Received: 21 September 2022 | Accepted: 28 December 2022

DOI: 10.1002/cai2.51

REVIEW

CANCER INNOVATION

Role of YES1 signaling in tumor therapy resistance

Hai Zhou[1] | **Dantong Sun**[2] | **Junyan Tao**[3] | **Mingjin Xu**[4] | **Xiaochun Zhang**[1] | **Helei Hou**[1]

[1]Precision Medicine Center of Oncology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China

[2]Department of Medical Oncology, National Cancer Center/National Clinical Research Center for Cancer/Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College, Beijing, China

[3]Qingdao Sixth People's Hospital, Qingdao, Shandong, China

[4]Department of Radiation Oncology, The Affiliated Hospital of Qingdao University, Qingdao, Shandong, China

Correspondence
Helei Hou, Precision Medicine Center of Oncology, The Affiliated Hospital of Qingdao University, 59 Haier Rd, Qingdao, Shandong 266000, China.
Email: houheleihhl@163.com and houhelei@qdu.edu.cn

Funding information
Special Funding for Qilu Sanitation and Health Leading Talents Cultivation Project; Key Research and Development Project of Shandong Province, Grant/Award Number: 2017GSF18147

Abstract

YES proto-oncogene 1 (YES1) is an SRC family kinase (SFK) that plays a key role in cancer cell proliferation, adhesion, invasion, survival, and angiogenesis during tumorigenesis and tumor development. Reports suggest that *YES1* amplification is associated with resistance to chemotherapeutic drugs and tyrosine kinase inhibitors (TKIs) in human malignancies. However, the mechanisms of drug resistance have not been fully elucidated. In this article, we review the literature on YES1 and discuss the implications of YES1 signaling for targeted therapy and chemotherapy resistance in malignancies. Moreover, recent advances in targeted therapy for *YES1*-amplified malignancies are summarized. Finally, we conclude that targeting YES1 may reverse drug resistance and serve as a valuable tumor treatment strategy.

KEYWORDS
YES1-amplified malignancies, chemotherapy resistance, molecular mechanisms, EGFR-TKIs

1 | BACKGROUND

Studies of driver mutations in malignancy, such as those in epidermal growth factor receptor (*EGFR*), anaplastic lymphoma kinase (*ALK*), and human epidermal growth factor receptor 2 (*HER2*), have provided more treatment options for patients with advanced malignancies [1–3]. However, some patients still do not benefit from targeted therapy because they either have acquired or primary resistance or lack targetable driver mutations. Drug resistance remains a serious problem in the course of treatment, which limits the application of targeted therapy and is one of the most important challenges in the treatment of malignancies today [4]. Therefore, there

Abbreviations: ALK, anaplastic lymphoma kinase; ANXA2, annexin A2; EGFR, epidermal growth factor receptor; EPHA2, erythropoietin-producing hepatocellular receptor A2; HER2, human epidermal growth factor receptor-2; MAPK, mitogen-activated protein kinase; mTOR, mammalian target of rapamycin; NSCLC, non-small cell lung cancer; SFK, Src family kinase; TKI, tyrosine kinase inhibitor; YAP1, YES1-associated protein 1; YES1, YES proto-oncogene 1.

is an urgent need to improve anticancer treatment strategies, including developing new drugs and addressing drug resistance.

YES proto-oncogene 1 (YES1) is one of the nine members of SRC family kinases (SFKs), and the other members are SRC, FYN, LYN, BLK, LCK, HCK, FGR, and YRK. YES1, SRC, and FYN are widely expressed in mammalian tissues, while LYN, LCK, FGR, BLK, and HCK are more expressed in the hematopoietic system [5]. SFK is an important nonreceptor tyrosine kinase (RTK) that can regulate the cellular function of normal cells. SFK signaling has been shown to be related to the growth, survival, invasion, adhesion, and migration of cancer cells, and plays a role in resistance to targeted therapy, endocrine therapy, chemotherapy, and radiotherapy [6, 7]. Recently, YES1 has received increasing attention for its potential oncogenic properties and its use as a biomarker in various tumors. Upon stimulation by RTKs, including EGRF, PDGFR, CSF1R, and FGFR, YES1 is recruited to activate and phosphorylate these membrane receptors that regulate downstream substrates and exert partial biological effects. *YES1* is the only member of the SFK family to show gene amplification in primary tumors of untreated patients [8]. Previous laboratory studies supported that *YES1* amplification mediates resistance to anti-HER2 drugs and EGFR-tyrosine kinase inhibitors (TKIs) among others [9, 10].

In this review, we describe the role of YES1 and its signaling in tumors, focusing on the role of *YES1* amplification in TKI and chemotherapy resistance. Recent advances in targeted therapy for *YES1*-amplified malignancies are analyzed. Targeting YES1 may reverse drug resistance and serve as a valuable therapeutic strategy in tumor treatment.

2 | FUNCTION AND SIGNALING OF YES1 IN TUMORS

It has been observed that YES1 plays a vital role in the occurrence and development of various malignant tumors such as non-small cell lung cancer (NSCLC), breast cancer, colorectal cancer, prostate cancer, esophageal cancer, gastric cancer, liver cancer, thyroid cancer, glioblastoma, pancreatic cancer, and melanoma [11–21]. We investigated genomic data from patients with somatic *YES1* amplification in various malignancies, including NSCLC, breast, colorectal, bladder, and prostate cancers, from the cBioPortal for Cancer Genomics databases. The prevalence of *YES1* amplification in various malignancies is shown in Figure 1. In addition, the correlation between YES1 expression from the Human Protein Atlas database and the prognosis of various tumors is shown in Figure 2. The results showed that high expression of YES1 was associated with shorter progression-free survival (PFS). Recent studies have shown that YES1 overexpression can promote the level of tumor-infiltrating regulatory T cells, thereby forming an immunosuppressive tumor microenvironment [22]. This might explain the poorer survival outcome of patients with high YES1 expression. Therefore, YES1 may be a predictor of decreased tumor PFS.

YES1 is associated with cell proliferation, migration, and metastasis. Overexpression of the nontyrosine protein kinase YES1 is associated with activation of the focal adhesion

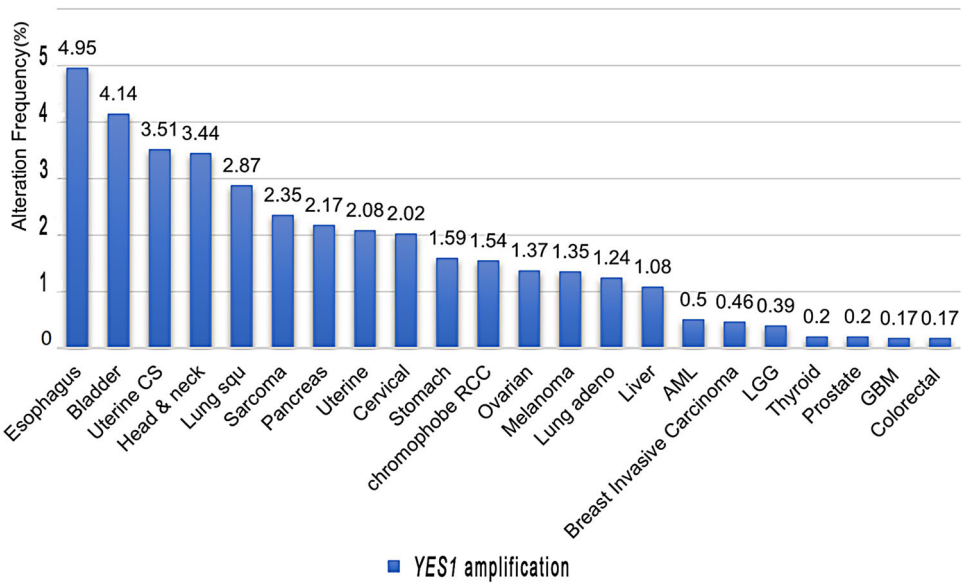

FIGURE 1 Prevalence of *YES1* amplification in tumors from the cBioPortal database. AML, acute myeloid leukemia; GBM, glioblastoma; LGG, low-grade glioma; RCC, renal cell carcinoma. YES1, YES proto-oncogene 1.

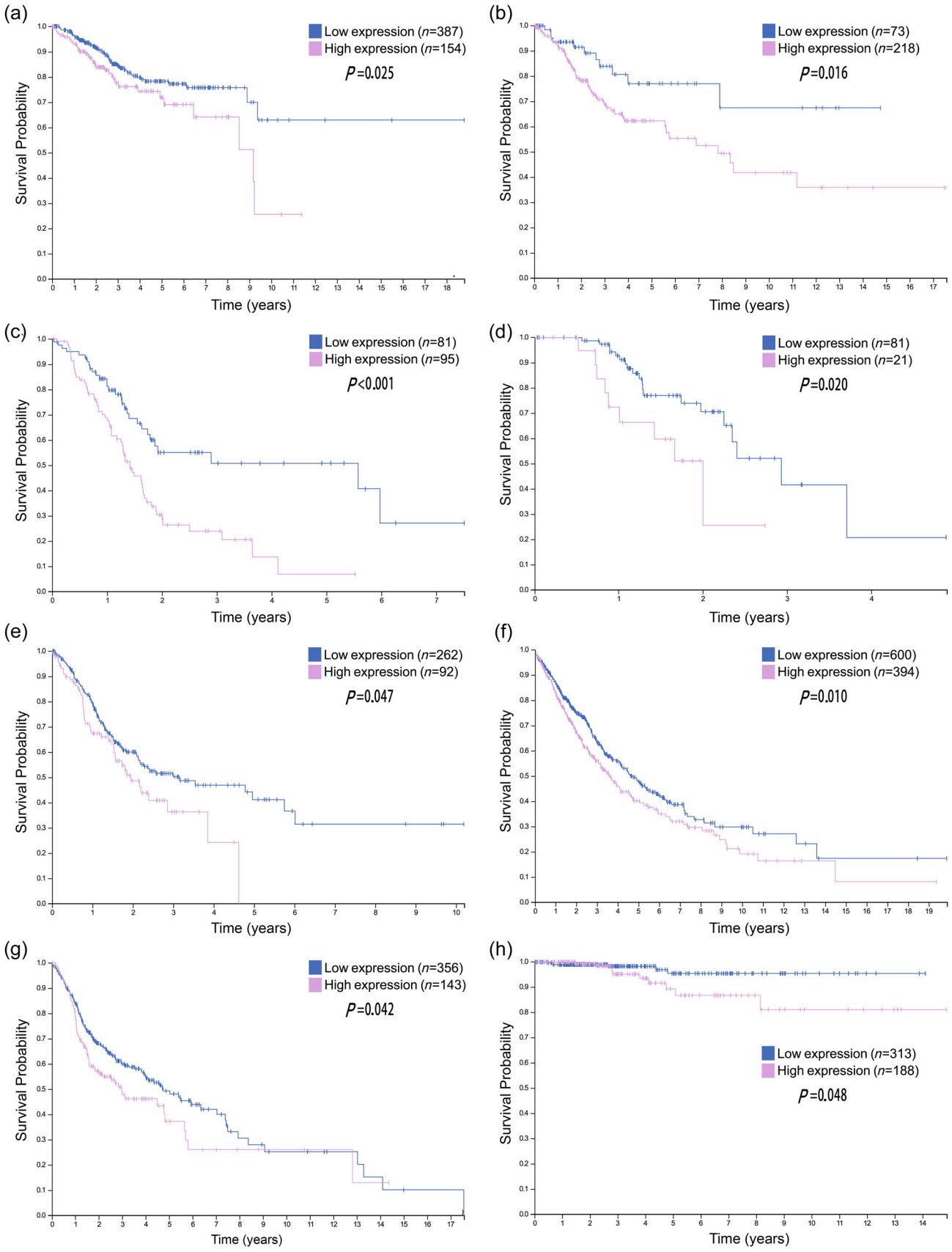

FIGURE 2 Expression of YES1 and its relationship to the prognosis of multiple tumors from the Human Protein Atlas database. (a) Endometrial cancer; (b) cervical cancer; (c) pancreatic cancer; (d) melanoma; (e) stomach cancer; (f) NSCLC; (g) head and neck cancer; (h) thyroid cancer. *Y*-axis: survival probability. *X*-axis: time (years). NSCLC, non-small cell lung cancer; YES1, YES proto-oncogene 1.

kinase [14], YES1-associated protein 1 (YAP1) [23], and mammalian target of rapamycin (mTOR) [24] pathways. Garmendia et al. [11] reported that amplification of *YES1* leading to YES1 overexpression is an altered oncogenic driver in NSCLC that induces tumor growth and metastatic spread. The underlying mechanism may be that YES1 promotes S6K and protein kinase B (AKT) phosphorylation and affects phosphatidylinositol-3-kinase (PI3K)/AKT/mTOR pathway. YES1 overexpression can also modulate the microenvironment to promote tumor growth. Several studies have shown that the circFUT8/miR-944/YES1 axis affects proliferation, migration, and invasion of NSCLC cells [25]. Several YES1-related signaling axes have also been reported in other cancers, and in malignant mesothelioma. YES silencing leads to cell growth inhibition, which is dependent on G1 cell cycle arrest and induction of apoptosis, and knockdown of YES decreases levels of cyclin D by inactivation of β-catenin signaling. RBM15-mediated m6A modification may promote hepatocellular carcinoma progression through the IGF2BP1-YES1-MAPK axis [26]. In gastric cancer, the EPHA2-YES1-Annexin A2 (ANXA2) axis has been confirmed to be a new invasion and metastasis pathway. Among them, YES1 activated by EPHA2 phosphorylates ANXA2 at Tyr24, leading to ANXA2 activation and increased ANXA2 nuclear distribution, which contributes to invasion and metastasis [27]. Furthermore, some microRNAs regulate tumor progression by interacting with YES1. For example, circ-ZNF124-regulated mir-498 directly binds to *YES1* messenger RNA and inhibits NSCLC progression by inactivating the Wnt/β-catenin signaling pathway. Moreover, a study showed that overexpression of mir-133a inhibits the proliferation of NSCLC cells. In gastric cancer, miR-140-5p affects phenotype by regulating *YES1* [16, 28–30]. Wang et al. [31] found that the levels of phosphorylated SFK, EGFR, AKT, and extracellular signal-regulated kinase 1 and 2 (ERK1/2) were significantly increased in *YES1*-amplified cells, and they confirmed that YES1 overexpression is upstream of abnormal activation of SFK, EGFR, AKT, and ERK1/2 signaling pathways. One study showed that YES1 is required for EGFR nuclear translocation [32]. In addition to the classic cytoplasmic EGFR signaling pathway, there is also a signaling pathway affected by nuclear EGFR [33–35], and the nuclear translocation of EGFR leads to resistance to multiple treatments such as targeted therapy, chemotherapy, and radiotherapy [36–40].

YAP1, originally identified as YES1-associated protein 1, is a key effector of the HIPPO signaling pathway and plays a vital role in anticancer drug resistance [41–43]. Literature data suggest that YES1 regulates YAP1 activity indirectly through serine phosphorylation and directly through nuclear localization, and the mechanism by which YES1 regulates YAP1 may also depend on the cellular environment [15, 44]. However, the molecular and functional relationship between YES1 and YAP1 is complex and has not been thoroughly elucidated.

3 | ROLE OF YES1 IN ANTICANCER THERAPY RESISTANCE

3.1 | YES1 resistance to EGFR-TKIs

To date, third-generation small-molecule TKIs targeting EGFR have been developed for the treatment of EGFR-mutant cancers. Despite high response rates to these EGFR-TKIs, resistance remains inevitable for most patients with malignancies. Studies have shown that *YES1* amplification is associated with acquired resistance to first-generation EGFR-TKIs [45, 46]. Yu et al. [45] first identified a patient who acquired *YES1* amplification after erlotinib treatment. Wei et al. [46] reported that YES1 expression was upregulated 1.5-fold in a stable gefitinib-resistant cell line, and these resistant cells responded to SFK-targeting dasatinib. However, none of the studies further elucidated how *YES1* amplification plays a role in acquired resistance to erlotinib and gefitinib. Garmendia et al. [11] reported that YES1 is one of the drivers of NSCLC tumor growth and progression, and YES1 overexpression was associated with *YES1* amplification. These investigators demonstrated that knockdown of YES1 expression by specific small interfering RNAs decreased the levels of phosphorylated S6K, a downstream effector of mTOR, and that YES1 overexpression resulted in increased levels of phosphorylated S6K, whereby YES1 maintained mTOR pathway activity. There is evidence that activation of mTOR confers resistance to erlotinib and gefitinib [47, 48]. Thus, although not directly validated, *YES1* amplification may be involved in resistance to EGFR-TKIs through activation of the mTOR pathway. Fan et al. [9] demonstrated that acquired amplification of *YES1* is a mechanism of resistance to EGFR inhibition and that activation of YES1 expression resulted in resistance to all three generations of EGFR-TKIs, including erlotinib, afatinib, and osimertinib. Ichihara et al. [49] demonstrated that amplification of *YES1* mediates acquired resistance to osimertinib. In their study, treatment of *YES1*-amplified cells with osimertinib alone inhibited phosphorylation of EGFR but not other downstream effectors (e.g., ERK, AKT, or S6). Therefore, *YES1* amplification may lead to osimertinib resistance by activating corresponding signaling pathways, such as AKT and MAPK pathways. Pharmacological or genetic inhibition of YES1 expression restored sensitization to osimertinib in cells with *YES1* amplification. Moreover, combined treatment with

osimertinib and SFK inhibitors inhibited both EGFR and downstream effector signaling, thereby increasing apoptosis in vitro. The relationship between *YES1* amplification and primary resistance to EGFR-TKIs remains unclear. We reported for the first time a case of primary afatinib-resistant lung adenocarcinoma patient carrying EGFR exon 21 L858R missense mutation and *YES1* amplification [50]. The potential role of YES1 in primary EGFR-TKI resistance needs further exploration.

3.2 | YES1 signaling mediates resistance to HER2-targeted drugs

HER2 is an RTK and a member of the ERBB protein family. To date, HER2-targeted therapy has made significant progress, and a variety of HER2-targeted drugs have come out one after another, including anti-HER2 antibodies (trastuzumab and pertuzumab), pan-HER inhibitors (afatinib and neratinib), and trastuzumab emtansine (T-DM1). Amplification of *YES1* has been reported as a mechanism of HER2-targeted drug resistance in various cancers, including gastric cancer, NSCLC, and breast cancer [10, 31, 51, 52]. Wang et al. [31] found that YES1 was overexpressed in T-DM1-resistant cells with *YES1* amplification. YES1 activates different proliferation-related signaling pathways, including EGFR, PI3K, and MAPK pathways, resulting in cross-resistance to all types of HER2-targeting drugs such as antibodies, antibody-drug conjugates, and small-molecule inhibitors. The interaction between YES1 and HER2 was elucidated by Takeda et al. [52], who believed that YES1 directly binds and activates HER2, and *YES1* amplification is the mechanism of neratinib resistance in HER2-driven breast and lung cancers. Multiple studies confirmed that the SRC family inhibitor dasatinib overcomes HER2-targeted drug resistance mediated by *YES1* amplification [10, 31, 51, 52]. As precision medicine continues to advance in cancer treatment, new therapeutic strategies need to be identified to overcome HER2-targeted drug resistance caused by *YES1* amplification.

3.3 | Role of YES1 in resistance to other TKIs

Iida et al. [32] found that YES1 overexpression leads to nuclear EGFR translocation and mediates cetuximab resistance in a NSCLC cell line. Fan et al. [9] reported that *YES1* amplification may lead to resistance to ALK-TKIs in NSCLC patients. In their study, among 17 patients with ALK fusion-driven, two patients with *YES1* amplification developed resistance to ALK-TKIs. However, these researchers did not further explore the specific mechanism of *YES1* amplification leading to ALK-TKI resistance. Lun et al. [53] demonstrated that overexpression of YES1 activates ERK1/2 in an MEK-independent manner in melanoma cells. In their study, YES1 expression activated ERK, which induced resistance to combination therapy with vemurafenib ($BRAF^{V600E}$ inhibitor) and CI1040 (MEK inhibitor). Therefore, this research group suggested that the overexpression of YES1 is one of the key mechanisms of drug resistance in melanoma cells carrying $BRAF^{V600E}$ mutation, and YES1 is one of the kinases that can induce BRAF-MEK combined inhibitory drug resistance. Kim et al. [54] revealed that YES1 expression was upregulated in a dose-dependent manner in nilotinib- and imatinib-resistant cell line models. The researchers believed that when the endogenous BCR-ABL oncoprotein is inactivated by TKI inhibitors, the activated YES1 kinase may provide another means to engage in survival pathways. However, YES1 expression in imatinib-resistant chronic myelogenous leukemia patients did not differ significantly between strong and poor responders. One explanation for this finding is the relatively small clinical sample size in this study. Therefore, further studies with larger clinical sample sizes are needed [54].

3.4 | YES1 regulates tumor cell sensitivity to chemotherapy

Paclitaxel, a tubulin-binding agent, is an antitubulin chemotherapy drug. Studies have shown that overexpression of SFKs mediates paclitaxel resistance in various cancer types, and inhibition of SFKs increases paclitaxel sensitivity [55]. Arima et al. [56] demonstrated that YES1 and its mitotic phosphorylation confer paclitaxel resistance. These researchers demonstrated that cyclin-dependent kinase 1-mediated phosphorylation of YES1 was associated with mitotic arrest and apoptosis in antitubulin chemotherapy. MiR-199a is a negative regulator of various cancers [57]. Chen et al. [58] confirmed that YES1 expression was directly regulated by miR-199a and found that miR-199a was negatively correlated with YES1 expression. Ectopic expression of miR-199a decreased the expression of YES1, whereas overexpression of YES1 downregulated the expression of miR-199a. Low miR-199a expression leads to overexpression of YES1, which mediates paclitaxel resistance in prostate cancer. Touil et al. [59] found that YES1 expression levels were increased by 5-fluorouracil (5-FU) chemotherapy that patients expressing high YES1 levels had a poorer prognosis. The YES1/YAP axis plays an important role in 5-FU

chemoresistance through the joint acquisition of stem cell-like phenotype and cell quiescence. Altogether, YES1 regulates sensitivity to chemotherapy, and high expression of YES1 may be one of the mechanisms of chemotherapy resistance. The role of YES1 in targeted therapy and chemotherapy resistance is shown in Figure 3.

3.5 | Novel therapies for *YES1*-amplified and YES1-overexpressing malignancies

Studies have shown that patients with *YES1* amplification may benefit from SFK inhibitors, such as dasatinib. Dasatinib restored the sensitivity of *YES1*-amplified lung cancer cells to EGFR-TKIs, such as osimertinib and gefitinib [46, 49]. Yoshioka et al. [51] showed that dasatinib monotherapy or combination therapy with afatinib overcame the acquired resistance to afatinib in *YES1*- and *HER2*-amplified gastric cancer cells. Other studies have shown that combination therapy with dasatinib can overcome acquired resistance to neratinib in *YES1*- and *HER2*-amplified breast and lung cancers, and acquired resistance to trastuzumab, lapatinib, and T-DM1 in *YES1*-amplified and HER2-positive breast cancers [10, 31, 52]. Recently, Hamanaka et al. [15] generated the YES1 inhibitor CH6953755. They demonstrated that *YES1* amplification is a potential driver in several tumor types. In their study, CH6953755 had selective antitumor activity against cancers with *YES1* amplification, both in vitro and in vivo.

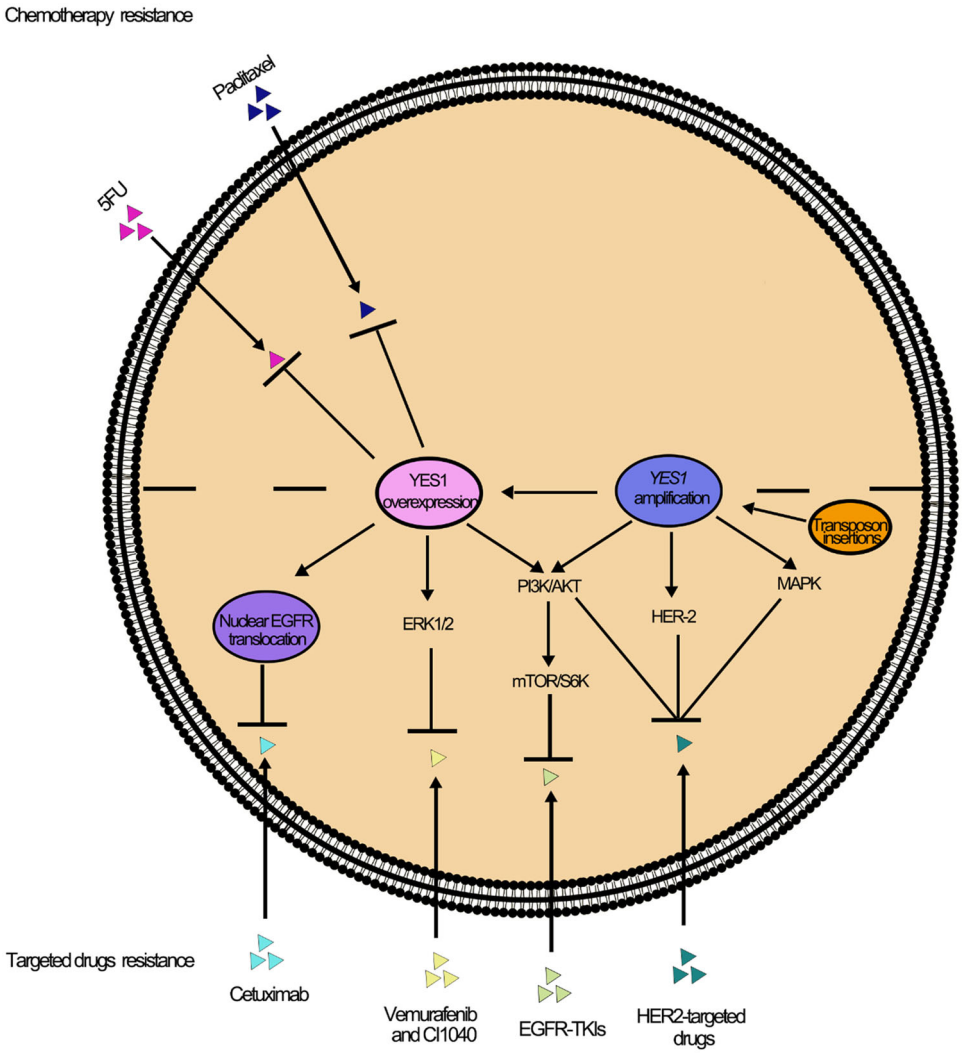

FIGURE 3 Role of YES1 signaling in resistance to targeted therapy and chemotherapy. AKT, protein kinase B; EGFR, epidermal growth factor receptor; ERK1/2, extracellular signal-regulated kinase 1 and 2; 5-FU, 5-fluorouracil; HER2, human epidermal growth factor receptor-2; mTOR, mammalian target of rapamycin; PI3K, phosphatidylinositol-3-kinase; TKI, tyrosine kinase inhibitor; YES1, YES proto-oncogene 1.

4 | CONCLUSION

YES1 is critical for resistance to cancer therapy, including multiple TKIs and chemotherapeutics. Targeting YES1 may reverse drug resistance and serve as a valuable therapeutic strategy in cancer treatment. Therefore, further studies are warranted to reveal the roles of YES1 overexpression and *YES1* amplification in resistance to anticancer therapy. In conclusion, YES1 and regulatory molecules of the YES1 signaling pathway have the potential to be used as novel, reliable and rational molecular targets for antimalignant tumor therapy.

AUTHOR CONTRIBUTIONS

Hai Zhou: Conceptualization (lead); writing—original draft (lead). **Dantong Sun**: Data curation (equal); writing—original draft (equal). **Junyan Tao**: Conceptualization (equal); writing—original draft (equal). **Mingjin Xu**: Data curation (supporting); writing—original draft (supporting). **Xiaochun Zhang**: Writing—review and editing (equal). **Helei Hou**: Funding acquisition (lead); project administration (lead); supervision (lead).

ACKNOWLEDGMENTS

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no data sets were generated or analyzed during the current study.

ETHICS STATEMENT

Not applicable.

INFORMED CONSENT

Not applicable.

ORCID

Hai Zhou http://orcid.org/0000-0002-3578-5755

REFERENCES

1. Ma WW, Adjei AA. Novel agents on the horizon for cancer therapy. CA Cancer J Clin. 2009;59(2):111–37. https://doi.org/10.3322/caac.20003
2. Ramalingam SS, Owonikoko TK, Khuri FR. Lung cancer: new biological insights and recent therapeutic advances. CA Cancer J Clin. 2011;61(2):91–112. https://doi.org/10.3322/caac.20102
3. Vogel CL, Cobleigh MA, Tripathy D, Gutheil JC, Harris LN, Fehrenbacher L, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Clin Oncol. 2002;20(3):719–26. https://doi.org/10.1200/JCO.2002.20.3.719
4. Glickman MS, Sawyers CL. Converting cancer therapies into cures: lessons from infectious diseases. Cell. 2012;148(6):1089–98. https://doi.org/10.1016/j.cell.2012.02.015
5. Schlessinger J. New roles for Src kinases in control of cell survival and angiogenesis. Cell. 2000;100(3):293–6. https://doi.org/10.1016/S0092-8674(00)80664-9
6. Zhang S, Yu D. Targeting Src family kinases in anti-cancer therapies: turning promise into triumph. Trends Pharmacol Sci. 2012;33(3):122–8. https://doi.org/10.1016/j.tips.2011.11.002
7. Ortiz MA, Mikhailova T, Li X, Porter BA, Bah A, Kotula L. Src family kinases, adaptor proteins and the actin cytoskeleton in epithelial-to-mesenchymal transition. Cell Commun Signaling. 2021;19(1):67. https://doi.org/10.1186/s12964-021-00750-x
8. Garmendia I, Redin E, Montuenga LM, Calvo A. YES1: a novel therapeutic target and biomarker in cancer. Mol Cancer Ther. 2022;21(9):1371–80. https://doi.org/10.1158/1535-7163.MCT-21-0958
9. Fan PD, Narzisi G, Jayaprakash AD, Venturini E, Robine N, Smibert P, et al. YES1 amplification is a mechanism of acquired resistance to EGFR inhibitors identified by transposon mutagenesis and clinical genomics. Proc Natl Acad Sci USA. 2018;115(26):E6030–38. https://doi.org/10.1073/pnas.1717782115
10. Takeda T, Yamamoto H, Kanzaki H, Suzawa K, Yoshioka T, Tomida S, et al. Yes1 signaling mediates the resistance to trastuzumab/lapatinib in breast cancer. PLoS One. 2017;12(2):e0171356. https://doi.org/10.1371/journal.pone.0171356
11. Garmendia I, Pajares MJ, Hermida-Prado F, Ajona D, Bértolo C, Sainz C, et al. YES1 drives lung cancer growth and progression and predicts sensitivity to dasatinib. Am J Respir Crit Care Med. 2019;200(7):888–99. https://doi.org/10.1164/rccm.201807-1292OC
12. Zhang G, Wang J, Zheng R, Song B, Huang L, Liu Y, et al. MiR-133 targets YES1 and inhibits the growth of triple-negative breast cancer cells. Technol Cancer Res Treat. 2020;19:153303382092701. https://doi.org/10.1177/1533033820927011
13. Barraclough J, Hodgkinson C, Hogg A, Dive C, Welman A. Increases in c-Yes expression level and activity promote motility but not proliferation of human colorectal carcinoma cells. Neoplasia. 2007;9(9):745–54. https://doi.org/10.1593/neo.07442
14. Chatterji T, Varkaris AS, Parikh NU, Song JH, Cheng CJ, Schweppe RE, et al. Yes-mediated phosphorylation of focal adhesion kinase at tyrosine 861 increases metastatic potential of prostate cancer cells. Oncotarget. 2015;6(12):10175–94. https://doi.org/10.18632/oncotarget.3391
15. Hamanaka N, Nakanishi Y, Mizuno T, Horiguchi-Takei K, Akiyama N, Tanimura H, et al. YES1 is a targetable oncogene in cancers harboring YES1 gene amplification. Cancer Res. 2019;79(22):5734–45. https://doi.org/10.1158/0008-5472.CAN-18-3376
16. Fang Z, Yin S, Sun R, Zhang S, Fu M, Wu Y, et al. miR-140-5p suppresses the proliferation, migration and invasion of gastric cancer by regulating YES1. Mol Cancer. 2017;16(1):139. https://doi.org/10.1186/s12943-017-0708-6
17. Feng H, Masaki T, Nonomura T, Morishita A, Jian G, Nakai S. Activation of c-Yes in hepatocellular carcinoma: a preliminary study. World J Gastroenterol. 2006;12(35):5743–5. https://doi.org/10.3748/wjg.v12.i35.5743
18. Liu L, Yang J, Zhu X, Li D, Lv Z, Zhang X. Long noncoding RNA H19 competitively binds miR-17-5p to regulate YES1

expression in thyroid cancer. FEBS J. 2016;283(12):2326–39. https://doi.org/10.1111/febs.13741
19. Kleber S, Sancho-Martinez I, Wiestler B, Beisel A, Gieffers C, Hill O, et al. Yes and PI3K bind CD95 to signal invasion of glioblastoma. Cancer Cell. 2008;13(3):235–48. https://doi.org/10.1016/j.ccr.2008.02.003
20. Je DW, O YM, Ji YG, Cho Y, Lee DH. The inhibition of SRC family kinase suppresses pancreatic cancer cell proliferation, migration, and invasion. Pancreas. 2014;43(5):768–76. https://doi.org/10.1097/MPA.0000000000000103
21. Liu W, Monahan KB, Pfefferle AD, Shimamura T, Sorrentino J, Chan KT, et al. LKB1/STK11 inactivation leads to expansion of a prometastatic tumor subpopulation in melanoma. Cancer Cell. 2012;21(6):751–64. https://doi.org/10.1016/j.ccr.2012.03.048
22. Redin E, Garmendia I, Lozano T, Serrano D, Senent Y, Redrado M, et al. SRC family kinase (SFK) inhibitor dasatinib improves the antitumor activity of anti-PD-1 in NSCLC models by inhibiting Treg cell conversion and proliferation. J Immunother Cancer. 2021;9(3):e001496. https://doi.org/10.1136/jitc-2020-001496
23. Sourbier C, Liao PJ, Ricketts CJ, Wei D, Yang Y, Baranes SM, et al. Targeting loss of the Hippo signaling pathway in NF2-deficient papillary kidney cancers. Oncotarget. 2018;9(12):10723–33. https://doi.org/10.18632/oncotarget.24112
24. Merhi A, Delrée P, Marini AM. The metabolic waste ammonium regulates mTORC2 and mTORC1 signaling. Sci Rep. 2017;7:44602. https://doi.org/10.1038/srep44602
25. Zhu H, Lu Q, Lu Q, Shen X, Yu L. Matrine regulates proliferation, apoptosis, cell cycle, migration, and invasion of non-small cell lung cancer cells through the circFUT8/miR-944/YES1 axis. Cancer Manag Res. 2021;13:3429–42. https://doi.org/10.2147/CMAR.S290966
26. Cai X, Chen Y, Man D, Yang B, Feng X, Zhang D, et al. RBM15 promotes hepatocellular carcinoma progression by regulating N6-methyladenosine modification of YES1 mRNA in an IGF2BP1-dependent manner. Cell Death Discov. 2021;7(1):315. https://doi.org/10.1038/s41420-021-00703-w
27. Mao L, Yuan W, Cai K, Lai C, Huang C, Xu Y, et al. EphA2–YES1–ANXA2 pathway promotes gastric cancer progression and metastasis. Oncogene. 2021;40(20):3610–23. https://doi.org/10.1038/s41388-021-01786-6
28. Shen Y, Chen F, Liang Y. MicroRNA-133a inhibits the proliferation of non-small cell lung cancer by targeting YES1. Oncol Lett. 2019;18(6):6759–65. https://doi.org/10.3892/ol.2019.11030
29. Li L, He L, Zhao JL, Xiao J, Liu M, Li X, et al. Retracted: MiR-17-5p up-regulates YES1 to modulate the cell cycle progression and apoptosis in ovarian cancer cell lines. J Cell Biochem. 2015;116(6):1050–9. https://doi.org/10.1002/jcb.25060
30. Gao F, Jia L, Han J, Wang Y, Luo W, Zeng Y. Circ-ZNF124 downregulation inhibits non-small cell lung cancer progression partly by inactivating the Wnt/β-catenin signaling pathway via mediating the miR-498/YES1 axis. Anticancer Drugs. 2021;32(3):257–68. https://doi.org/10.1097/CAD.0000000000001014
31. Wang L, Wang Q, Xu P, Fu L, Li Y, Fu H, et al. YES1 amplification confers trastuzumab-emtansine (T-DM1) resistance in HER2-positive cancer. Br J Cancer. 2020;123(6):1000–11. https://doi.org/10.1038/s41416-020-0952-1
32. Iida M, Brand TM, Campbell DA, Li C, Wheeler DL. Yes and Lyn play a role in nuclear translocation of the epidermal growth factor receptor. Oncogene. 2013;32(6):759–67. https://doi.org/10.1038/onc.2012.90
33. Lin SY, Makino K, Xia W, Matin A, Wen Y, Kwong KY, et al. Nuclear localization of EGF receptor and its potential new role as a transcription factor. Nat Cell Biol. 2001;3(9):802–8. https://doi.org/10.1038/ncb0901-802
34. Brand TM, Iida M, Li C, Wheeler DL. The nuclear epidermal growth factor receptor signaling network and its role in cancer. Discov Med. 2011;12(66):419–32.
35. Shah P, Chaumet A, Royle SJ, Bard FA. The NAE pathway: autobahn to the nucleus for cell surface receptors. Cells. 2019;8(8):915. https://doi.org/10.3390/cells8080915
36. Dittmann K, Mayer C, Kehlbach R, Rodemann HP. Radiation-induced caveolin-1 associated EGFR internalization is linked with nuclear EGFR transport and activation of DNA-PK. Mol Cancer. 2008;7:69. https://doi.org/10.1186/1476-4598-7-69
37. Liccardi G, Hartley JA, Hochhauser D. EGFR nuclear translocation modulates DNA repair following cisplatin and ionizing radiation treatment. Cancer Res. 2011;71(3):1103–14. https://doi.org/10.1158/0008-5472.CAN-10-2384
38. Hsu SC, Miller SA, Wang Y, Hung MC. Nuclear EGFR is required for cisplatin resistance and DNA repair. Am J Transl Res. 2009;1(3):249–58.
39. Li C, Iida M, Dunn EF, Ghia AJ, Wheeler DL. Nuclear EGFR contributes to acquired resistance to cetuximab. Oncogene. 2009;28(43):3801–13. https://doi.org/10.1038/onc.2009.234
40. Huang WC, Chen YJ, Li LY, Wei YL, Hsu SC, Tsai SL, et al. Nuclear translocation of epidermal growth factor receptor by Akt-dependent phosphorylation enhances breast cancer-resistant protein expression in gefitinib-resistant cells. J Biol Chem. 2011;286(23):20558–68. https://doi.org/10.1074/jbc.M111.240796
41. Lin L, Sabnis AJ, Chan E, Olivas V, Cade L, Pazarentzos E, et al. The Hippo effector YAP promotes resistance to RAF- and MEK-targeted cancer therapies. Nat Genet. 2015;47(3):250–6. https://doi.org/10.1038/ng.3218
42. Ghiso E, Migliore C, Ciciriello V, Morando E, Petrelli A, Corso S, et al. YAP-Dependent AXL overexpression mediates resistance to EGFR inhibitors in NSCLC. Neoplasia. 2017;19(12):1012–21. https://doi.org/10.1016/j.neo.2017.10.003
43. Ciamporcero E, Shen H, Ramakrishnan S, Yu Ku S, Chintala S, Shen L, et al. YAP activation protects urothelial cell carcinoma from treatment-induced DNA damage. Oncogene. 2016;35(12):1541–53. https://doi.org/10.1038/onc.2015.219
44. Rosenbluh J, Nijhawan D, Cox AG, Li X, Neal JT, Schafer EJ, et al. β-catenin-driven cancers require a YAP1 transcriptional complex for survival and tumorigenesis. Cell. 2012;151(7):1457–73. https://doi.org/10.1016/j.cell.2012.11.026
45. Yu HA, Suzawa K, Jordan E, Zehir A, Ni A, Kim R, et al. Concurrent alterations in EGFR-mutant lung cancers associated with resistance to EGFR kinase inhibitors and characterization of MTOR as a mediator of resistance. Clin Cancer Res. 2018;24(13):3108–18. https://doi.org/10.1158/1078-0432.CCR-17-2961
46. Wei N, Song Y, Zhang F, Sun Z, Zhang X. Transcriptome profiling of acquired gefitinib resistant lung cancer cells

reveals dramatically changed transcription programs and new treatment targets. Front Oncol. 2020;10:1424. https://doi.org/10.3389/fonc.2020.01424

47. Morgillo F, Woo JK, Kim ES, Hong WK, Lee HY. Heterodimerization of insulin-like growth factor receptor/epidermal growth factor receptor and induction of survivin expression counteract the antitumor action of erlotinib. Cancer Res. 2006;66(20):10100–11. https://doi.org/10.1158/0008-5472.CAN-06-1684
48. Fei SJ, Zhang XC, Dong S, Cheng H, Zhang YF, Huang L, et al. Targeting mTOR to overcome epidermal growth factor receptor tyrosine kinase inhibitor resistance in non-small cell lung cancer cells. PLoS One. 2013;8(7):e69104. https://doi.org/10.1371/journal.pone.0069104
49. Ichihara E, Westover D, Meador CB, Yan Y, Bauer JA, Lu P, et al. SFK/FAK signaling attenuates osimertinib efficacy in both drug-sensitive and drug-resistant models of EGFR-mutant lung cancer. Cancer Res. 2017;77(11):2990–3000. https://doi.org/10.1158/0008-5472.CAN-16-2300
50. Tao J, Sun D, Hou H. Role of YES1 amplification in EGFR mutation-positive non-small cell lung cancer: primary resistance to afatinib in a patient. Thorac Cancer. 2020;11(9):2736–9. https://doi.org/10.1111/1759-7714.13583
51. Yoshioka T, Shien K, Takeda T, Takahashi Y, Kurihara E, Ogoshi Y, et al. Acquired resistance mechanisms to afatinib in HER2-amplified gastric cancer cells. Cancer Sci. 2019;110(8):2549–57. https://doi.org/10.1111/cas.14089
52. Takeda T, Yamamoto H, Suzawa K, Tomida S, Miyauchi S, Araki K, et al. YES1 activation induces acquired resistance to neratinib in HER2-amplified breast and lung cancers. Cancer Sci. 2020;111(3):849–56. https://doi.org/10.1111/cas.14289
53. Lun XK, Szklarczyk D, Gábor A, Dobberstein N, Zanotelli VRT, Saez-Rodriguez J, et al. Analysis of the human kinome and phosphatome by mass cytometry reveals overexpression-induced effects on cancer-related signaling. Mol Cell. 2019;74(5):1086–102.e5. https://doi.org/10.1016/j.molcel.2019.04.021
54. Kim TM, Ha SA, Kim HK, Yoo J, Kim S, Yim SH, et al. Gene expression signatures associated with the in vitro resistance to two tyrosine kinase inhibitors, nilotinib and imatinib. Blood Cancer J. 2011;1(8):e32. https://doi.org/10.1038/bcj.2011.32
55. Le XF, Bast Jr., RC. Src family kinases and paclitaxel sensitivity. Cancer Biol Ther. 2011;12(4):260–9. https://doi.org/10.4161/cbt.12.4.16430
56. Arima Y, Hayashi H, Kamata K, Goto TM, Sasaki M, Kuramochi A, et al. Decreased expression of neurofibromin contributes to epithelial–mesenchymal transition in neurofibromatosis type 1. Exp Dermatol. 2010;19(8):e136–41. https://doi.org/10.1111/j.1600-0625.2009.01017.x
57. Wang Q, Ye B, Wang P, Yao F, Zhang C, Yu G. Overview of microRNA-199a regulation in cancer. Cancer Manag Res. 2019;11:10327–35. https://doi.org/10.2147/CMAR.S231971
58. Chen L, Cao H, Feng Y. MiR-199a suppresses prostate cancer paclitaxel resistance by targeting YES1. World J Urol. 2018;36(3):357–65. https://doi.org/10.1007/s00345-017-2143-0
59. Touil Y, Igoudjil W, Corvaisier M, Dessein AF, Vandomme J, Monté D, et al. Colon cancer cells escape 5FU chemotherapy-induced cell death by entering stemness and quiescence associated with the c-Yes/YAP axis. Clin Cancer Res. 2014;20(4):837–46. https://doi.org/10.1158/1078-0432.CCR-13-1854

How to cite this article: Zhou H, Sun D, Tao J, Xu M, Zhang X, Hou H. Role of YES1 signaling in tumor therapy resistance. Cancer Innovation. 2023;2:210–218. https://doi.org/10.1002/cai2.51