Chapter 4

PTEN – A MOLECULE THAT CANCERS ABUSE TO OVERCOME THEIR ACLILLES HEELS

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ABSTRACT

Oncogenic mutations drive some types of cancers. An example is the epidermal growth factor receptor (EGFR) gene mutation in lung cancer. EGFR-mutated lung cancers are highly dependent upon an aberrantly activated EGFR signaling pathway; therefore, they often respond dramatically to treatment with EGFR tyrosine kinase inhibitors (TKIs). However, approximately 10% of EGFR-mutated lung cancers show inherent resistance (de novo resistance) to EGFR-TKIs. Additionally, most patients who initially respond to EGFR-TKIs eventually develop acquired resistance. To overcome inherent or acquired resistance to EGFR-TKIs, researchers have identified several molecules involved in these resistances. Because down-regulation of the PI3K-AKT pathway is required for TKI-induced apoptosis in EGFR-mutated lung cancers, some researchers include PTEN as a candidate molecule that affects both inherent and acquired resistance to EGFR-TKIs. An example of in vitro inherent resistance is seen in the H1650 lung cancer cell line, which harbors an EGFR mutation and homozygous deletion of PTEN. PTEN reconstitution by stable retroviral expression increased susceptibility to TKI-induced apoptosis in this cell line. In clinical samples, 1 out of 24 EGFR-mutated lung cancers also harbored a homozygous PTEN deletion. However, PTEN expression is reportedly regulated by several mechanisms, including genetic aberrations, transcriptional silencing and protein instability. In patients treated with EGFR-TKIs, favorable survival

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was seen in patients with high PTEN expression. Many researchers established in vitro acquired resistance models to EGFR-TKIs from sensitive cells using chronic exposure to the drug. Several independent groups have obtained acquired resistance models with PTEN down-regulation due to diverse mechanisms of PTEN inactivation. In clinical samples, loss of PTEN protein expression was also observed in tumors sampled after EGFR-TKI treatment failure. In addition to EGFR-mutated lung cancers, PTEN inactivation has been reported as a resistance mechanism to molecular targeted therapy against oncogenic drivers in several cancers; e.g., breast cancers with HER2 overexpression, melanoma with BRAF mutation, gastrointestinal stromal tumor with c-KIT mutation, and leukemia with fusion genes. PTEN inactivation has been garnering attention as a cause of inherent or acquired resistance to molecular target therapy.

**Keywords:** Inherent resistance, acquired resistance, molecular target therapy, oncogenic drivers, lung cancer

**INTRODUCTION**

Recent advances in technologies for molecular analyses have accelerated identification of somatic genetic aberrations in several types of cancers. Although these efforts have shown cancer cells to harbor numerous genetic aberrations [1-3], researchers have found that some types of cancers depend their proliferation and survival on a single mutated proto-oncogene [4]. Therefore, these mutated proto-oncogenes (oncogenic drivers) are, so to speak, the Achilles’ heels of these cancers, and are potential molecular targets for their treatment.

A success story in this field is epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI) treatment for lung cancers with EGFR-activating mutations. Lung cancers with EGFR mutation have been shown to respond dramatically to orally available EGFR-TKIs, whereas those without EGFR mutation do not [5, 6]. However, approximately 10 % of lung cancers with EGFR mutations show inherent resistance (de novo resistance) to EGFR-TKIs [7-9]. In addition, almost all lung cancers with EGFR mutations become refractory to EGFR-TKIs within a few years, despite initial dramatic responses (acquired resistance) [10].

In this chapter, we firstly describe lung cancers with EGFR mutation, EGFR-TKI treatment for EGFR-mutated lung cancers, and resistance to EGFR-TKIs, briefly. Next, we summarize recent reports regarding the role of PTEN in inherent or acquired resistance to EGFR-TKIs in lung cancers with EGFR mutation. We also discuss the role of PTEN inactivation in inherent or acquired resistance mechanisms to target therapy against oncogenic drivers in cancers originating from other organs.

**LUNG CANCERS WITH EGFR MUTATION AND TREATMENT EFFECTS OF EGFR-TKIS**

Lung cancer is one of the most commonly diagnosed cancers worldwide (1.61 million cases in 2008) and the leading cause of cancer-related mortality worldwide (1.38 million deaths in 2008) [11]. Of the several lung cancer histologies, adenocarcinoma is the most common in many countries. Lung cancer with EGFR mutation is one of the major
molecularly defined subtypes, especially in lung adenocarcinomas, which account for about 40% of non-small cell lung cancers in East-Asians and 10% in Caucasians [5].

EGFR is one of four members of the human EGF receptor (HER) family of receptor tyrosine kinases. Activated EGFR leads to a downstream signaling network, including the MAPK and PI3K/AKT pathways, that regulate fundamental processes of cell proliferation, apoptosis suppression, angiogenesis, invasion, and metastasis (Figure 1A) [12]. In lung cancer, somatic activating EGFR mutations occur within the intracellular tyrosine kinase domain (mutations are frequently identified in exons 18–21), and mutant EGFR becomes constitutively activated without ligand binding. As lung cancers with EGFR mutations depend on signaling from these mutated EGFR for proliferation and survival, mutated EGFR is the potential Achilles’ heel for these cancers. Lung cancer cell lines with EGFR mutations are highly sensitive to siRNA-mediated EGFR knockdown or exposure to EGFR-TKIs (Figure 1B) [13-16], and lung cancer patients with EGFR mutations respond very well to orally available EGFR-TKIs, gefitinib, erlotinib, and afatinib [7-9, 17, 18].

Figure 1. Schema of PTEN inactivation as a resistance mechanism to EGFR-TKI in lung cancer cells with EGFR mutation. (a) In lung cancer cells with EGFR mutation, downstream signaling of aberrantly activated EGFR, including the PI3K–AKT pathway, is constitutively activated. PTEN both negatively regulates the PI3K–AKT pathway, and mediates degradation of activated EGFR. (b) Upon treatment with EGFR-TKI, lung cancer cells with EGFR mutation lapse into apoptosis. (c) However in lung cancer cells with concurrent EGFR mutation and PTEN inactivation, cancer cells can survive due to sufficient PI3K accumulation and AKT activation through other growth factor receptors other than inhibited EGFR. In addition, it is also suggested that PTEN inactivation raises EGFR activity by impairing EGFR degradation.
However, some lung cancers with EGFR mutations show inherent resistance to EGFR-TKIs, and almost all lung cancers with EGFR mutations that initially respond to EGFR-TKIs acquire resistance within a few years [10, 19]. Secondary mutation of EGFR that occurs in its gatekeeper position (T790M mutation) is the most common mechanism of acquired resistance [20] but is a rare event in inherent resistance [21]. Mechanisms affecting molecules other than EGFR have also been reported to mediate inherent and acquired resistance; e.g. gene amplification of MET proto-oncogene, high-level expression of hepatocyte growth factor (HGF), gene amplification of CRKL adaptor protein, NFκB activation, and gene amplification of ERBB2, in addition to PTEN inactivation that is described circumstantially in this chapter [10, 22].

**PTEN ABERRATIONS IN LUNG CANCERS**

The PI3K-AKT anti-apoptotic and proliferation pathway is downstream of EGFR; the PTEN tumor suppressor gene negatively regulates this pathway [23-26], without a redundancy of this gene. Inactivation of PTEN reportedly occurs through mutations, deletions, transcriptional silencing, or protein instability in a wide spectrum of human cancers [27]. In lung cancers, especially for lung adenocarcinomas that often harbor EGFR mutation, mutation of the PTEN gene or PTEN gene copy deletion is rare [28-31]. However, loss of PTEN protein expression (as analyzed by immunohistochemistry) is reported to occur in 24–68% of cases [31]. Possible reasons for these counterintuitive results are the heterogeneity of lung adenocarcinomas, and differences in antibodies, staining methods, and cut-off values [32]. Most of these studies did not distinguish lung cancers with EGFR mutation from other molecular subtypes of lung cancers, but Yanagawa, and colleagues reported that 27% of lung cancers with EGFR mutations were PTEN–, while 44% of lung cancers without EGFR mutation were PTEN– [31], suggesting relatively lower rate of PTEN inactivation in lung cancers with EGFR mutation.

In several cancer types, including lung cancer, loss of PTEN protein reportedly predicted poor prognosis [33-40], or poorer response to chemotherapeutic drugs [41-47].

**PTEN’S ROLE IN INHERENT RESISTANCE TO EGFR-TKIS IN LUNG CANCERS WITH EGFR MUTATIONS**

Less than 10% of lung cancers with EGFR mutations are inherently resistant to EGFR-TKIs; e.g., disease control rate of gefitinib or erlotinib in a phase III study of first-line setting was reported to be 93 ~ 97 % [7-9]. Down-regulation of the PI3K-AKT pathway is required for EGFR-TKI-induced apoptosis in lung cancers with EGFR mutations, [48] and inactivation of PTEN represents a common cause of PI3K pathway activation in human cancers [49]. Researchers thus include PTEN in analyses for inherent and acquired resistance mechanisms to EGFR-TKIs.

The H1650 lung cancer cell line carries EGFR-TKI inherent resistance by PTEN homozygous deletion (Table 1) [50].
Table 1. Roles of PTEN inactivation in resistance mechanism to molecular target therapy (in vitro models)

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Cetuximab; a recombinant anti-EGFR human/mouse chimeric monoclonal antibody.
Gefitinib and Erlotinib; reversible EGFR-TKIs.
CL-387,785; an irreversible EGFR-TKI.
Sunitinib; a multitarget TKI with sensitivity for c-KIT, PDGFR, VEGFR.
Imatinib; a multitarget TKI with sensitivity for BCR-ABL, c-KIT, and PDGFR.
EGR1; early growth response 1 (a transcription factor which regulates PTEN expression).

Although the H1650 cell line harbors EGFR exon 19 deletion mutation (del E746–A750), this cell line is resistant to erlotinib; with a half-maximal inhibitory concentration (IC_{50}) value of more than 2 μM, contrasting with HCC827 cells or PC9 cells which harbor the same EGFR deletion mutation and have IC_{50} values of less than 0.05 μM [50, 51]. Wild-type PTEN reconstitution in H1650 cells reportedly increases susceptibility to erlotinib-induced apoptosis; treating H1650 cells with a combination of erlotinib and an AKT inhibitor led to reduced viability compared with cells treated with erlotinib alone. Silencing of PTEN expression in PC9 cells also led to a significantly decreased fraction of apoptotic cells when
treated with erlotinib. These results suggest that the PTEN homozygous deletion confers inherent resistance to EGFR-TKIs in EGFR-mutated lung cancers, although PTEN homozygous deletion is reportedly uncommon, as 1-in-24 [50] or 1-in-17 [31] patients whose lung cancers have EGFR mutations. The PC14 lung cancer cell line with the same EGFR exon-19 deletion mutation [52] is another model of inherent EGFR-TKI resistance with loss of PTEN expression (Table 1) [53, 54]. However, the mechanism of PTEN inactivation in PC14 cells was not homozygous deletion but hypermethylation in the PTEN promoter region. Clinical implications of PTEN inactivation through hypermethylation in lung cancer is unclear, as hypermethylation frequency of PTEN promoter region reportedly varies (0–35%) [26, 55–58]. Among EGFR-TKI-treated patients whose lung cancers had EGFR mutations, loss of PTEN protein expression correlated significantly with worse overall survival [59].

ACQUIRED PTEN INACTIVATION MAY CAUSE RESISTANCE TO EGFR-TKIS IN LUNG CANCER WITH EGFR MUTATION

An in vitro model suggests that lung cancers lose PTEN expression during their progression. PC9/f9 cells and PC9/f14 cells are highly metastatic sub-lines established from the PC9 lung cancer cells described above [60], and are reported to lose PTEN expression due to histone deacetylation [53], and to show inherent resistance to an EGFR-TKI, gefitinib (Table 1) [54]. A histone deacetyltransferase (HDAC) inhibitor restored PTEN expression in PC9/f9 cells and PC9/f14 cells; in addition, combined treatment with gefitinib and the HDAC inhibitor induced significant growth inhibition in these cells [53]. Chin and colleagues suggested that treatment with cisplatin, a representative agent of cytotoxic chemotherapy for lung cancer, conferred erlotinib insensitivity through loss of PTEN expression [52]. They chronically exposed PC9 cells to cisplatin for 3 months to obtain cisplatin-resistant PC9 cells. In the analyses of cisplatin resistant PC9 cells, the authors identified that the resistant cells showed cross resistance to erlotinib, and that the resistant cells lost PTEN expression (Table 1). However, Rho and colleagues observed quite different results in this setting. They established cisplatin-resistant cells from lung cancer cell lines with EGFR mutations (PC9 and HCC827 cells), and found that the IC₅₀ value and apoptotic fractions after exposure to EGFR-TKIs were almost the same between the parent cells and resistant cells, although baseline PTEN expression was reduced in the resistant cells [61]. Furthermore, overall survival of patients whose lung cancers had EGFR mutations in phase III trials that compared EGFR-TKIs and platinum doublet chemotherapy as first-line treatments were almost the same (most patients in the platinum doublet arm were received EGFR-TKI in second-line treatment or later) [7, 62]. Therefore, it is unclear whether EGFR-TKI is the optimal and exclusive first-line treatment for patients whose lung cancers have EGFR mutations.

MOLECULAR MECHANISMS OF RESISTANCE BY PTEN INACTIVATION IN LUNG CANCER WITH EGFR MUTATION

How does PTEN modify drug resistance in lung cancers with EGFR mutation? PTEN lipid phosphatase activity would be essential in this point, because reintroduction of wild-type
PTEN, but not G129E mutant PTEN (which lacks lipid phosphatase activity), restored sensitivity to EGFR-TKI in A431 PTEN-deficient cell line model using PTEN siRNA [63]. As PTEN negatively regulates the PI3K-AKT pathway, PTEN inactivation has been thought to allow sufficient phosphatidylinositol 3,4,5-triphosphate accumulation and AKT activation through growth factor receptors other than inhibited EGFR (Figure 1C). Consistent with this, sustained phosphorylation of AKT was observed in PTEN-deficient EGFR mutated lung cancer cells treated with EGFR-TKIs [50, 51, 64], and acquired resistance by PTEN inactivation can be overcome by co-treatment with an AKT inhibitor [64].

In addition to these effects by PTEN inactivation, Vivanco and colleagues identified a different molecular mechanism that confers resistance to EGFR-TKIs by PTEN inactivation [63]. They found increased EGFR activity in PTEN-knockdown cells compared to parent cells, and that PTEN promotes ubiquitylation and degradation of activated EGFR. Therefore, they suggested that PTEN inactivation increases EGFR activity by impairing degradation, and causes resistance to EGFR-TKIs (Figure 1C); this agrees with an observation that more complete EGFR kinase inhibition overcame PTEN-associated resistance to EGFR-TKIs [63].

Other molecular mechanisms of resistance by PTEN inactivation, reduction of direct SRC dephosphorylation and suppressed BIM expression, have also been reported in other cancer types, and are summarized below in the paragraph of “PTEN’s role in resistance mechanisms to target therapy in cancer types other than lung cancers with EGFR mutation.”

**PTEN’s Role in Acquired Resistance to EGFR-TKIs in Lung Cancers with EGFR Mutation**

To analyze molecular mechanisms underlying acquired resistance to EGFR-TKIs, many researchers have established in vitro acquired resistance cell line models. Lung cancer cell lines with EGFR mutations are highly sensitive to EGFR-TKIs as described above (IC$_{50}$ values of these cell lines to EGFR-TKIs are around 0.005–0.05 μM). The researchers chronically exposed these sensitive cells to increasing concentration of EGFR-TKIs or high concentration of EGFR-TKIs (IC$_{50}$ values rose to several μM) after 3–9 months [15, 16, 65]. Some of these cell line models with acquired resistance contained clinically well validated resistance mechanisms such as $EGFR$ T790M secondary mutation [16, 48, 66, 67], whereas several independent groups have obtained cell line models with PTEN inactivation due to diverse mechanisms (Table 1).

An early report on PTEN in acquired resistance to EGFR inhibitors in lung cancer cells with $EGFR$ mutations utilized cetuximab, a recombinant anti-EGFR human/mouse chimeric monoclonal antibody that can induce antibody-dependent cell cytotoxicity [68, 69]. Kim and colleagues established a cell line with acquired resistance to cetuximab from HCC827 cells by chronic exposure to increasing concentrations of cetuximab for 6 months [70]. Because AKT phosphorylation was maintained in these cetuximab-resistant HCC827 cells, they analyzed PTEN status, comparing acquired resistance cells with the parent cells. Although there was no difference in PTEN mRNA expression levels between acquired resistance cells and parent cells, expression of PTEN protein was obviously lower in the acquired resistance cells. As treatment with a proteosomal inhibitor, MG-132, restored expression of PTEN protein and sensitivity to cetuximab, they concluded that increased PTEN instability led to
acquired cetuximab resistance. Obviously, these cetuximab-resistant HCC827 cells were cross-resistant to an EGFR-TKI, gefitinib.

Yamamoto and colleagues observed that another lung cancer cell line with EGFR mutation, PC9 cells, also acquired resistance to gefitinib by loss of PTEN expression [51]. In their acquired resistant PC9 cells to gefitinib with PTEN loss, nuclear translocation of the EGFR transcription factor, which regulates PTEN expression, was suppressed, therefore they concluded this to be the molecular mechanism of PTEN inactivation in their acquired resistant cells.

Wang and colleagues suggested that miRNAs are a part of the PTEN inactivation mechanism. They established HCC827 cells with acquired resistance to gefitinib. Based on a previous observation that miR-214 induces cisplatin resistance by targeting PTEN in ovarian cancer [71], they analyzed expression levels of miR-214 and mRNA and protein expression levels of PTEN, and identified increased expression of miR-214 and down-regulation of PTEN in the gefitinib-resistant HCC827 cells compared with parent cells. Knockdown of miR-214 re-sensitized the gefitinib-resistant HCC827 cells. Expression of PTEN mRNA can also be suppressed by miR-21. Up-regulation of this miRNA reportedly causes cancer cell proliferation, invasion, and chemo- or radio-resistance by targeting PTEN in non-small cell lung cancer [72], hepatocellular cancer [73], or gastric cancer cells [74].

As described above, EGFR T790M secondary mutation is the most common cause of acquired resistance to EGFR-TKIs. Irreversible or T790M-specific EGFR-TKIs, which can bind to EGFR regardless of the presence of T790M mutation, are expected to overcome this type of resistance. To imitate this situation, we first established cells with acquired resistance to erlotinib from HCC827 cells by chronic exposure, which gave HCC827 cells with T790M mutation. Because this cell line was sensitive to an irreversible EGFR-TKI, CL-387,785, we next established a cell line with acquired resistance to CL-387,785 from the HCC827 erlotinib-resistant cells with T790M mutation, using chronic exposure. Analysis of cells resistant to CL-387,785 showed down-regulated PTEN, suggesting that PTEN also affects “secondary” acquired resistance to EGFR-TKIs after acquisition of T790M mutation. In clinical specimens, loss of PTEN protein expression in tumors sampled after EGFR-TKI treatment failure, but not in those sampled before treatment, was also observed [75].

**PTEN’s Role in Resistance Mechanisms to Target Therapy in Cancer Types Other Than Lung Cancers with EGFR Mutation**

As PTEN inactivation is reported to be a predictor factor for poor response to conventional chemotherapeutic drugs in several types of cancers [45, 46, 76], does PTEN also cause resistance to molecular target therapies that suppress oncogenic drivers in cancer types other than lung cancers with EGFR mutation? Several reports that analyzed clinical specimens or in vitro model-based studies suggest that this is the case.

A431 epidermoid cells constitutively overexpress EGFR and are sensitive to EGFR-TKIs. Yamasaki and colleagues established erlotinib-resistant A431 cells by chronic exposure to the drug, and identified PTEN down-regulation with undetermined mechanism as the cause of acquired resistance (Table 1) [77].
Glioblastoma is a highly aggressive human brain tumor; about 20% harbor a EGFR mutation that confer constitutive activation of EGFR due to an in-frame deletion of exons 2–7 within the extra-cellular ligand-binding domain—the so-called EGFR variant III (vIII) mutation. Reportedly, 10–20% of unselected glioblastoma patients respond to EGFR-TKIs, and the majority of responding tumors expressed the EGFR vIII mutation. However some glioblastoma with EGFR vIII mutation show inherent resistance to EGFR-TKIs; loss of PTEN has been reported to be highly correlated with treatment failure [78].

On the other hand, it is not clear whether PTEN inactivation confers resistance to molecular target therapy in cancers with oncogenic drivers other than EGFR. Reportedly, PTEN knockdown did not protect cancer cell lines harboring amplification of MET (MKN45 and EBC1 cells) or PDGFR-alpha (H1703 and TS543 cells) from cell death in response to MET kinase inhibitors or PDGFR inhibitors, respectively [63]. However, recent studies have reported effect of PTEN inactivation on inherent or acquired resistance to molecular target therapy in breast cancers that overexpress human epidermal growth factor receptor-2 (HER2), BRAF-mutated melanoma, c-KIT-mutated gastrointestinal stromal tumor (GIST), and leukemias with FIP1-like 1 (FIP1L1)/platelet-derived growth factor receptor-alpha (PDGFR-alpha) fusion, or breakpoint cluster region-abelson (BCR-ABL) fusion, as described below.

For patients with breast cancers that overexpress HER2, trastuzumab, a humanized antibody that targets HER2, is a successful, rationally designed therapy, with considerable clinical efficacy. It extends overall survival of certain patients with HER2-overexpressing breast cancer, but its overall response remains modest: approximately 26% when used as a single therapy and 40–60% when used in combination with systemic chemotherapy [79-81]. The most prevalent inherent resistance mechanisms include constitutive activation of the PI3K pathway owing to PTEN deficiency [82] of PI3KCA gene mutation [83]. In analyses of PTEN-deficient breast cancer cells or PTEN-knockdown breast cancer cells with HER2 overexpression, Zhang and colleagues reported that PTEN dephosphorylate SRC directly and specifically by its protein phosphatase activity [84]. SRC is a non-receptor tyrosine kinase that interacts with multiple receptor tyrosine kinases through its SH2 domain, and facilitates RTK-mediated signaling [85, 86]. Therefore, they conclude that SRC activation is a molecular mechanism through which PTEN loss confers trastuzumab resistance in breast cancer cells with HER2 overexpression [84].

Paraiso and colleagues analyzed melanoma cells with V600E mutation in the BRAF gene [76]. Recent clinical trials of vemurafenib or dabrafenib, the selective BRAF inhibitors, revealed a prolonged progression-free and overall survival compared with dacarbazine chemotherapy [87, 88]. Using BRAF mutated melanoma cell lines with and without PTEN expression, the authors observed that vemurafenib-inducible apoptosis was significantly lower in cell lines with PTEN loss, suggesting that PTEN induces resistance to BRAF inhibitors in melanoma cells with BRAF mutation. In addition, they found PTEN loss to reduce apoptosis by suppressing the expression of the proapoptotic protein BIM [76].

In contrast to melanoma, vemurafenib shows limited single-agent clinical activity in colorectal cancers with BRAF mutations. By comparing colorectal cancer cell lines and melanoma cell lines with BRAF mutations, Mao and colleagues observed greater PI3K/AKT pathway activation in colorectal cancer cell lines, and that colorectal cancer cell lines with PTEN or PIK3CA mutations were less sensitive to growth inhibition by vemurafenib-analog PLX4720 [89].
Loss of PTEN has also been reported as an acquired resistance mechanism to molecular target therapy in cancers originating from other organs (Table 1). Yang and colleagues established sunitinib-resistant cells from GIST cells (GIST-T1 cells) that harbor a c-KIT mutation and are initially sensitive to sunitinib. Sunitinib is a small-molecule TKI with sensitivity for c-KIT, PDGFR-alpha/beta, vascular endothelial growth factor receptor etc., and used to treat patients with imatinib-resistant GIST [90]. The established resistant cells to sunitinib showed cross-resistance to imatinib, and had PTEN loss due to methylation of the gene’s promoter region. Forced PTEN expression in resistant cells sensitized them to sunitinib-mediated growth arrest and apoptosis [91].

Epigenetic silencing of the PTEN gene was also reported as an acquired resistance mechanism to imatinib, a small molecule inhibitor of BCR-ABL, c-KIT, and PDGFR-alpha/beta, in leukemia cells [92]. Nishioka and colleagues established imatinib-resistant chronic eosinophilic leukemia (CEL) EOL-1 sub-lines by culturing cells with increasing concentrations of imatinib for 6 months. CEL cells harbor FIP1L1/PDGFR-alpha fusion kinase and are initially highly sensitive to imatinib [93]. Established resistant cells showed epigenetic silencing of the PTEN gene, and forced expression of PTEN or anti-epigenetic agents restored sensitivity of these resistant cells to imatinib. In addition, hypermethylation of the promoter region of the PTEN gene was identified in leukemia cells derived from patients with CEL, chronic myeloid leukemia (CML) with BCR-ABL fusion gene, and Philadelphia+ acute lymphoblastic leukemia (AML) who acquired resistance to imatinib [92]. This evidence suggests the role of PTEN in inherent and acquired resistance to molecular target therapy for oncogenic drivers in cancers other than lung cancers with EGFR mutations.

**CONCLUSION**

Here, we reviewed the effect of PTEN in inherent and acquired resistance to molecular target therapy in several types of cancers harboring known oncogenic drivers, such as lung cancers with EGFR mutation. As PTEN dysfunction can occur at several steps, the question of how PTEN status should be tested in clinical samples remains open. Establishment of appropriate evaluation protocols for PTEN status, and treatment strategies to overcome resistance by PTEN inactivation would be applied to several types of cancers with known oncogenic drivers, and may improve outcomes of patients suffering from these types of cancers.

**REFERENCES**


PTEN – A Molecule That Cancers Abuse to Overcome Their Achilles-Heels


