

CDK4/6 Inhibitors' Resistance Mechanisms

Subjects: **Biology**

Contributor: Federica Villa , Alessandra Crippa , Davide Pelizzoni , Alessandra Ardizzoia , Giulia Scartabellati , Cristina Corbetta , Eleonora Cipriani , Marialuisa Lavitrano , Antonio Ardizzoia

Cyclin-dependent kinase (CDK) 4 and its functional homolog CDK6 are two structurally related kinases with biochemical and biological similarities. Despite having few differences in some of their activities, these enzymes are constantly expressed throughout the cell cycle and, with their partners, D-cyclins, are fundamental for integrating mitogenic and antimitogenic extracellular signals, among which stimulating factors, cytokines, cell–cell contacts and other factors are included, representing a boundary between the environment and the cell cycle machinery. The cyclin D-CDK4/6 complex is a driving force that controls the transition from the G1 to the S phases. Also, the INK4 (the cyclin D-CDK4/6 inhibitor molecule) retinoblastoma protein (pRb) pathway regulates cellular proliferation by controlling the G1 to the S cell cycle checkpoint. The dysregulation of this pathway is frequently observed in cancer and contributes to cell cycle progression and persistent growth. CDK4/6 mediates the transition from the G1 phase to the S phase by associating with D-type cyclins and regulating the phosphorylation state of pRb. Unphosphorylated pRb binds and represses the functions of the E2 family (E2F) transcription factors; upon phosphorylation, pRb dissociates from the E2F transcription factors, freeing them to be able to participate in DNA replication and cell division.

CDK 4/6 inhibitors

cell-cycle-specific and non-specific resistance

1. Cell-Cycle-Specific Mechanisms

Multiple factors involved in the regulation of the cell cycle are associated with a resistance to CDK4/6is, the loss of drug target genes, and the overexpression of other genes involved in the progression of the cell cycle (**Figure 1**).

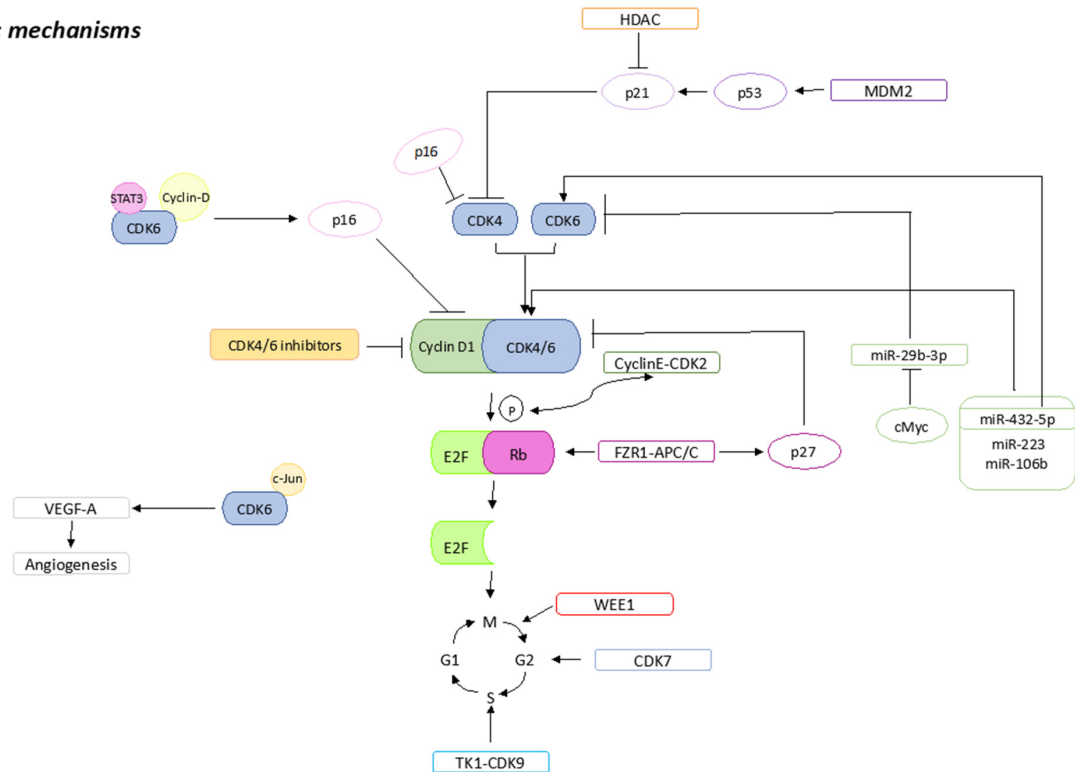
Cell cycle-specific mechanisms

Figure 1. Cell-cycle-specific mechanisms that could be associated with CDK4/6is resistance. Sharp arrows (→) indicate stimulation, blunt arrows (⊥) indicate inhibition.

1.1. pRb Loss or Mutations

pRb is a tumor suppressor protein coded by the RB transcriptional corepressor 1 (RB1) that plays a pivotal role as a cell cycle checkpoint factor. In fact, it is involved in the control of the CDK4/6 pathway, one of the main targets of the CDK4/6is drugs and whose loss, most frequently caused by inactivating mutations of RB1, is the main reason for the resistance to CDK4/6is [1][2]. In this case, in spite of this loss, the cell cycle progresses through other molecular pathways, such as the E2F and the cyclin E-CDK2 axis, thus bypassing its dependence on CDK4/6 and causing resistance to CDK4/6is [3]. It has been suggested that administration of cyclin E-CDK2 inhibitors with CDK4/6is may be a valid solution to overcoming resistance [4].

1.2. p16 Amplification

p16 is a tumor suppressor protein belonging to the INK4 family involved in cell cycle regulation if pRb is functional. It is an inhibitor of CDK4, and it has been reported to be an accurate biomarker of pRb loss in different tumors [5][6]. p16 amplification is frequently found in BC, and this leads to lower levels of CDK4, thus representing the loss of a target of CDK4/6is. Moreover, p16 amplification is frequently caused by the loss of pRb, thus leading again to resistance to CDK4/6is ex vivo [7]. Palafox et al. suggested that high p16 protein levels and heterozygous RB1 loss-of-function mutations could be predictive in order to identify the CDK4/6is resistance in BC. Moreover, they demonstrated that targeting the p16-CDK4/6 interaction sensitizes p16-overexpressing tumor cells to CDK4/6is [8].

1.3. CDK2 Amplification

Cyclin E is encoded by the CCNE1 gene and its association with CDK2 is involved in cell cycle progression from phase G1 to S. Its main role is the pRb phosphorylation, resulting in complete release of E2F [9]. It has been widely reported that CCNE1 overexpression is responsible for the resistance to CDK4/6is. In fact, cells losing their dependence on CDK4/6 use bypass mechanisms, such as CDK2 amplification, to keep up with cell cycle progression [10][11]. Moreover, there is a study that reports that the CDK2 upregulation in ER+ breast cancer is also controlled by TROJAN. TROJAN is a noncoding RNA that can bind to NKRF (NF-Kappa-B-repressing factor) and inhibit its interaction with RELA. This binding leads to CDK2 overexpression and, as aforementioned, leads to CDK4/6is resistance [12].

1.4. E2F Amplification

As a pRb transcription factor, E2F plays an important role in cell cycle regulation. As aforementioned, D-CDK4/6 phosphorylates the pRb leading to E2F release with concurrent transcription of proteins (such as cyclin E) necessary for cell cycle progression. At the same time, cyclin E transcription leads to cyclin E-CDK2 formation, which further phosphorylates pRb. For these reasons, the E2F amplification leads cells to evade CDK4/6 cell cycle regulation thus, driving resistance to their inhibitors [1][2][9][13].

1.5. CDK7 Overexpression

CDK7 regulates the cell cycle by activating the CDK-activating kinase (CAK) and participates in G1 and G2 phases [14]. Martin et al. reported that its overexpression is involved in CDK4/6is resistance [15]. However, details of its involvement in CDK4/6is resistance are not clear, and further studies are needed to better understand its role.

1.6. CDK6 Amplification

The CDK6, together with the CDK4, plays a pivotal role in the cell cycle progression, and its function is mainly kinase-dependent. However, it also upregulates the transcription of p16 in the presence of STAT3 and cyclin D in a kinase-independent way [16]. Moreover, together with c-Jun, CDK6 upregulates the vascular endothelial growth factor A (VEGF-A) which is responsible for cancer progression and drug resistance due to its ability to induce angiogenesis [17]. It was also demonstrated that a particular drug that specifically degrades CDK6 was able to overcome the CDK4/6is resistance [8].

1.7. WEE1 Overexpression

WEE1 is a serine/threonine kinase involved in guaranteeing an accurate DNA replication and, in coordination with CDK1, it is responsible for inhibiting DNA-damaged cells from entering mitosis. Most importantly, it plays a key role in the transition from G2 to M phase of the cell cycle. Its role in the CDK4/6is resistance is not clear; however, it was reported that its inhibition in resistant cells could partially restore the CDK4/6 sensitivity [18].

1.8. MDM2 Overexpression

Mouse double minute 2 homolog (MDM2) is a negative regulator of p53 which is involved in the activation of p21 (a CDK inhibitor), thus leading to cell cycle arrest [19][20]. MDM2 overexpression leads to interruption of cell senescence and hence CDK4/6is resistance. For this reason, MDM2 inhibitors may be useful in treating patients' resistant to CDK4/6is, despite further studies being needed [21].

1.9. HDACs Activation

Histone deacetylases (HDACs) are responsible for removing the acetyl group from the histones' ϵ -N-acetyl lysins, playing a crucial role in gene expression regulation [22]. Moreover, they inhibit p21, which interacts with cyclin D [23]. Recently, it has been reported that the CDK4/6i palbociclib resistance may be conferred by HDAC5 depletion through disruption of palbociclib-induced histone deacetylation and suppression of oncogenic gene expression. Thus, the HDAC5 deficiency in cancer cells could be useful to drive the clinical use of CDK4/6is [24].

1.10. FZR1 Loss

Fizzy and the cell division cycle 20-related 1 (FZR1) is a co-activator of the ubiquitin-ligase APC/C that, once activated, can interact with pRb during the cell cycle phase G1 [25]. Ruijtenberg et al. showed that FZR1 is a substrate of cyclin D-CDK4/6 and that, once phosphorylated, it loses its ability to activate APC/C. They further demonstrated that knockdown of both FZR1 and APC/C leads cells to bypass their dependence on cyclin D-CDK4/6 for the progression of the cell cycle [26]. The involvement of the APC/C-FZR1 complex in the downregulation of CDK2/4/6 is particularly interesting because it can also upregulate p27 (a CDK inhibitor) through S-phase kinase-associated protein 2 (SKP2) degradation [27]. For all these reasons, the FZR1 loss is linked to resistance to CDK4/6is.

1.11. TK1 Activation

Thymidine kinase 1 (TK1) is an enzyme important for thymidine metabolism during the synthesis of DNA. In resting cells, TK1 activity is low and it increases gradually until it reaches its peak during the S phase. However, it was reported to be continuously overexpressed in patients with different malignancies [28]. It has been demonstrated that TK1 activity is associated with OS and PFS in patients with advanced BC [29]. Moreover, Del Re et al. analyzed exosomal mRNA expression of TK1 and CDK9 in patients with ER+/HER2- mBC enrolled in the ECLIPS biomarker study, showing that higher mRNA expression levels of both of them were linked to palbociclib resistance [30].

1.12. miRNAs Expression

In recent years, microRNA (miRNAs) expression in cancer has been widely studied, due to its important role in cancer progression [31]. Among the different miRNAs identified, some were found to be linked to CDK4/6is resistance, such as miR-432-5p, miR-223, and miR-106b [32]. In particular, miR-432-5p was reported to induce

resistance through CDK6 overexpression [33]. Moreover, the oncogene c-Myc could reduce the inhibitory effect of miR-29b-3p on CDK6 by downregulating miR-29b-3p, thus inducing BC resistance to palbociclib [34].

1.13. S6K1 Amplification

Ribosomal protein S6 kinase beta-1 (S6K1) is a serine/threonine protein kinase that acts downstream of the mTORC1 complex and regulates cell size, protein translation and cell proliferation [35]. Recently, it has been reported that S6K1 amplification is responsible for primary resistance to CDK4/6is, mainly linked to c-Myc overexpression that induces hyperactivation of cyclins/CDKs. The authors also suggested the use of mTOR inhibitors combined with CDK4/6is to overcoming resistance [36].

2. Cell-Cycle-Non-Specific Mechanisms

Cell-cycle-non-specific mechanisms include the overexpression of factors that are upstream of the cell cycle, such as FGFR and PI3K/AKT/mTOR, resulting in decreased efficacy of CDK4/6is (Figure 2).

Cell cycle-nonspecific mechanisms

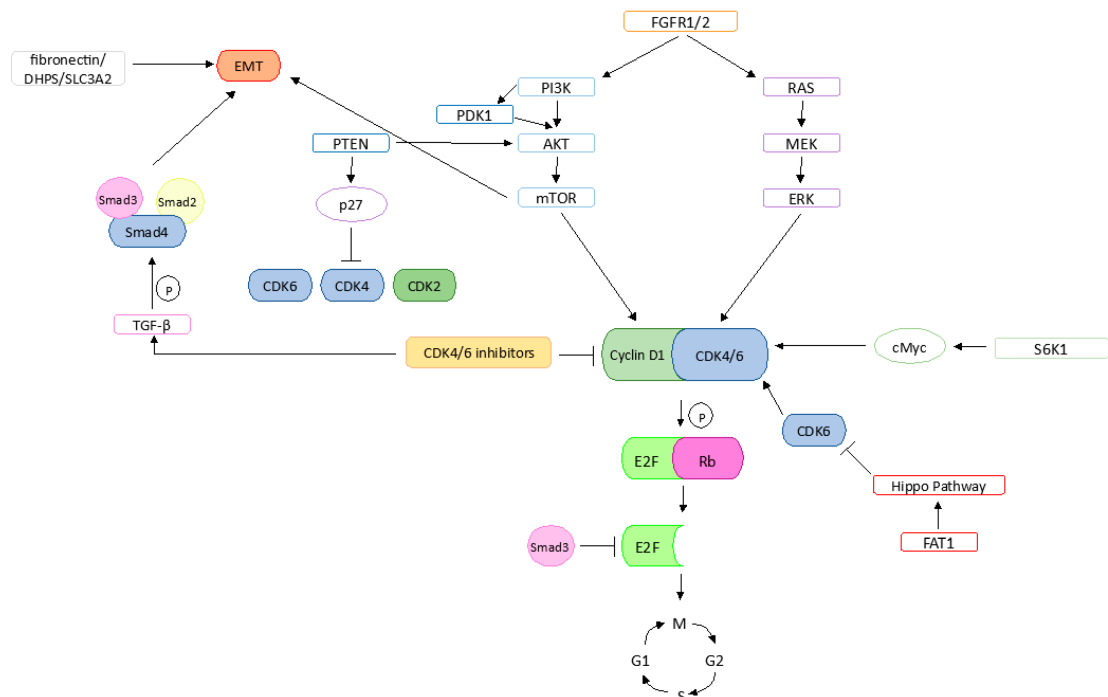


Figure 2. Cell-cycle-non-specific mechanisms that could be associated with CDK4/6is resistance. Sharp arrows (→) indicate stimulation, blunt arrows (⊥) indicate inhibition.

2.1. FGFR Pathway Activation

The fibroblast growth factor receptor 1 (FGFR1) is a tyrosine kinase involved mostly in cell proliferation, differentiation and survival [37]. Mutations in FGFR1 have been widely reported in different cancers, including BC [38]. Different studies report that FGFR1 and FGFR2 are linked to CDK4/6is resistance. In particular, it was reported

that this resistance was caused by the amplification of FGFR1, which led to the activation of PI3K/AKT and RAS/MEK/ERK signaling pathways [39]. In addition, a recent study demonstrated that giving a specific FGFR1 tyrosine kinase-inhibitor to resistant cells could revert the resistance [40]. Finally, it was shown that the FGFR2-activating mutation in ER+ BC could contribute to palbociclib resistance and, when the cells were given a high dose of FGFR inhibitors, they could be completely resensitised to the drug. [41]. These studies suggest a potential therapeutic approach to overcoming such resistance.

2.2. PI3K/AKT/mTOR Pathway Activation

Many studies have reported a main role of the PI3K/AKT/mTOR activation in CDK4/6is resistance. In particular, high levels of pyruvate dehydrogenase kinase 1 (PDK1, a protein kinase that acts downstream of PI3K) and activation of the AKT pathway (phospho-S477/T479 AKT) were reported in ribociclib-resistant BC cells. Moreover, inhibition of PDK1 led to higher sensitivity to ribociclib in these cells [42]. Another study revealed that mTORC1/2 may also be involved in CDK4/6is resistance: inhibition of mTOR in ER+ BC results in a decrease in cyclin D1 protein, pRb phosphorylation, and so E2F mediated transcription. In addition, they found that even if cells resistant to CDK4/6is reactivated the CDK-pRb-E2F pathway, they still were sensitive to mTORC1/2 inhibitors [43]. Also, the protein phosphatase and tensin homolog (PTEN) plays a pivotal role in the regulation of the AKT/mTOR pathway. Costa et al. showed that its loss caused a CDK4/6i (ribociclib) resistance by AKT activation. Its loss translated into p27 downregulation which, again, turned into activation of CDK2 and CDK4 [44]. Moreover, knockdown of PTEN in CDK4/6is-sensitive cell lines led to the upregulation of CDK6 and resistance to abemaciclib [45]. These data suggest a wide range of drugs that could be used in combination with CDK4/6is in order to prevent/revert resistance.

2.3. MAPK Pathway Activation

The mitogen-activated protein kinase (MAPK) pathway (RAS/RAF/MEK/ERK) is one of the main pathways downstream of FGFR1. It has been reported that selumetinib, a MEK1/2 inhibitor, in association with fulvestrant and palbociclib could inhibit BC proliferation in patients resistant to CDK4/6is [46]. Moreover, it was shown how the overexpression of KRAS, a member of the RAS family, was involved in palbociclib and fulvestrant resistance [47].

2.4. Hippo Pathway Inhibition by FAT1

The Hippo pathway is a pathway reported to have a tumor-suppressive role [48]. FAT atypical cadherin 1 (FAT1) is a cadherin that interacts both with the Hippo pathway and β -catenin, and it is reported to act as a tumor suppressor gene [49]. Interestingly, a study of 348 patients treated with CDK4/6is showed loss of FAT1 in patients who became resistant to CDK4/6is. The resistance was probably caused by the fact that FAT1 loss led to Hippo pathway inhibition, which turned into CDK6 overexpression [50]. However, another study reported that more genetic alterations are needed besides FAT1 loss to have CDK6 overexpression [45]. This suggests that more in-depth studies need to be performed to clarify this pathway and to understand whether its targeting could have a therapeutic effect.

2.5. Epithelial–Mesenchymal Transition

Epithelial–mesenchymal transition (EMT) consists of the transition of cells from an epithelial to a mesenchymal phenotype. EMT is linked with tissue morphogenesis. However, it has been widely reported to be linked also with tissue invasion, drug resistance and metastasis of cancer [51]. It has been reported that inhibition of the CDK4/6 can induce EMT by activating TGF- β -Smad and PI3K/AKT/mTOR pathways. Once activated, TGF- β can phosphorylate and so activate Smad2 and Smad3. These can create a complex with Smad4 and activate EMT transcription factors [52]. In addition, Smad3 inhibition leads to CDK4/6is resistance, probably because it is no longer able to block E2F from the pRb-E2F complex [53][54]. Moreover, TGF- β can lead to EMT through activation of the PI3K/AKT/mTOR pathway [55]. Recently, it has also been reported that the fibronectin/DHPS/SLC3A2 signaling axis may be involved in the resistance to CDK4/6is. Galler et al. showed that the targeting of this signaling axis improved palbociclib sensitivity in pRb-negative BC cells [56].

2.6. Apoptosis Failure

The combination of ET with CDK4/6 inhibition has a predominantly cytostatic effect, thus leading to reduced apoptosis [57]. For this reason, it has been suggested that a combination therapy using CDK4/6is and BCL2 inhibitors could inhibit proliferation and induce apoptosis of cancer cells. Moreover, this approach reduced the proliferation of regulatory T cells in the tumor microenvironment [58].

2.7. Stemness Properties

In the last few years, many studies have reported a central role of cancer stem cells (CSCs) in drug resistance. CSCs are a population of cells capable of self-renewal and differentiation potential. Moreover, they show many alterations in different pathways, and for different reasons, and at dates not completely clear, they also play a main role in drug resistance [59]. Interestingly, Wang et al. found that ER+ BC cells treated with palbociclib developed resistance by showing a senescence-like phenotype, which went on to promote stemness. Particularly, PFKFB4 played a major role in this transformation by enhancing glycolysis, and its downregulation resulted in higher palbociclib sensitivity [60]. Thus, even if more studies are needed, targeting CSCs could be a promising therapeutic approach.

References

1. Malumbres, M.; Sotillo, R.; Santamaría, D.; Galán, J.; Cerezo, A.; Ortega, S.; Dubus, P.; Barbacid, M. Mammalian Cells Cycle without the D-Type Cyclin-Dependent Kinases Cdk4 and Cdk6. *Cell* 2004, 118, 493–504.
2. O’Leary, B.; Finn, R.S.; Turner, N.C. Treating Cancer with Selective CDK4/6 Inhibitors. *Nat. Rev. Clin. Oncol.* 2016, 13, 417–430.

3. Finn, R.S.; Crown, J.P.; Lang, I.; Boer, K.; Bondarenko, I.M.; Kulyk, S.O.; Ettl, J.; Patel, R.; Pinter, T.; Schmidt, M.; et al. The Cyclin-Dependent Kinase 4/6 Inhibitor Palbociclib in Combination with Letrozole versus Letrozole Alone as First-Line Treatment of Oestrogen Receptor-Positive, HER2-Negative, Advanced Breast Cancer (PALOMA-1/TRIO-18): A Randomised Phase 2 Study. *Lancet Oncol.* 2015, 16, 25–35.
4. Huang, J.; Zheng, L.; Sun, Z.; Li, J. CDK4/6 Inhibitor Resistance Mechanisms and Treatment Strategies (Review). *Int. J. Mol. Med.* 2022, 50, 128.
5. Shapiro, G.I.; Edwards, C.D.; Kobzik, L.; Godleski, J.; Richards, W.; Sugarbaker, D.J.; Rollins, B.J. Reciprocal Rb Inactivation and P16INK4 Expression in Primary Lung Cancers and Cell Lines. *Cancer Res.* 1995, 55, 505–509.
6. Lukas, J.; Parry, D.; Aagaard, L.; Mann, D.J.; Bartkova, J.; Strauss, M.; Peters, G.; Bartek, J. Retinoblastoma-Protein-Dependent Cell-Cycle Inhibition by the Tumour Suppressor P16. *Nature* 1995, 375, 503–506.
7. Dean, J.L.; McClendon, A.K.; Hickey, T.E.; Butler, L.M.; Tilley, W.D.; Witkiewicz, A.K.; Knudsen, E.S. Therapeutic Response to CDK4/6 Inhibition in Breast Cancer Defined by Ex Vivo Analyses of Human Tumors. *Cell Cycle* 2012, 11, 2756–2761.
8. Palafox, M.; Monserrat, L.; Bellet, M.; Villacampa, G.; Gonzalez-Perez, A.; Oliveira, M.; Brasó-Maristany, F.; Ibrahim, N.; Kannan, S.; Mina, L.; et al. High P16 Expression and Heterozygous RB1 Loss Are Biomarkers for CDK4/6 Inhibitor Resistance in ER+ Breast Cancer. *Nat. Commun.* 2022, 13, 5258.
9. Gladden, A.B.; Diehl, J.A. Cell Cycle Progression without Cyclin E/CDK2: Breaking down the Walls of Dogma. *Cancer Cell* 2003, 4, 160–162.
10. Etemadmoghadam, D.; Au-Yeung, G.; Wall, M.; Mitchell, C.; Kansara, M.; Loehrer, E.; Batzios, C.; George, J.; Ftouni, S.; Weir, B.A.; et al. Resistance to CDK2 Inhibitors Is Associated with Selection of Polyploid Cells in CCNE1-Amplified Ovarian Cancer. *Clin. Cancer Res.* 2013, 19, 5960–5971.
11. Herrera-Abreu, M.T.; Palafox, M.; Asghar, U.; Rivas, M.A.; Cutts, R.J.; Garcia-Murillas, I.; Pearson, A.; Guzman, M.; Rodriguez, O.; Grueso, J.; et al. Early Adaptation and Acquired Resistance to CDK4/6 Inhibition in Estrogen Receptor-Positive Breast Cancer. *Cancer Res.* 2016, 76, 2301–2313.
12. Jin, X.; Ge, L.P.; Li, D.Q.; Shao, Z.M.; Di, G.H.; Xu, X.E.; Jiang, Y.Z. LncRNA TROJAN Promotes Proliferation and Resistance to CDK4/6 Inhibitor via CDK2 Transcriptional Activation in ER+ Breast Cancer. *Mol. Cancer* 2020, 19, 87.
13. Diehl, J.A. Cycling to Cancer with Cyclin D1. *Cancer Biol. Ther.* 2002, 1, 226–231.

14. Schachter, M.M.; Merrick, K.A.; Larochelle, S.; Hirschi, A.; Zhang, C.; Shokat, K.M.; Rubin, S.M.; Fisher, R.P. A Cdk7-Cdk4 T-Loop Phosphorylation Cascade Promotes G1 Progression. *Mol. Cell* 2013, 50, 250–260.
15. Martin, L.-A.; Pancholi, S.; Ribas, R.; Gao, Q.; Simigdala, N.; Nikitorowicz-Buniak, J.; Johnston, S.; Dowsett, M. Abstract P3-03-09: Resistance to Palbociclib Depends on Multiple Targetable Mechanisms Highlighting the Potential of Drug Holidays and Drug Switching to Improve Therapeutic Outcome. *Cancer Res.* 2017, 77 (Suppl. S4).
16. Tigan, A.S.; Bellutti, F.; Kollmann, K.; Tebb, G.; Sexl, V. CDK6-a Review of the Past and a Glimpse into the Future: From Cell-Cycle Control to Transcriptional Regulation. *Oncogene* 2016, 35, 3083–3091.
17. Kollmann, K.; Heller, G.; Schneckenleithner, C.; Warsch, W.; Scheicher, R.; Ott, R.G.; Schäfer, M.; Fajmann, S.; Schlederer, M.; Schiefer, A.I.; et al. A Kinase-Independent Function of CDK6 Links the Cell Cycle to Tumor Angiogenesis. *Cancer Cell* 2016, 30, 359–360.
18. Matheson, C.J.; Backos, D.S.; Reigan, P. Targeting WEE1 Kinase in Cancer. *Trends Pharmacol. Sci.* 2016, 37, 872–881.
19. Efeyan, A.; Ortega-Molina, A.; Velasco-Miguel, S.; Herranz, D.; Vassilev, L.T.; Serrano, M. Induction of P53-Dependent Senescence by the MDM2 Antagonist Nutlin-3a in Mouse Cells of Fibroblast Origin. *Cancer Res.* 2007, 67, 7350–7357.
20. Cox, L.S. Multiple Pathways Control Cell Growth and Transformation: Overlapping and Independent Activities of P53 and P21Cip1/Waf1/Sdi1. *J. Pathol* 1997, 183, 134–140.
21. Portman, N.; Chen, J.; Lim, E. MDM2 as a Rational Target for Intervention in CDK4/6 Inhibitor Resistant, Hormone Receptor Positive Breast Cancer. *Front. Oncol.* 2021, 11, 777867.
22. Sabnis, G.J.; Goloubeva, O.; Chumsri, S.; Nguyen, N.; Sukumar, S.; Brodie, A.M.H. Functional Activation of the Estrogen Receptor- α and Aromatase by the HDAC Inhibitor Entinostat Sensitizes ER-Negative Tumors to Letrozole. *Cancer Res.* 2011, 71, 1893–1903.
23. Dash, B.C.; El-Deiry, W.S. Phosphorylation of P21 in G2/M Promotes Cyclin B-Cdc2 Kinase Activity. *Mol. Cell. Biol.* 2005, 25, 3364–3387.
24. Zhou, Y.; Jin, X.; Ma, J.; Ding, D.; Huang, Z.; Sheng, H.; Yan, Y.; Pan, Y.; Wei, T.; Wang, L.; et al. HDAC5 Loss Impairs RB Repression of Pro-Oncogenic Genes and Confers CDK4/6 Inhibitor Resistance in Cancer. *Cancer Res.* 2021, 81, 1486–1499.
25. Ramanujan, A.; Tiwari, S. APC/C and Retinoblastoma Interaction: Cross-Talk of Retinoblastoma Protein with the Ubiquitin Proteasome Pathway. *Biosci. Rep.* 2016, 36, e00377.
26. The, I.; Ruijtenberg, S.; Bouchet, B.P.; Cristobal, A.; Prinsen, M.B.W.; Van Mourik, T.; Koreth, J.; Xu, H.; Heck, A.J.R.; Akhmanova, A.; et al. Rb and FZR1/Cdh1 Determine CDK4/6-Cyclin D

- Requirement in *C. Elegans* and Human Cancer Cells. *Nat. Commun.* 2015, 6, 5906.
27. Fujita, T.; Liu, W.; Doihara, H.; Wan, Y. Regulation of Skp2-P27 Axis by the Cdh1/Anaphase-Promoting Complex Pathway in Colorectal Tumorigenesis. *Am. J. Pathol.* 2008, 173, 217–228.
 28. He, Q.; Zou, L.; Zhang, P.A.; Lui, J.X.; Skog, S.; Fornander, T. The Clinical Significance of Thymidine Kinase 1 Measurement in Serum of Breast Cancer Patients Using Anti-TK1 Antibody. *Int. J. Biol. Markers* 2000, 15, 139–146.
 29. Bjöhle, J.; Bergqvist, J.; Gronowitz, J.S.; Johansson, H.; Carlsson, L.; Einbeigi, Z.; Linderholm, B.; Loman, N.; Malmberg, M.; Söderberg, M.; et al. Serum Thymidine Kinase Activity Compared with CA 15-3 in Locally Advanced and Metastatic Breast Cancer within a Randomized Trial. *Breast Cancer Res. Treat.* 2013, 139, 751–758.
 30. Del Re, M.; Bertolini, I.; Crucitta, S.; Fontanelli, L.; Rofi, E.; De Angelis, C.; Diodati, L.; Cavallero, D.; Gianfilippo, G.; Salvadori, B.; et al. Overexpression of TK1 and CDK9 in Plasma-Derived Exosomes Is Associated with Clinical Resistance to CDK4/6 Inhibitors in Metastatic Breast Cancer Patients. *Breast Cancer Res. Treat.* 2019, 178, 57–62.
 31. Lin, S.L.; Chang, D.C.; Ying, S.Y.; Leu, D.; Wu, D.T.S. MicroRNA MiR-302 Inhibits the Tumorigenicity of Human Pluripotent Stem Cells by Coordinate Suppression of the CDK2 and CDK4/6 Cell Cycle Pathways. *Cancer Res.* 2010, 70, 9473–9482.
 32. Pulito, C.; Cristaudo, A.; La Porta, C.; Zapperi, S.; Blandino, G.; Morrone, A.; Strano, S. Oral Mucositis: The Hidden Side of Cancer Therapy. *J. Exp. Clin. Cancer Res.* 2020, 39, 210.
 33. Cornell, L.; Wander, S.A.; Visal, T.; Wagle, N.; Shapiro, G.I. MicroRNA-Mediated Suppression of the TGF- β Pathway Confers Transmissible and Reversible CDK4/6 Inhibitor Resistance. *Cell Rep.* 2019, 26, 2667–2680.e7.
 34. Ji, W.; Zhang, W.; Wang, X.; Shi, Y.; Yang, F.; Xie, H.; Zhou, W.; Wang, S.; Guan, X. C-Myc Regulates the Sensitivity of Breast Cancer Cells to Palbociclib via c-Myc/MiR-29b-3p/CDK6 Axis. *Cell Death Dis.* 2020, 11, 760.
 35. Fingar, D.C.; Blenis, J. Target of Rapamycin (TOR): An Integrator of Nutrient and Growth Factor Signals and Coordinator of Cell Growth and Cell Cycle Progression. *Oncogene* 2004, 23, 3151–3171.
 36. Mo, H.; Liu, X.; Xue, Y.; Chen, H.; Guo, S.; Li, Z.; Wang, S.; Li, C.; Han, J.; Fu, M.; et al. S6K1 Amplification Confers Innate Resistance to CDK4/6 Inhibitors through Activating c-Myc Pathway in Patients with Estrogen Receptor-Positive Breast Cancer. *Mol. Cancer* 2022, 21, 171.
 37. Turner, N.; Grose, R. Fibroblast Growth Factor Signalling: From Development to Cancer. *Nat. Rev. Cancer* 2010, 10, 116–129.

38. Luqmani, Y.A.; Graham, M.; Coombes, R.C. Expression of Basic Fibroblast Growth Factor, FGFR1 and FGFR2 in Normal and Malignant Human Breast, and Comparison with Other Normal Tissues. *Br. J. Cancer* 1992, 66, 273–280.
39. Turner, N.; Pearson, A.; Sharpe, R.; Lambros, M.; Geyer, F.; Lopez-Garcia, M.A.; Natrajan, R.; Marchio, C.; Iorns, E.; Mackay, A.; et al. FGFR1 Amplification Drives Endocrine Therapy Resistance and Is a Therapeutic Target in Breast Cancer. *Cancer Res.* 2010, 70, 2085–2094.
40. Sobhani, N.; Fassel, A.; Mondani, G.; Generali, D.; Otto, T. Targeting Aberrant FGFR Signaling to Overcome CDK4/6 Inhibitor Resistance in Breast Cancer. *Cells* 2021, 10, 293.
41. Mao, P.; Kusieli, J.; Cohen, O.; Wagle, N. Abstract PD4-01: The Role of FGF/FGFR Axis in Resistance to SERDs and CDK4/6 Inhibitors in ER+ Breast Cancer. *Cancer Res.* 2018, 78 (Suppl. S4), PD4-01.
42. Jansen, V.M.; Bholra, N.E.; Bauer, J.A.; Formisano, L.; Lee, K.M.; Hutchinson, K.E.; Witkiewicz, A.K.; Moore, P.D.; Estrada, M.V.; Sánchez, V.; et al. Kinome-Wide RNA Interference Screen Reveals a Role for PDK1 in Acquired Resistance to CDK4/6 Inhibition in ER-Positive Breast Cancer. *Cancer Res.* 2017, 77, 2488–2499.
43. Michaloglou, C.; Crafter, C.; Siersbaek, R.; Delpuech, O.; Curwen, J.O.; Carnevalli, L.S.; Staniszezewska, A.D.; Polanska, U.M.; Cheraghchi-Bashi, A.; Lawson, M.; et al. Combined Inhibition of MTOR and CDK4/6 Is Required for Optimal Blockade of E2F Function and Long-Term Growth Inhibition in Estrogen Receptor-Positive Breast Cancer. *Mol. Cancer Ther.* 2018, 17, 908–920.
44. Costa, C.; Ye, W.; Ly, A.; Hosono, Y.; Murchi, E.; Walmsley, C.S.; Huynh, T.; Healy, C.; Peterson, R.; Yanase, S.; et al. PTEN Loss Mediates Clinical Cross-Resistance to CDK4/6 and PI3K α Inhibitors in Breast Cancer. *Cancer Discov.* 2020, 10, 72–85.
45. Li, Q.; Jiang, B.; Guo, J.; Shao, H.; Del Priore, I.S.; Chang, Q.; Kudo, R.; Li, Z.; Razavi, P.; Liu, B.; et al. INK4 Tumor Suppressor Proteins Mediate Resistance to CDK4/6 Kinase Inhibitors. *Cancer Discov.* 2022, 12, 356–371.
46. Formisano, L.; Lu, Y.; Servetto, A.; Hanker, A.B.; Jansen, V.M.; Bauer, J.A.; Sudhan, D.R.; Guerrero-Zotano, A.L.; Croessmann, S.; Guo, Y.; et al. Aberrant FGFR Signaling Mediates Resistance to CDK4/6 Inhibitors in ER+ Breast Cancer. *Nat. Commun.* 2019, 10, 1373.
47. Raimondi, L.; Raimondi, F.M.; Pietranera, M.; Di Rocco, A.; Di Benedetto, L.; Miele, E.; Lazzeroni, R.; Cimino, G.; Spinelli, G.P. Assessment of Resistance Mechanisms and Clinical Implications in Patients with KRAS Mutated-Metastatic Breast Cancer and Resistance to CDK4/6 Inhibitors. *Cancers* 2021, 13, 1928.
48. Dey, A.; Varelas, X.; Guan, K.L. Targeting the Hippo Pathway in Cancer, Fibrosis, Wound Healing and Regenerative Medicine. *Nat. Rev. Drug Discov.* 2020, 19, 480–494.

49. Finn, R.S.; Crown, J.P.; Ettl, J.; Schmidt, M.; Bondarenko, I.M.; Lang, I.; Pinter, T.; Boer, K.; Patel, R.; Randolph, S.; et al. Efficacy and Safety of Palbociclib in Combination with Letrozole as First-Line Treatment of ER-Positive, HER2-Negative, Advanced Breast Cancer: Expanded Analyses of Subgroups from the Randomized Pivotal Trial PALOMA-1/TRIO-18. *Breast Cancer Res.* 2016, 18, 67.
50. Li, Z.; Razavi, P.; Li, Q.; Toy, W.; Liu, B.; Ping, C.; Hsieh, W.; Sanchez-Vega, F.; Brown, D.N.; Da Cruz Paula, A.F.; et al. Loss of the FAT1 Tumor Suppressor Promotes Resistance to CDK4/6 Inhibitors via the Hippo Pathway. *Cancer Cell* 2018, 34, 893–905.e8.
51. Bae, S.N.; Arand, G.; Azzam, H.; Pavasant, P.; Torri, J.; Frandsen, T.L.; Thompson, E.W. Molecular and Cellular Analysis of Basement Membrane Invasion by Human Breast Cancer Cells in Matrigel-Based in Vitro Assays. *Breast Cancer Res. Treat.* 1993, 24, 241–255.
52. Lamouille, S.; Xu, J.; Derynck, R. Molecular Mechanisms of Epithelial-Mesenchymal Transition. *Nat. Rev. Mol. Cell Biol.* 2014, 15, 178–196.
53. Zelivianski, S.; Cooley, A.; Kall, R.; Jeruss, J.S. Cyclin-Dependent Kinase 4-Mediated Phosphorylation Inhibits Smad3 Activity in Cyclin D-Overexpressing Breast Cancer Cells. *Mol. Cancer Res.* 2010, 8, 1375–1387.
54. Yang, J.; Song, K.; Krebs, T.L.; Jackson, M.W.; Danielpour, D. Rb/E2F4 and Smad2/3 Link Survivin to TGF-Beta-Induced Apoptosis and Tumor Progression. *Oncogene* 2008, 27, 5326–5338.
55. Du, B.; Shim, J.S. Targeting Epithelial-Mesenchymal Transition (EMT) to Overcome Drug Resistance in Cancer. *Molecules* 2016, 21, 965.
56. Geller, C.; Maddela, J.; Tuplano, R.; Runa, F.; Adamian, Y.; Güth, R.; Soto, G.O.; Tomaneng, L.; Cantor, J.; Kelber, J.A. Fibronectin, DHPS and SLC3A2 Signaling Cooperate to Control Tumor Spheroid Growth, Subcellular EIF5A1/2 Distribution and CDK4/6 Inhibitor Resistance. *bioRxiv* 2023.
57. Johnston, S.; Puhalla, S.; Wheatley, D.; Ring, A.; Barry, P.; Holcombe, C.; Boileau, J.F.; Provencher, L.; Robidoux, A.; Rimawi, M.; et al. Randomized Phase II Study Evaluating Palbociclib in Addition to Letrozole as Neoadjuvant Therapy in Estrogen Receptor-Positive Early Breast Cancer: PALLET Trial. *J. Clin. Oncol.* 2019, 37, 178–189.
58. Whittle, J.R.; Vaillant, F.; Surgenor, E.; Policheni, A.N.; Giner, G.; Capaldo, B.D.; Chen, H.R.; Liu, H.K.; Dekkers, J.F.; Sachs, N.; et al. Dual Targeting of CDK4/6 and BCL2 Pathways Augments Tumor Response in Estrogen Receptor-Positive Breast Cancer. *Clin. Cancer Res.* 2020, 26, 4120–4134.
59. Zeng, X.; Liu, C.; Yao, J.; Wan, H.; Wan, G.; Li, Y.; Chen, N. Breast Cancer Stem Cells, Heterogeneity, Targeting Therapies and Therapeutic Implications. *Pharmacol. Res.* 2021, 163,

105320.

60. Wang, S.; Bei, Y.; Tian, Q.; He, J.; Wang, R.; Wang, Q.; Sun, L.; Ke, J.; Xie, C.; Shen, P. PFKFB4 Facilitates Palbociclib Resistance in Oestrogen Receptor-Positive Breast Cancer by Enhancing Stemness. *Cell Prolif.* 2023, 56, e13337.
-

Retrieved from <https://encyclopedia.pub/entry/history/show/112956>