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Cell Cycle Regulation via the p53, PTEN, and BRCA1 Tumor Suppressors

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Abstract

Multiple cell cycle regulatory proteins play an important role in oncogenesis. Cancer cells may arise from dysregulation of various genes involved in the regulation of the cell cycle. In addition, cyclin-dependent kinase inhibitors are regarded as key regulators for cancer cell proliferation. Accordingly, permission of impaired cells by cell cycle checkpoints suppresses carcinogenesis. P53, a multifunctional protein, controls G1-S transition, which is the strongest tumor suppressor involved in the regulation of cell cycle. The p53 is stimulated by cellular stress like oxidative stress. Upon activation, p53 leads to cell cycle arrest and promotes DNA repair; otherwise, it induces apoptosis. One of the target effectors of p53 is the phosphatase and tensin homolog deleted on chromosome 10 (PTEN). The tumor suppressor PTEN is a dual-specificity phosphatase which has protein phosphatase activity and lipid phosphatase activity that antagonizes PI3K/AKT activity. The PI3K/AKT cell survival pathway is shown as regulator of cell proliferation. The p53 cooperates with PTEN and might be an essential barrier in development of cancers. BRCA1 plays an important role in DNA repair processes related to maintenance of genomic integrity and control of cell growth. The inactivation of these tumor suppressor proteins confers a growth advantage of cancer. This chapter summarizes the function of several tumor suppressors in the cell cycle regulation.

Keywords: p53, PTEN, BRCA1, AKT, MDM2, p21WAF1, protein interaction, protein expression, cell signaling, DNA repair, cell cycle regulation

1. Introduction

Mechanisms of cell cycle are predominantly controlled by p53 tumor suppressor [1, 2]. The p53 transcription factor can bring G1 arrest of the cell cycle by transactivating several downstream molecules [3, 4], which regulates various signaling pathways involved in the cellular response to genome stress and DNA damage. Through the stress-induced activation, p53 triggers the expression of target genes that protect the genetic reliability of cells [5]. Germinal mutations of the *p53* gene constitute an etiological base of Li-Fraumeni syndrome, which is a sporadic heterogeneous autosomal dominant inherited oncogenic disorder [6]. BRCA1, a famous breast cancer tumor suppressor, is associated with breast and ovarian cancer risk and genetic susceptibility [7]. Studies have shown that p53 as well as BRCA1 plays a key role in DNA damage responses [8]. In addition, BRCA1 could work together with phosphatase and tensin homolog deleted in chromosome 10 (*PTEN*), which is also a tumor suppressor gene that is deleted or mutated in a range of human cancers [7, 9], and may be a critical protection in development of several tumors [7, 9]. Actually, PI3K/AKT pathway is constitutively active in BRCA1 defective human cancer cells [10]. Both *PTEN* and *BRCA1* genes are documented as one of the most frequently deleted and/or mutated in various human cancers. Loss or decrease of these *PTEN* or *BRCA1* activities, by either mutation or reduced expression, seems to have a critical role in various cancer developments. *PTEN* prevents the activation of PI3K/AKT pathway by dephosphorylating the membrane phospholipid PIP3 [11]. Loss of *PTEN* results in increased AKT recruitment to the plasma membrane and stimulates the signaling pathway. Mutations in *PTEN* genome are the cause of distinctive hamartoma syndromes (*PTEN*-related Proteus syndrome, Cowden syndrome, Proteus-like syndrome, Bannayan-Riley-Ruvalcaba syndrome) with higher risk for a development of several tumors [12]. Furthermore, *BRCA1* and *PTEN* have been shown to be involved in a complex linkage on the interaction with the p53 as presented in Figure 1. Although they are functionally distinct, mutual cooperation has been proposed. These tumor suppressors regulate diverse cellular activities including DNA damage repair, cell cycle arrest, cell differentiation, cell proliferation, cell migration, and cell apoptosis [13]. Importantly, mutations in all of these genes have been associated with increased risk of developing cancers. This review summarizes the function of the tumor suppressors in DNA repair and cell cycle regulation. We will also discuss the role of cellular signaling through protein interaction pathways for the potential implications in the fundamental DNA repair and cell cycle regulation.

2. Characteristics of *p53*, *PTEN*, and *BRCA1*

The *p53* gene encodes a nuclear 393-amino-acid protein which is a transcription factor (Figure 2). The p53 tumor suppressor plays an essential role in regulating cellular processes including cell cycle arrest, apoptosis, cell metabolism, and cell senescence. Inactivation of *p53* gene is related to the development of most types of cancers [14], suggesting that *p53* also plays a critical role in preventing normal cells to becoming cancer cells. In addition, importance of *p53* as an inherited cancer susceptibility gene has been revealed in the Li-Fraumeni syndrome [15].

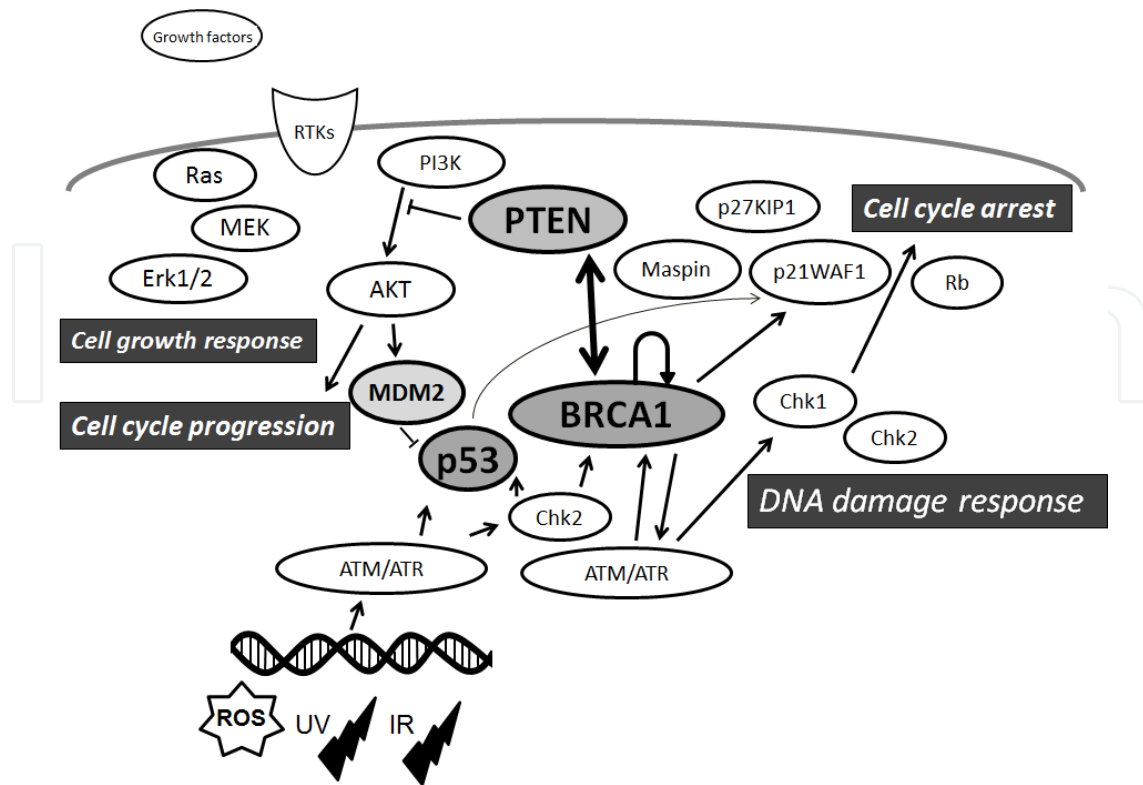


Figure 1. Schematic illustration of the integrative signaling model of tumor suppressors including p53, PTEN, and BRCA1 is shown. Typical examples of molecules known to act on the cell proliferation, DNA damage response, and cell cycle regulation via the regulatory pathway are shown. Note that some critical pathways have been omitted for clarity.

Multiple mechanisms have been shown to accomplish the regulation of p53 activity, which controls the selectivity of p53 for specific transcriptional targets [16]. Discharge of p53 from normal repression by binding with molecules such as MdmX or Mdm2 may be a crucial step in the activation of p53 [17, 18]. Functional activation of p53 links with its higher DNA-binding ability, transcriptional activation, then increased expression of the target genes of p53, which are all related to cell cycle regulation and/or cellular apoptosis.

PTEN tumor suppressor gene is also frequently deleted and mutated in several human cancers [19]. The gene product is a 53-kDa protein with homology to tensin and protein tyrosine phosphatases. Human genomic locus of the *PTEN* consists of 9 exons on chromosome 10q23.3 encoding a 5.5-kb mRNA that postulates a 403-amino-acid open reading frame [20]. Schematic construction of the predicted PTEN protein is presented in Figure 2. The PTEN protein consists of amino-terminal phosphatase, carboxyl-terminal C2, and PDZ (PSD-95, DLG1, and ZO-1) binding domains [21]. The structure offers PTEN with its preference for acidic phospholipid substrates including phosphatidylinositol 3,4,5-triphosphate (PIP3), as the PTEN CX5R(S/T) motif resides within an active site that surrounds the catalytic core with three basic residues, which are critical for PTEN lipid phosphatase activity [22]. PTEN negatively regulates the activity of PI3K/AKT signaling through converting PIP3 into phosphatidylinositol 4,5-bisphosphate (PIP2) [23]. PIP3 is the principal second messenger of the PI3K pathway that

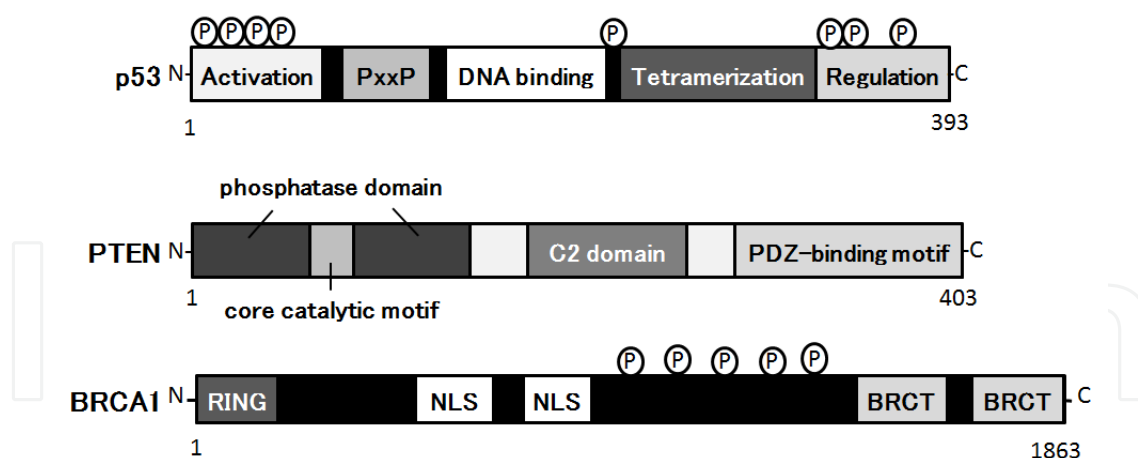


Figure 2. Schematic structures of p53, PTEN, and BRCA1 proteins are shown. The predicted consensual domain structures for each protein are depicted. The functionally key sites including the sites of protein phosphorylation are shown. Note that the sizes of protein are modified for clarity. Activation = transactivation domain; PxxP = proline-rich region; RING = (Really Interesting New Gene) finger domain, NLS = Nuclear Localization Signal, BRCT = BRCA1 C Terminus; C2 domain = a protein structural domain involved in targeting proteins to cell membranes; PDZ = a common structural domain in signaling proteins (PSD95, Dlg, ZO-1, etc.)

mediates receptor tyrosine kinase (RTK) signaling to the cell survival kinase AKT. In general, growth factors stimulate RTKs, then activate PI3K and AKT. Upon activation, the inositol ring phosphorylated by PI3K serves to fix AKT to the plasma membrane, where it is sequentially phosphorylated and completely activated by 3-phosphoinositide-dependent kinases PDK1 and PDK2 [24]. Subsequently, activated AKT phosphorylates target proteins involved in cell survival, cell cycling, proliferation, and cell migration [25]. PTEN may act as a regulator of keeping basal levels of PIP3 under a threshold for those signaling activation. Overexpression of PTEN inhibits cell growth by supporting cell cycle arrest, which requires the lipid phosphatase activity of PTEN [26], which correlates with reduced levels and nuclear localization of cyclin-D1 [27], an important molecule of cell cycle regulated by PTEN and AKT. In addition, PTEN induces the cell cycle arrest by upregulating the cell cycle inhibitor p27KIP1 [28]. However, studies have shown many tumor suppressive activities for PTEN that are working within the nucleus, where catalysis of PIP3 does not appear to characterize a main function of the enzyme. The nuclear PTEN activities may include the regulation of genomic stability and several gene expression, indeed despite that the central role of PTEN is as a negative regulator of the PI3K pathway. PTEN activity can be regulated by posttranslational regulation including phosphorylation, oxidation, and acetylation [29, 30].

BRCA1 cDNA encodes for 1863-amino-acid protein with two nuclear localization signals (NLS) and an amino terminal conserved RING finger motif which is the shared motif present in E3 ubiquitin ligases [31] (Figure 2). The RING finger domain interacts with E2 ubiquitin ligases and applies E3 ligase activity [32]. Knock-in mice with deficient *BRCA1* activity exhibit diverse genomic instability and tumor-forming phenotypes [33]. Exon 11 encodes an unstructured region of the *BRCA1* protein that is phosphorylated by the ATM and Chk2 kinases in a DNA-damage-dependent manner [34, 35], and the specific function of *BRCA1* may be regulated by

phosphorylation. BRCA1 becomes more phosphorylated after exposure to the DNA-damaging agents [36]. The carboxyl-terminal domain of BRCA1 is involved in association with specific phosphorylated proteins [37]. Because BRCA1 plays a crucial role in maintaining genome stability, the mutation of BRCA1 is associated with increased genomic instability in cells, which consequently accelerates the mutation rate of the other critical genes. Inherited BRCA1 germline mutation is revealed as a genetic susceptibility leading to high risk of breast and ovarian cancers [38]. Although *BRCA1* gene mutations are rare in breast and/or ovarian cancers, BRCA1 protein expression is often decreased in sporadic cancer specimens. Principally, the role of BRCA1 in cell cycle control has been understood by its ability to interact with various cyclin proteins and various cyclin-dependent kinases [39, 40].

3. Relationship among PTEN, p53, BRCA1, and MDM2

The PTEN and p53 complex augments the p53-DNA binding and the transcriptional action [41], which may upregulate the expression of PTEN itself and p21WAF1, which is a key molecule involved in cell cycle arrest [42]. Indeed, a superior function of p53 is to work as a transcription factor by attaching to the definite DNA consensus sequence on the p53 responsive genes. Consequently, p53 indirectly inhibits production of PIP3 by inducing the expression of this PTEN. In addition, PTEN associates with p53 and regulates the transcriptional activity of p53 by modulating its DNA binding. PTEN is also required for the maintenance of p53 acetylation [43], which is essential for target gene transcription. An adjacent function of PTEN as a tumor suppressor is accomplished through the stabilization of the p53 protein. PTEN and p53 form a complex in the nucleus under hypoxic conditions [44]. Nuclear PTEN is sufficient to reduce cancer progression in a p53-dependent manner [45]. In addition, the nuclear PTEN seems to mediate DNA damage repair through modulating the activity of DNA repair molecules. The PI3K-dependent activation of AKT indirectly leads to the inhibition of p53 functions by activating another tumor suppressor MDM2 [46]. Activation of AKT has the potential of reducing the p53-mediated cell cycle checkpoints through phosphorylation and appropriation of p21WAF1 [47]. By the way, several PI3K inhibitors favorably reduce proliferation of BRCA1-defective breast cancer cells. For example, BEZ235 inhibits not only PI3K/mTOR but also ATM/ATR [48, 49]. It is possible that ATM pathways are involved in upregulation of the PI3K/AKT pathway in BRCA1-defective cancer cells. In contrast, BRCA1 may regulate the PI3K/AKT pathway by acting on upstream kinases of AKT. Overexpression of wild-type BRCA1 could further reduce basal phosphorylation of AKT levels in MCF7 cells [10, 50]. In addition, reduced levels of PTEN are associated with radio-resistance which can be suppressed by the ectopic PTEN expression [51, 52].

MDM2 controls carcinogenesis, whose mRNA level is also transcriptionally regulated by p53 in response to DNA damage [53]. MDM2 protein and subcellular localization are post-translationally modulated by AKT [53]. Besides inhibiting the PI3K/AKT signaling, PTEN also promotes translocation of the MDM2 into the nucleus. Furthermore, PTEN modulates *MDM2* transcription by negatively regulating its promoter [41]. PTEN controls *MDM2* promoter activity through its lipid phosphatase activity, independent of the p53 activity [53]. In *PTEN*-

null cells, *MDM2* promoter activity is upregulated, resulting in increased *MDM2* expression [53]. *MDM2* also regulates the activity of p53 protein by transferring the nuclear p53 protein into the cytoplasm and by promoting the degradation of the p53 protein [54]. *PTEN* upregulates the p53 level as well as its activity by downregulating *MDM2* transcription [55]. However, in the absence of p53, *PTEN* may have a role in inhibiting *MDM2*-mediated carcinogenesis through regulation of *MDM2* transcription. The p53 and *MDM2* complex transports from the nucleus into the cytoplasm, where *MDM2* serves as an E3 ubiquitin ligase [56]. Therefore, p53 and *MDM2* form a regulatory feedback loop in which p53 positively regulates *MDM2* activity. Inactivation of either gene should result in lower protein levels of the other gene. The ability of *PTEN* to inhibit the nuclear entry of *MDM2* increases the cellular content. The *BRCA1* carboxyl-terminal region can also stimulate transcription of the p53-responsive promoter of *MDM2* [57]. *BRCA1* has been shown to affect the gene transcription, but how it does so remains elusive. Essentially, the most important molecule for the DNA damage recognition may be *ATM*, which is a key checkpoint kinase that phosphorylates various proteins including *BRCA1* and/or p53 in response to the DNA damage [58]. *BRCA1* activates the CDK inhibitor p21^{WAF1} and the p53 tumor suppressor protein, which regulates several genes that control the cell cycle checkpoints [59, 60]. Inhibition of this important DNA repair pathway seems to block the mechanisms that are required for normal cell survival in the presence of oncogenic mutations due to DNA damage.

4. Involvement of the p53-PTEN-MDM2-BRCA1 loop in cell cycle regulation

The levels of p53 could vary and is positively related to the amount of DNA damage [61]. Low levels of p53 may induce cell cycle arrest, whereas high levels of p53 may induce apoptosis. On the other hand, growth factor-activated *AKT* signaling supports progression of cell cycle by acting on several factors involved in the G1/S or G2/M cell cycle transitions. Because the ability of p53 to induce cell cycle arrest and/or cell apoptosis can be provoked by cell survival signals including the *AKT* pathway, the cell growth signal circuitously leads to the inhibition of p53 by triggering its negative regulators [62]. The p53 protein also regulates *BRCA1* transcription both in vitro and in vivo, and *BRCA1* participates in p53 accumulation after irradiation through regulation of its phosphorylation and *MDM2* expression [63]. *MDM2* can act as a modifier of *BRCA1* mutant and may accelerate breast and ovarian carcinogenesis [64]. In addition, p53 and *PTEN* are known to interact and to regulate each other at the transcription as well as protein level, which could be at the important control machinery for switching between survival and death. Given the ability of *PTEN* to stabilize p53 protein through provoking the *AKT*-*MDM2* complex or by increasing p53 acetylation, the decreased p53 activity in *PTEN*-lacking tumor cells could be plausible. *PTEN* and *BRCA1* may be regulated and interact with each other at multiple levels including transcription, protein modulation, and protein stability. Therefore, the p53-*PTEN*-*MDM2*-*BRCA1* loop in cell cycle regulation now becomes dominant (Figure 3). These cross talks are frequently a combination of reciprocally antagonistic pathways, which may often serve as an additional regulatory effect on the

expression of key genes involved in cell cycle and carcinogenesis. Interestingly, genistein, which is a soy isoflavone, brings regulation between PTEN and p53 to support cell cycle arrest [65]. Genistein induces PTEN expression and nuclear accumulation, which elicits a sequence of PTEN-dependent nuclear p53 accumulation and recruitment of the PTEN/p53 complex to the p53 binding sites [65], then attenuates expression of cell proliferative genes [65]. In addition, genistein inhibits cell proliferation and induces cell apoptosis more proficiently in BRCA1-mutant cells than in cells expressing wild-type BRCA1 protein [66]. BRCA1-mutant breast cancer cells are highly sensitive to genistein treatment, and AKT could be genistein targets in these cells [66]. Accordingly, genetic variants in the molecules of p53, PTEN, BRCA1, and MDM2 may play roles in tumor suppressor network mediating a susceptibility to cancer. Remarkably, it has also been presented that zinc deficiency modulates the p53-PTEN-BRCA1-MDM2 signaling network in normal cells [67].

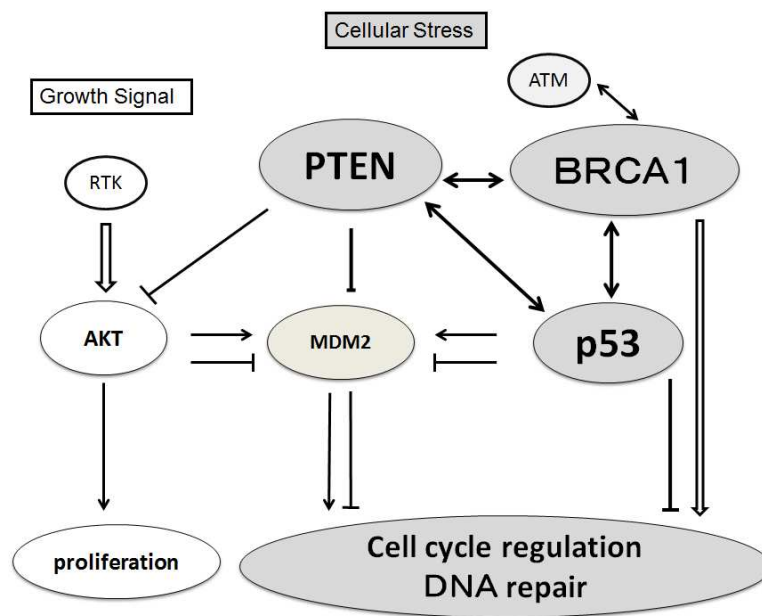


Figure 3. Suggestion of various regulatory loops involving the p53-PTEN-MDM2-BRCA1 network on cell cycle regulation. Interactions are shown as arrows to mean activation, while hammerheads, to mean inhibition. Expression of these tumor suppressor genes is regulated by genetic, epigenetic, and transcriptional changes, which may result in the DNA repair and cell cycle regulation in a cell. Downregulation of the function can contribute to genomic instability, which promotes malignant transformation of cells. Note that some critical pathways have been omitted for clarity.

5. Perspective

In unstressed cells, p53 may be regularly kept at low levels by its negative regulator MDM2. This feedback loop among the p53-PTEN-MDM2-BRCA1 may function for the accurate regulation of the DNA repair and cell cycle (Figure 3). When stressed, the tumor suppressor p53 predominantly induces cell cycle arrest or apoptosis in the response to DNA damage. Indeed, the regulation is crucial for the effective design of novel cancer therapeutics. Further

mechanistic studies are needed in order to understand the exact molecular mechanisms for the effective treatment of cancers with the functional alterations in the cellular signaling loop. Targets within this pathway could provide strategies therapeutically valuable for several cancer treatments. It is important to investigate the linkage among the molecules, and elucidation of interaction-specific functions may provide insight into regulatory aspects of these tumor suppressors as well as opportunities for therapeutic intervention. Such molecular interactions may sustain the biological plausibility that the combination of variants of the p53-PTEN-MDM2-BRCA1 network could result in more comprehensive. Genetic analysis for germline mutations in these key genes allows for the identification of characters at increased risk of cancers. However, they may be regulated and interact with each other at multiple levels including transcription, protein modulation, and protein stability. Obviously, understanding the regulation is crucial for the effective design of novel cancer prevention and therapeutics. Further studies are needed to understand molecular mechanisms in more detail.

6. Abbreviations

ATM: ataxia telangiectasia-mutated

BRCA1: breast cancer susceptibility gene 1

HDM2: human homolog of MDM2

LOH: Loss of heterozygosity

MDM2: murine double minute 2

NEDL1: NEDD4-like ubiquitin protein ligase-1

NF- κ B: nuclear factor kappaB

NLS: Nuclear Localization Signal

mTOR: mammalian target of rapamycin

PDZ: PSD-95, DLG1, and ZO-1

PEST: proline, glutamic acid, serine and threonine

PTEN: phosphatase and tensin homolog deleted on chromosome 10

PIP2: phosphatidylinositol 4,5- bisphosphate

PIP3: phosphatidylinositol 3,4,5-triphosphate

PI3K: phosphoinositide-3 kinase

RING: really interesting new gene finger domain

RTK: receptor tyrosine kinase

ROS: reactive oxidative species

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