Biotechnology and Molecular Biology Review Vol. 3 (2), pp. 024-031, April 2008
Available online at http://www.academicjournals.org/BMBR
ISSN 1538-2273 © 2008 Academic Journals

Standard Review

The retinoblastoma binding protein 6 is a potential target for therapeutic drugs

Monde Ntwasa

School of Molecular and Cell Biology, University of the Witwatersrand, Wits, 2050. South Africa. E-mail: monde.ntwasa@wits.ac.za. Tel: 27 11 7176254. Fax: 27 11 717 6351.

Accepted 18th April, 2008

The retinoblastoma binding protein 6 (RBBP6) proteins (also called P-53 Associated Cell Testis Derived (PACT)) are highly upregulated in esophageal cancer and enhance the activity of MDM2, a p53 inhibitor with ubiquitin ligase activity that is overexpressed in many human cancers. Mammalian RBBP6 binds the tumour suppressor proteins p53 and the retinoblastoma protein (Rb). The invertebrate orthologues, on the other hand, have not been shown experimentally to have these properties and they have no obvious sequence features that are similar to the mammalian p53- and Rb-binding domains. General features of RBBP6 proteins such as a highly conserved N-terminal ubiquitin-like domain and a RING-finger indicate that they may be involved in proteolytic degradation of substrate proteins via the proteasome pathway. They have recently been found to act downstream hedgehog in certain normal developmental processes. This may implicate RBBP6 proteins in a wider range of human cancers. These data imply that antagonists of RBBP6 can be used as effective antitumour agents to treat tumours that have functional p53.

Key words: p53, RBBP6, PACT, SNAMA, cell cycle, apoptosis, cancer.

INTRODUCTION

RBBP6 proteins are found only in eukaryotes. The mammalian RBBP6 protein binds to the tumour suppressor proteins p53 and Rb and promotes p53 degradation by enhancing the activity of Mdm2 , the key p53 negative regulator (Li et al., 2007; Scott et al., 2003; Simons et al., 1997). The *Drosophila* orthologue called SNAMA has not been shown to bind p53 but is involved in apoptosis and is essential for embryonic development (Mather et al., 2005) while the yeast one, Mpe1 is involved in pre-mRNA processing (Vo et al., 2001).

p53 and Rb are key regulators of the cell cycle and p53 also plays an important role in maintaining genome integrity through its role in nucleotide excision repair systems (Wang et al., 2003). In normal cells p53 is kept at low levels by MDM2, a RING finger protein that mediates its ubiquitination and proteasome degradation. *Drosophila* is peculiar in this regard because it seems to lack a MDM2 homologue. RBBP6 proteins have a characteristic highly conserved ubiquitin-like N-terminal domain called the Domain With No Name (DWNN) ((Mather et al., 2005; Pugh et al., 2006)). Overall, the vertebrate and invertebrate proteins have generally low homology but show high level of homology at the N-terminal domain. When compared with one another, the mammalian sequences have high identity in the p53 and Rb binding regions. These were experimentally delineated in the mouse P2P-R (Figure 3) (Witte and Scott, 1997) (see also Table 1).

In addition to the highly conserved DWNN, RBBP6 proteins show various combinations of other sequence features such as the CCHC zinc finger, a RING-finger-like (RFL) motif, lysine-rich, and proline-rich regions, coiled-coils and RS regions. This suggests that these proteins may interact with a number of proteins and indeed that they could have multiple functions. The RS

Abbreviations: RBBP6: retinoblastoma binding protein 6; Rb: retinoblastoma protein; P2P-R: proliferation potential protein-related; MDM2: mouse double mutant 2.

Table 1. RBBP6 orthologues that have been experimentally characterized.

Organism	Isoform	Name	Accession number	Length	Reference
Mouse (Chr 7)	One	PACT/P2P-R	NP_035377	1560	(Witte and Scott, 1997) (Simons et al., 1997)
	Two	RBBP6	P97868	1790	Predicted
	Three	RBBP6	XP_145621	786	Predicted
	Four	DWNN	NP_778188, NM_175023	123	(Mather et al., 2005; Pugh et al., 2006)
Human (Chr. 16)	One	RBBP6	NP_008841.	1792	(Pugh et al., 2006)
	Two	RBBP6/RBQ-1	NP_061173/X85133	1758	(Sakai et al., 1995)
	Three	DWNN	NP_116015.	118	(Mather et al., 2005; Pugh et al., 2006)
Fruitfly (Chr 2R)		SNAMA/Mnm^{p}	NP_611884, CG3231-PA	1231	(Jones et al., 2006; Mather et al., 2005)

region is often found in proteins that are involved in RNA processing and indeed Mpe1 has been shown to be involved in the 3' mRNA cleavage complex (Vo et al., 2001).

Interestingly, the mammalian RBBP6 N-terminal DWNN can exist as an independent splice isoform in the same manner as ubiquitin. Furthermore, the mammalian proteins have a conserved di-glycine peptide closer to and downstream the final conserved proline in DWNN. This feature is noteworthy because in ubiquitin the di-peptide is crucial for conjugation of ubiquitin to other proteins. It can be speculated that DWNN represents another form of protein modification that is similar to ubiquitination.

Evidence found in *Drosophila* indicates that the RBBP6 protein, SNAMA/Mnm^{p}, plays an important role in cell proliferation and cell survival and is directly implicated in nucleic acid metabolism and apoptosis during development. Furthermore, SNAMA/Mnm^{p} acts downstream hedgehog in the morphogenetic furrow during the development of the compound eye of the fly (Jones et al., 2006; Mather et al., 2005). The involvement of RBBP6 protein in the hedgehog pathway may widen the number of pathological conditions in which RBBP6 proteins are involved as hedgehog is implicated in a number of human tumors and developmental abnormalities.

The role that RBBP6 proteins play in regulation of the cell cycle and more especially the influence they have on the prototypical tumor suppressors, p53 and Rb, underscores their importance as targets for anticancer therapy. Inhibitors of these proteins should prevent p53 degradation and increase apoptosis in tumour cells. Indeed small molecule inhibitors of the E3 ubiquitin called nutlins have been tried in retinoblastoma cells and found to induce p53-mediated cell death (Laurie et al., 2007). Antisense oligonucleotides have also been used to inhibit expression of the Mdm2 gene (Bianco et al., 2005; Wang et al., 2001; Zhang et al., 2005). Other approaches could target the p53-RBBP6 interface. Again such approaches have been explored in attempts to design molecules that interfere with p53-Mdm2 interaction (Justin K. Murray, 2007).

Evolution of structural features of vertebrate RBBP6 proteins

Invertebrate and vertebrate RBBP6 family members have acquired a number of structural features in their sequence through evolution. Even the DWNN has acquired interesting structural features that appear late in evolution (Figure 1). For instance the di-glycine peptide that follows the conserved proline (asterisk) is found in mammals and birds but is absent in plants, arthropods and fish indicating that this may be a late evolutionary event.

The new protein modules acquired through evolution, probably confer new functions to the RBBP6 proteins. For instance more recent organisms in evolution such as insects, mammals and birds have acquired the lysine-rich region, arginine–rich region, and the RS region (Figure 2.). Other late evolutionary features are the p53 and Rb-binding domains (Figures 3 and 4). These were mapped in the mouse isoform, PACT/P2P-R (Witte and Scott, 1997). It is therefore possible that through evolution this family acquired new functions such as apoptosis and DNA repair. This region of the mammalian sequence also interacts with MDM2, a ubiquitin-ligase that negatively regulates p53 (Li et al., 2007). The role of RBBP6 proteins in invertebrates is likely to be somewhat different with respect to p53 because in addition to the lack of an obvious MDM2 homologue in the *Drosophila* genome, an MDM2 binding site seems to be absent in *Drosophila* p53.

RBBP6 proteins and the tumor suppressors

The role of RBBP6 proteins in cell cycle processes is in-

Figure 1. Alignment of DWNN of plant, vertebrate and invertebrate RBBP6 proteins. The asterisk refers to the conserved proline. The arrows indicate the di-glycine peptides that are conserved in mammals. In ubiquitin, a similar conserved di-glycine at position 75 and 76 is crucial for conjugation of the ubiquitin moiety to itself or to other proteins that are targeted for proteasome degradation.

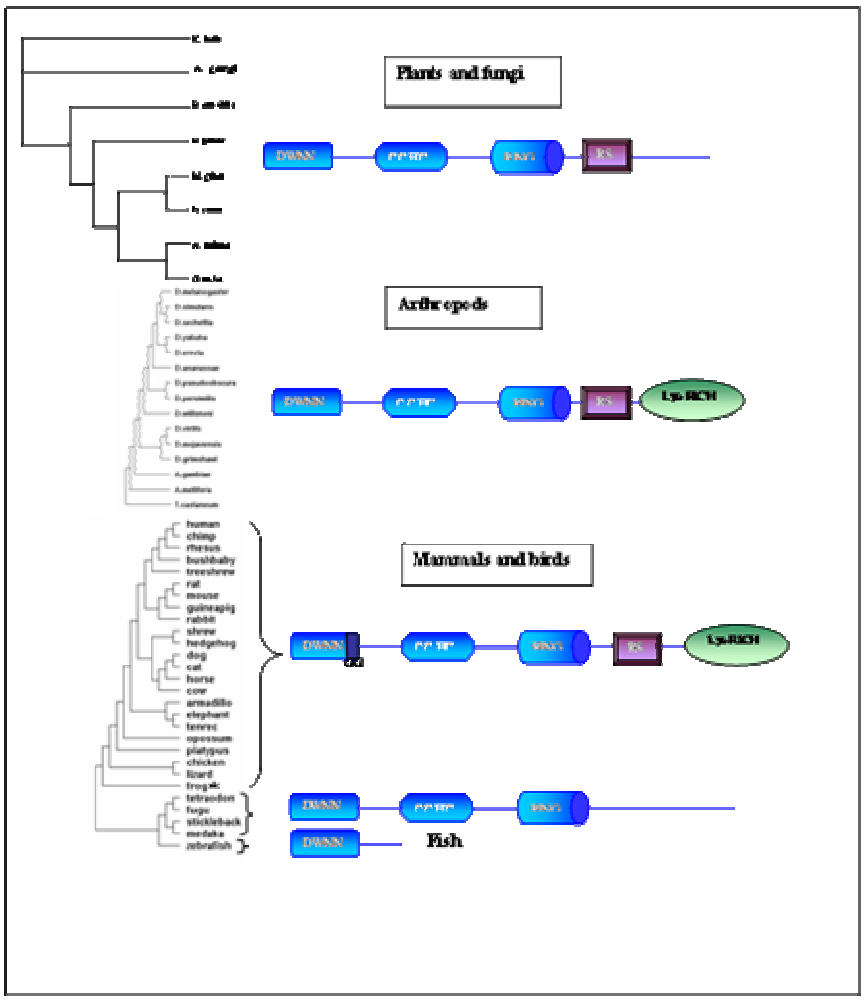

Figure 2. Domains structure of RBBP proteins. The phylogenetic trees show how these structures have evolved. Note that the fish orthologues lack the zinc finger and the RING finger motif – but exist as an independent DWNN with a short C-terminal extension.

Figure 3. Sequence alignment of vertebrate RBBP6 proteins sequences. Alignment human (*Homo sapiens*) chick (*G. gallus*), Rat (*R. norvegicus*), mouse (*M. musculus*) and worm (*C. elegans*) protein sequences. This alignment and Phylogenetic three (insert) was produced by using DNAMAN shows conserved regions of the proteins.

dicated by subcellular localization in nuclear spec-kles, expression in mitotically active cells, by aberrant apoptosis when perturbed and by association with cellular differentiation (Gao and Scott, 2002; Gao and Scott, 2003; Gao et al., 2002; Robert et al., 2003; Scott et al., 2003; Scott et al., 2005; Witte and Scott, 1997). RBBP6 proteins are widely expressed in many tumor cell lines and are upregulated in esophageal cancer (Yoshitake et al., 2004). They are normally expressed in the heart, lung, liver skeletal muscle and most prominently in the

testis (Witte and Scott, 1997).

Many cancers are caused by alterations in tumor suppressor proteins such as breast cancer 1 and breast cancer 2 (BRCA1 and BRCA2) (Greenberg, 2008), patched (Chidambaram et al., 1996), E2F (Du and Dyson, 1999; Du et al., 1996) and many others, resulting in aberrant proliferation of cells. Tumor suppressor proteins have therefore become important targets for anticancer therapy. Controlling the activity of tumor suppressor regulatory proteins is also a growing area of drug discovery.

The role of RBBP6 proteins as negative regulators of p53 was elucidated in the mouse system where RBBP6/PACT was shown to negatively affect p53 levels by enhancing the activity of MDM2. In these experiments the essential part that RBBP6 plays is emphasized by the fact that embryos lacking a functional RBBP6/PACT (*Pact*$^{-/-}$) had a reduced size, were developmentally retarded and died before E7.5. Moreover, lethality caused by the disruption of the *PACT* gene was partially rescued by a *p53* null mutation (Li et al., 2007). Notably, the *Pact*$^{-/-}$ phenotype is similar to that of *mdm2*$^{-/-}$ mice which also die during embryogenesis. This phenotype is also rescued by the concomitant absence of p53 indicating that MDM2 and RBBP6/PACT are critical for maintaining optimum p53 levels (Luna et al., 1995). These results are a significant contribution to the understanding of the relationship between p53 and RBBP6 proteins.

MDM2 interacts with and negatively regulates two key tumor suppressor proteins, p53 (Jones et al., 1995; Luna et al., 1995; Michael and Oren, 2003) and Rb (Xiao et al., 1995) and is amplified in a number of human tumors. In addition to this, MDM2 promotes cell cycle progression by stimulating the S-phase transcription factors E2F/DP1 (Martin et al., 1995). MDM2 is associated with aberrant p53 gene expression and with invasiveness of hepatocellular carcinoma (Qiu et al., 1997). MDM2 splice isoforms that lack the p53 binding domain are associated with advanced malignancy in ovarian tumors, in bladder and breast cancers and in human astrocytic neoplasms indicating that MDM2 can promote malignant cell proliferation independently of p53 (Matsumoto et al., 1998; Sigalas et al., 1996). p53 was also found to be stable in glioblastoma cells despite the amplification of MDM2 splice isoforms (Kraus et al., 1999).

Because it is rare for proteins to bind both p53 and Rb it is speculated that RBBP6 proteins may act as scaffold for the assembly of tumor suppressor proteins (Li et al., 2007). This view is consistent with an earlier view that proposed a formation of a complex that comprises an RBBP6 protein in matrix attachment regions (MARS) to influence gene transcription and chromatin organization (Scott et al., 2003). In addition the mammalian proteins occur in isoforms including one which has a coiled coil domain that is encoded by a separate exon (Figure 4).

Coiled coils in proteins often control oligomerisation and are associated with the cytoskeleton, the Golgi, centromeres, centrosomes, the nuclear matrix, and chromatin. This feature indicates that this isoform may dimerize and perform a unique role.

The structural and functional features of RBBP6 proteins, namely, involvement in the cell cycle and association with key tumor suppressor proteins, p53 and RB make them attractive candidate targets for anticancer therapy. The RBBP6 functional relative, MDM2, is already a promising target of anticancer therapeutic agents. For example, small molecule MDM2 inhibitors have been developed as anticancer agents by exploiting the p53-MDM2 interface. These are either non-genotoxic molecules that bind to the p53 binding pocket in MDM2 without interfering with normal p53 activity or mimetic peptides (Sakurai et al., 2004; Secchiero et al., 2007).

RBBP6 proteins and hedgehog signaling

Hedgehog signaling is involved in many human congenital diseases and in many cancers. A catalogue of pathological conditions that involve the hedgehog pathway lists abnormalities in the central and peripheral nervous systems, the circulatory system, the gut, the kidney and many bone related abnormalities (McMahon et al., 2003). Moreover cyclins D and E, which are regulators of the Rb/E2F pathway, acting in some cases downstream of hedgehog and its receptor patched (Ptc) (Figure 5), are implicated in many human cancers (Donnellan and Chetty, 1999). This is a highly conserved pathway in both vertebrates and invertebrates.

Recent experiments demonstrate that the *Drosophila* RBBP6 protein, SNAMA/Mnm^{p} acts downstream hedgehog during development of the *Drosophila* eye (Jones et al., 2006). This was the first report that links RBBP6 proteins with the hedgehog pathway. Hedgehog signaling is known to control cell cycle exit via the Dpp-dependent pathway and cell cycle reentry via a Notch dependent pathway in the *Drosophila* retina. RBF, the *Drosophil*a homologue of Rb, acts downstream hedgehog in the *Drosophila* retina during cell differentiation when it mediates cell cycle exit in a Notch-dependent pathway. During cell cycle reentry RBF is antagonized by a Notch-dependent mechanism resulting in the release of the transcription factor, dE2F1 into the nucleus (reviewed by (Neumann, 2005). E2F is physiologically inhibited in a complex with Rb and is released, upon phosphorylation of Rb, into the nucleus to activate or repress genes that are involved in various cellular functions, such as cell cycle phase transitions, DNA synthesis, mitosis, apoptosis, DNA repair and differentiation depending on the context and source of the signal (DeGregori, 2005).

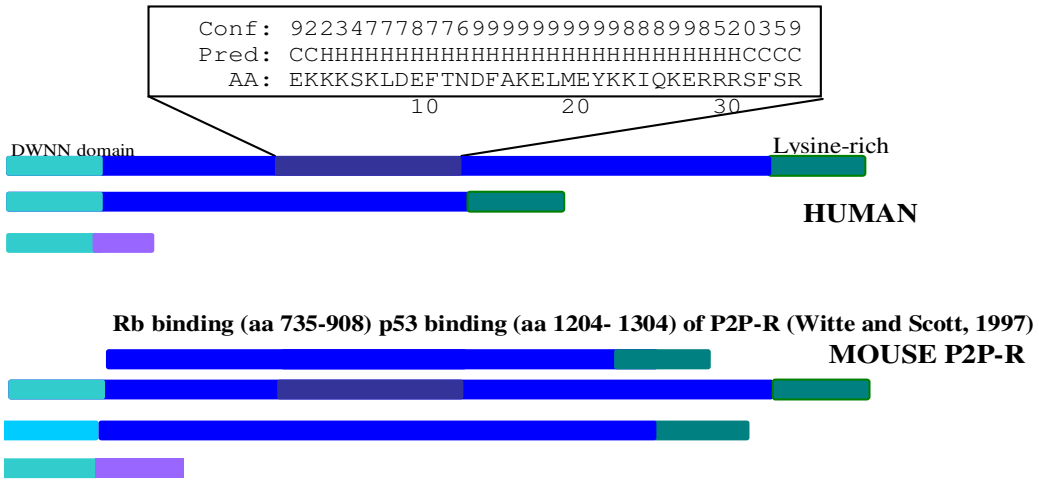

Figure 4. Schematic representation of mouse and human RBBP6 proteins. The Rb and p53-binding domains of the mouse P2P-R proteins were delineated experimentally. The dark blue block shows the coiled coil region that is missing in other isoforms and in invertebrate proteins.

The role of the *Drosophila* RBBP6 protein, SNAMA/-Mnm^{p}, in the hedgehog pathway probably entails the control of dE2F inhibition by interacting with RBF. It could then influence cell cycle exit or reentry in a context dependent manner.

Taken together all these results suggest a potential for RBBP6 proteins to catalyze the degradation of either Rb or p53 in a proteasome-dependent manner. This scenario would be consistent with an earlier proposal that the *Drosophila* protein SNAMA/Mnm^{p} suppresses apoptosis directly or negatively regulates a proapoptotic molecule (Mather et al., 2005). RBBP6 family members therefore provide another level of intervention in the fight against cancer and probably other diseases that are caused by aberration in hedgehog signaling. These include several human con-genital malformations such as brachydactyly and some limb defects. Hedgehog signaling is involved in several other processes affecting development of the central nervous tissue, the gut, the circulatory system, the respi-ratory system, the neural crest, and others (McMahon et al., 2003). It is, however, not clear yet how RBBP6 proteins influence the hedgehog pathway. Further work is required to dissect this pathway before therapeutic interventions targeting its components can be designed. The signaling pathway depicted in Figure 5 could provide basis for speculation about the influence of RBBP6 proteins in the hedgehog pathway, but more experimental evidence is required.

Conclusions

The regulatory effect that RBBP6 proteins have on key tumor suppressors illustrates that they represent a noteworthy class of potential targets for anticancer therapy. Inhibition of these proteins is likely to elevate the levels of p53 in tumor cells thus promoting apoptosis. These strategies involve small molecule antagonists that perturb protein-protein interactions between the tumor suppressors and the E3 ligases. Antisense oligonucleo-tides are also being explored to prevent expression of these enzymes.

Further work needs to be done to refine these strate-gies because there are still formidable challenges. For example, specific and targeted inhibitors are required because the E3 ligases have diverse substrates and are required for normal cell function. However, local (subcon-junctival) delivery of the small molecule, nutlin-3, seems to have been successful in preclinical retinoblas-toma models reinforcing the feasibility of this approach (Laurie et al., 2007). Delivery techniques where the inhibitor is confined to the diseased tissue may help avoid extensive damage to normal tissue.

Future prospects

It has to be confirmed experimentally that RBBP6 pro-teins have ubiquitin-like activities and their function in different cell types must be elucidated. Protein-protein interaction studies to further delineate the RBBP6-p53 and RBBP6-Rb interfaces should contribute significantly in drug design. Structural studies of these proteins will also help design antagonists that could be useful in the-rapy. Cell based assays and animal models that over express RBBP6 proteins will help screen for molecules

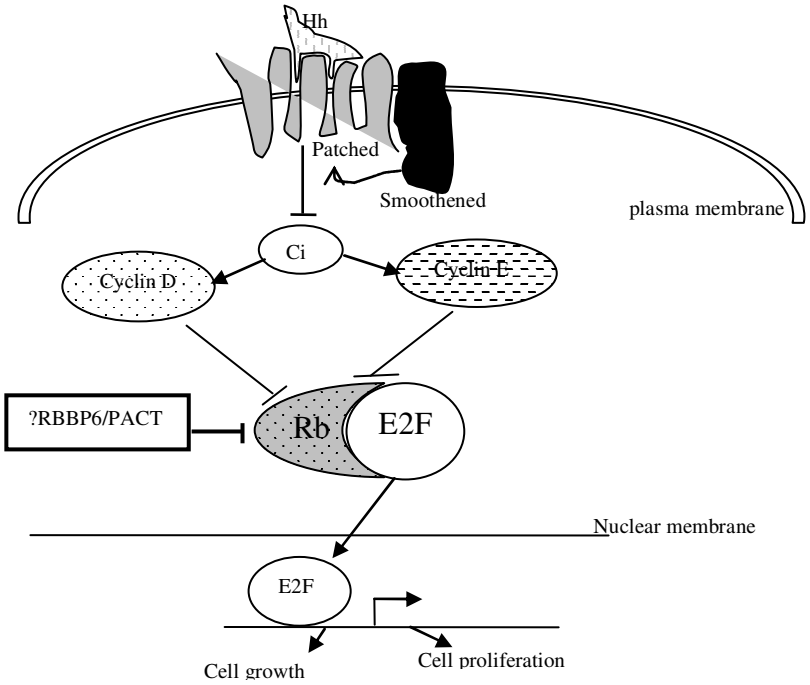

Figure 5. Simplified hedgehog signaling pathway. RBBP6 proteins probably promote cell proliferation and growth by negatively regulating Rb. Binding of hedgehog to patched, its receptor, leads to the release of smoothened (Smo) and to the subsequent activation of downstream molecules. This leads to phosphorylation of Rb by cyclin D or cyclin E and its dissociation from E2F. E2F is a transcription factor that activates or represses transcription of genes that are involved in cell proliferation and cell growth.

that could be used in cancer therapy or in managing developmental defects.

REFERENCES

Bianco R, Ciardiello F, Tortora G (2005). Chemosensitization by antisense oligonucleotides targeting MDM2. Curr. Cancer Drug Targets, 5: 51-56.

Chidambaram A, Goldstein AM, Gailani MR, Gerrard B, Bale SJ, DiGiovanna JJ, Bale A E, Dean M (1996). Mutations in the Human Homologue of the Drosophila patched Gene in Caucasian and African-American Nevoid Basal Cell Carcinoma Syndrome Patients. Cancer Res. 56: 4599-4601.

DeGregori J (2005). E2F and cell survival: Context really is key. Developmental Cell 9, 442-444.

Donnellan R, Chetty R (1999). Cyclin E in human cancers. Faseb. J. 13: 773–780.

Du W, Dyson N (1999). The role of RBF in the introduction of G1 regulation during Drosophila embryogenesis. EMBO. J. 18: 916-925.

Du W, Vidal M, Xie J, Dyson N (1996). RBF, a novel RB-related gene that regulates E2F activity and interacts with cyclin E in Drosophila. Genes & Dev. Vol 10: 1206-1218.

Gao S, Scott RE (2002). P2P-R protein overexpression restricts mitotic progression at prometaphase and promotes mitotic apoptosis. J. Cell. Physiol. 193: 199-207.

Gao S, Scott RE (2003). Stable overexpression of specific segments of the P2P-R protein in human MCF-7 cells promotes camptothecin-induced apoptosis. J. Cell Physiol. p. 197.

Gao S, White MM, Scott RE (2002). P2P-R protein localizes to the nucleus of interphase cells and the periphery of chromosomes in mitotic cells which show maximum P2P-R immunoreactivity. J. Cell Physiol. 191: 145-154.

Greenberg R (2008). Recognition of DNA double strand breaks by the BRCA1 tumor suppressor network. Chromosoma Epub ahead of print.

Jones C, Reifegerste R, Moses K (2006). Characterization of Drosophila mini-me, a gene required for cell proliferation and survival. Genetics 173: 793-808.

Jones SN, Roe AE, Donehower LA, Bradley A (1995). Rescue of embr-ryonic lethality in Mdm2-deficient mice by absence of p53. Nature 378: 206-208.

Justin K, Murray SHG (2007). Targeting protein-protein interactions: Lessons from p53/MDM2. Peptide Science 88: 657-686.

Kraus A, Neff F, Behn M, Schuermann M, Muenkel K, Schlegel J (1999). Expression of alternatively sliced mdm2 transcripts correlates with stabilized wild-type p53 protein in human gliblastoma cells. Int J Cancer: 80: 930–934.

Laurie N, Schin-Shih C, MAyer D (2007). Targeting MDM2 and MDMX in retinoblastoma. Curr Cancer Drug Targets 7: 689-695.

Li L, Deng B, Xing G, Teng Y, Tian C, Cheng X, Yin X, Yang J, Gao X, Zhu Y, et al provide all other name (2007). PACT is a negative regulator of p53 and essential for cell growth and embryonic development. Proc. Natl. Acad. Sci. USA 104: 7951-7956.

Luna RM, d O, Wagner DS, Lozano G (1995). Rescue of early embryonic lethality in mdm2-deficient mice by deletion of p. 53.

Nature 378: 203-206.
Martin K, Trouche D, Hagemeier C, Sorensen TS, Thangue NBL, Kouzarides T (1995). Stimulation of E2F/DP1 transcriptional activity my MDM2 oncoporotein. Nature 375: 691-694.
Mather A, Rakghotho M, Ntwasa M (2005). SNAMA, a novel protein with a DWNN domain and a RING finger-like motif:A possible role in apoptosis. Biochim. Biophys. Acta. 1727: 169-176.
Matsumoto R, Tada M, Nozaki M, Zhang C-L, Sawamura Y, Abe H (1998). Short alternative splice transcripts of the mdm2 oncogene correlate to malignancy in human astrocytic neoplasms. Cancer Res 58: 609-613.
McMahon A, Ingham P, Tabin C (2003). Developmental roles and clinical significance of hedgehog signaling. Curr. Top Dev. Biol. 53: 1-114.
Michael D, Oren M (2003). The p53-Mdm2 module and the ubiquitin system. Seminars in Cancer Biology 13: 49-58.
Neumann CJ (2005). Hedgehogs as negative regulators of the cell cycle. Cell Cycle 4: 1139-1140.
Pugh DJR, Eiso AB, Faro A, Lutya PT, Hoffmann E, Rees DJG (2006). DWNN, a novel ubiquitin-like domain, implicates RBBP6 in mRNA processing and ubiquitin-like pathways. BMC Struct. Biol. 6: 1-12.
Qiu S-J, Ye S-L, Wu Z-Q, Tang Z-Y, Liu Y-K (1997). The expression of the mdm2 gene may be related to the aberration of the p53 gene in human hepatocellular carcinoma. J. Cancer Res. Clin. Oncol. 124: 253-258.
Robert SE, Giannakouros T, Gao S, Peidis P (2003). Functional Potential of P2P-R: Role in the Cell Cycle and Cell Differentiation Related to its interactions With Proteins That Bind to Matrix associated Regions of DNA. J. Cell. Biochem. 90: 6-12.
Sakai Y, Saijo M, Coelho K, Kishino T, Niikawa N, Taya Y (1995). cDNA sequence and chromosomal localisation of a novel human protein, RBQ-1 (RBBP6), that binds to the retinoblastoma gene product. Genomics 30: 98-101.
Sakurai K, Chung HS, Kahne D (2004). Use of a retroinverso p53 peptide as an inhibitor of MDM2. J. Am. Chem. Soc. 126: 16288-16289.
Scott RE, Giannakouros T, Gao S, Peidis P (2003). Functional potential of P2P-R: A role in the cell cycle and cell differentiation related to its interactions with proteins that bind to matrix associated regions of DNA? J. Cell. Biochem. 90: 6-12.
Scott RE, White-Grindley E, Ruley HE, Chesler EJ, Williams RW (2005). P2P-R expression is genetically coregulated with components of the translation machinery and with PUM2, a translational repressor that associates with the P2P-R mRNA. J. Cell Physiol. 204: 99-105.
Secchiero P, Corallini F, Gonelli A, Dell'Eva R, Vitale M, Capitani S, Albini A, Zauli G (2007). Antiangiogenic activity of the MDM2 antagonist Nutlin-3. Circ. Res. 100: 61-69.
Sigalas I, Calvert A, Anderson J, Neal D, Lunec J (1996). Alternatively spliced mdm2 transcripts with loss of p53 binding domain sequences: transforming ability and frequent detection in human cancer. Nat Med 2: 912-917.
Simons A, Melamed-Bessudo C, Wolkowicz R, Sperling J, Sperling R, Eisenbach L, Rotter V (1997). PACT: cloning and characterization of a cellular p53 binding protein that interacts with Rb. Oncogene 14: 145-155.
Vo LTA, Minet M, Schmitter J, Lacroute F, Wyers F (2001). Mpe1, a zinc knuckle protein, is an essential component of yeast cleavage and polyadenylation factor required for the cleavage and polyadenylation of mRNA. Mol. Cell. Biol. 21: 8346-8356.
Wang H, Nan L, Yu D, Agrawal S, Zhang R (2001). Antisense Anti-MDM2 oligonucleotides as a novel therapeutic approach to human breast cancer: In vitro and in vivo activities and mechanisms. Clin. Cancer Res. 7: 3613-3624.
Witte MM, Scott RE (1997). The proliferation potential protein-related (P2P-R) gene with domains encoding heterogeneous nuclear ribonucleoprotein association and Rb1 binding shows repressed expression during terminal differentiation. Proc. Natl. Acad. Sci. USA. 94: 1212-1217.
Xiao Z.-X, Chen J, Levine AJ, Modjtahedi N, Xing J, Sellers WR, Livingstone DM (1995). Interaction between the retinoblastoma protein and the oncoprotein MDM2. Nature. 375: 694-698.
Yoshitake Y, Nakatsura T, Monji M, Senju S, Matsuyoshi H, Tsukamoto H, Hosaka S, Komori H, Fukuma D, Ikuta Y, et al provide all other name (2004). Proliferation potential-related protein, an ideal esophageal cancer antigen for imunotherapy, identified using complimentary DNA microarray analysis. Clin. Cancer Res. 10: 6437-6448.
Zhang R, Wang H, Agrawal S (2005). Novel antisense anti-MDM2 mixed-backbone oligonucleotides: Proof of principle, in vitro and in vivo activities, and mechanisms. Curr. Cancer Drug Targets, 5: 43-49.