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REVIEW

Census and evaluation of p53 target genes

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The tumor suppressor p53 functions primarily as a transcription factor. Mutation of the *TP53* gene alters its response pathway, and is central to the development of many cancers. The discovery of a large number of p53 target genes, which confer p53's tumor suppressor function, has led to increasingly complex models of p53 function. Recent meta-analysis approaches, however, are simplifying our understanding of how p53 functions as a transcription factor. In the survey presented here, a total set of 3661 direct p53 target genes is identified that comprise 3509 potential targets from 13 high-throughput studies, and 346 target genes from individual gene analyses. Comparison of the p53 target genes reported in individual studies with those identified in 13 high-throughput studies reveals limited consistency. Here, p53 target genes have been evaluated based on the meta-analysis data, and the results show that high-confidence p53 target genes are involved in multiple cellular responses, including cell cycle arrest, DNA repair, apoptosis, metabolism, autophagy, mRNA translation and feedback mechanisms. However, many p53 target genes are identified only in a small number of studies and have a higher likelihood of being false positives. While numerous mechanisms have been proposed for mediating gene regulation in response to p53, recent advances in our understanding of p53 function show that p53 itself is solely an activator of transcription, and gene downregulation by p53 is indirect and requires p21. Taking into account the function of p53 as an activator of transcription, recent results point to an unsophisticated means of regulation.

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INTRODUCTION

The tumor suppressor p53 and its encoding genes are the most studied protein and gene in literature, with a total of more than 80 000 entries in PubMed. p53 was mistakenly discovered almost four decades ago as an oncogene that is overexpressed in cancer, and has since become known as the most important tumor suppressor, and 'the guardian of the genome'.[1,2] This is evidenced by reports that *TP53*, the gene that encodes for p53, is the most frequently mutated gene in cancer.[3] p53 is activated in response to stress signals—DNA damage, oncogene activation, ribosomal stress and hypoxia[4] —and leads to growth suppression by inducing cell cycle arrest or cell death. The prevailing function of the p53 tumor suppressor is the transcriptional control of target genes that regulate numerous cellular processes, including cell cycle and apoptosis.[5,6] Typically, p53 binds to the target genes as a tetramer, which comprises two dimers that each binds a decameric half-site with the consensus sequence RRRCWWGYYY (R = A/G, W = A/T, Y = C/T).[7–10] The discovery of the first p53 target genes, including *CDKN1A* (*p21, CIP1, WAF1*),[11,12] *GADD45A*[13] and *MDM2*,[14,15] inspired numerous researchers to identify additional genes that mediate the tumor suppressor function. Recent genome-wide analyses have identified from one hundred[16] up to thousands[17] of potential p53 target genes.

The aim of the present survey is to compile an updated list of p53 target genes from individual gene analyses and high-throughput studies that will serve as a resource, and to evaluate the regulation of these genes based on the frequency of their identification in independent studies. Results from a recent meta-analysis of 20 genome-wide p53 gene expression profiles, and 15 p53 binding profiles, document that many p53 target genes are regulated across cell types as well as treatments.[18] Moreover, a comparison of binding studies shows that functional p53 binding is independent of cell type and treatment.[19] In the present survey, a p53 target gene is defined as a protein-coding gene that is differentially regulated following p53 activation or inactivation, and that is bound by p53 near the gene locus.

SURVEY OF 346 TARGET GENES DERIVED FROM 319 INDIVIDUAL GENE STUDIES

Similar to the discovery of the first p53 target genes, many additional p53 targets have been identified in studies that focused on one up to a few individual genes. The criterion of a target gene that is bound as well as regulated by p53 is met by 346 genes described in 319 such 'individual gene studies' (Supplementary Table S1). Taking into consideration that some of these studies investigated several target genes, and that some target genes were reported in more than one study, a total of 399 gene-study pairs were found (Supplementary Table S1). More than one study on a target gene was included in the list if it provided information on the p53-dependent regulation that added to or was different from what was reported in the initial study. The 319 individual studies were published between 1992 and 2016, with a maximum of 26 studies published in 2006 (Figure 1a). Of the 346 genes, 246 were reported as activated by p53, 91 as repressed and 9 as both activated and repressed (Figure 1b). The 319 studies (399 gene-study pairs) investigated 358 human genes, 47 mouse genes, 5 rat genes and 1 bovine gene (Figure 1c). When a study investigated gene regulation in multiple species, the human data was focused.

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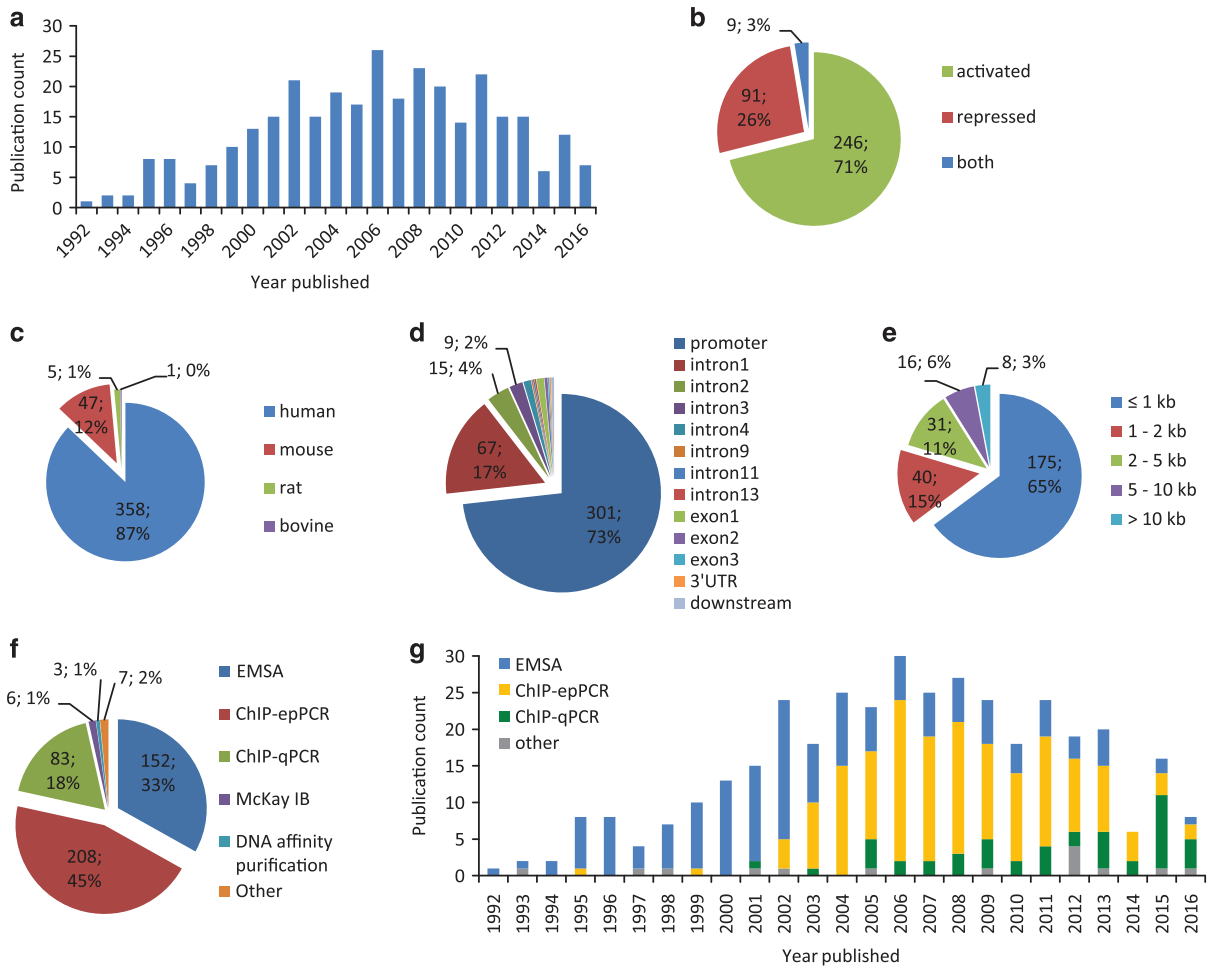

Figure 1. Survey of 346 target genes derived from 319 individual gene studies. (**a**) The number of studies reporting individual p53 target genes published in a particular year. (**b**) Genes were reported as activated, repressed or both activated and repressed by p53. (**c**) Experiments were carried out in cells from human, mouse, rat or bovine. Some studies used cells from more than one species. (**d**) Binding of p53 is located in different parts of the gene. (**e**) p53 binding sites are located in varying distances from the TSS. Some genes display multiple p53 binding sites. (**f**) Various methods have been used to identify p53 binding sites. Some studies used more than one method. (**g**) The number of publications that used a particular method to identify p53 binding compared with the publication year. Some studies used multiple methods.

p53 most frequently binds in the promoter region (5′-untranslated region (UTR) and upstream) of genes. Introns (particularly intron 1) also frequently harbor p53 binding sites, whereas p53 seldom binds to the coding region (Figure 1d). Precise location of the p53 binding site has been reported for 266 of the 399 gene-study pairs. In general, the number of p53 binding events decreases with increasing distance from the transcriptional start site (TSS). Proximal p53 binding—that is, within 1 kb from the TSS—occurs most frequently, whereas distal binding—at >10 kb from the TSS—is rarely reported (Figure 1e). It is important to note, however, that studies on individual genes are biased for analyzing promoters. The most common technique used to identify p53 binding is chromatin immunoprecipitation followed by end point PCR (ChIP-epPCR), which was applied 208 times. Electromobility shift assays (applied 152 times) and ChIP followed by real-time PCR (ChIP-qPCR, applied 83 times) have also been frequently used. Other techniques such as the McKay immunoblots (McKay IB, applied six times) and DNA affinity purifications (applied three times) are rarely used (Figure 1f). Use of the ChIP technique replaced use of electromobility shift assay over time, but the outdated ChIP-epPCR has not yet been fully replaced by ChIP-qPCR (Figure 1g).

SURVEY OF 3509 TARGET GENES DERIVED FROM 16 HIGH-THROUGHPUT DATA SETS

In recent years, genome-wide analyses aimed at identifying p53 target genes have each identified shared candidates, as well as those that are unique.[16,18,20–30] In these analyses, candidate p53 target genes were uncovered by integrating p53-dependent gene expression profiles with p53 binding profiles. As mentioned above, genes that are regulated and bound by p53 are considered to be candidate p53 target genes. Given that three studies harbored two data sets each,[20,22,26] 16 data sets were extracted from 13 genome-wide studies of p53 target genes,[16,18,20–30] yielding a total of 3509 candidate p53 target genes in the 16 data sets (Supplementary Table S2). From 121[16] to 1341[26] candidate p53 target genes were documented in the individual data sets. Notably, the majority of genes (2261 out of 3509; 64.4%) was identified exclusively in one data set (Figure 2a). Only two genes—*CDKN1A*[11,12] and *RRM2B*[31]—were identified in all 16 data sets. This is particularly surprising, given that some data sets were derived from the same combination of cell type and treatment (HCT116 cells treated with 5-FU[16,29] and MCF-7 cells treated with Nutlin-3a[21,25]), and indicates that the individual data sets harbor numerous false positives and false negatives. Table 1 displays the

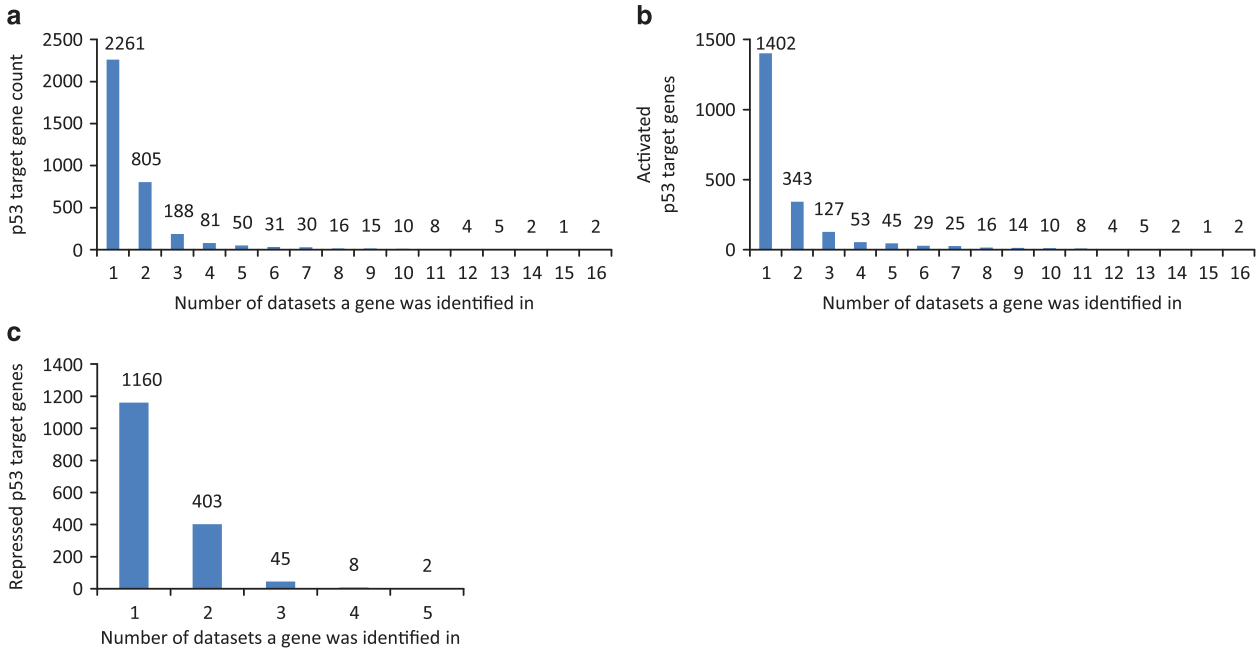

Figure 2. Survey of 3509 target genes derived from 16 high-throughput data sets. (**a**) The number of potential p53 targets is compared with the number of data sets that commonly identify them. (**b**) The number of genes is displayed that is identified by an increasing number of data sets as being directly activated by p53. (**c**) The number of genes is displayed that is identified by an increasing number of data sets as being directly repressed by p53.

top 116 genes that are identified as p53-activated targets in at least six data sets. In addition to *CDKN1A* and *RRM2B*, well-known p53 target genes were identified in the majority of data sets, including *MDM2*,[14,15] *GDF15*,[32] *SUSD6* (*TMPS, DRAGO, KIAA0247*),[33,34] *GADD45A*,[13] *PLK3*,[35] *BTG2*,[36] *TIGAR* (*C12orf5*),[35,37] *TNFRSF10B*,[38,39] *PPM1D*,[40] *BAX*,[41–43] *AEN*,[44] *PLK2*,[45] *SESN1*,[46] *FAS*[47–49] and *KITLG*[50] (Supplementary Table S2). Well-known p53 target genes that did not meet the criteria of a published p53 target (this occurred usually because p53 gene binding was not investigated; see above) included *SFN* (*14-3-3 sigma*),[51] *SESN2*,[52] *TNFRSF10C*[39] and *TNFRSF10D*,[39] and these genes were identified in multiple data sets as well. Thus, the number of data sets that agree on a gene being a p53 target represents a ranking of confidence, which is supported by recent meta-analysis results.[18] Genes that were identified only in a small number of data sets are more likely to be false positives.

When p53 target genes are grouped into those that are activated by or repressed by p53, it is evident that the majority of data sets exclusively identified target genes that are activated by p53. In contrast, target genes that are repressed by p53 were not commonly identified (Figures 2b and c). This finding is in agreement with the current model that describes p53 solely as a transcriptional activator, and not as repressor.[53]

TARGET GENE ACTIVATION BY P53

The p53 tumor suppressor binds target genes through p53 response elements (REs) that comprise two decameric half-sites with the consensus sequence RRRCWWGYYY, separated by a spacer of 0–13 bp. In addition, results from multiple studies suggest that p53 can bind and transactivate target genes through noncanonical binding sites, particularly through half-sites.[22,54–56] A recent comparison of multiple genome-wide p53 binding studies, however, showed that spacers and half-sites have no role in functional p53 binding.[19]

Activation of p53 is induced by cell stress including DNA damage, oncogene activation, ribosomal stress or hypoxia.[4] DNA damage, for example, initiates a series of p53 pulses that ultimately lead to target gene activation.[57] The p53 transcription factor uses two transactivation domains to drive gene expression[58] and the transactivation of target genes requires cooperative interaction between the p53 molecules at DNA REs.[23,59] Target genes were reported to be activated by p53 with varying kinetics through stimulus- and promoter-specific recruitment of transcription initiation components and polymerase II.[60–63] Genome-wide data, however, do not support promoter-specific activities of p53, but instead suggest unsophisticated p53 binding.[19]

P53 BINDING: LOCATION, LOCATION, LOCATION

How differences in the location of p53 binding, relative to the TSS of a given gene, influence the gene's regulation is not known. To identify p53 target genes, the genome-wide studies have used thresholds for p53 binding that range from 5 kb[22] to 100 kb[16] relative to the TSS, but the general consensus is that the number of p53 binding events declines with increasing distance from the TSS.

Analysis of the 346 reported p53 target genes shows that binding to most p53 target genes occurs within 1 kb of the TSS (Figure 1e), which is in agreement with results from a previous smaller census of p53 target genes that reported a decline in transactivation potential with distance from the TSS.[5] This observation is further supported by the control of gene transcription largely through proximal promoters.[64] A recent genome-wide meta-analysis also found that proximal p53 binding, within 2.5 kb from the TSS, strongly correlates with transactivation of p53 target genes.[18] Of note, the meta-analysis data provides evidence that distal p53 binding also correlates with target gene activation, although to a lesser degree.[18] And, long-distance transactivation is reportedly mediated by the binding of p53 to enhancers.[30,65,66] Finally, gene downregulation through distal enhancer interference by p53 binding has been reported for mouse embryonic stem cells,[17] but is not supported by data from humans.[18,19]

The finding that p53 binding occurs at intronic sites (Figure 1d) indicates that p53 can promote alternative transcription initiation, which leads to the formation of transcripts that differ in the length

Table 1. Top 116 genes identified as activated p53 targets in at least 6 out of 16 genome-wide data sets

Gene symbol	Literature	No. of genome-wide data sets	Gene symbol	Literature	No. of genome-wide data sets	Gene symbol	Literature	No. of genome-wide data sets
CDKN1A	11,12	16	*HSPA4L*		9	*PLCL2*		7
RRM2B	31	16	*ISCU*	54	9	*PRKAB1*	35,201	7
MDM2	14,15	15	*PHLDA3*	233	9	*PTP4A1*	234	7
GDF15	32	14	*SERPINB5*	235	9	*SPATA18*	236	7
SUSD6	33,34	14	*SLC12A4*		9	*TGFA*	161	7
BTG2	36	13	*TRAF4*	179	9	*TLR3*	237	7
DDB2	165	13	*TRIM22*	223	9	*ZNF219*		7
GADD45A	13	13	*CCDC90B*		8	*ZNF337*		7
PLK3	35	13	*CES2*	238	8	*ZNF79*	160	7
TIGAR	35,37	13	*DYRK3*		8	*ARHGEF3*		6
RPS27L	239,240	12	*FAM13C*		8	*CD82*	241	6
TNFRSF10B	38,39	12	*FAM198B*		8	*CDIP1*	242	6
TRIAP1	189	12	*FAM212B*		8	*CERS5*		6
ZMAT3	243	12	*KITLG*	50	8	*CSF1*	244	6
BAX	41–43	11	*NADSYN1*		8	*DUSP14*		6
BLOC1S2		11	*NTPCR*		8	*EPS8L2*		6
PGF	160	11	*ORAI3*		8	*FAM210B*		6
POLH	170	11	*SESN2*	52	8	*FUCA1*	160,196	6
PPM1D	40	11	*SLC30A1*		8	*GRHL3*		6
PSTPIP2		11	*TM7SF3*		8	*HHAT*		6
SULF2	245	11	*TMEM68*		8	*IER5*	246	6
XPC	166	11	*WDR63*		8	*IGDCC4*		6
AEN	44	10	*ZNF561*		8	*IKBIP*		6
ANKRA2		10	*ACER2*		7	*LAPTM5*		6
FAS	47–49	10	*ANXA4*		7	*MAST4*		6
GPR87	247	10	*APOBEC3C*		7	*MICALL1*		6
NINJ1	160	10	*ASCC3*		7	*PADI4*	248	6
PLK2	45	10	*ASTN2*		7	*PANK1*	199,200	6
SERTAD1		10	*ATF3*	249	7	*PMAIP1*	182	6
SESN1	46	10	*BBC3*	181	7	*PRDM1*	250	6
TP53I3	251,252	10	*CPE*		7	*RAP2B*	253	6
TP53INP1	254	10	*DCP1B*		7	*RNF19B*		6
ABCA12	255	9	*EDA2R*	256	7	*RRAD*	257	6
CCNG1	219	9	*ENC1*		7	*SAC3D1*		6
CMBL		9	*EPHA2*	258	7	*SYTL1*		6
CYFIP2	259	9	*FDXR*	202	7	*TNFRSF10D*	39	6
DRAM1	209	9	*FOSL1*		7	*TSPAN11*		6
FBXO22	240	9	*LIF*	260	7	*VWCE*		6
FBXW7	159	9	*PGPEP1*		7			

of their 5′-UTR, or their first exon. In case of *MDM2*, for example, p53 binding to the first intron leads to the formation of transcripts that differ from the constitutionally expressed *MDM2* isoform.[67,68] Thus, alternate transcription initiation enables p53 to induce transcripts that may differ in their function from the longest isoforms.

TRANSCRIPTIONAL DOWNREGULATION BY P53

Numerous mechanisms have been proposed for mediating gene downregulation in response to p53 activation[69–72] (Figure 3). In 1993, p53 was first reported to bind to coactivators, including the TATA-box binding protein,[73,74] the CCAAT-box binding factor (NF-Y)[75] and specificity protein 1 (Sp1) that binds to GC-boxes,[76] and to interfere with their transactivator function. While many additional coactivators are believed to be blocked by p53, NF-Y[77] and Sp1[78,79] are the coactivators most commonly linked to p53-dependent gene downregulation through a mechanism of p53 interference. Note, however, that interference of p53 with coactivators is not supported by results of genome-wide analyses:[53] phylogenetically conserved TATA-boxes, CCAAT-boxes and GC-boxes are not enriched among genes that are downregulated in response to p53 activation.

The most commonly reported model for p53-dependent gene downregulation involves the direct binding of p53 to the target gene promoter (Supplementary Table S1). In these cases, p53 binds either through a consensus p53 RE,[80,81] a head-to-tail oriented p53 RE,[82–84] a p53 RE with changed dinucleotide core[85] or by piggy-backing on coactivators, such as NF-Y[86] or Sp1.[87,88] Reports of direct repression of many target genes by p53, however, have been contradicted in the literature (Table 2). The current model describes p53 solely as a transcriptional activator and not as repressor,[53] and is supported by multiple genome-wide analyses.[18,19,23,24,89] The survey presented here also shows little conformity among potential p53 repressed targets (Figure 2c).

In 1997, the cyclin-dependent kinase (CDK) inhibitor p21 (CDKN1A) was initially documented to be necessary for p53-dependent downregulation of the cell cycle genes *CDK1* (*Cdc2*) and *Cyclin A2*.[90,91] Following these reports, numerous cell cycle genes were found to be downregulated via the p53-p21 pathway.[92–97] From cell cycle research, we know that CDKs are crucial for inactivation of repressor complexes formed by the pocket proteins RB, p107 and p130, and by the E2F transcription factors. Consistent with this notion, p130 and E2F4 are recruited to cell cycle gene promoters when p21 is activated by p53.[98,99] RB, too, is important for p53-dependent downregulation of multiple genes.[100–103] The pocket proteins p107 and p130, together with E2F4, are members of the multiprotein repressor complex DREAM that binds cell cycle genes during quiescence.[104–106] Further, the DREAM complex is stabilized and recruited to target gene promoters when p21 is activated by p53.[107–114] However, how DREAM and RB coordinate their efforts to mediate p53-

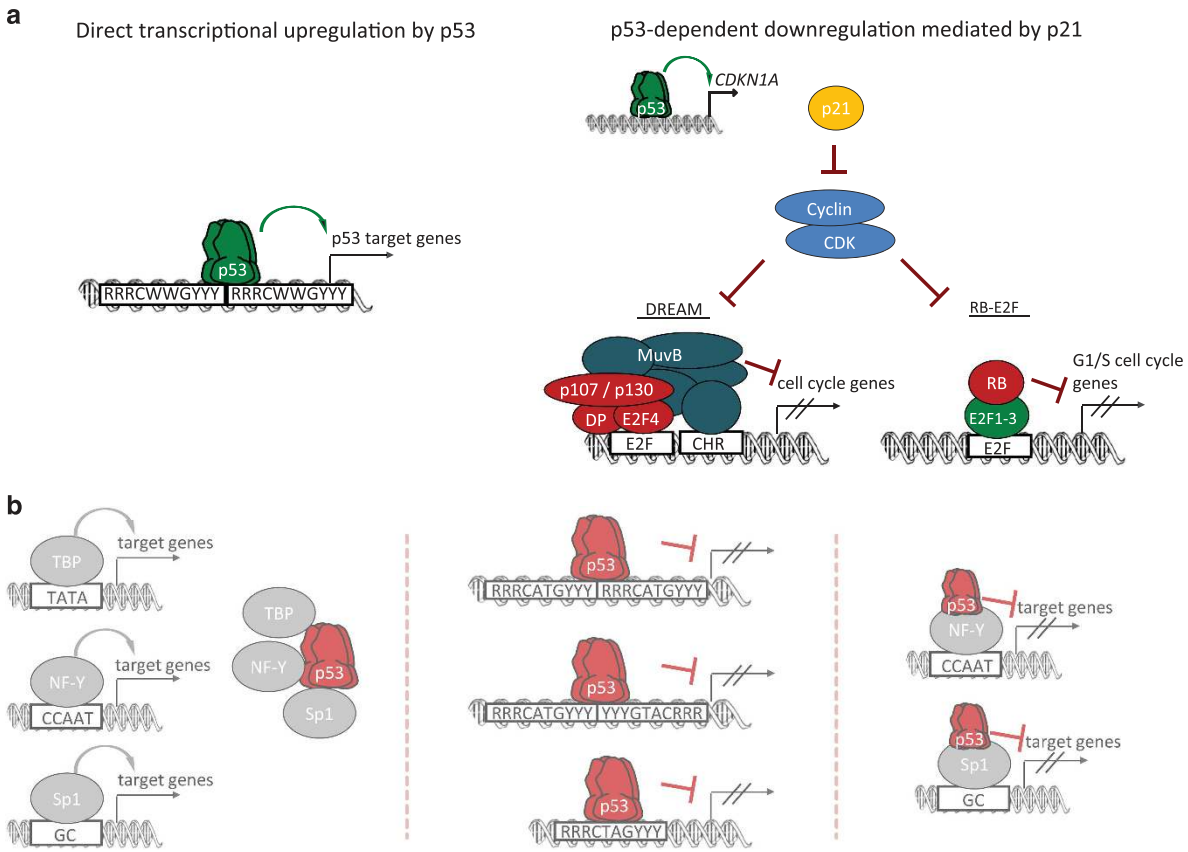

Figure 3. Mechanisms of p53-mediated transcription control. (**a**) Mechanisms involving direct target gene activation by p53 and indirect repression through p53-p21-DREAM/RB are supported by genome-wide data. (**b**) Mechanisms involving the sequestration of coactivators or direct target gene repression by p53 are not supported by genome-wide data.

dependent gene downregulation is not fully understood. Genome-wide analyses show that most genes downregulated by p53 are cell cycle genes[115] and targets of the DREAM complex.[18] Recent results from p21-knockout cells show that, in general, p21 is required for p53-dependent gene downregulation.[18,116] Collectively, these results indicate that p21 not only mediates p53-dependent downregulation of cell cycle genes but also identifies p21 as being part of most, if not all, pathways that mediate gene downregulation by p53.

E2F7 is a p53 target gene[117] and encodes a transcriptional regulator of cell cycle genes,[118] and its role in mediating p53-dependent downregulation is unclear: Carvajal *et al.*[117] reported that E2F7 and p21 are required for p53-dependent downregulation of G1/S cell cycle genes; Schlereth *et al.*,[59] however, found that E2F7 but not p21 was required for mediating downregulation of G1/S genes, and Benson *et al.*[119] revealed that E2F7 likely is not involved in p53-mediated downregulation of cell cycle genes. Notably, genome-wide data supports the possibility that E2F7, in conjunction with DREAM and RB, downregulates G1/S cell cycle genes in response to p53 activation.[53]

Several noncoding RNAs were reported to mediate p53-dependent gene regulation—these include microRNAs[120] and long noncoding RNAs,[121] such as *TUG1*,[122,123] *miR-34*,[124] *lincRNA-p21*,[125] *PANDA*[126] and *PINT*.[127] Nonetheless, results based on different experimental approaches have limited consistency. For example, results of experiments that used overexpression or knockdown of *miR-34* or *lincRNA-p21*[124,125] barely overlapped with those that used knockout mice.[128,129] In the case of *lincRNA-p21*, the low stability and low copy numbers found make it unlikely that *lincRNA-p21* directly regulates many target genes.[129] Furthermore, many *lincRNA-p21* target genes identified in mice[125] are not regulated by p53 in humans.[53] Given that gene downregulation by p53 is governed by p21 in general,[18,116] it remains open for future investigations how noncoding RNAs coordinate their efforts with p21, to mediate gene downregulation by p53. One such mechanism was suggested for *lincRNA-p21*, which supports p21 upregulation in response to p53 activation.[129]

EVALUATING REPRODUCIBILITY

Table 2 shows the contradictions and limited reproducibility found in the literature on p53-dependently repressed genes. Individual gene studies and genome-wide analyses report potential targets that are directly repressed by p53, and that are likely to be false positives (Supplementary Table S1 and Figure 2c). Reproducibility issues, however, are not limited to reports on directly repressed p53 target genes: of 242 protein-coding genes that are reportedly directly activated by p53 (Supplementary Table S1), only 150 (62.0%) have been identified in at least one out of 16 genome-wide data sets (Supplementary Table S2). These 16 genome-wide data sets cover a broad range of cell types and treatments, and recent findings indicate that p53 binds target genes independent of cell type and treatment.[19] However, 92 of the genes that are reportedly directly activated p53 targets are not supported by any of the 16 genome-wide data sets, including *BNIP3L*,[130] *ESR1*,[131] *FDFT1*, *FDPS*, *LDLR*,[132] *PARK2*,[133] *POMC*,[134] *SHBG*,[135] *Toll-like receptors 2, 4, 5, 8* and *10*[136] and *ULK1* and *ULK2*[137] (Supplementary Table S2). The reason behind this lack of reproducibility is unclear, but it points to a need for caution in interpreting research findings that have not been reproduced by independent approaches and by a number of investigators. It is well known that research findings can have limited

Table 2. Genes reported as being directly repressed by p53, and contradictory findings

Gene	*Reports of direct repression*	*Reported contradictions*
ABCB1 (MDR1)	82	Activated, not repressed[261] Not bound or regulated by p53[53]
ANLN	262	Repression requires p107/p130[263]
BCL2	190,191	Not bound or regulated by p53[53]
BIRC5 (Survivin)	264–267	Not bound by p53[92,107,268] Repression requires p21[92,93,107] Repression requires p107/p130[263]
BNIP3	269	Not bound or regulated by p53[53]
CCNB1	270,271	Not bound by p53[53,108] Repression requires p21[53,92,94,100,108] Repression requires p107/p130[263]
CCNB2	86	Repression requires p21[95,101,109] Repression requires p107/p130[263]
CD44	83	Not bound by p53[53] Not regulated by p53[53,272]
CDC20	273	Not bound by p53[53] Repression requires p21[93,96] Repression requires p107/p130[263]
CDC25B	274	Repression requires p21[95]
CDC25C	275,276	Not bound by p53[107] Repression requires p21[92,107] Repression requires p107/p130[263]
CDK1 (CDC2)	86,276	Not bound by p53[53] Repression requires p21[53,90,92,94,98,100,101] Repression requires p107/p130[263]
CKS2	277	Repression requires p107/p130[263]
CRYZ	262,278	Not bound or regulated by p53[53]
ECT2	279	Repression requires p107/p130[263]
HSPA8	262,278	Not bound or regulated by p53[53]
ID2	280	Not bound or regulated by p53[53]
LASP1	281	Not bound or regulated by p53[53]
MAD1L1	278,282	Not bound by p53[53] Repression requires p21[93,102] Repression requires p107/p130[263]
ME1	80	Not bound or regulated by p53[53]
ME2	80	Not bound or regulated by p53[53]
ME3	80	Not bound or regulated by p53[53]
NEK2	283	Not bound by p53[53] Repression requires p21[53,93]
PCNA	284	Activated, not repressed[169,285]
PLK1	286,287	Not bound by p53[107] Repression requires p21[97,107] Repression requires p107/p130[263]
POLD1	288	Not bound by p53[108] Repression requires p21[92,108]
PRC1	289	Repression requires p21[93] Repression requires p107/p130[263]
PTK2 (FAK)	290	Not bound or regulated by p53[53]
RAD51	173	Repression requires p21[94]
SCD	262	Repression requires p21[291]
TPT1 (TCTP)	84	Not bound or regulated by p53[53]

reproducibility,[138] and while some of these false findings are caused by chance, many others may be the consequences of prevailing biases.[138] The survey of 319 studies on individual genes together shows that p53 target gene research still relies on the error-prone ChIP-epPCR methodology, which may promote false findings (Figure 1g). Notably, the ChIP technique in general can produce false findings. Transcription factors undergo fast turnover at non-functional binding sites that can be fixated during ChIP protocol, thereby leading to false-positive hits,[139] and ChIP signals vary in general relative to formaldehyde crosslinking time.[140,141] In addition, sometimes polyclonal antibody batches are used that do not contain the same antibody. To predict functional sites that lead to target gene activation, recent approaches now rely on ranking p53 binding sites based on multiple genome-wide data sets.[18,19,56]

Here, p53 target genes are ranked by the number of data sets that report them as potential p53 target genes. The data sets include 16 genome-wide data sets and one literature-based data set, as described above (Supplementary Table S2). To be considered as high-confidence p53 target gene, a protein-coding gene was required to be identified as a p53-activated target in at least three of the 17 data sets, which ensures identification by at least two independent approaches. These criteria were met by 343 genes (Supplementary Table S3). Such an integrative approach identifies target genes that may have been missed in some data sets but have been identified in several others, and displays genes that are identified only in a small number of data sets and have a higher likelihood of being false positives.

FUNCTION OF HIGH-CONFIDENCE P53 TARGET GENES

To identify biological processes that are enriched among direct p53 target genes, a gene ontology (GO) term enrichment analysis was performed of the 343 genes that were considered as high-confidence p53 targets. As expected, GO terms associated with cell cycle arrest, apoptosis and metabolism, processes that are central to the p53 response and tumor suppression, are highly enriched for these target genes (Supplementary Table S4). Taken together, high-confidence p53 target genes function in multiple processes that include, but are not limited to, cell cycle arrest, DNA repair, apoptosis, metabolism, autophagy, translation control and feedback mechanisms (Figure 4).

Cell cycle arrest

P53 uses cell cycle checkpoints to induce G1/S[142,143] and G2/M cell cycle arrest.[144] *CDKN1A* (*p21*, *WAF1*, *CIP1*) was among the first p53 target genes[11,12] to be identified and is now recognized as an encoder for a major cell cycle checkpoint control protein.[145] Indeed, p21 is required for p53-mediated G1/S[146–148] and also for G2/M cell cycle arrest.[149] P21 functions primarily by binding to and inhibiting CDKs, and in addition, p21 halts the cell cycle by blocking PCNA, which is required for DNA replication.[150,151] Importantly, inhibition of CDKs leads to stabilization and activation of RB, and of the RB-related DREAM complex. As for p21, RB is also required for cell cycle arrest.[100,152] Stabilization of the DREAM complex and its recruitment to target gene promoters leads to indirect p53-mediated downregulation of cell cycle genes such as *CDK1*, *Cyclin A* and *B*, *CDC25C*, *MYBL2* (*B-MYB*), *PLK1* and hundreds more, all of which are required for cell cycle progression.[18,108,114] Taken together, p21 is sufficient to induce cell cycle arrest.[153] The p53 target genes *BTG2*[36,154,155] and *GADD45A*[13,156] can also induce G1/S and G2/M cell cycle arrest, respectively. *SFN* (*14-3-3 sigma*) encodes for a protein that removes cell cycle proteins from the nucleus and is also required for the G2/M arrest.[51,157] FBXW7 ubiquitin ligase is a component of the SCF complex and mediates degradation of several cell cycle proteins,[158] and its β-isoform is induced by p53.[159] Notably, p53 also activates *PGF*,[160] *TGFA*[161] and *KITLG*[50] that encode for growth factors that can stimulate cell proliferation.

DNA repair

Given that p53 is activated in response to DNA damage, it is not surprising that several of its target genes encode for DNA repair proteins.[162,163] Although the p53-mediated DNA damage response appears not to be part of p53's function as tumor suppressor,[164] it does support cell viability. The p53 target genes *DDB2*[165] and *XPC*[166] encode for proteins related to nucleotide excision repair. *RRM2B* encodes for a ribonucleotide reductase that

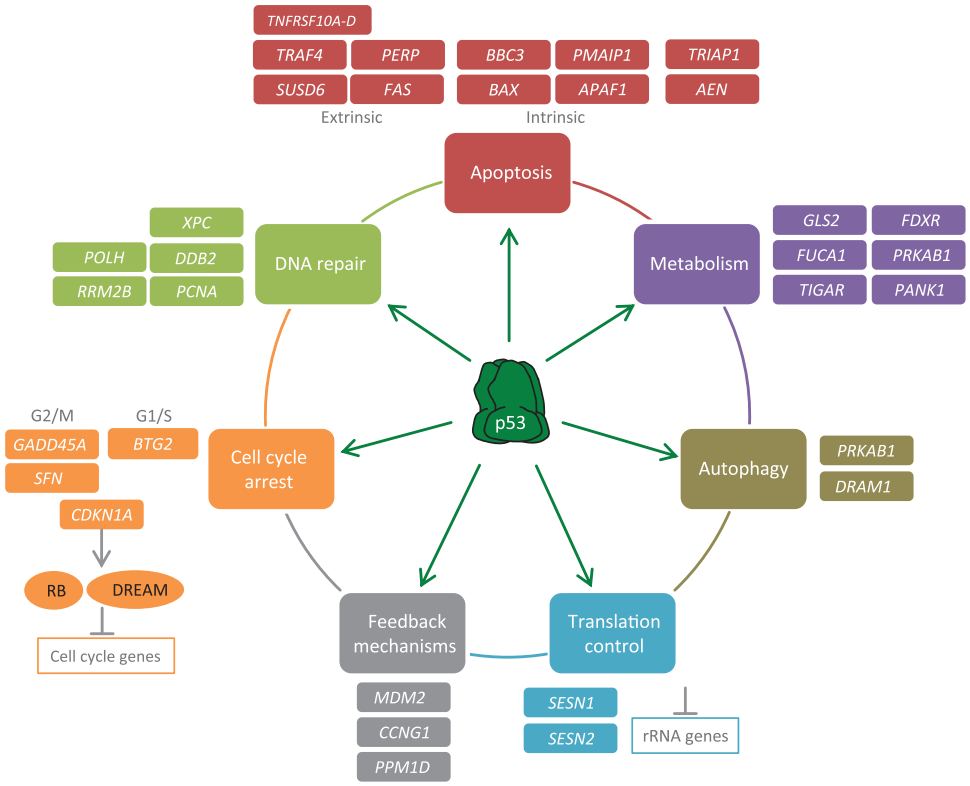

Figure 4. p53 directly activates target genes that mediate various functions. Proteins encoded by p53 target genes function in multiple processes that include, but are not limited to, cell cycle arrest, DNA repair, apoptosis, metabolism, autophagy, translation control and feedback mechanisms.

fuels DNA repair by supplying precursors, and is targeted by p53.[31] And, although PCNA is a crucial component of the replication fork during the cell cycle, it also functions in DNA repair.[167] Therefore, the regulation of *PCNA* is cell cycle-dependent,[168] and is activated by p53.[169] Through the activation of *POLH*, p53 specifically recruits a DNA polymerase that can accurately replicate damaged DNA.[170,171]

Many genes that encode DNA repair proteins are cell cycle-regulated and are downregulated by p53 through the p53-p21-DREAM pathway. Although several DNA repair genes, including *MSH2*,[172] *RAD51*[173] and *RECQL4*,[87] were thought to be direct p53 targets, it has become evident that they are indirectly repressed through the DREAM complex.[18,108,114] Also, genes encoding for proteins of the Fanconi anemia DNA repair pathway are indirectly downregulated by p53 through p21 and DREAM.[174] Interestingly, some cell cycle genes, including *PCNA, POLH* and *AEN*, are targeted by both DREAM and p53: in these cases, the transcriptional activator p53 opposes the repressive DREAM complex, leading to target gene activation.[18] The DNA repair genes *PMS2* and *MLH1* were also believed to be p53-activated targets,[175] but meta-analysis data show this unlikely to be the case[18] (Supplementary Table S2).

Apoptosis

Apoptosis, both intrinsic and extrinsic, is induced via p53 target genes.[176,177] The extrinsic apoptosis signaling pathway is largely controlled by the tumor necrosis factor (TNF) receptor family. TNF receptors include the p53-induced targets *FAS*[47–49] and *TNFRSF10A–D*;[38,39] these can be activated by external stimuli such as binding with FASL or TNF-α, thereby leading to caspase-dependent apoptosis.[178] The gene that encodes for the TNF receptor-associated protein 4 (*TRAF4*) is also a p53 target.[179] Additional apoptosis-inducing transmembrane proteins are encoded by the p53 targets *PERP*[180] and *SUSD6* (*TMPS*; *KIAA0247*).[33] On the other hand, the intrinsic apoptosis pathway is regulated by the BCL-2 family of proteins, which control the release of cytochrome *c* from the mitochondria. Several proapoptotic BCL-2 family members, including *BAX*,[41–43] *BBC3* (*PUMA*)[181] and *PMAIP1* (*NOXA*),[182] are activated by p53. When released from the mitochondria, cytochrome *c* binds to APAF1 and procaspase 9 to form the apoptosome. *APAF1* is activated by p53 too.[183–185] The p53 target gene *AEN* encodes for an apoptosis-enhancing nuclease that further supports apoptosis through digestion of double-stranded DNA.[44] Apoptosis also can be activated by ceramide,[186] and p53 appears to directly upregulate the ceramide synthase-encoding genes *CERS5* (Table 1) and *CERS6*[187] and to induce ceramide production.[188] Although many p53 target genes encode for apoptosis-promoting proteins, the p53 target *TRIAP1* encodes for an inhibitor of apoptosis.[189] Additional BCL-2 family members reported as p53 targets include *BCL2*[190,191] and *BID*[192]—but these are not directly regulated by p53 according to meta-analysis data[18] (Supplementary Table S2). *AIFM1* (*AIF*; apoptosis-inducing factor), also proposed as a p53 target,[193] appears not to be regulated by p53.

Metabolism

Target genes directly regulated by p53 participate in multiple metabolic pathways.[194,195] The TP53-induced glycolysis and apoptosis regulator, encoded by p53 target gene *TIGAR* (*C12orf5*), functions in glycolysis by degrading fructose-2,6-bisphosphate, and thereby opposing the Warburg effect.[37] The carbohydrate fucose is degraded through a fucosidase that is encoded by the p53 target *FUCA1*.[196] GLS2 catalyzes the hydrolysis of glutamine to glutamate and ammonia and is encoded by a direct p53 target gene.[197,198] *PANK1* is a p53 target, which encodes for a key regulatory enzyme in the biosynthesis of

coenzyme A.[199,200] *PRKAB1* is also targeted by p53 and encodes for AMP-activated protein kinase beta-1 subunit, which is involved in phosphorylation and inactivation of acetyl-coenzyme A carboxylase and β-hydroxy β-methylglutaryl-coenzyme A reductase, key enzymes involved in regulating *de novo* biosynthesis of fatty acids and cholesterol.[201] The p53 target *FDXR* encodes a mitochondrial flavoprotein that initiates electron transport for cytochromes *P*450, which receive electrons from NADPH.[202]

Several additional genes, including *SCO2*,[203] *PARK2* (*Parkin*),[133] *LPIN1*,[204] *CPT1C*,[205] *SLC2A3* (*GLUT3*),[206] *SLC2A4* (*GLUT4*)[207] and *ME1*, *ME2* and *ME3*,[80] are involved in metabolism and are believed to be directly regulated by p53. However, according to meta-analysis data these genes are not regulated by p53 in humans[18] (Supplementary Table S2).

Autophagy

Autophagy is another cellular program that is triggered by cell stress and p53.[195,208] The p53 target gene *DRAM1* encodes a lysosomal membrane protein that is required for the induction of autophagy by p53.[209] AMPK, which p53 activates by direct activation of *PRKAB1*, blocks the mammalian target of rapamycin (mTOR) pathway, and leads to autophagy.[201,210] P53 can further block mTOR activity through its direct target genes *SESN1* and *SESN2*.[211] And, although *ULK1* and *ULK2*, which encode autophagy-activating kinases, were thought to be regulated by p53,[137] their regulation by p53 is not supported by meta-analysis data[18] (Supplementary Table S2).

Translation control

Protein biosynthesis and mRNA translation are both influenced by p53. When cells undergo stress and p53 becomes active, mRNA translation and protein biosynthesis is repressed, to inhibit cell growth. Induction of p53 leads to downregulation of rRNA genes[212,213] and of genes that are required for import and export of ribosomal proteins from the nucleus.[214] In addition, p53 uses two direct target genes, *SESN1* and *SESN2*, to block mTOR and to repress mRNA translation.[211,215]

Feedback regulation

Through activation of its target genes, p53 activates several feedback loops, both positive and negative.[216] The best known feedback loop uses *MDM2*, a p53 target gene that encodes a ubiquitin ligase, which mediates degradation of p53.[14,15,217] MDM2 function is supported through cyclin G1, which activates MDM2 through dephosphorylation[218] and *CCNG1* is a p53 target itself.[219] *PPM1D* (*WIP1*) is also a p53 target and encodes for a phosphatase that confers a negative feedback loop through p53 dephosphorylation and cell cycle checkpoint abrogation.[40,220,221] Members of the TRIM protein family, such as PML (TRIM19)[222] and TRIM22,[223] are transcriptionally activated by p53 and have been shown to alter the p53 response.[224]

Through p21, p53 is engaged in additional feedback loops. CDK inhibition by p21 leads to the activation of RB and suppression of activating E2Fs. E2F1 signals positive and negative feedback to p53.[225] E2F1 can induce ARF, which blocks MDM2-mediated p53 degradation,[226] and it can also induce SIRT1, which impairs p53 function through deacetylation.[227]

Additional genes believed to be involved in feedback loops as p53 targets include *SIAH1*,[228] *RCHY1* (*Pirh2*)[229] and *RFWD2* (*COP1*),[230] but these are not regulated by p53 according to meta-analysis data[18] (Supplementary Table S2).

OUTLOOK

For a number of decades, the study of p53 led to increasingly complex models of its function: 'If genius is the ability to reduce the complicated to the simple, then the study of p53 makes fools of us all'.[231] However, recent meta-analysis approaches that enabled comparisons of multiple genome-wide data sets of p53 binding and gene regulation, have started to simplify our understanding of p53 function:

- The transcription factor p53 itself is solely an activator of transcription.[53,232]
- Gene downregulation by p53 is indirect and requires p21.[18,116]
- Functional p53 binding sites are independent of cell type and treatment.[19]
- Most functional p53 binding sites are found in proximal promoters[18] (Figure 1e).
- Functional p53 binding sites consist of two decameric half-sites, and likely do not contain spacers in between.[19,56]
- Noncanonical binding sites, including half-sites, appear to be non-functional.[19]
- P53 mostly acts alone to activate target genes, and does not depend on cofactors binding to the same promoter.[19]
- The number of true p53 target genes is limited, and likely does not exceed a few hundred[18] (Figure 2a and Supplementary Tables S2 and S3).

Given recent advances in our understanding of p53 function, one can envision that genome-wide data integration approaches will answer additional questions and clarify further obscurities.

CONFLICT OF INTEREST

The author declares no conflict of interest.

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