Targeting PTEN in Colorectal Cancers

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Abstract

Phosphatase and tensin homolog (PTEN) is a tumour suppressor that represents one of the most common targets for genetic defect in human cancer. PTEN controls an array of physiopathological processes related to cell proliferation, differentiation, DNA/chromosome integrity, apoptosis and invasiveness. PTEN dephosphorylates not only proteins, but also phosphoinositides generated by phosphatidylinositol 3-kinase, thus counteracting the Akt signalling pathway. Interestingly, PTEN can also exert some biological functions independently of its catalytic activity.

A feature of colorectal cancers is the relatively low incidence of PTEN mutation or deletion, whereas PTEN downregulation occurs in approximately one third of tumours. PTEN inactivation may be even higher when changes in posttranslational modifications and/or mislocalization of the tumour suppressor are accounted for. Strategies based on pharmacologically-induced restoration of wild-type PTEN function in colon cancer cells could therefore be considered, to impact cell growth, trigger apoptosis, and sensitize tumour cells to therapeutic agents.

This review details current knowledge of the mechanisms regulating PTEN expression, activity and function. It also focuses on the use of small molecules targeting positive or negative PTEN regulators and summarizes alternative strategies that could be used to alter PTEN conformation/activity. Finally, we propose an outline of a personalized approach to restore PTEN function in colon cancer cells.

1. Background

PTEN (phosphatase and tensin homolog deleted on chromosome ten)/MMAC (mutated in multiple advanced cancers) was identified in 1997 by two groups as a candidate tumour suppressor gene located at 10q23 (Li et al. 1997a; Steck et al. 1997). In parallel, in a study screening for new dual-specificity phosphatases the same gene was identified and named TEP-1 (TGF-β-regulated and epithelial cell-enriched phosphatase) (Li and Sun 1997b). Homozygous inactivation of PTEN occurs in a large fraction of glioblastomas, melanoma cell lines, advanced prostate cancers and endometrial carcinomas (Teng et al. 1997). Depending on tissue type, PTEN inactivation can occur either as an early (*e.g.* endometrium), or late event (*e.g.* prostate cancers, glioblastomas). PTEN is one of the most common targets for genetic defect in human cancer. Haploinsufficiency or inactivation of a single PTEN allele is sufficient for cancer development. Germ-line mutations in PTEN cause three autosomal dominant inherited cancer syndromes (Cowden disease, Lhermitte-Duclos disease, and Bannayan-Zonana syndrome) characterized by hamartomas, and an increased prevalence of breast and thyroid malignancies. $Pten^{+/-}$ mice mimic the effects of some germ-line mutations of the human tumour suppressor gene (Di Cristofano et al. 1998; Suzuki et al. 1998; Podsypanina et al, 1999). $Pten^{-/-}$ mice exhibit early embryonic lethality, whereas heterozygotes show increased tumour incidence, consistent with its identification as a tumour suppressor gene.

PTEN encompasses 403 amino acids and is characterized by five functional domains: a short N-terminal PtdIns(4,5)P2 (PIP2)-binding domain, a phosphatase domain, a membrane-targeting C2 domain, and a C-terminal tail containing PEST sequences and a PDZ binding motif in its C-terminus (Figure). The PDZ binding motif permits binding to PDZ domain-containing proteins that often direct the assembly of multiprotein complexes at membrane-cytoskeletal interfaces.

PTEN is a multifunctional protein endowed with phosphatase activity. It has been reported that PTEN dephosphorylates the protein substrates FAK, SHC, IRS1, Dvl2 and PTK6 (Gu et al. 1998; Shi et al. 2014; Shnitsar et al. 2015; Wozniak et al. 2017). The tyrosine residue 138 of PTEN appears to be critical for PTEN protein phosphatase activity (Davidson et al. 2010). Importantly, PTEN dephosphorylates not only proteins, but also the phosphoinositides generated by phosphatidylinositol 3-kinase activity. PtdIns(3,4,5)P3 is known to exert its function by recruiting proteins that contain pleckstrin homology (PH) domains to the membrane, such as Btk, PKB/Akt, PLC-γ, Gab1, P-Rex1, PDK1, and Grp1 (Lemmon 2007). PtdIns(3,4,5)P3 effectors promote activation of Rac GTPases and F-actin polymerization at the leading edge of migrating cells. Through its lipid phosphatase activity PTEN counteracts the PI3K/Akt signalling cascade to decrease cell proliferation (Furnari et al. 1998), promote apoptosis (Stambolic et al. 2001; Szado et al. 2008) and revert invasiveness (Kotelevets et al. 2001, see also "PI3K as therapeutic target" by Raquel Seruca and Sofia Fernandes, in this issue). PTEN can autodephosphorylate threonine 383 and threonine 366 in its C-terminal tail (Figure) (Raftopoulou et al. 2004; Tibarewal et al. 2012).

The many somatic PTEN mutations identified in human cancers impact PTEN stability, subcellular localisation, and/or the lipid phosphatase/both lipid and protein phosphatase activities (Georgescu et al. 2000; Yang et al. 2017; Furnari et al. 1998).

PTEN also exerts some biological activities independently of its catalytic activity. For example, PTEN directly interacts with the tumour suppressor Tp53, enhancing its stability and transcriptional activity (Freeman et al. 2003; Tang and Eng 2006). The C-terminal domain of PTEN physically interacts with the forkhead-associated domain

of the Microspherule Protein 1 (MSP58) and inhibits its oncogenic activity (Okumura et al 2005). The isolated C2 domain of PTEN is also able to mimic effects of full-length PTEN in the control of both cell migration and glandular morphogenesis in 3D colorectal cancer cell systems (Raftopoulou et al. 2004; Leslie et al. 2007; Lima-Fernandes et al. 2011; Javadi et al. 2017). Nuclear PTEN also interacts with the anaphase-promoting complex (APC/C), promotes APC/C association with CDH1 (CDC20 homolog 1), and thereby enhances the tumour-suppressive activity of the APC-CDH1 complex, in a phosphatase-independent manner (Song et al. 2011). Interestingly, the knockin of mutant phosphatase-defective alleles of PTEN in mouse models reveals that heterozygous mice bearing one mutant allele ($Pten^{C124S/+}$ and $Pten^{G129E/+}$) have a higher tumour burden than $Pten^{+/-}$ counterparts with one full null allele. This suggests that heterooligomerization of wild-type with mutant PTEN inhibits PTEN tumour suppressor activity (Papa et al. 2014).

Due to the significant progress in high-throughput technologies, vast amounts of multidimensional data relevant to the biology of colorectal cancers have been generated (http://www.colonatlas.org) (Chisanga et al. 2016). Colorectal cancers (CRC) arise through the stepwise accumulation of genetic alterations leading from normal epithelia to aberrant crypt foci, adenoma, carcinoma and metastatic disease (Fearon and Vogelstein 1990; Kotelevets et al. 2016), and follow three molecular pathways to genome instability characterized by *i)* chromosomal instability (CIN), *ii)* high microsatellite instability (MSI-H), or *iii)* CpG island methylator phenotype (CIMP). A more detailed classification of primary colorectal cancers based on intrinsic gene expression profiles, resulting in the four biologically distinct consensus molecular subtypes (CMS1 – 4) was recently proposed to facilitate the translation of molecular subtypes into the clinic (Guinney et al. 2015).
According to The Cancer Genome Atlas Network, APC, TP53, KRAS, PIK3CA, FBXW7, SMAD4, TCF7L2 and NRAS are the most frequently mutated genes in CRC (cancer genome atlas network 2017). Molecular analysis of PTEN status in sporadic colorectal cancers revealed that PTEN mutation is a relatively rare event. COSMIC v84 (URL http://cancer.sanger.ac.uk/cosmic/, released February 13 2018), reports that 335 out of 6361 human colonic tumour samples exhibited PTEN mutations (5.27%, 2.02% according to Lin et al. 2015), whereas PTEN mutations were found in 37.8% of endometrial cancers. PTEN mutation in CRC was associated with the subgroup displaying microsatellite instability (mutation rate estimated to 19% in this subgroup), suggesting that PTEN might be a target of defective mismatch repair function in colorectal carcinogenesis. In line with this, the PTEN coding region contains several repeat sequences, including two poly(A) tracts in exons 7 and 8 (Goel et al. 2004). These mutations were found regardless of the antero-posterior localization of the tumour, with a slightly higher incidence in the cecum and proximal colon (Loree et al. 2017).
The loss of *PTEN* copy number was identified in 1.56% of tumour samples. Nevertheless, PTEN downregulation occurs in 33% of colon cancer samples. PTEN inactivation in colonic tumours might therefore be underestimated and could occur via other non-genomic mechanisms such as aberrant regulation of posttranslational modifications and/or mislocalization of the tumour suppressor. Nuclear-cytoplasmic partitioning of PTEN is a promising biological marker: the absence of nuclear PTEN is associated with more aggressive disease in patients with colorectal cancer or other types of cancer (Zhou et al. 2002; Tachibana et al. 2002; Whiteman et al. 2002; Perren et al. 2000; Fridberg et al. 2007).

Experimental studies demonstrate that restoration of PTEN expression sensitizes tumour cells to conventional as well as targeted therapies and immunotherapies. Since PTEN mutation is uncommon in CRC, targeting the multiple levels of PTEN regulation constitutes an attractive strategy to explore with the goal of re-establishing/potentiating its tumour suppressor activities and to manage tumour cell responses to chemotherapies.

2. Targeting PTEN in colorectal cancers

PTEN exerts pleiotropic activity and fulfils a complex array of physio-pathological processes related to cell proliferation (cell cycle arrest in G1 or in G2-M), differentiation, DNA and chromosomal integrity (Shen et al 2007), apoptosis (increased susceptibility) and invasiveness (inhibition). PTEN expression is therefore subjected to fine-tuning at transcriptional, post-transcriptional and post-translational levels (Figure). The importance of maintaining appropriate PTEN expression is highlighted by the fact that even a subtle reduction in PTEN levels is sufficient to promote cancer susceptibility (Carracedo et al. 2011).

2.1 Transcriptional level

Epigenetic PTEN regulation

Hypermethylation of CpG islands in promoters is associated with gene silencing and PTEN silencing might therefore result from promoter methylation independently of copy number loss. The analysis of *PTEN* promoter methylation might be biased by contamination of the methylated *PTEN* pseudogene. In colonic cell lines, *PTEN* promoter methylation is a rare event (Hesson et al. 2012). In contrast, however, *PTEN* promoter methylation was observed in approximately 30% of colorectal tumour samples (lin et al. 2015; Yazdani et al. 2016). Interestingly, sulforaphane, an organosulfur compound present in cruciferous vegetables such as broccoli, Brussels sprouts and cabbages induces DNA demethylation and restores PTEN expression in cultures of mammary cell lines (Lubecka-Pietruszewska et al. 2015). Other epigenetic inhibition of PTEN expression involves the histone methyltansferase activity of the Polycomb Repressive Complex 2 that is reversed by the selective antagonist 3-deazaneplanocin A (Benoit et al. 2013).

This provides a rationale for epigenetic therapies based on the use of DNA demethylating agents, such as 5-azacytidine and 5-aza-2'-deoxycytidine, or of selective inhibitors of histone methyltransferase. Such compounds are under clinical trial for cancer treatment (16 trials referenced at URL: https://clinicaltrials.gov/, accessed on 1st March 2018 concern azacytidine derivatives in colorectal cancers, 13 trials evaluate histone methyltransferase inhibitors in different types of cancers).

The *PTEN* pseudogene *PTENpg1* is located on chromosome 9, and encodes a long noncoding RNA (lncRNA) that regulates PTEN both positively and negatively at transcriptional and posttranscriptional levels (Johnsson et al. 2013). *PTENpg1* is transcribed in the sense orientation and in antisense under three isoforms: unspliced, spliced antisense alpha and antisense beta. It is proposed that the antisense alpha recruits the EZH2 histone methyltransferase and the DNA methyltransferase 3A (DNMT3a) to the *PTEN* promoter leading to *PTEN* silencing. The nuclear export of the *PTENpg1* sense RNA which lacks a poly-A tail is facilitated by *PTENpg1* antisense beta. Due to its strong homology with *PTEN*, cytoplasmic sense *PTENpg1* transcript acts as a "sponge" to "mop up" the microRNAs targeting *PTEN* (Figure and see below) (Poliseno et al. 2010).

Transcription factors

A series of transcription factors bind directly to the PTEN promoter and either activate or repress PTEN transcription (Figure).

Inducing factors include the early growth response transcriptional factor 1 (EGR1) (Virolle et al. 2001), the peroxisome proliferator activated receptor gamma (PPARγ) (Patel et al. 2001), activating transcription factor 2 (ATF2) (Shen et al. 2006), the nuclear factor of activated T cell (NFAT) (Wang et al. 2011) and the tumour suppressor, Tp53 (Stambolic et al. 2001).

In contrast, PTEN is transcriptionally repressed by c-Jun (Hettinger et al. 2007), nuclear factor-kappa B (NFκB) (Xia et al. 2007; Ghosh-Choudhury et al. 2010)), and the zinc finger-like proteins SNAIL and SLUG involved in epithelial-mesenchymal transition (Escriva et al. 2008; Uygur et al. 2015).

These transcription factors and their upstream effectors therefore constitute targets to enhance PTEN transcription. Examples include the PPARγ agonist rosiglitazone, induction of EGR-1 following irradiation, activation of NFAT by butyrate a short-chain fatty acid produced by fermentation of dietary fibers by colonic microbiota, statins or selective inhibitors to target NFkB.

2.2 Posttranscriptional modulation

MicroRNAs (miRNAs) are a class of small non-coding RNAs containing 18-24 nucleotides. These short RNAs can negatively regulate gene expression by complementary binding to the 3-untranslated region (3'-UTR) of target transcripts, leading to translation inhibition and/or mRNA degradation (Figure). One single miRNA may target the expression of many different genes. Conversely, one transcript may be targeted by distinct miRNAs. MiRNAs are usually transcribed as miRNA precursors, which are processed by the DGCR8–Drosha complex, to produce a 60- to 70-nucleotide pre-miRNA. This pre-miRNA is exported to the cytoplasm and further cleaved by the Dicer complex into the mature form of miRNA. The mature miRNA is then loaded onto the Argonaute protein, forming a miRNA–protein complex known as the RNA-induced silencing (RISC). A subgroup of miRNAs termed oncomiRs, exert oncogenic action through the binding and downregulation of tumour suppressor transcripts.

So far, 19 miRNA known to directly target PTEN have been identified in colorectal cancers, including miR-17 and miR-92a (cluster miR-17-92) (Tanaka et al. 2016; Zhang et al. 2013); miR-20b (Zhu et al. 2014) and miR-106a (cluster miR-106a-363) (Qin et al. 2018); miR-21 (Zhu et al. 2014); miR-26b (Fan et al. 2018); miR-29a (Wang et al. 2016); miR-32 (Wu et al. 2013); miR-103 (Geng et al. 2014); miR-106b (Zheng et al. 2015); miR-130b (Colangelo et al. 2013); miR-135b (Xiang et al. 2014); miR-181a (Wei et al. 2014); miR-200a (Li et al. 2016); miR-200c (Chen et al. 2014); miR-221 (Xue et al. 2013); miR-494 (Sun et al. 2014); miR-543 (Sun et al. 2016); miR-582 (Song et al. 2017). In contrast, miR-22 suppresses the growth, migration and invasion of colorectal cancer cells through targeting Sp1 transcripts, resulting in PTEN up-regulation (Xia et al. 2017).

MiRNAs expression could therefore be targeted at different levels, *i.e.* transcription, processing, or via depletion or inactivation using antisense sequence or small molecule inhibitors (Nguyen and Chang 2018). As a proof of concept, the high throughput analysis of a library of pharmacologically active compounds allowed the identification of small molecule inhibitors of the (onco)mir-21 (Gumireddy et al. 2008). Anti-miRNA-221 sensitizes human colorectal carcinoma cells to radiation by upregulating PTEN (Xue et al. 2013). The MEK inhibitor PD0325901 suppresses

expression of the miR-17-92 cluster and up-regulates PTEN in human colonic HT-29 cells (Tanaka et al. 2016).
The RNA-binding proteins Musashi-1/2 overexpressed in CRC bind *PTEN* transcripts leading to loss of the PTEN protein and to activation of the Akt pathway (Wang et al. 2015; Li et al. 2015; see Figure). The emerging role of Musashi proteins in carcinogenesis motivated several groups to screen libraries of small molecules in order to identify compounds that might disrupt the binding of Musashi proteins to RNA. Gossypol, a natural phenol derived from the cotton plant, was identified following screening. Interestingly, this inhibitor of RNA-binding proteins suppresses tumour growth in a mouse xenograft model and might constitute the basis for the development of more selective compounds (Kudinov et al. 2017).

2.3 PTEN translation/PTEN isoforms

In addition to the initial PTEN sequence encompassing 403 amino acid residues, longer isoforms have been recently identified (Hopkins et al. 2013; Liang et al. 2014; Tzani et al. 2016). These isoforms originate via translation from alternative start codons, distinct from the canonical AUG, and characterized by an extra in frame N-terminal sequence of 72 (PTEN-O), 131 (PTEN-N), 146 (PTEN-M/PTEN-β) and 173 amino acid residues (PTEN-L/PTEN-α) (Pulido et al. 2014; Tzani et al. 2018). Translation of the PTEN-L isoform was reported to be under the control of the eukaryotic translation initiation factor 2A (eIF2a) (Liang et al. 2014). All these isoforms retain phosphatase activity and downregulate the PI3K/Akt pathways. Nevertheless, the N-terminal extension affects their subcellular localization. PTEN-L interacts with canonical PTEN to increase PTEN-induced kinase 1 (PINK1) levels and collaborates in mitochondrial bioenergetics through regulation of cytochrome c oxidase activity and ATP production (Liang et al. 2014). PTEN-M is localized to the nucleolus, where it binds and dephosphorylates, nucleolin, the nucleolar phosphoprotein resulting in inhibition of rDNA transcription, ribosomal biogenesis and cell proliferation (Liang et al. 2017).
PTEN-L harbours an N-terminal signal peptide secretion signal, is secreted from cells and can enter into other neighbouring cells (Figure). As an exogenous agent, PTEN-L antagonizes PI3K signalling and induces tumour cell death *in vitro* and in mouse tumours xenograft after intraperitoneal injection (Hopkins et al. 2013). By providing a means to restore a functional tumour suppressor protein to tumour cells, PTEN-L may have therapeutic implications. In this context, a variant of this isoform was engineered by replacement of the native leader sequence of PTEN-L with a leader sequence from human light-chain immunoglobulin G (IgG) to enhance cell-mediated protein delivery to neighbouring cancer cells (Lavictoire et al. 2018). Another prospect might be to exploit surrounding neighbouring non-transformed cells to produce PTEN-L. The eukaryotic translation initiation factor 2 (eI2F) plays an important role in the translation of this isoform (Liang et al. 2014).

2.4 Posttranslational regulation

In the case where PTEN is expressed, several approaches could be devoted to increase its activity, including posttranslational modulation, stabilization of active conformations and modulating its subcellular localization.

Phosphorylation

PTEN is subjected to phosphorylation, mainly on serine/threonine residues located in the C-terminus (Thr366, Ser370, Ser380, Thr382, Thr383 and Ser385) (Odriozola et

al. 2007). Casein kinase 2 (CK2) phosphorylates PTEN sequentially on Ser-385, Ser-380, Thr-383, Thr-382, and Ser-370, and reduces phosphatase activity and proteolysis by 70% (Torres and Pulido 2001; Cordier et al. 2012; Fragoso and Barata 2015) (Figure). Despite T cell acute lymphoblastic leukemia (T-ALL) cells displaying normal levels of wild type *PTEN* mRNA and exhibiting PTEN overexpression, hyperphosphorylation of PTEN on the phosphorylation sites in its C-terminus by CK2, results in decreased PTEN lipid phosphatase activity and hyperactivation of the PI3K/Akt pathway (Silva et al 2008). Incubation of T-ALL cell lines with the selective CK2 inhibitor CX-4945 reverses Akt activation and triggers apoptosis (Buontempo et al. 2014). Interestingly, CK2 is also overexpressed in CRC and colonic cell lines treated with CK2 inhibitor display decreased proliferation and invasiveness (Zou et al. 2011).

It has been proposed that phosphorylation of the C-terminal Ser380, Thr382, Thr383, Ser385 cluster induces a "closed" less active cytoplasmic form that has decreased plasma membrane targeting and increased conformational compaction (Vazquez et al. 2000; Vazquez 2001; Das et al. 2003; Bolduc et al. 2013; see Figure). Intramolecular interaction of the phosphorylated C-terminal tail with basic residues within the N-terminal PIP2-binding motif, the catalytic and C2 domains maintains PTEN in its "closed" form (Rahdar et al. 2009). Mutation of the C-terminal residues disrupts the intramolecular interaction promoting an "open" form of PTEN with increased plasma membrane association to control PIP3 levels (Rahdar et al. 2009; Lima-fernandes et al. 2014). The "open" PTEN conformation also favours PTEN translocation to the nucleus (Nguyen et al. 2015) where it functions in DNA repair and genome stability independently of its lipid phosphatase activity (see below, PTEN ubiquitination). PTEN is also inhibited by the GSK-3β (phosphorylation of Ser362 and 366) and the MASTs (Microtubules associated Kinase 205, MAST3, phosphorylation of C-terminal tail) Ser/Thr kinases (Al-Khouri et al. 2005; Cordier et al. 2012; Fragoso and Barata 2015; Valiente et al. 2005). In contrast, phosphorylation of Ser-229/Thr-223 and Thr-319/Thr-321 amino acid residues by ROCK (RhoA-associated kinase) in the PTEN C2 domain enhances PTEN phosphatase activity (Li et al. 2005; Lima-Fernandes et al. 2011). Activation of ATM serine/threonine kinase (ataxia telangiectasia mutated) by DNA damage induces PTEN phosphorylation at Ser 113 leading to PTEN nuclear translocation and induction of autophagy (Chen et al. 2015). The interaction of glioma tumour suppressor candidate region 2 gene product, GLTSCR2/ 'protein interacting with carboxyl terminus 1' (PICT-1) with PTEN favors phosphorylation of Ser-380 (Okahara et al. 2004).

PTEN is also a substrate for tyrosine kinases. Src phosphorylates PTEN at Tyr-240 and Tyr-315 leading to a decrease in phosphatase activity and stability of the tumour suppressor (Lu et al. 2003). Phosphorylation of tyrosine 336 by the tyrosine kinases Rak and FAK results in inhibition of PTEN polyubiquitination by NEDD4-1 and degradation by the proteasome (Yim et al. 2009; Tzenaki et al. 2015).

The polo-like kinase 1 (PLK1) is a regulator of many cell cycle-related events, including mitotic entry and the G2/M checkpoint, coordination of the centrosome and cell cycle, regulation of spindle assembly and chromosome segregation. PLK1 phosphorylates PTEN *in vitro* on Ser-380, Thr-382, and Thr-383, but not Ser-385. *In vivo*, only the Ser-380 amino-acid residue is significantly phosphorylated and this is associated with PTEN accumulation on chromatin (Choi et al. 2014). PTEN and PLK1 can reciprocally regulate each other. PTEN inhibits PLK1 by inducing its dephosphorylation, or by promoting the association of the E3 ligase APC/C with its

activator CDH1, which induces the degradation of mitotic cyclins (Cyclins A and B), as well as mitotic kinases including PLK1 (Song et al. 2011; Zhang et al. 2016).
So far, few studies have reported the mechanisms related to PTEN dephosphorylation. The N-myc downstream-regulated gene 2 (NDRG2) is a molecular partner of PTEN that recruits protein phosphatase 2A (PP2A) resulting in dephosphorylation of PTEN at the Ser380, Thr382 and Thr383 (Nakahata 2013). Interestingly, NDRG2 is frequently down-regulated in CRC. The Tyrosine phosphatase SHP-1 dephosphorylates PTEN in Src transfected cells and restores PTEN stability (Lu et al. 2003). Some orally bioavailable small molecule activators of PP2A (SMAPs) efficiently inhibited the growth of KRAS-mutant lung cancers in mouse xenografts and transgenic models (Sangodkar et al. 2018).

Oxidation

PTEN is subjected to reversible inactivation by reactive oxygen species (ROS) produced by the membrane associated Duox1/2, NAPDH oxidase (Noxs) and mitochondrial oxidative stress. Hydrogen peroxide (H_2O_2) inactivates PTEN by promoting oxidation of the critical Cys124 residue in the catalytic domain of PTEN and forming an intramolecular disulfide bond with Cys71 (Lee et al. 2002; Leslie et al. 2003). This inhibition is reversed by thioredoxin (Figure). This regulation process might occur under physiological conditions. Accordingly, it has been proposed that cell stimulation by EGF triggers PI3Kinase activation that induces NOXs activation. The resulting ROS inactivate PTEN leading to further accumulation of PIP3 to complete a positive feedback loop (Kwon et al. 2004). Binding of thioredoxin-1 to PTEN Cys212 of the C2 domain of PTEN inhibits PTEN membrane translocation and activation (Meuillet et al. 2004).
Hypoxia, a hallmark of tumours, promotes transcriptional inhibition of AIF (tumour apoptosis-inducing factor) through HIF-1 (hypoxia induced factor-1), resulting in oxidative inactivation of PTEN and epithelial–mesenchymal transition of colorectal cancer (Xiong et al. 2016).
Oxidation of PTEN-binding partners can also affect PTEN activity. For example, the oncogene DJ-1 binds to PTEN and reduces its catalytic activity. Oxidation of DJ-1 increases its affinity for PTEN, resulting in more profound decreases in PTEN activity (Kim et al. 2009*)*. ROS might also affect PTEN indirectly via pro-inflammatory redox-sensitive pathways, such as NF-κB.
Scavengers of ROS, such as sodium pyruvate, which reacts with H_2O_2 to yield sodium acetate, carbon dioxide and water and anti-inflammatory agents therefore constitute approaches to restore PTEN activity.

S-nitrosylation

Ischemia, superoxide anion, hydrogen peroxide and nitric oxide (NO) can trigger S-nitrosylation of protein cysteine residues. It was reported that low NO concentrations lead to S-nitrosylation of Cys-83 leading to PTEN inactivation (Numajiri et al. 2011)
The NO scavenger c-PTIO efficiently prevents PTEN S-nitrosylation.

Acetylation

The Histone Acetylase (PCAF)/ lysine acetyltraansferase 2B (KAT2B) has been reported to promote PTEN acetylation on Lys125 and Lys128 in response to growth factor stimulation (Okumura et al., 2006). As these residues are within the catalytic pocket, acetylation negatively regulates its enzymatic activity. PTEN is also acetylated on Lys402, which is located within the C-terminal PDZ-domain-binding

motif of PTEN, by CREB-binding protein (CREBBP) favouring PTEN interaction with proteins with PDZ domains (Ikenoue et al. 2008). CREBBP and the sirtuin SIRT1 have been identified as the main PTEN acetyltransferase and deacetylase, respectively. Interestingly, PCAF forms a complex with CREBBP.
It has also been recently demonstrated that non-selective Histone Deacetylase (HDAC) or HDAC6-specific inhibitors switch PTEN into an open conformation and induce its membrane translocation through acetylation at Lys163, resulting in the inhibition of cell proliferation, migration and invasion, as well as xenograft tumour growth in athymic mice (Meng et al. 2016). Such inhibitors may be clinically relevant to treat tumours with wild-type PTEN.

Mono/ polyubiquitinylation proteasome
PTEN is regulated by ligation of the protein modifiers ubiquitin (76 amino acids) on the Lys amino-acid residues 13 and 289. NEDD4 was identified as an E3 ligase that ubiquitylates PTEN (Wang et al. 2007). Other E3 ligases have also been reported to target PTEN, including X-linked inhibitor of apoptosis protein (XIAP) and WWP2. Polyubiquitination of PTEN leads to its degradation by the proteasome complex, whereas monoubiquitylation is essential for PTEN nuclear import (Wang et al. 2007, Trotman et al. 2007 (Figure). Although NEDD4 proved to be overexpressed in colorectal cancer (Kim et al. 2008), its effect on the growth and morphology of human colonic cell lines seems to be independent of PTEN (Eide et al. 2013).
The monoubiquitylation of PTEN and its nuclear compartmentalization, is reversed by the deubiquitylase USP7 (Song et al. 2008). Nuclear exclusion of PTEN has been associated with cancer progression. Some inhibitors of USP7 are under development in several bio-pharmaceutical companies (Zhou et al. 2018)

Sumoylation
PTEN can be modified by the small ubiquitin-like modifier (SUMO) on Lys254 and Lys266 in the C2 domain. SUMOylation, principally at Lys266, in the CBR3 loop, which plays a major role in PTEN membrane association, was shown to promote binding to the plasma membrane via electrostatic interactions (Huang et al. 2012). This leads to decreased PI3K/AKT signalling, suppression of anchorage-independent cell growth and tumour growth *in vivo*. Subsequently it was shown that SUMOylation of Lys254 controls PTEN nuclear localization (Figure). Following cell exposure to either γ-irradiation or DNA-damaging chemotherapeutic agents, SUMO conjugated PTEN was excluded from the nucleus in an ATM protein kinase manner. Cells lacking nuclear PTEN were hypersensitive to DNA damage.

Several other studies have shown that there may be competition between SUMOylation and ubiquitination. Gonzalez-Santamaria et al. (2012), showed that Lys289 can also be SUMOylated. As Lys289 is also a major site for PTEN monoubiquitination, which drives nuclear import, competition for modification on this site would be predicted to affect nucleocytoplasmic partitioning. In another study, PTEN SUMOylation was shown to be enhanced by the SUMO E3 ligase PIASxα, resulting in reduced PTEN polyubiquitination and increased stability, culminating in negative regulation of the PI3K/AKT pathway, cell proliferation inhibition and tumour suppression (Wang et al. 2014).

Ribosylation

PTEN can also be ribosylated by tankyrases (TNKS1 and TNKS2) on Glu40/Glu150 in the phosphatase domain and Asp326 in the C2 domain. This promotes the recognition of PTEN by an E3 ubiquitin ligase, RNF146, leading to subsequent PTEN ubiquitination and degradation. Knockdown of TNKS1/2 in colorectal cancer cell lines resulted in the inhibition of tumour growth in PTEN-expressing cells but not in PTEN-depleted cells. This indicates that targeting TNKS in tumour cells may only be effective in wild-type PTEN contexts. Interestingly, expression of tankyrases was found to be negatively correlated with PTEN levels in human colon carcinomas. Combined, all these findings support the rationale to explore the development of tankyrase inhibitors as potential anti-cancer agents.

Other postranslational modifications of PTEN

PTEN is also subject to S-sulfydration on both Cys71 and Cys124, which has been proposed to prevent the S-nitrosylation associated with inhibition of PTEN catalytic activity. PTEN can also be methylated on Lys313 by the oncogenic protein methyltransferase SET and MYND domain containing 2 (SMYD2), which has been proposed to result in negative regulation of PTEN activity and increased PI3K/AKT signalling (Nakakido et al. 2015).

2.5 Protein-Protein Interactions

PTEN interacts with many effector systems through its different domains (lipid binding, catalytic, C2 domain and the PDZ binding motif in the C-terminus) which are crucial for its localization and for organization in a variety of submembranous complexes associated with cell signal mediators, including ion channels, transmembrane receptors and regulatory enzymes (Harris and Lim 2001; Kotelevets et al. 2005, Chastre et al. 2009, Lima-Fernandes et al. 2011).

The cellular activity of PTEN is thus commonly modulated via inclusion in multiprotein signalosomes (Figure).

Modulating protein–protein interactions involved in disease pathways is an attractive strategy for developing drugs, but remains a challenge to achieve. One approach is to target certain domains within proteins that mediate these interactions (Berg 2003; Arkin et al. 2004). One example of such a domain is the PDZ domain (Dev et al. 2004). Proteins with PDZ domains usually encompass a series of such domains alone or combined with other protein-protein interaction domains, and act as scaffolding molecules allowing the organization of effector proteins as signalosomes and their targeting to selective cellular subdomains.

A series of proteins with PDZ domains interact with the C-terminus of PTEN, These include MAGI-1/2/3, NHERF, MAST3, hDLG1. We demonstrated that PTEN was recruited to E-cadherin junctional complexes through the interaction with the 2nd PDZ domain of MAGI-1, whereas the C-terminus of β-catenin interacts with PDZ5. The colocalization of PTEN and PI3K and their antagonistic activities on PIP3 levels allows the subtle regulation of junctional complex activities (Kotelevets et al. 2001; 2005; Chastre et al. 2009). Subsequently, we identified by yeast two-hybrid analysis human DLG, a protein with multiple PDZ domains, as a binding partner for the PTEN PDZ-BD and demonstrated Dlg1-PTEN interaction in colonic HT-29 epithelial cells (Kotelevets, unpublished data).

Recently, Zaric *et al* identified MAGI-1 as a celecoxib-induced inhibitor of Wnt/β-catenin signalling with tumour- and metastasis-suppressive activity in colon cancer cells. They reported that this Cox-2 inhibitor upregulated MAGI-1 in human colonic

cell lines, and that MAGI-1 overexpression attenuated primary tumour growth and spontaneous lung metastasis in an orthotopic model of colorectal cancer (Zaric et al. 2012). One interesting point that was not addressed in their study concerns the role of PTEN in this process. Interestingly, another study reported that celecoxib promoted the membrane translocation of PTEN and the inactivation of Akt. (Zhang and Gan 2017). Taken together, these data suggest that inhibition of Cox-2 leads to increased expression of MAGI-1 and the subsequent targeting of PTEN to the plasma membrane.

The widespread occurrence of PDZ domains as organizers of signalling pathways makes them an important subject for biological studies. Changes in the expression of several PDZ domain-containing proteins have been associated with cancers (Nagayama et al. 2004; Park et al. 2006*).* The therapeutic usefulness of inhibiting PDZ-based protein-protein interactions has been clearly demonstrated by using peptide and nonpeptide small molecules (Aarts et al. 2002; LeBlanc et al. 2010*).* Because PDZ domains have well-defined binding sites, they are promising targets for drug discovery. However, there is still much to learn about the function of these domains before drugs targeting PDZ interactions can become a reality. The first cell-permeable inhibitor of a PDZ interaction was reported in a study that described how the interaction between the PDZ domain of MAGI and the PDZ motif of PTEN was irreversibly blocked by a low-molecular-mass compound. The interaction between MAGI and PTEN is thought to regulate the activity of the kinase Akt/PKB. Compound treatment of HCT116 cells expressing endogenous PTEN, MAGI and Akt/PKB showed enhanced AKT activity (Fujii et al. 2003*)*. By creating analogue libraries, the structure of the compound was suggested to be a useful starting point for finding class- and domain-selective inhibitors. Further chemical optimization could render the compound useful as a tool for exploring the effects and side effects of inhibiting PDZ interactions *in vivo* (Fujii et al.2006*).*

The multifunctional scaffolding proteins β-arrestins (β-arrs) control distinct functional outputs of PTEN to regulate cell proliferation, migration and multicellular assembly. β-arr binding to PTEN increases its lipid phosphatase activity and inhibits cell proliferation. However, during cell migration of glioma cells, β-arr binds the C2 domain of PTEN to inhibit its lipid phosphatase-independent anti-migratory function (Lima-Fernandes et al. 2011). β-arr1 also binds the C2 domain of PTEN as part of a membrane-associated regulatory complex incorporating the Cdc42 GTPase-activating protein ARHGAP21 and Cdc42 (Figure). This complex controls Cdc42-dependent mitotic spindle formation and lumen formation in 3D cultures of colorectal cancer cells. Disruption of the complex provokes mitotic spindle misorientation and abnormal multilumen formation that are evocative of colorectal cancer (Javadi et al. 2017).

PTEN interacts *via* its phosphatase domain with homodimers of the p85α regulatory subunit of the PI3K (PIK3R1). Importantly, this interaction positively regulates the lipid phosphatase activity of PTEN and impairs PTEN degradation by competing with the E3 ligase WWP2 (Rabinovsky et al. 2009; Chagpar et al. 2010; Cheung et al. 2015). Thus, PIK3CA overexpression or PIK3R1 mutations could lead to PI3K pathway hyperactivation by decreasing PTEN expression and activity.

Many disparate proteins interact with PTEN and negatively regulate its tumour suppressing activity by a wide variety of mechanisms. These proteins include DJ-1, α-mannosidase 2C1 (Man2C1), shank-interacting protein–like 1 (SIPL1), and PI(3,4,5)P3-dependent RAC exchange factor2a (PREX2a) (He et al. 2011; He et al. 2010; Fine et al. 2009**)**. Man2C1, PREX2a and SIPL1 bind directly to PTEN and inhibit its lipid phosphatase activity**.**
Furthermore, paxillin, an important adaptor protein of focal adhesions, was identified as an interaction partner of PTEN (Herlevsen et al. 2007). A recent study showed that PTEN downregulates paxillin expression in human colon cancer tissues via the PI3K/AKT/NF-κB pathway and that paxillin expression contributes to colon tumourigenesis (Zhang et al. 2015).

Greater understanding of the pathophysiological relevance *in vitro* and *in vivo* will be critical in strategies for developing drugs toward modulating protein-protein interactions.

2.6 Controlling PTEN conformation and subcellular localization

In addition to the bioactive small molecules targeting positive or negative PTEN regulators mentioned above, the development of alternative strategies to control PTEN conformation and subcellular localization might constitute powerful approaches to restore or enhance PTEN tumour suppressor activity. As a proof of concept, Nguyen et al screened a library of randomly mutated human PTEN and identified mutations that increase its recruitment to the plasma membrane. This enhanced PTEN (ePTEN) exhibited an eightfold increase in ability to suppress PIP3 signalling (Nguyen et al. 2014). These findings open up interesting new perspectives on pharmacological strategies that could therefore be harnessed to achieve enhanced forms of PTEN using small molecule conformational activators/stabilisers. In relation to this, an intramolecular bioluminescence resonance energy transfer (BRET)-based biosensor of PTEN with PTEN sandwiched between the energy donor Renilla luciferase (Rluc) and the energy acceptor yellow fluorescent protein (YFP) was recently described that can report signal-dependent conformational changes of PTEN in live cells (Lima-Fernandes et al. 2014; Misticone et al. 2016). The PTEN biosensor could therefore potentially be used as conformational readout in high-throughput screens to identify small molecules that enhance or restore PTEN function.
Another interesting point concerns the balance in the subcellular localisation of PTEN at the plasma membrane, in the cytosol, mitochondria, endoplasmic reticulum and nucleus. Some strategies succeeded in targeting PTEN to the plasma membrane (Meng et al. 2016; Zhang and Gan 2017) to exert tumour suppressor activity. Whether the nuclear pool of PTEN is affected remains an interesting question. Enhancing PTEN targeting to the endoplasmic reticulum may promote Ca2+ release and sensitivity to apoptosis. As stated above promoting PTEN nuclear exclusion should sensitize cancer cells to genotoxic agents. Based on the observation that cancer cells are more prone to export nuclear PTEN, further studies are required to delineate the benefit to induce pharmacological nuclear exclusion of PTEN and the impact on neighbouring non-transformed cells.
Another level of complexity resides in the heterogeneous PTEN distribution at the plasma membrane and its contribution as a member of molecular signalling complexes. During chemotaxis, PTEN and PI3K exhibit a reciprocal pattern of localization, PI3K being located at the leading edge and PTEN at the rear (Li et al.

2005). PTEN is also recruited to E-cadherin junctional domains and likewise PTEN is also recruited to the plasma membrane with β-arr2 following GPCR stimulation. Complementary approaches, such as the development of permeant bi-functional nanobodies might allow to target PTEN in specific subdomains.

3. Toward targeted therapies

Experimental models of carcinogenesis using transgenic mice reveal that PTEN inactivation cooperates with the main genetic alterations identified in human CRC, including KRAS activation, and APC and TGFBR2 inactivation, to promote cancer progression (Davies et al. 2014; Shao et al. 2007; Marsh et al. 2008; Yu et al 2013). Restoring PTEN expression/activity should therefore benefit all patients with colorectal cancer, regardless of the subtype. Nevertheless, particular attention should be devoted in the case of activation of downstream effectors controlled by PTEN, such as Akt1 mutation (Carpten et al. 2007).

It should be underlined that as for other targeted therapies, the strategy proposed here will require the identification of patients who are most likely to respond to the treatment and to define the appropriate and personalized approach to restore PTEN activity. Due to the higher rate of PTEN mutations in the subgroup of patients with CRC high microsatellite instability (15% of CRC), the MSI-h status of the tumour will direct to PTEN sequencing. Typing of CRC for MSI and analysis of gene mutations, e.g. *KRAS* are performed routinely in clinical practice. In the case of PTEN deletion or mutation, (since genome editing is far away from being used in the clinic) an alternative approach would be to take advantage of PTEN deficiency-related defects in homologous recombination. This defect sensitizes tumour cells to inhibitors of polyadenosine diphosphate ribose polymerase (PARP), involved in the repair of DNA double-strand breaks (Dillon and Miller 2014). Five clinical trials are evaluating the efficiency of PARP inhibitors in connection with PTEN status (NCT02286687, NCT02401347, NCT03207347, NCT03016338, NCT02576444)

In as far as PTEN is wild-type, immunohistological analysis of PTEN accumulation, subcellular localisation, and activation of downstream PI3K targets (Akt, S6k) could be monitored to provide information on the level of dysregulation (transcriptional, post-transcriptional, post-translational).

Ex vivo testing of organotypic CRC slices cultured on porous membrane supports would permit to simultanenously screen a series of selected compounds, based on the level of PTEN dysregulation identified by immunochemistry and to assess the restoration of the activity of the tumour suppressor. A series of permeant fluorescent labeled probes are now available to monitor *in situ* tissue response to treatment : live or dead cells, enzyme activities (*e.g.* caspases). Proof of concept to test individual tumour responses to anti-cancer drugs was recently provided using a 96-well plate-based microfluidic device that allows to expose organotypic slices to multiple compounds either simultaneously or sequentially (Chang et al. 2014).

It is also conceivable to optimize the identification of PTEN defects in these organotypic slices using fluorescently-labelled permeant nanobodies targeting selective PTEN epitopes and/or downstream effector systems FRET could then be used as readout to report changes in PTEN conformation or subcellular localisation, or upon molecular assembly of signalosomes, *e.g.* TORC1 complex.

4. Conclusions and prospects

This review illustrates the diversity and complexity of the mechanisms that can downregulate PTEN function during carcinogenesis. Restoring/enhancing PTEN activity in colonic cancer cells may represent a promising therapeutic approach, since it would be predicted to directly impact cell growth, trigger apoptosis, but also increase tumour cell sensitivity to therapeutic agents. This is a critical issue, since anti-cancer treatments have dose-limiting toxicities.
Further studies are required to elucidate the cross-talk between PTEN and other (anti/)oncogene pathways during carcinogenesis, and their significance in terms of resistance to chemotherapies. Nevertheless, knowledge gleaned in how PTEN signalling is regulated will provide the basis to explore the potential of a personalized approach to restore/enhance PTEN activity in cancer.

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Legend for Figure

Schematic overview of PTEN structure, biological functions and regulation by epigenetic, transcriptional, post-transcriptional and post-translational mechanisms
Upper Panel : Structure of canonical PTEN and post-translational modifications

Lower Panel : Effector systems controlling PTEN accumulation, activity and subcellular localisation. For details see the text.