-value.[7] The data on differentially expressed genes after expression of HPV-16 E6 or HPV-18 E6 from the study by Rozenblatt-Rosen et al. (GSE38467) were filtered with log-fold change of 0.25 and an adjusted p-value of 0.05.[21] The data from the report by Kracikova et al. (GSE30753) were filtered solely with an adjusted p-value of 0.05, the same criteria were used in the original study.[22] The thresholds for the Goldstein et al. data (GSE30137) were set to an absolute log-fold change of 0.5 and an adjusted p-value of 0.05.[23] The expression data from Rashi-Elkeles et al. represent a meta-study on different data sets. For filtering, the sum of the Z-values from the individual studies is used; larger than 10 is counted as "increased", less than -10 is counted as "repressed".[20]

For every gene, the genomic location is shown, i.e. chromosome, strand, transcription start and stop, and start and stop of the coding sequence. Primarily, the annotations of the canonical transcripts for the human genome version hg19 were taken from the UCSC Genome Browser database.[423] Only in cases where no annotation was available at the UCSC Genome Browser

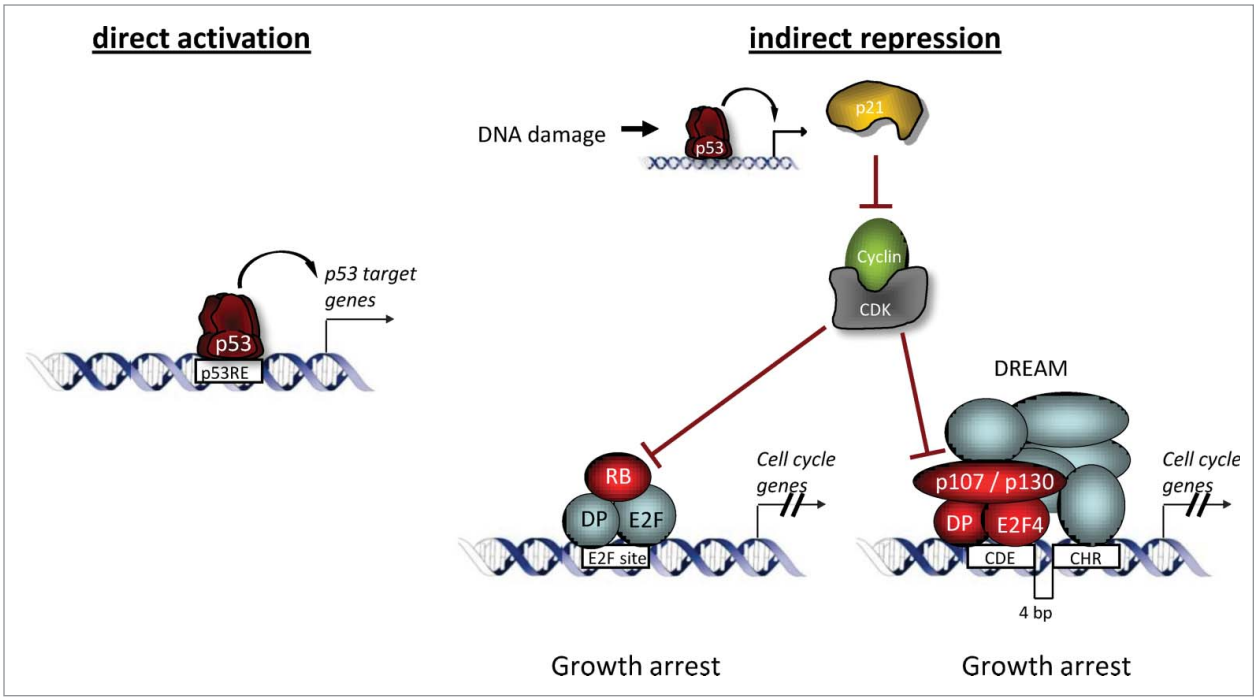


Figure 6. The tumor suppressor p53 is not a direct repressor of transcription, it solely activates its target genes upon binding to DNA. In order to activate transcription, the p53 tetramer binds to the p53 RE of its target gene. The transcription factor p53 acts as repressor by activation of the p53-p21-DREAM/RB pathway ultimately leading to indirect p53-dependent transcriptional repression.

database, the annotation from Ensembl human genome version GRCh37 was used.[424] Additionally, mappings to the different database identifiers are provided if available including UCSC canonical transcript ID, Ensembl gene ID, HUGO gene symbol, and Affymetrix microarray IDs (**Table S1**).

ChIP peaks from 6 genome-wide p53 binding studies were annotated 25 kb around the TSS.[6-9,24,25] In 4 of the 6 studies, ChIP peaks originate from several experiments. In case of 2 data sets in one report, all ChIP peaks were included in our analysis.[6,8] To reduce the number of false positive annotated p53 ChIP peaks, we filtered for peaks which occurred in at least 2 data sets in cases where 3 or 4 experiments were performed.[7,9] Furthermore, ChIP peaks occurring in more than one experiment from the same study were merged into one peak using BEDTools.[425] All ChIP peaks from the 6 studies that overlap by at least one base pair were merged. From this set of p53 ChIP peaks, only those peaks were selected for further analysis that were found in at least 2 studies. For each gene, the location of the p53 peaks is annotated for each study as well as the *p53 ChIP Score* showing the number studies for which peaks in the promoter of this gene were found (**Table S1**).

Search for phylogenetically conserved binding motifs

Several binding sites were annotated in the promoter regions of the genes. CHR (TTTGAA, TTTAAA, CTTGAA, TAGGAA), E2F (TTSSSSS), TATA (TATATA, TATAA), CCAAT (CCAAT), and SP1 (GGGCGG, GGCGGG) sites were searched in the region of 200 bp around the TSS on both strands that were not extended into the coding sequence or genes located upstream of the TSS. PhastCons conservation scores [426] obtained from the multiz46 alignment of placental mammalia [427] were used to calculate average phylogenetic sequence conservation. Only those hits were annotated that have an average PhastCons conservation score of at least 0.8 (**Table S1**).

Meta-analysis of "default targets"

An extensive literature search for potential direct p53 target genes was performed that started with 2 reviews [13,428] and includes about 300 reports in total (**Table S2**). We included all target genes that were reported as differentially expressed upon p53 induction and bound by p53 in proximity of their locus (**Table S2**). All reported p53 target genes were compiled and classified as repressed (−1) or activated (+1) by p53 (**Table S3**).

Additionally, we included potential p53 target genes from genome-wide studies that combined p53 binding data (ChIP-PET, ChIP-chip, ChIP-seq) with p53-dependent expression data from microarray analyses.[5-9] Two studies contained 2 data sets each from ChIP-seq combined with expression data following 2 different treatments to activate p53.[6,8] We included the 2 data sets of each study separately in our analysis. As both data sets originate from experiments with similar conditions, we assigned a lower score (0.75) when a gene was found as p53 target gene in these data sets in order to not overweigh the study's influence on our meta-analysis (**Table S3**). Next, we combined 2 genome-wide p53 binding data sets,[24,25] that previously had not been compared to expression data, with 6 genome-wide p53 dependent expression studies.[7,19-23] From this combination, we included genes as potential p53 targets that were identified as

bound by p53 in at least one of the binding studies and as regulated in at least one expression study, assigning a score of 0.25 for each study in which the gene was identified as bound or regulated by p53 (**Tables S1** and **S3**).

For every gene the *Default Target Score* was calculated as the sum of the scores from the individual data sets. Thus, it represents the direction of regulation as well as the confidence of the classification. We considered a gene as a "default target" that was reported in at least 3 data sets, which corresponds to a *Default Target Score* greater than 2 (**Table S3**).

DREAM, p130, RB, and E2F7 binding data

The promoter regions 200 bp upstream and downstream from the TSS, but not extending into the coding sequence or genes located upstream of the TSS, were overlayed with peaks from 4 ChIP-chip experiments measuring binding of E2F4, p130, LIN9, and LIN54 proteins as indicators for DREAM complex binding [341] as described previously.[408] ChIP-seq peaks for DNA bound by p130, RB,[340] and E2F7 [373] were overlayed with an extended promoter region of 1000 bp around the TSS. Again, the promoter regions were truncated to not overlap with the coding sequence or genes located upstream of the TSS. ChIP peaks for p130 and RB were restricted to those with a false discovery rate ≤ 0.1 (**Table S1**).

Cell culture, FACS, chromatin immunoprecipitation, RNA extraction, and semi-quantitative real-time PCR

Experiments were performed as described previously.[357]

Primer

Real-time PCR primer for ChIP analyses

GAPDHS: for 5′-AGACCAGCCTGAGCAAAAGA-3′, rev 5′-CTAGGCTGGAGTGCAGTGGT-3′;[356, 357] *CDKN1A*: for 5′-CTGAGCCTCCCTCCATCC-3′, rev 5′-GAGGTCTCCTGTCTCCTACCATC-3′;[356, 357] *MDM2*: for 5′-TCGGGTCACTAGTGTGAACG-3′, rev 5′-TGAACACAGCTGGGAAAATG-3′; *ABCB1*: for 5′-TTATCCCAGTACCAGAGGAGGA-3′, rev 5′-TGCTTTGGAGCCATAGTCAT-3′; *BCL2*: for 5′-ATCCTTCCCAGAGGAAAAGC-3′, rev 5′-ATCAAGTGTTCCGCGTGATT-3′; *BNIP3*: for 5′-AGCGTTTCTGGGGCGCACCTTG-3′, rev 5′-GGGACTGGGAGGCACTTTTCAGAGGA-3′;[251] *CCNB1*: for 5′-CCTGATTTTCCCATGAGAGG-3′, rev 5′-GGATCACACATTAGCAACGGG-3′;[254] *CD44*: for 5′-TTTACGGTTCGGTCATCCTC-3′, rev 5′-TGCTCTGCTGAGGCTGTAAA-3′;[262] *CDC20*: for 5′-TAAAGCCCCAAGGGGATAAG-3′, rev 5′-CGTGTGTTTGTCTCGTTTGC-3′; *CDK1*: for 5′-AACTGTGCCAATGCTGGGAG-3′, rev 5′-AGCCAGCTTTGAAGCCAAGT-3′;[258] *CRYZ*: for 5′-TCCACCATGATTGTGAGACC-3′, rev 5′-CAAACATTTACCTGACACCCA-3′;[260] *HSPA8*: for 5′-TGGGTAGATGGGTCCTTCAT-3′, rev 5′-AATAGTGCCCATCACCTCCT-3′;[260] *ID2*: for 5′-GAACGCGGAAGAACCAAG-3′, rev 5′-GGCTCGGCTCAGAATGAA-3′; *LASP1*: for 5′-AGCGTTCAGGAGGATCCAA-3′, rev 5′-AGCGCTCTCAGGCTGACT-3′; *MAD1L1*: for 5′-ACTGGGAAGGTAGCCTAGTAGCATA-3′, rev 5′-AGCCTCCTCGGACAAACTTGC-3′;[260] *ME1*: for 5′-GGAAACTGCACCAACTGTGA-3′, rev 5′-TAAACATGCGGGTTGGCTAT-3′; *ME2-RE1*: for 5′-GTTGCCCAGGCTGGAGTG-3′, rev 5′-CTGTAATCCCAGCACTTT-3′;[285] *ME2-RE3*: for 5′-AAGTTGGAGACCACCCTGTG-3′, rev 5′-GCTAGAGTGCAGTGGCATGA-3′; *ME3*: for 5′-GTTGCGATCCCGTGGCTG-3′, rev 5′-ACCGCAGGTCAGACTGAC-3′;[285] *NEK2*: for 5′-TGCAACCCCATGCTCTGTTAC-3′, rev 5′-TCACGCCTATAATCCTAGCAC-3′;[289] *PTK2*: for 5′-CTCCAACCTCGCCTTTTGC-3′, rev 5′-GGGACTTAGAAGTCCACTGG-3′;[306] *TPT1*: for 5′-TAGGGAGCGCCCCGAGAGTT-3′, rev 5′-GTGACGTGGCACGAAGAG-3′.[320]

Real-time PCR primer for expression analyses

GAPDH: for 5′-GACCCCTTCATTGACCTCAAC-3′, rev 5′-CACGACGTACTCAGCGCC-3′; *U6*: for 5′-AACGCTTCACGAATTTGCGT-3′, rev 5′-CTCGCTTCGGCAGCACA-3′;[357] *L7*: for 5′-GCACTATCACAAGGAATATAGGCAG-3′, rev 5′-CCCATGCAATATATGGCTCTAC-3′;[356] *CDKN1A*: for 5′-GGAAGACCATGTGGACCTGT-3′, rev 5′-GGATTAGGGCTTCCTCTTGG-3′; *MDM2*: for 5′-GTGAATCTACAGGGACGCCA-3′, rev 5′-CTGATCCAACCAATCACCTGAA-3′;[351] *PPM1D*: for 5′-CAACTGCCAGTGTGGTCATC-3′, rev 5′-CGATTCACCCCAGACTTGTT-3′; *ABCB1*: for 5′-CATGATGCTGGTGTTTGGAG-3′, rev 5′-AGGCACCAAAATGAAACCTG-3′; *BCL2*: for 5′-ACTTGTGGCCCAGATAGGCACCCAG-3′, rev 5′-CGACTTCGCCGAGATGTCCAGCCAG-3′;[245] *BNIP3*: for 5′-TCCTCTTTAAACACCCGAAGCGCA-3′, rev 5′-ATCCGATGGCCAGCAAATGAGAGA-3′;[251] *CCNB1*: for 5′-AAGAGCTTTAAACTTTGGTCTGGG-3′, rev 5′-CTTTGTAATGCCTTGATTTACCATG-3′;[254] *CD44*: for 5′-CCACGTGGAGAAAAATGGTC-3′, rev 5′-CATTGGGCAGGTCTGTGAC-3′;[262] *CDC20*: for 5′-CGCCAACCGATCCCACAG-3′, rev 5′-CAGGTTCAAAGCCCAGGC-3′;[328] *CDK1*: for 5′-TGGGGTCAGCTCGTTACTCA-3′, rev 5′-CACTTCTGGCCACACTTCATTTA-3′;[258] *CRYZ*: for 5′-GAGTGATAGTTGTTGGCAGCAGAG-3′, rev 5′-TGCTGAAATTCCTCCTTGGTTG-3′;[260] *HSPA8*: for 5′-GCCGTTTGAGCAAGGAAGACA-3′, rev 5′-CAGCAGTCTGATTCTTATCAAGCC-3′;[260] *ID2*: for 5′-TCAGCCTGCATCACCAGAGA-3′, rev 5′-CTGCAAGGACAGGATGCTGAT-3′;[275] *LASP1*: for 5′-GTATCCCACGGAGAAGGTGA-3′, rev 5′-TGTCTGCCACTACGCTGAAA-3′;[281] *MAD1L1*: for 5′-CAGGGTGACTATGACCAGAGCAG-3′, rev 5′-TCAGCTCTGCCACCTCCTTG-3′;[260] *ME1*: for 5′-GGATTGCACACCTGATTGTG-3′, rev 5′-TCTTCATGTTCATGGGCAAA-3′; *ME2*: for 5′-ATGGGCTTGTACCAGAAACG-3′, rev 5′-TGCTGCAAGAAGACCTGCTA-3′; *ME3*: for 5′-CAGCAGAGTGACCTGGACAA-3′, rev 5′-CTTCTGGCCAAGAATTCAGC-3′; *NEK2*: for 5′-AGTGCAAGGACCTGAAGAAAAG-3′, rev 5′-TCAATATCTGACAGGGCTTGAG-3′;[289] *PTK2*: for 5′-GTGCTCTTGGTTCAAGCTGGAT-3′, rev 5′-ACTTGAGTGAAGTCAGCAAGATGTGT-3′;[306] *TPT1*: for 5′-GATCGCGGACGGGTTGT-3′, rev 5′-TTCAGCGGAGGCATTTCC-3′.[320]

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

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The opinions expressed in this publication are those of the authors and do not necessarily reflect the views of the funders.

Author Contributions

MF conceived the study. LS and MF performed the computational analyses. MF performed the experiments. KE supervised the study. MF and KE, including segments provided by LS, wrote the manuscript. All authors read and approved the final article.

Supplemental Material

Supplemental data for this article can be accessed on the publisher's website.

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