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THE MECHANISM OF ACTION OF THE TUMOUR SUPPRESSOR GENE PTEN

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Intracellular levels of phosphorylation are regulated by the coordinated action of protein kinases and phosphatases. Disregulation of this balance can lead to cellular transformation. Here we review knowledge of the mechanisms of one protein phosphatase, the tumour suppressor PTEN/MMAC/TEP-1 apropos its role in tumorigenesis and signal transduction. PTEN plays an important role in the phosphatidyl-inositol-3-kinase (PI3-K) pathway by catalyzing degradation of phosphatidylinositol-(3,4,5)-triphosphate generated by PI3-K. This inhibits downstream targets mainly protein kinase B (PKB/Akt), cell survival and proliferation. PTEN contributes to cell cycle regulation by blockade of cells entering the S-phase of the cell cycle, and by upregulation of $p27^{Kip1}$ which is recruited into the cyclin E/cdk2 complex. PTEN also modulates cell migration and motility by regulation of the extracellular signal-related kinase – mitogen activated protein kinase (ERK-MAPK) pathway and by dephosphorylation of focal adhesion kinase (FAK). We also emphasize the increasingly important role that PTEN has from an evolutionary point of view. A number of PTEN functions have been elucidated but more information is needed for utilization in clinical application and potential cancer therapy.

INTRODUCTION

PTEN (**p**hosphatase and **ten**sine homolog deleted on chromosome ten)/MMAC (**m**utated in **m**ultiple **a**dvanced **c**ancers) has been identified simultaneously by two research groups as a candidate tumour suppressor gene located at 10q23[1, 2]. Another group identified the same gene in the search for new dual-specificity phosphatases and named it TEP-1 (**T**GF-β regulated and **e**pithelial cell-enriched **p**hosphatase)[3]. Overall, PTEN is one of the most common targets of mutation in human cancer, with a mutation frequency approaching that of p53. PTEN is also mutated in inherited cancer predisposition disorders.

A variety of cellular functions have been reported for PTEN using different experimental model organisms; regulation of cell division, cell survival, apoptosis and cell migration in human and mouse cells, involvement in the dauer formation in Caenorhabditis elegans, regulation of cell size in Drosophila eye development and having a role in sporulation in Saccharomyces cerevisiae[4].

The PTEN cDNA encodes a 403-amino-acid peptide with relative molecular mass of 55 kD[1, 3, 5, 6, 7]. Two major transcripts of approximately 2 and 5kb and several other minor RNA species have been detected in a wide variety of cell lines and immunological in situ detections indicate different localisation of the PTEN protein[8]. In xenografts from prostate tumour tissue were observed exclusively cytoplasmic staining, which supports the suggested role of PTEN as a signal transduction molecule connecting the cytoskeleton to intracellular signaling pathway[9]. Immunohistochemical analysis of tissue sections from a group of glioblastomas (GBMs) shows perinuclear cytoplasmic and nuclear staining[10]. Two distinct patterns of positive staining were observed. All of the tumour cells were either homogenously or heterogenously stained for PTEN. Positivity of PTEN was also present in vascular endothelial cells and neurons. In archival paraffin tissue section from resected prostate cancer PTEN expression was seen in the cytoplasm of the secretory cells with a granular staining pattern[11].

STRUCTURE OF THE PTEN MOLECULE IN RELATION TO ITS FUNCTION

The crystal structure study of PTEN reveals two major domains: an N-terminal phosphatase domain consisting of five stranded β-sheets surounded by six α-helices, connected via a flexible internal loop to the C-terminal domain consisting of two antiparallel β-sheets linked by two short α-helices[12]. The N-terminal domain with 179-residues (residues 7–185) has significant homology to the cytoskeletal protein tensine and auxilin. Tensine binds to actin and participates in the assembly of the signaling complex at focal adhesion, downstream

of which lie pathways that regulate cellular integrity, cell-to-cell communication, cell-microenvironment interactions and cell migration. Auxilin is involved in the transport of synaptic vesicles[8].

The 166 residues of C-terminal domain contains the protein tyrosine phosphatase (PTP) motif and has a structure similar the dual specifity phosphatase (DSP). The phosphatase active site of PTEN with its basic charge is important for Phosphatidyl-Inositol-3,4,5-tri--Phosphate (Ptd-Ins-3,4,5-P_3) binding (Fig. 1). The C-terminal has a structure similar to the C2 domain that mediates the Ca^{+2}-dependent membrane recruitment of several signaling proteins. The PTEN C2 domain lacks the Ca^{+2} ligands, and in this respect it is similar to the C2 domains of the Ca^{+2} – independent protein kinase C (PKC) isotypes. The in vitro membrane binding activity of PTEN does not require Ca^{+2}. It is strongly suggested that PTEN binds to phospolipid membranes and its lipid binding activity is important for its tumour suppressor function. The C2 and phosphatase domains associate across an extensive interface that is adjacent to the phosphatase active site and consists of conserved residues frequently mutated in cancer (Fig. 1, 2). The PTEN C2 domain may help recruit PTEN to the membrane and also serve to position and orient the catalytic domain optimally with respect to the membrane-bound substrate[13].

The PTEN HCXXGRXXR motif forms a loop (P-loop, residues 123–130) located at the bottom of the active site pocket, in common with PTPs and DSPs (Fig. 1). In the PTEN HCXXGRXXR motif the Cys-124 and Arg-130 residues are essential for catalysis and the His-123 and Gly-127 residues are important for the conformation of the P loop[14]. The PTEN has a second anion-binding site adjacent to the catalytic phosphate-binding site, called the TI loop (Fig. 1). Mutations of Thr-167 or Gln-171 on the TI loop, Lys-125 in the conserved basic residues in the PTEN active site motif and His-93 resulted in reductions of enzymatic activity toward Ptd-Ins-3,4,5-P_3 about 75%[13].

The C-terminus of PTEN has a consensus binding motif – **p**ostsynaptic density protein (PSD95)/**D**rosophila disc large tumour suppressor (dlg)/tight junction protein **Z**O1 (PDZ-binding motif) and this may interact with PDZ domain-containing proteins[15]. The PDZ binding site of PTEN is represented by the aminoacids: Ile-Thr-Lys-Val and it is unnecessary for the function of some systems[16, 17]. Other studies have shown that PDZ binding site associates with members of membrane--associated guanylate kinases (MAGI). In the absence of an interaction between PTEN and MAGI 2 or MAGI 3, the ability of PTEN to decrease Akt phosphorylation is impaired, suggesting that the PDZ binding site contributes to the PTEN function in some models[17, 18, 19, 20]. In human breast cancer tissue a stop codon mutation in PTEN has been identified that adds a short carboxyl extension, destroying the PDZ binding site in PTEN[21]. It has recently been shown that an interaction of PDZ domain with MAGI-2 stabilises the PTEN protein and enhances its activity, and threonine phosphorylation of the PDZ-binding motif both inhibits and stimulates PDZ-binding[12].

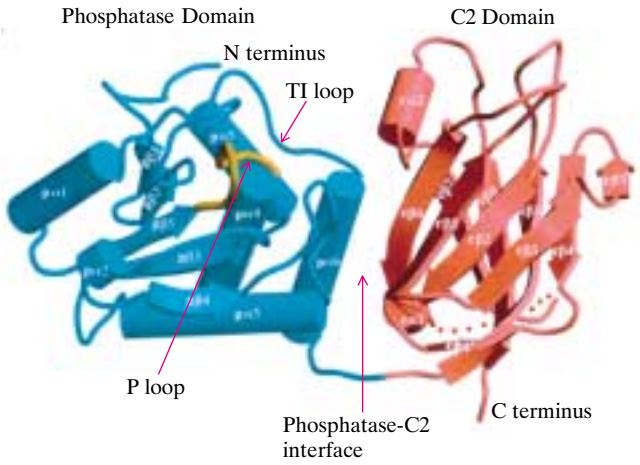

Fig. 1. The crystal structure of PTEN with phosphatase domain, C2 domain, phosphatase-C2 interface, TI loop and P loop. Adapted according to the article: Crystal structure of the PTEN tumour suppressor: implications for its phosphoinositide phosphatase activity and membrane association (*Cell 99, 323–334, 1999*).

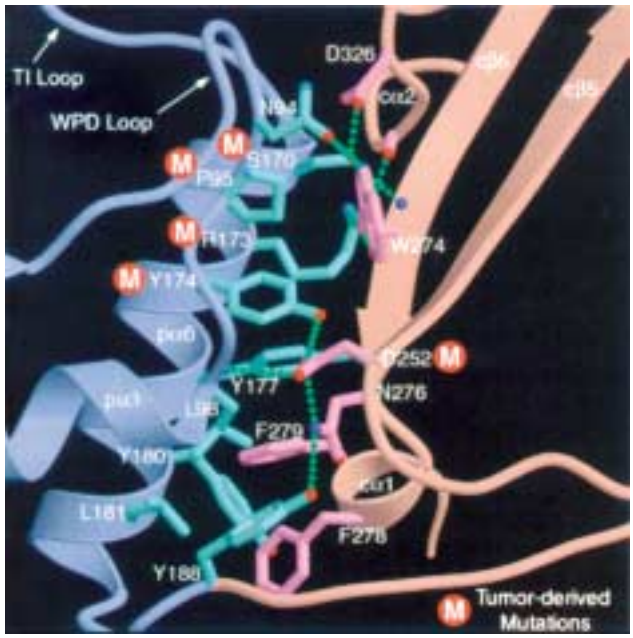

Fig. 2. Phosphatase-C2 interface with many residues participating in hydrogen binding networks have been found mutated in tumours. Adapted according to the article: Crystal structure of the PTEN tumour suppressor: implications for its phosphoinositide phosphatase activity and membrane association (*Cell 99, 323–334, 1999*).

Several growth factors induce PTEN phosphorylation, probably at tyrosine residues 240, 315, and 336. This is followed by decreased protein stability and enzymatic activity[21]. A large number of PTEN nonsense or frameshift mutations found in tumours are targeted to the C-terminal domain of the protein, suggesting an important role for this domain in the regulation of the PTEN tumour suppressor activity. C-terminal PTEN domain is rich in phosphorylation sites, and phosphorylation of the PTEN C terminus has been recently reported to affect PTEN protein stability and function. It is constitutively phosphorylated by protein casein kinase CK2 at Ser 370 and Ser 385 residues. This suggests the role of phosphorylation as a regulatory mechanism of PTEN biological activity by modulating its stability to proteasome-mediated degradation. However it is still not proven that the stability of the protein can reflect the localization of PTEN within a subcellular compartment[22].

Two novel alternatively spliced transcripts of the human PTEN gene, encoding protein products with altered C-terminal amino acid sequences in comparison with full length PTEN have been identified. PTEN-Δ is generated by inclusion of the 5 end of intron H between exon 8 and 9, resulting in a truncated coding sequence. PTEN-B is generated by alternative splicing of the end of exon 5. The generated open reading frame is truncated, and it encounters a stop codon after only five aminoacids. The coexpression of full length PTEN and two splicing variants have been demonstrated in normal lymphocytes and in non-malignant prostate cell lines. PTEN-Δ and PTEN-B are likely to be short-lived structures with limited phosphatase activity. The low-stability of PTEN protein homologues could imply they act as competitors for substrates or they could be stabilised by interaction with other molecular structures[12].

PHOSPHATASE ACTIVITY

The level of phosphorylation within cells is tightly regulated by the action of protein kinases and protein phosphatases. Disregulation of the activity of either of these players can lead to cellular tranformation. Many protein tyrosine kinases are proto-oncogenes and it has been postulated that some protein phosphatases may act as tumour suppressors. PTEN is a member of the PTP gene superfamily. PTP superfamily members can be further subdivided into classic PTP and dual specificity phosphatase families, comprising: cdc25A, B, and C (enzymes that specifically dephosphorylate and activate cyclin-dependent kinases), BVP (a baculovirus phosphatase), human VHR (a protein related to the vaccinia virus VH1 phosphatase), MKP1 (MAP kinase phosphatase 1, an enzyme that specifically dephosphorylates and activates mitogen activated protein kinase MAPK), the yeast cdc14 (an enzyme involved in the control of cell cycle progression), and the family of prenylated protein tyrosine phosphatases PRL1, 2, and 3. PTEN is a dual specificity protein phosphatase, dephosphorylates phosphotyrosine, phosphoserine, and/or phosphothreonine. It has phosphoinositide 3-phosphatase activity and plays an important role in the modulation of the phosphatidylinositol 3-kinase (PI3-K) pathway[8]. Overexpression of PTEN reduces insulin induced Ptd-Ins-3,4,5-P_3 without affecting insulin-induced PI3-K activation. Transfection of the catalytically inactive mutant of PTEN (C124S) causes Ptd-Ins-3,4,5-P_3 accumulation in the absence of insulin stimulation. PTEN catalyzes dephosphorylation of Ptd-Ins-3,4,5-P_3, at position 3 on the inositol ring. Ptd-Ins-3,4,5-P_3 is an important second messenger involved in cell growth signaling. It is specifically produced from Ptd-Ins-(4,5)-P_2 by PI3-K upon stimulation by a variety of ligands (Fig. 3). Ptd-Ins-3,4,5-P_3 can directly activate protein kinase B (PKB/Akt), which regulates cell survival and cell proliferation (Fig. 3). PTEN has Ptd-Ins-3,4,5-P_3 3-phosphatase activity and may act in vivo as a regulator of Ptd-Ins-3,4,5-P_3, which produces a substrate that can be recycled by PI3-K[15] (Fig. 3).

PI 3-K, PKB/Akt SURVIVAL SIGNALING PATHWAY

Several papers establish a link between the PI3-K/Akt pathway and human cancers via defects in PTEN[23]. Association with PI3-K and elevated levels of specific lipid products of the enzyme Ptd-Ins-3,4,5-P_3 correlate with the transforming ability of several oncoproteins. Growth factor stimulation and oncoprotein transformation correlate with increase in vivo levels of Ptd-Ins-3,4-P_2 and Ptd-Ins-3,4,5-P_3. These lipids are absent from quiescent cells but appear within seconds to minutes of stimulation with growth factors, platelet derived growth factor (PDGF), nerve growth factor (NGF), or insulin-like growth factor (IGF-1). These lipids act as membrane-embedded second messengers. A variety of cytosolic signaling proteins have evolved the ability to bind to one or both of these lipids as a mechanism of recruitment to the membrane[24]. Akt was discovered as the product of a retrovirus-encoded oncogene that transforms lymphoid cells[25]. There are three mammalian isoforms of Akt: Akt1, Akt2 and Akt3[26]. The protein products have a catalytic domain with close similarity to the protein kinase A (PKA) and PKC family of protein kinases, and Akt has been independently termed PKB as a PKC homologue[27]. The first evidence that PKB/Akt is regulated via a pathway involving PI3-K came from studies of PDGF-dependent PKB/Akt activation in fibroblasts[28]. The N-terminal PH domain of PKB/Akt acts as an autoinhibitory domain. This domain has a high affinity for Ptd-Ins-3,4-P_2 and Ptd-Ins-3,4,5-P_3. Binding to these phosphoinositides localizes PKB/Akt to the membrane and opens up the catalytic site. Protein-serine/threonine kinase, PDK1, also has the PH domain that binds Ptd-Ins-3,4-P_2 and Ptd-Ins-3,4,5-P_3 tightly, allowing it to colocalize with PKB/Akt and phosphorylate the activation loop. The full function of PKB/Akt requires phosphorylation at a second C-terminal site by a distinct kinase.

Activation of PI3-K and PKB/Akt has been shown to provide a survival signal in response to NGF, IGF-1, PDGF, interleukin-3 (IL-3) and the extracellular matrix[29]. PKB/Akt is likely to send survival signals by phosphorylating multiple targets, including the Bcl-2 family member Bad rendering it incapable of blocking Bcl-2 or Bcl-x_L activity[30] and the cell death pathway enzyme caspase-9[31] (Fig. 3). PKB/Akt catalyzes phosphorylation of another serine/threonine kinase, glycogen synthase kinase 3 (GSK3), and this results in GSK3 inhibition[32] (Fig. 3). GSK3 promotes cyclin D proteolysis. Thus by catalyzing GSK3 inhibition PKB/Akt may contribute to cyclin D accumulation and cell cycle entry[33]. The forkhead transcription factors FKHR, FKHRL1 and the protein-serine/threonine kinase $p70^{S6kinase}$ are also activated by the PI3-K pathway (Fig. 3). The forkhead transcription factors are inactive in PTEN null cells. Reconstitution of FKHR activity, in the absence of PTEN, can induce both cell cycle arrest and apoptosis in PTEN null cells[34, 35]. $P70^{S6kinase}$ may contribute to cell growth by regulating translation of key mRNAs[36]. Normally, PKB/Akt activity is low in the absence of growth factor stimulation. PTEN-deficient tumor cell lines, as well as immortalized fibroblasts and tumours derived from PTEN-deficient mice, exhibit high basal levels of PKB/Akt phosphorylation. Reconstitution of wild-type (wt) PTEN expression restores normal PKB/Akt regulation[23]. PTEN action can be overcome by expression of the constitutively active form of PKB/Akt. These results indicate that deregulation of the PI3-K/PKB/Akt signal transduction pathway may contribute to a large percentage of human cancers.

ROLE IN CELL CYCLE REGULATION

Overexpression of wt PTEN in MCF-7 breast cancer cell line leads to the suppression of cell growth through the blockade of cell cycle progression[37], an increased abundance of cyclin dependent kinase (cdk) inhibitor $p27^{Kip1}$, a decrease in the protein level of cyclin D_1 and inhibition of PKB/Akt phosphorylation. Expression of the phosphatase-dead PTEN mutant, C124S, has the opposite effect on the abundance of $p27^{Kip1}$, cyclin D_1 and PKB/Akt phosphorylation. The G129E mutant which does not have lipid phosphatase activity but retains protein phosphatase activity behaves like C124S except for a decreasing cyclin D_1 level similar to that of wt PTEN. The lipid phosphatase branch of PTEN upregulates $p27^{Kip1}$ by blocking PI3-K signaling, whereas the protein phosphatase branch down-regulates cyclin D_1. Furthermore, either estrogen or insulin abrogates PTEN-mediated upregulation of $p27^{Kip1}$ and partially blocks PTEN-mediated growth supression. In contrast, the combination of estrogen and insulin eliminates the upregulation of $p27^{Kip1}$, downregulation of cyclin D_1 and it completely blocks PTEN-mediated growth suppression[38]. In glioblastoma cell lines, $p27^{Kip1}$ is recruited into cyclin E/cdk2 immunocomplexes when PTEN is overexpressed in PTEN-mutant, but not in PTEN wt cells. The recruitment of $p27^{Kip1}$ to this complex leads to reduction in cyclin E/cdk2 kinase activity by 80%, an overall diminution of phosphorylation levels in endogenous retinoblastoma protein (pRb) and G_1 cell cycle arrest. These effects culminate in a substantial reduction in the number of cells reaching the S-phase of the cell cycle. Cdk4-associated kinase activity, levels of $p21^{Waf1/Cip1}$ and cyclin E in immuno-complexes were unaffected[39].

ERK-MAPK SIGNALING PATHWAY AND ROLE IN REGULATION OF CELL MOTILITY

It was discovered that PTEN can exert a growth suppressive effect by blocking insulin-stimulated phosphorylation of mitogen-activated protein kinase (MAPK). The Ras/MAPK pathway is the central signal transduction pathway involved in the regulation of a broad range of cellular functions. Well-defined nuclear targets of this pathway include a member of the Ets family of transcription factors, ETS-2. Its phosphorylation on the threonine residue 72 in Ras-dependent fashion leads to an increase in ability to transactivate target genes. ETS-2 expression correlates with cell proliferation and it can activate the promoter of cyclin D_1, a key positive regulator of the G_1/S cell cycle progression. Induction of wt PTEN in the MCF-7 cell line

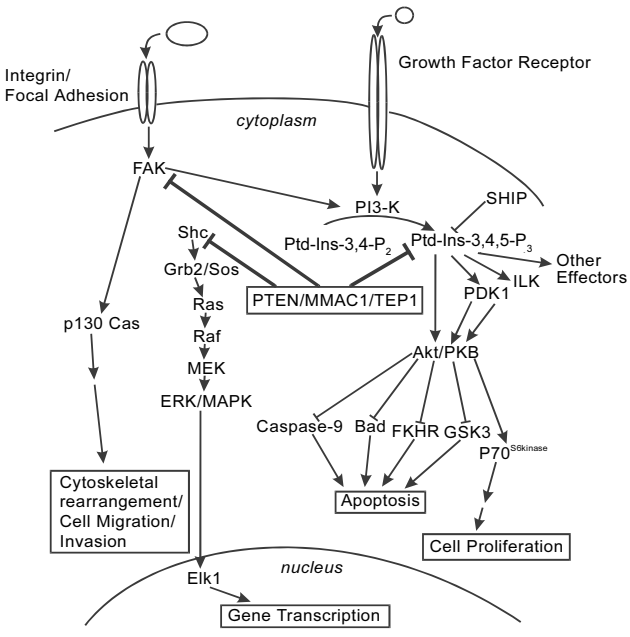

Fig. 3. Proposed model for PTEN/MMAC1/TEP1 mode of action. Schematic view of the known targets of negative regulation by PTEN, either via its protein tyrosine phosphatase activity or its phosphoinositide 3-phosphatase activity. Adapted according to the article: PTEN in signal transduction and tumorigenesis (*Eur. J. Biochem. 263, 605–611, 1999*).

resulted in marked decrease in phosphorylation levels of ETS-2, PKB/Akt, and extracellular signal-related kinase (ERK) members of the MAPK family ERK1/2, in contrast to the phosphatase-dead C124S PTEN mutant[40]. PTEN may block the MAPK pathway at some point upstream of MAPK or ERK (MEK) that might be common to both the integrin- and growth factor-mediated signaling pathway. PTEN most likely does not directly dephoshorylate ETS-2, but instead acts upstream of ETS-2 and ERK, and thus indirectly inhibits ETS-2 phosphorylation. Ras has been suggested as an initial component between integrin- and growth factor-mediated MAPK signaling pathways. The ability of PTEN to inhibit both integrin- and growth factor-mediated MAPK signaling pathways might be due to PTEN inhibiting Ras activation (Fig. 3). Upstream MEK, Ras activation, SH_2-phosphotyrosine-binding adapter protein (Shc) phosphorylation, and its interaction with the adapter protein Grb_2 are inhibited, but the EGF receptor, c-Jun NH_2-terminal kinase (JNK) and PKB/Akt phosphorylation are not affected (Fig. 3). The Ras inhibition can be overcome by expression of activated Ras and overexpression of an activated downstream component of the pathway, MEK1, can antagonize the biological effect of PTEN on cell spreading and focal contact formation[41]. It has been shown that the G129E mutant of PTEN, which lacks lipid phosphatase activity but retains protein phosphatase activity, can still inhibit integrin-mediated cell migration, spreading, focal adhesions, and tumour cell invasion, whereas protein and lipid phosphatase dead mutant C124S of PTEN can not, demonstrating an important role of protein phosphatase activity in PTEN function. PTEN directly associates with the focal adhesion kinase (FAK) and can reduce its tyrosine phosphorylation as well as its potential downstream effector, p130 Crk-associated substrate ($p130^{Cas}$) (Fig. 3). Furthermore, overexpression of FAK or $p130^{Cas}$ can antagonize the effects of PTEN on cell migration and invasion. MAPK activation may partially antagonizes PTEN function with partial rescue of cell spreading on fibronectin impaired by PTEN. This inhibition of PTEN was associated with effects on Shc phosphorylation. Shc links tyrosine kinases to Ras signaling by recruiting the Grb_2-Sos complex to the plasma membrane in a tyrosine phosphorylation-dependent manner. PTEN can inhibit tyrosine phosphorylation of both FAK and Shc (Fig. 3). Both proteins are implicated in integrin signaling and both can bind and potentially activate the Ras-MAPK pathway. PTEN, Shc and FAK regulate cell movement through two different mechanisms: one is the pathway from Shc through the MAPK pathway leading to the stimulation of random cell motility, and the other is from FAK through $p130^{Cas}$ leading to stimulation of directionally persistent cell migration. These two pathways are counterbalanced and integrated with the actions of PTEN[42].

STRUCTURE AND FUNCTION AT DIFFERENT EVOLUTIONARY LEVELS

One homolog of mammalian PTEN found in Caenorhabditis elegans is abbreviated as CePTEN. The amino-terminal region of CePTEN contains the phosphatase catalytic domain, and this region shares 38% sequence identity with the corresponding domain of human PTEN. The carboxyl-terminal region of CePTEN has lower levels of sequence homology than to human PTEN. CePTEN is involved in dauer formation and lifespan regulation and is encoded by the daf-18 gene. The dauer state is essentially a state of hibernation that is normally only entered under conditions of starvation or overcrowding. The nr2037 CePTEN mutation reveals a deletion that removes 990 nucleotides of the gene spanning parts of intron 2 and exon 3. This mutation abolishes the phosphatase activity of CePTEN. A strain homozygous form nr2037 is viable and shows no obvious abnormalities in development or morphology when grown under well fed conditions. The daf-18 nr2037 homozygotes at high-saturation growth densities or under starvation conditions failed to form dauers (a dauer defective phenotype). The dauer defective phenotype can be rescued by germ-line transformation with the wt CePTEN gene. Daf-18 nr2037 mutants have a shorter lifespan than wt animals by about 30%. This provides genetic evidence that CePTEN/daf-18 is one of the rate-limiting factors controlling the onset of aging in Caenorhabditis elegans[43].

The PTEN gene homologue, TEP1, exists in the budding yeast Saccharomyces cerevisiae. In the absence of a functional TEP1 gene, yeast cells grow normally, but homozygous diploids display resistence to the PI3-K inhibitor wortmanin and lithium ions. Neither TEP1 haploids nor diploids have altered life spans. TEP1 RNA is present throughout the cell cycle, and levels are dramatically upregulated during meiotic development. The spores produced in homozygous TEP1 mutants indicate a specific defect in the trafficking or deposition of dityrosine, a major component of yeast spore walls, on the surface. The maturation of the spore wall and its connection to the meiotic cell is analogous to the interaction of epithelial cells with the extracellular matrix. Perturbation of these cell contacts is important in carcinogenesis and suggests that analysis of TEP1 in yeast will be directly applicable to understanding the role of its homolog PTEN as a tumour suppressor in humans[44].

The Drosophila (dPTEN) and human PTEN gene product are similar in length and share 44% sequence similarities in both the N-terminal phosphatase domain and the C-terminal region. Both dPTEN defective heterozygotes and homozygotes die in the early larval stage. The size of the dPTEN mutant cells in the eye are much larger then neighboring wt cells. Overexpression of PTEN in proliferating cells of the eye disc results in dramatic reduction of eye size in a dose-dependent manner. Even multiple copies of PTEN can completely

eliminate the eye. Flow cytometry analysis after PTEN overexpression shows the cell cycle arrest in the G_2 or G_2/M phase in proliferating cells and cell death analysis shows apoptosis in differentiating cells during eye development. The small eye phenotype of PTEN overexpression is suppressed by overexpression of wt Drosophila PI3-K (D-PI3-K) and enhanced by overexpression of the dominant negative D-PI3-K. These results clearly indicate that PTEN and PI3-K function antagonistically in Drosophila. In this study no PTEN effect on cell migration was observed. Furthermore, signals from the insulin receptor can be antagonized by PTEN function, as in Caenorhabditis elegans and mammals. This argues for a PTEN function as a major conserved negative regulator in the insulin signaling pathway[4].

Homozygous mutant mice lacking exons 3–5 of the PTEN gene (mPTEN$^{3-5}$) had severely expanded and abnormally patterned cephalic and caudal regions at day 8, 5 of gestation. Embryonic death occurred by day 9, 5 and was associated with defective chorio-allantoic development. Heterozygous mPTEN$^{3-5}$ had an increased incidence of tumours, especially T-cell lymphomas and γ-irradiation reduced the time lapse of tumour formation. DNA analysis of these tumours revealed the deletion of the mPTEN gene due to loss of heterozygosity (LOH) of the wt allele. Tumours associated with LOH in mPTEN T-cell lymphomas and teratocarcinomas showed elevated phosphorylation of PKB/Akt, thus providing a functional connection between mPTEN and protooncogene PKB/Akt involved in the development of lymphomas. The PTEN heterozygous (PTEN+/–) mice are highly susceptible to the development of various types of tumours. PTEN+/– mice show impaired Fas-mediated apoptosis and may develop lethal autoimmune disorders[45]. It is described PTEN-knockout mouse embryos which display regions of increased proliferation. PTEN-deficient immortalized mouse embryonic fibroblast exhibit decreased sensitivity to cell death, providing in vivo evidence that PTEN negatively regulates cell survival signaling pathways[45]. Surprisingly, as one scales the evolutionary ladder, PTEN plays an increasingly important role. In Caenorhabditis elegans the PTEN homolog is only required for the dauer response to starvation. Analogous to the dauer formation, sporulation in yeast is a developmental state that is activated in response to starvation. The PTEN homolog in yeast plays a role in this process, although it is not essential for the formation of viable spores. The Drosophila PTEN homolog is required for viability and regulation of cell size in eye development. Finally, the inactivation of PTEN in mice results in embryonic lethality and a tendency for the development of tumours in the heterozygous state[44].

SUMMARY

Several lines of evidences have confirmed the role of PTEN as a tumour suppressor both in vitro and in vivo. PTEN participates in the regulation of normal cell growth and survival. Mutation of PTEN directly contributes to cell transformation and neoplastic growth. We have made an effort here to summarise current knowledge of the PTEN molecular structure in relation to its function. PTEN has been demonstrated to be involved in the regulation of a variety of biological phenomena such as cell survival, proliferation or apoptosis. PTEN affects the PKB/Akt pathway by reducing the level of the second messenger Ptd-Ins-3,4,5-P_3, cell cycle by upregulation of p27^{Kip1}, cell adhesion as well as migration through regulation of FAK and MAPK activation. Many aspects of the PTEN biology remain unclear and further investigation will be necessary for their elucidation and for practical application of these findings to cancer therapy.

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