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Targeting Unique Features of Quiescent Cancer Stem Cells to Overcome Resistance and Recurrence in Cancer Therapy: A Review

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Review Article

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ABSTRACT

Quiescent cancer stem cells (QCSC) are non-proliferating cells that survive in the G0 phase and have low ki-67 expression and high p27 expression. QCSCs have the ability to evade most chemotherapy, and some subsequent treatments may result in a higher proportion of quiescent cancer stem cells in the tumor. QCSCs are also associated with cancer recurrence rates because they can re-enter the cell cycle to proliferate when tumor environmental conditions are favorable. QCSCs cause high rates of drug resistance and tumor recurrence, therefore it is necessary to understand the properties of QCSCs. QCSCs have a mechanism that regulates the transition between the proliferative phase and the stationary phase in cancer cells, therefore it is necessary to find new treatments to eliminate QCSCs in tumors. In this review, the authors discuss the mechanisms of QCSCs in inducing drug resistance and tumor recurrence as well as therapies to target QCSCs so that the rate of drug resistance and tumor recurrence can be reduced, including in

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this review: (i) identifying reactive quiescent cancer cells and eliminating them through anticancer reagents. cell cycle dependent; (ii) modulating the transition from the quiescent to the proliferative phase; and (iii) eliminate QCSC by targeting its unique features. Targeting cancer cells that are in proliferating and stationary phase may ultimately be used as a more effective therapeutic strategy for cancer treatment.

Keywords: Quiescent cancer stem cells; targeting unique features; targeted therapy.

1. INTRODUCTION

"Cancer is a chronic disease that is very threatening to human life. Many strategies have been discovered in cancer treatment including chemotherapy, radiotherapy, surgery and targeted therapy. The incidence of cancer in women has stabilized and decreased slightly in men in the last decades, and cancer death rates have also decreased" [1]. However, not all types of cancer can be treated with traditional cancer treatment [2]. Recurrence, metastasis, resistance, heterogeneity to chemotherapy, evasion of immunological surveillance and radiotherapy are the main factors causing cancer treatment failure [3]. "This failure can be described by the characteristics of the cancer stem cells" [4]. "Cancer stem cells can cause cancer recurrence, metastasis, radiation resistance, and multidrug resistance through their ability to survive in the G0 phase so that in a favorable environment they can give rise to new cancer" [5]. Therefore, cancer stem cells are currently considered the most important target for cancer treatment.

"Cancer stem cells were first identified in leukemia patients in the 1990s, and isolated through the expression of surface markers CD34+ and CD38−" [6,7]. "Cancer stem cells can express surface markers such as nestin, CD44, and CD133 and are found in many non-solid and solid tumors" [8,9]. "CSCs can proliferate to produce tumors through self-renewal mechanisms and differentiation into several cellular subtypes" [10]. Intracellular and extracellular factors are factors that can be used as drug targets for cancer treatment because they can control CSC activity [11]. To understand the properties of CSCs, through this review we summarize the therapeutic methods targeting cancer stem cells that are effective for cancer therapy in both basic biomolecular research and clinical studies.

1.1 Characteristics of Quiescent Cancer Stem Cells

"Quiescent cancer stem cells (QCSC) are non-proliferating cells arrested in the G0 phase, characterized by low ki-67 expression and high p27 expression. QCSC has the ability to avoid most chemotherapy, and some subsequent treatments may result in a higher proportion of quiescent cancer stem cells in the tumor. QCSC is also related to cancer recurrence rates because they can re-enter the cell cycle to proliferate when tumor environmental conditions are favorable. QCSCs are also associated with cancer recurrence rates because they can re-enter the cell cycle to proliferate when tumor environmental conditions are favorable. QCSCs cause high rates of drug resistance and tumor recurrence, therefore it is necessary to understand the properties of QCSCs". [92] "QCSCs have a mechanism that regulates the transition between the proliferative phase and the stationary phase in cancer cells, therefore it is necessary to find new treatments to eliminate QCSCs in tumors. In this review, the authors discuss the mechanisms of QCSCs in inducing drug resistance and tumor recurrence as well as therapies to target QCSCs so that the rate of drug resistance and tumor recurrence can be reduced, including in this review: (i) identify reactive quiescent cancer cells and eliminate them using cell cycle-dependent anticancer reagents; (ii) modulating the transition from the quiescent to the proliferative phase; and (iii) eliminate QCSC by targeting its unique features. Targeting cancer cells that are in proliferating and stationary phase may ultimately be used as a more effective therapeutic strategy for cancer treatment" [12].

1.2 Cancer Stem Cell Pathways as targets for Cancer Therapy

1.2.1 Wnt signaling pathway in CSCs

"Wnts include large protein ligands that influence the establishment of cell polarity and cell fate" [14]. "The Wnt pathway is very complex consisting of 19 Wnt ligands and more than 15 receptors" [15]. "The Wnt signaling pathway consists of canonical Wnt signaling (via the FZD-LRP5/6 receptor complex, leading to β-catenin derepression) and non-canonical Wnt signaling

(via the FZD receptor and/or ROR1/ROR2/RYK co-receptors, activating PCP signaling , RTK, or Ca2+ cascade)" [16]. In canonical Wnt signaling, i.e. in the absence of Wnt ligands (Fig. 2. Inactive Wnt signaling state), glycogen synthase kinase 3β (GSK3β) phosphorylates β-catenin and through ubiquitination of β-TrCP200 results in degradation of β-catenin as well as inhibiting β-catenin translocation from the cytoplasm to the nucleus [17]. In contrast, in the presence of Wnt ligands such as Wnt3a and Wnt1, they associate with the Fzd receptor and LRP co-receptor (Fig. 3. Active Wnt signaling).

GSK3β and CK1α are phosphorylated by LRP receptors [18]. "The Axin complex releases β-Catenin to enter the nucleus. In addition, the association of β-catenin with LEF/TCF results in increased recruitment of histone modifying coactivators, such as Pygo, BCL9, CBP/p300, and BRG1, to carry out transcriptional activation. β-catenin is not involved in noncanonical Wnt signaling. During Wnt/PCP signaling, Dvl activation occurs through the binding mechanism of Wnt ligands and ROR-Frizzled receptors" [19]. Dvl has a role in inhibiting the binding of the cytoplasmic protein DAAM1 and the small GTPase Rho [20], where the small GTPase Rac1 and Rho can trigger JNK (c-Jun N-terminal kinase) and ROCK (Rho kinase). This leads to rearrangement of transcriptional and/or cytoskeletal responses [21]. "Phospholipase C activity activates G protein-induced Wnt/Ca2+ signaling. This leads to downstream calcium-dependent cytoskeletal and/or transcriptional responses as well as calcium fluxes within the cell" [22, 23].

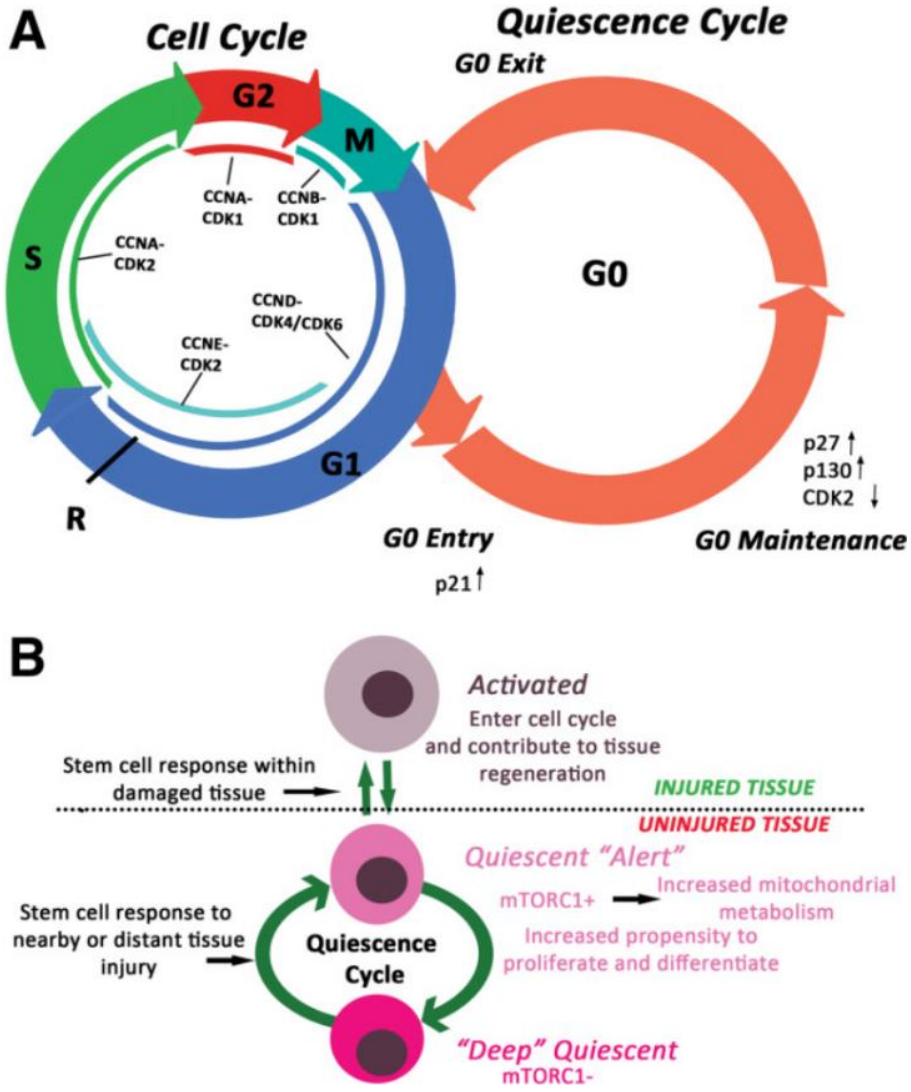

Fig. 1. The cell cycle and the quiescence cycle [13]

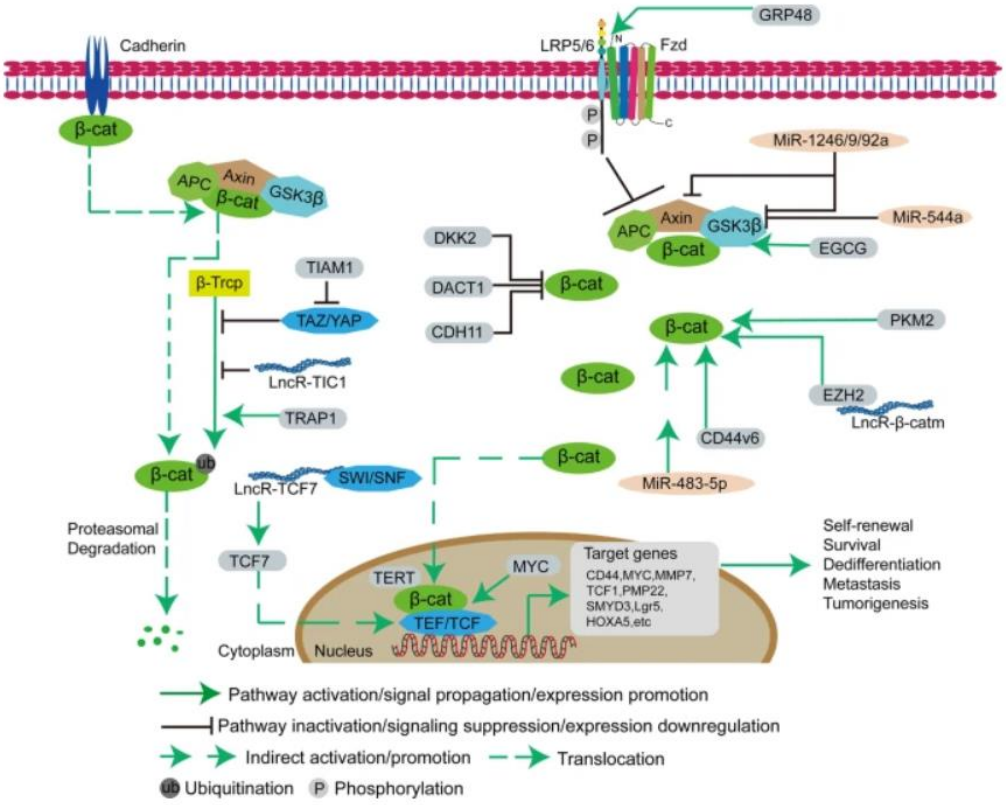

Fig. 2. Inactive wnt signaling state [17]

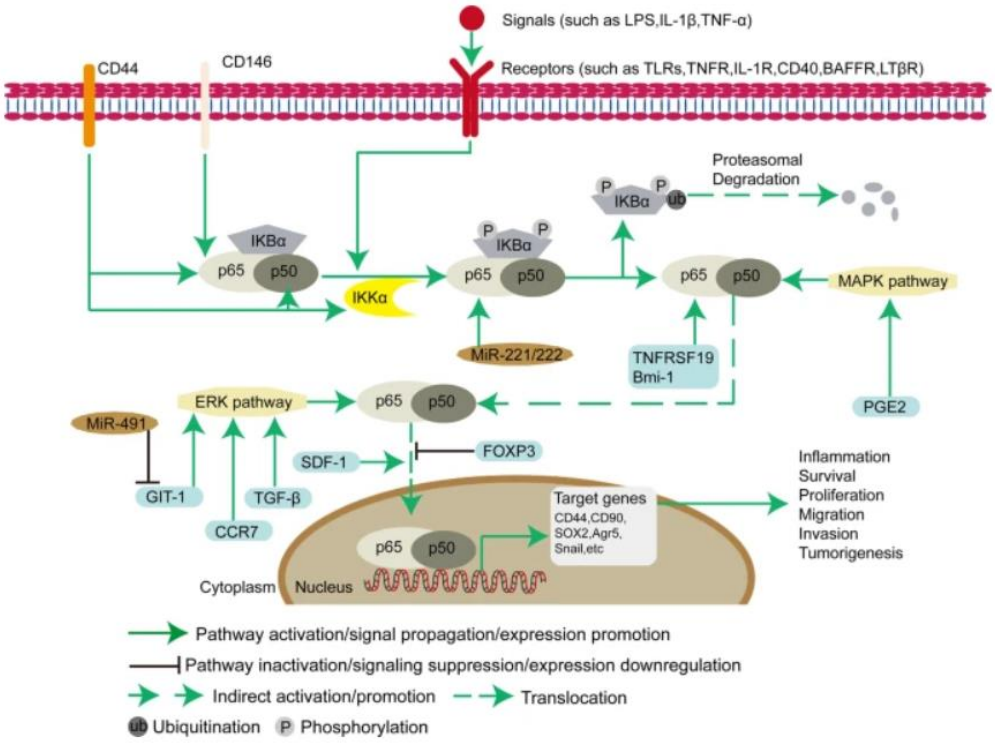

Fig. 3. Active Wnt signaling state [17]

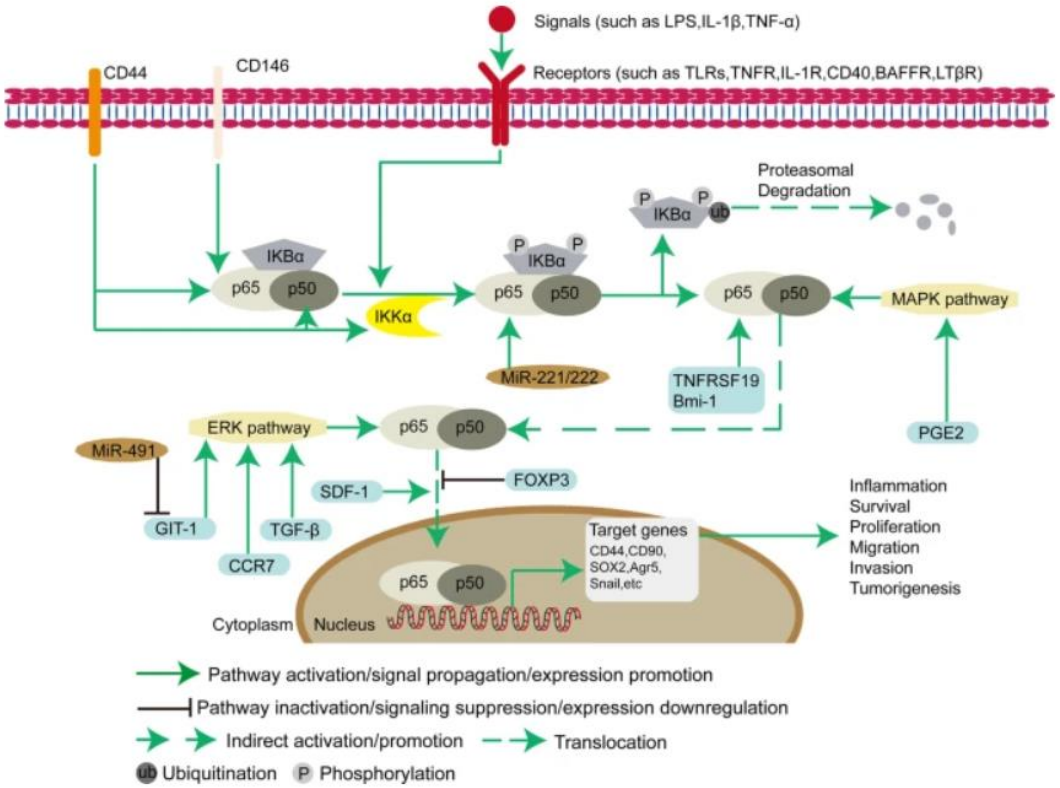

Fig. 4. NF-κB signaling pathway in CSCs [24]

1.2.2 NF-κB signaling pathway in CSCs

The NF-κB pathway has an important role in regulating CSC self-renewal, inflammation, maintenance and metastasis (Fig. 4). CD44+ cells induce self-renewal, CSC maintenance and metastasis, through increasing the expression of IKKα, RelA, RelB, as well as mediating nuclear activation of the p50/RelA dimer (p65/p50) [24]. "Activation of the NF-κB pathway of noncanonical cells is induced by high levels of NIK to regulate self-renewal and metastasis of breast CSCs" [25]. "Stromal cell-derived factor-1 (SDF-1) also has a role in regulating p65 translocation from the cytoplasm to the nucleus" [26]. "In colorectal CSCs, Prostaglandin E2 (PGE2) contributes to tumor formation, maintenance, and metastasis through activating NF-κB in the EP4-PI3K (phosphoinositide 3-kinase) and EP4-MAPK pathways" [27]. "In cell proliferation, metastasis, and apoptosis involving important mediators such as chemokines, low molecular weight proinflammatory cytokines" [28]. "Interaction between C-C chemokine receptor 7 with chemokine ligand 21 results in inhibition of apoptotic mechanisms and induces survival and migration in CD133+ pancreatic cancer-like cells by increasing the expression of p65 and extracellular signal-regulated kinase 1/2 (Erk1/2)" [28].

In addition, in gastric CSCs there was an increase in p65 protein in the integration site of the specific B cell murine leukemia virus Moloney 1 (Bmi-1) as well as MicroRNA also plays an important role in promoting CSC proliferation [28]. Inhibition of PTEN expression and subsequent induction of AKT phosphorylation resulting in increased p65, p-p65, and COX2 resulted in Mir-221/222 promoting self-renewal, migration, and invasion in breast CSCs [29].

1.2.3 JAK-STAT signaling pathway in CSCs

The JAK/STAT pathway induces ESC survival, self-renewal, hematopoiesis as well as neurogenesis [30]. In CSCs, this pathway is activated through sustained activation of STAT3, and significantly has the effect of enhancing cell survival and stemness maintenance in breast CSCs [31]. Cell renewal, migration, and invasion in non-small cell lung CSCs are induced by IL-10 [32]. The JAK1/STAT3 pathway in CD126+ high ALDH endometrial CSCs is activated by IL-6 [33]. In addition, IL-6 through activation of the downstream gene Oct4 in breast cancer induces

the conversion of non-stem cancer cells into cancer stem-like cells [34]. The JAK1/STAT6 pathway in ovarian CSCs is also activated by Oct4 [35]. Erythropoietin and IL-6 activate the JAK2/STAT3 pathway in CD44+CD24− as well as breast and colorectal CSCs [36,37,38]. JAK2/STAT3 signaling is activated by retinol-binding protein 4 via the STRA6 receptor in colon CSCs [39]. Through the JAK1/STAT3 pathway, HIF-1α promotes self-renewal of glioma stem-like cells [40]. AJUBA is a scaffolding protein that plays a role in the regulation of cell adhesion, proliferation, differentiation, and migration and through the JAK1/STAT1 pathway plays a role in increasing cell survival and proliferation of colorectal CSCs [41].

1.2.4 PI3K/AKT/mTOR signaling pathway in CSCs

Phosphatidylinositol-3-kinase (PI3K) is an intracellular phosphatidylinositol kinase [42]. Phosphatidylinositol-3-kinase (PI3K) consists of the p110 catalytic and p85 regulatory subunits, which have serine/threonine (Ser/Thr) kinase and phosphatidylinositol kinase activities [43]. AKT is a serine/threonine kinase that has three isoforms including AKT1, AKT2, and AKT3 [44]. The AKT protein is an important effector for PI3K and can also be a response to PI3K. The mammalian target of rapamycin complex (mTOR) is the main downstream target gene of AKT, which is a conserved serine/threonine kinase. The mammalian target of rapamycin complex (mTOR) forms two different multiprotein complexes including mTORC1 and mTORC2 [45]. mTORC1 consists of mTOR, raptor, mLST8, and two negative regulators including DEPTOR and PRAS40 [46,47]. At serine residue 473, mTORC2 phosphorylates AKT leading to full activation of the AKT protein [48].

Recent research shows that in glioblastoma multiforme, mutations in the PTEN gene have the effect of inhibiting PI3K/mTOR signaling. However, deletion of the PTEN gene in neural stem cells can cause increased cell growth, invasiveness in vivo, resistance to cell apoptosis as well as increased cell migration properties [49]. Inactivation of PTEN and activation of protein kinase B have been found in myeloproliferative neoplasia and leukemia [50]. Therefore, the PI3K/mTOR signaling pathway is critical in regulating cell proliferation and survival. In non-small cell lung cancer [51], breast cancer [52], prostate cancer [53], Burkitt lymphoma [54], esophageal adenocarcinoma [55], and colorectal cancer [56] improper activation of PI3K/mTOR signaling normal was found.

1.3 Targeting Unique Features QCCs to Overcome Resistance and Recurrence in Cancer Therapy

Eradicating all cancer cells, both proliferating cancer cells and quiescent cancer cells, is the main goal of optimal cancer treatment (Fig. 5). Because QCC and proliferating cells have different characteristics, it is necessary to find a QCC elimination strategy. We found several characteristics of QCC, but cannot cover all of them, because they have been studied separately in different studies.

a. Quiescent cancer cells exhibit altered mitochondrial activity

One study showed that inhibiting mitochondrial OXPHOS is a effective strategy to against cancer cells that reside in environments of nutrient deprivation and hypoxia. A study showed that in melanoma cells, the endogenous cell cycle inactive marker p27 induced an increase in GFP signal and the endogenous cell cycle active marker ki-67 caused an increase in mCherry signal. The authors identified a group of cancer cells expressing low levels of ki-67 and high levels of p27, which are thought to be in a quiescent state. Compared with other cells, these QCC show high levels of c-Myc expression and stimulate mitochondrial OXPHOS activity by transactivating genes encoding OXPHOS enzymes, including isocitric dehydrogenase subunit 3 (IDH3) [57].

Inhibition of mitochondrial OXPHOS has the effect of reducing cell viability in quiescent cells by a small molecule inhibitor of mitochondrial complex I, IACS-010759 [57], whereas it does not significantly affect the viability of cells active in the cell cycle [58]. This suggests that overcoming drug resistance in QCC can be done by targeting mitochondrial OXPHOS. Similar results have been shown by other studies, where glucose-deficient multicellular tumor spheroids (MCTS) with the QCC population as the core, then screened 1,600 compounds with a documented clinical history and identified five molecules that showed selective MCTS activity including niclosamide, nitazoxanide, closantel, pyrvinium pamoate, and salinomycin. These experiments showed that the five identified compounds were proven to inhibit mitochondrial respiration. In this study it can also be concluded

that MCTS containing the QCC population is very dependent on oxidative phosphorylation from glycolysis [59]. In another study, three different models, namely monolayer, proliferative MCTS, and quiescent MCTS, used HCT116 colon carcinoma cancer cells and examined the gene expression profiles on a panel of compounds targeting various processes (mitochondrial inhibitors, kinase inhibitors, autophagy inhibitors, mTOR inhibitors, MEK, etc.). Further research found that after exposure to OXPHOS inhibitors, the mevalonate pathway was significantly upregulated. The combination of the mitochondrial inhibitor nitazoxanide and the cholesterol synthesis inhibitor zaragozic acid can result in a strong reduction in cancer cell colony formation. However, the combination of nitazoxanide with irinotecan, the PI3K/mTOR dual inhibitor BEZ235, or the autophagy inhibitor Lys05 did not cause increased toxicity against quiescent MCTS, but suggests that inhibition of the mevalonate pathway is a promising strategy to optimize the effects of OXPHOS inhibitors on QCC [60].

Other studies also show that disruption of mitochondrial fatty acid β-oxidation (FAO) can induce apoptosis in cells. Targeting mitochondrial metabolism in QCC could be a fundamental principle of cell plasticity and a potential novel therapeutic option [61]. We also reported that the mitochondrial inhibitor VLX600, was able to eliminate not only proliferating cancer cells but also quiescent cancer cells, due to the bioenergetic disruption effect following mitochondrial inhibition [62]. The main source of ATP production in mitochondria. Mitochondria also play an important role in building macromolecules, regulating signaling processes, regulating intrinsic cell apoptosis, maintaining ROS homeostasis and cancer metastasis [63,64]. Therefore, it makes sense that the presence of mitochondria is necessary in QCC. Mitochondrial targeting, such as OXPHOS, may be a promising strategy to eliminate QCC in cancer cells [57,58,59,60,65].

b. Quiescent cancer cells cannot tolerate exacerbated autophagy

Quiescent cancer cells in solid tumors are usually located in areas far from blood vessels, causing a state of lack of nutrients and oxygen. Previous studies showed that VLX600 exhibited high toxicity effects against quiescent cancer cells through inhibiting mitochondrial induction mechanisms and autophagy [62]. In another study, quiescent cancer cells were treated with an inhibitor of ULK1, a key kinase that activates autophagy in combination with standard chemotherapy treatment (CPT-11), and were able to undergo apoptosis and were unable to regrow after treatment [66].

Saikosaponin A is a Bupleurum derivative compound that deactivates the Akt-mTOR signal and can worsen autophagy and can effectively eliminate silent prostate cancer cells that are resistant to various drugs. In addition, administration of saikosaponin A can be administered during the docetaxel treatment interval and can cause potent cell death in vitro and in vivo. This research shows that saikosaponin A can increase the effectiveness of therapy and prevent cancer recurrence by targeting QCCs [67].

c. Quiescent cancer cells have high levels of DYRK1B

A family of tyrosine-regulated kinases that have dual specificity belongs to the CMGC(DYRK) group consisting of DYRK1A, DYRK1B, DYRK2, DYRK3, and DYRK4 which includes mitogen-activated protein kinase (MAPK), cyclin-dependent kinases (CDKs), glycogen synthase kinase (GSK), and CDK-like kinases (CLKs) [68]. Studies have shown that there is a strong increase in DYRK1B family members when tumor cells exit the cell cycle after mitogen deprivation or pharmacological inhibition of proliferation pathways in various types of cancer cells such as breast, melanoma, colon, pancreatic and ovarian carcinomas [69,70,71]. Conversely, due to RNA interference there is a decrease in DYRK1B levels which allows C2C12 myoblasts to re-enter the cell cycle [72]. DYRK1B plays an important role in maintaining cancer cells in the stationary phase. DYRK1B is able to control the checkpoint in S phase by stabilizing the cyclin-dependent kinase inhibitor p27Kip1 and inducing cyclin D degradation [73,74]. DYRK1B also stabilizes the DREAM complex consisting of E2F, DP, RB, and MuvB, which is an important coordinator in phosphorylating LIN52 at Ser28 to keep the cell in the G0 quiescent state [75].

In addition, upregulating antioxidant gene expression and reducing intracellular reactive oxygen species levels, DYRK1B has a pro-survival role [76,77]. Substantial evidence suggests that quiescent cancer cell apoptosis can occur, as depletion or inhibition of DYRK1B

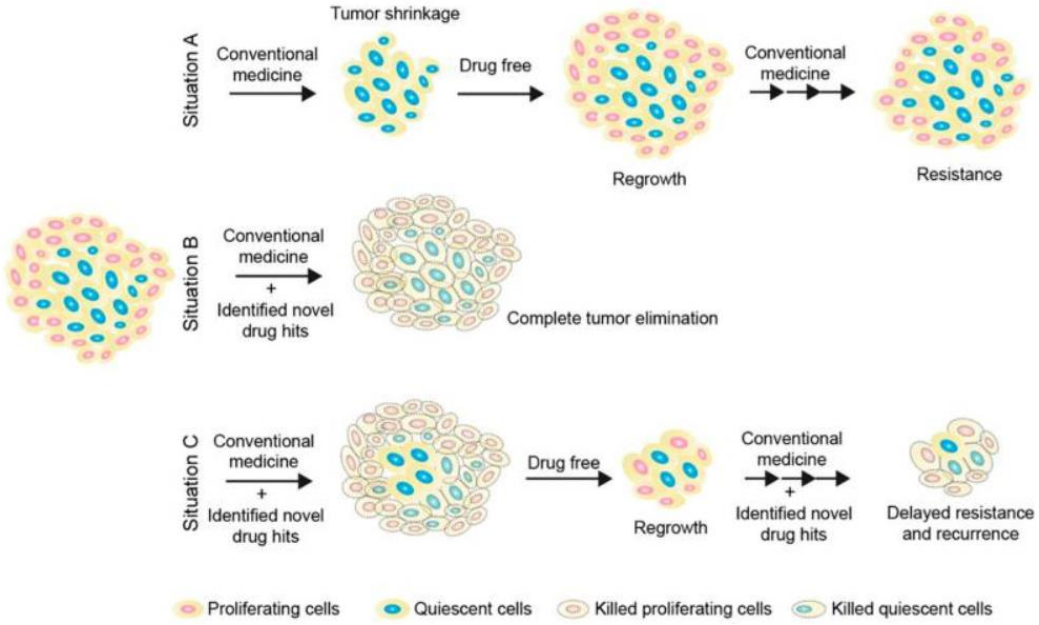

Fig. 5. Elimination of tumor cells by targeting both proliferative and quiescent cancer cell populations

promotes cell cycle re-entry and increases with high DYRK1B expression [78,79,80]. Furthermore, DYRK1B inhibitors were shown to sensitize cells to the cytotoxic effects of anticancer drugs targeting proliferating cells [81,82]. In conclusion, targeting increased DYRK1B levels in QCC may disrupt the quiescent state and eliminate it further through anticancer reagents targeting proliferating cells.

d. Quiescent cancer cells have the potential to upregulate the c-YES/YAP signaling axis

A cytoplasmic non-receptor protein (c-YES) belonging to the SRC kinase (SFK) family and has been shown to have a function as a biomarker in various types of tumors as well as oncogenic properties [83]. In cancer cells with poor prognosis, c-YES is overexpressed [84,85]. Some patients treated with EGFR and ALK inhibitors, have c-YES amplification becoming resistant to targeted therapy [86,87]. Recent studies have shown that, HT29 colon cancer cells, a 5-FU resistant clonal cell population can enter a quiescent G0 state that can revert to the cell cycle when re-exposed when the 5-FU concentration is higher. These quiescent cells showed high levels of c-YES/YAP signal expression. In colon cancer with liver metastases after 5-FU-based neoadjuvant chemotherapy had higher levels of YES1 and YAP transcripts, and also had a positive correlation with shorter patient survival as well as colon cancer recurrence [84].

Recent studies showed that 5-FU induced quiescence of cancer cells could result in high levels of YAP and decreased levels of c-Myc and cyclin E1, which was associated with overall survival and shorter disease-free time [88]. Overall, the therapeutic targets are thought to have the potential to kill drug-resistant quiescent cancer cells via the c-Yes/YAP signaling pathway.

e. Quiescent cancer cells have immune evasion capabilities

Metastasis occurs after resection of the primary tumor, through an unknown mechanism with a small number of cancer cells disseminating and persisting as a latent entity. Latent carcinoma cells (LCC) from breast and lung tumors can easily enter a quiescent state in 2% serum low mitogen medium (MLM), whereas the apoptosis marker caspase-3 remains unchanged for one month as a potential entity in the corresponding organs. These quiescent LCC cells still have tumorigenic potential and can induce metastasis. Further studies revealed that this QCC led to escape from immune surveillance and downregulation of NK cell activators via DKK1 protein expression [89].

These findings suggest that quiescent metastases can trigger immunological elimination

of latent metastases through selective reactivation of NK cell ligands in cells. Recent research also revealed that in breast tumor cells, QCCs overexpress the silent marker p27 and are able to resist T cell attack by establishing an immunosuppressive niche. QCC associated genes with chemoresistance such as Kdm5a, Kdm5b, Car9, hypoxia (Hif1a), and glucose transporter including Slc2a1 or Glut1. However, the expression levels of Cd81, Il12a, and Il12b, which represent key cytokines for T cell responses [90], were lower in the QCC niche. These studies suggest that QCC can induce immunotherapy resistance by creating a hypoxic immunosuppressive environment locally to block T cell function and restore T cell function to eliminate QCC so as to counter immunotherapy resistance [91].

2. CONCLUSION

QCC have the ability to evade most cancer treatments and have been associated with resistance to stem cell cancer as well as recurrence. QCC can re-enter the proliferation phase when tumor environmental conditions are favorable. Accumulating research aimed at finding QCC therapy options in cancer cells has revealed several clues to overcome resistance and recurrence of cancer therapy. Here, we review and discuss recent research advances in QCC treatment including reactivating quiescent cancer cells and eliminating them through cell cycle-dependent anticancer reagents, modulating the switch from quiescence to proliferation; and eliminate QCC by targeting its unique features.

Currently, there are many obstacles in cancer treatment to face QCC. Further research is still needed to understand the characteristics of QCC, the regulatory mechanisms of proliferative and stationary phase transitions in cancer cells, and discover new strategies to eliminate QCC in solid cancer cells. This is a long-term challenge and still requires further research in the future.

CONSENT AND ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Siegel RL, Miller KD, Jemal A. Cancer statistics. CA Cancer J. Clin. 2019;69:7–34.
2. Sun Y. Translational horizons in the tumor microenvironment: Harnessing breakthroughs and targeting cures. Med. Res. Rev. 2015;35:408–436.
3. Batlle E, Clevers H. Cancer stem cells revisited. Nat. Med. 2017;23:1124–1134.
4. Reya T, Morrison SJ, Clarke MF, Weissman IL. Jn Stem cells, cancer, and cancer stem cells. Nature. 2001;414: 105.
5. Chen W, Dong J, Haiech J, Kilhoffer MC, Zeniou M. Cancer stem cell quiescence and plasticity as major challenges in cancer therapy. Stem Cells Int. 2016;1740936(2016).
6. Lapidot T, et al. A cell initiating human acute myeloid leukaemia after transplantation into SCID mice. Nature. 1994;367:645–648.
7. Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. Nat. Med. 1997;3:730–737.
8. Shimokawa M, et al. Visualization and targeting of LGR5(+) human colon cancer stem cells. Nature. 2017;545:187–192.
9. Shibata M, Hoque MO. Targeting cancer stem cells: A strategy for effective eradication of cancer. Cancers. 2019;11:732.
10. Visvader JE, Lindeman GJ. Cancer stem cells: Current status and evolving complexities. Cell Stem Cell. 2012;10:717–728.
11. Ajani JA, Song S, Hochster HS, Steinberg IB. Cancer stem cells: The promise and the potential. Semin. Oncol. 2015;42(Suppl. 1):S3–S17.
12. Emma Lindell, Lei Zhong, Xiaonan Zhang. Quiescent Cancer Cells—A Potential Therapeutic Target to Overcome Tumor Resistance and Relapse. Int J Mol Sci. 2023 Feb;24(4):3762. Published online 2023 Feb 13.
    DOI: 10.3390/ijms24043762
13. Mohammad Rumman, Jyotsna Dhawan, Moustapha Kassem. Concise Review: Quiescence in Adult Stem Cells: Biological Significance and Relevance to Tissue

Regeneration. Stem Cells Journals. Published: 15 June 2015.
Available:https://doi.org/10.1002/stem.2056

14. Logan CY, Nusse R. The Wnt signaling pathway in development and disease. Annu. Rev. Cell Dev. Biol. 20, 781–810 (2004).
15. Kahn M. Can we safely target the WNT pathway? Nat. Rev. Drug Discov. 2014;13:513–532.
16. Katoh M. Canonical and non-canonical WNT signaling in cancer stem cells and their niches: Cellular heterogeneity, omics reprogramming, targeted therapy and tumor plasticity (Review). Int. J. Oncol. 2017;51:1357–1369.
17. Latres E, Chiaur DS, Pagano M. The human F box protein beta-TRCP associates with the Cul1/Skp1 complex and regulates the stability of beta-catenin. Oncogene. 1999;18:849–854.
18. Metcalfe C, Mendoza-Topaz C, Mieszczanek J, Bienz M. Stability elements in the LRP6 cytoplasmic tail confer efficient signalling upon DIX-dependent polymerization. J. Cell Sci. 2010;123:1588–1599.
19. Tree DR, et al. Prickle mediates feedback amplification to generate asymmetric planar cell polarity signaling. Cell. 2002;109:371–381.
20. Habas R, Kato Y, He X. Wnt/Frizzled activation of Rho regulates vertebrate gastrulation and requires a novel Formin homology protein Daam1. Cell. 2001;107:843–854.
21. Kikuchi A, Yamamoto H, Sato A, Matsumoto S. New insights into the mechanism of Wnt signaling pathway activation. Int. Rev. Cell. Mol. Biol. 2011;291:21–71.
22. Gao C, Chen YG. Dishevelled: The hub of Wnt signaling. Cell. Signal. 2010;22:717–727.
23. Thompson JJ, Williams CS. Protein phosphatase 2A in the regulation of Wnt signaling stem cells, and cancer. Genes. 2018;9:121.
24. Gonzalez-Torres C, et al. NF-kappaB participates in the stem cell phenotype of ovarian cancer cells. Arch. Med. Res. 2017;48:343–351.
25. Vazquez-Santillan K, et al. NF-kappaBeta-inducing kinase regulates stem cell phenotype in breast cancer. Sci. Rep. 2016;6:37340.
26. Kong L, et al. Overexpression of SDF-1 activates the NF-kappaB pathway to induce epithelial to mesenchymal transition and cancer stem cell-like phenotypes of breast cancer cells. Int. J. Oncol. 2016;48:1085–1094.
27. Wang D, Fu L, Sun H, Guo L, DuBois RN. Prostaglandin E2 promotes colorectal cancer stem cell expansion and metastasis in mice. Gastroenterology. 2015;149; 1884–1895:e1884.
28. Smith HA, Kang Y. The metastasis-promoting roles of tumor-associated immune cells. J. Mol. Med. 2013;91:411–429.
29. Zhang L, et al. CCL21/CCR7 axis contributed to CD133+ pancreatic cancer stem-like cell metastasis via EMT and Erk/NF-κB pathway. Plos One. 2016;11:e0158529.
30. Chambers I. The molecular basis of pluripotency in mouse embryonic stem cells. Cloning Stem Cells. 2004;6:386–391.
31. Zhou J, et al. Activation of the PTEN/mTOR/STAT3 pathway in breast cancer stem-like cells is required for viability and maintenance. Proc. Natl Acad. Sci. USA. 2007;104:16158–16163.
32. Yang L. et al. IL-10 derived from M2 macrophage promotes cancer stemness via JAK1/STAT1/NF-kappaB/Notch1 pathway in non-small cell lung cancer. Int. J. cancer. 2019;145:1099–1110.
33. Van Der Zee M, et al. IL6/JAK1/STAT3 signaling blockade in endometrial cancer affects the ALDHhi/CD126+ stem-like component and reduces tumor burden. Cancer Res. 2015;75:3608–3622.
34. Kim SY, et al. Role of the IL-6-JAK1-STAT3-Oct-4 pathway in the conversion of non-stem cancer cells into cancer stem-like cells. Cell. Signal. 2013;25: 961–969.
35. Ruan Z, Yang X, Cheng W. OCT4 accelerates tumorigenesis through activating JAK/STAT signaling in ovarian cancer side population cells. Cancer Manag. Res. 2019;11:389–399.
36. Marotta LL, et al. The JAK2/STAT3 signaling pathway is required for growth of CD44(+)CD24(−) stem cell-like breast cancer cells in human tumors. J. Clin. Invest. 2011;121:2723–2735.

37. Zhang X, et al. Human colorectal cancer-derived mesenchymal stem cells promote colorectal cancer progression through IL-6/JAK2/STAT3 signaling. Cell Death Dis. 2018;9:25.
38. Zhou B, et al. Erythropoietin promotes breast tumorigenesis through tumor-initiating cell self-renewal. J. Clin. Invest. 2014;124:553–563.
39. Song JI, Grandis JR. STAT signaling in head and neck cancer. Oncogene. 2000;19:2489–2495.
40. Almiron Bonnin DA, et al. Secretion-mediated STAT3 activation promotes self-renewal of glioma stem-like cells during hypoxia. Oncogene. 2018;37:1107–1118.
41. Jia H, et al. The LIM protein AJUBA promotes colorectal cancer cell survival through suppression of JAK1/STAT1/IFIT2 network. Oncogene. 2017;36:2655–2666.
42. Tasian SK, Teachey DT, Rheingold SR. Targeting the PI3K/mTOR pathway in pediatric hematologic malignancies. Front. Oncol. 2014;4:108.
43. Vanhaesebroeck B, Guillermet-Guibert J, Graupera M, Bilanges B. The emerging mechanisms of isoform-specific PI3K signalling. Nat. Rev. Mol. Cell. Biol. 2010;11:329–341.
44. Wang Q, Chen X, Hay N. Akt as a target for cancer therapy: More is not always better (lessons from studies in mice). Br. J. Cancer. 2017;117:159–163.
45. Loewith R, et al. Two TOR complexes, only one of which is rapamycin sensitive, have distinct roles in cell growth control. Mol. Cell. 2002;10:457–468.
46. Kim DH, et al. mTOR interacts with raptor to form a nutrient-sensitive complex that signals to the cell growth machinery. Cell. 2002;110:163–175.
47. Sancak Y, et al. PRAS40 is an insulin-regulated inhibitor of the mTORC1 protein kinase. Mol. Cell. 2007;25:903–915.
48. Knowles MA, Platt FM, Ross RL, Hurst CD. Phosphatidylinositol 3-kinase (PI3K) pathway activation in bladder cancer. Cancer Metastasis Rev. 2009;28:305–316.
49. Duan S, et al. PTEN deficiency reprogrammes human neural stem cells towards a glioblastoma stem cell-like phenotype. Nat. Commun. 2015;6: 10068.
50. Yuzugullu H, et al. A PI3K p110beta-Rac signalling loop mediates Pten-loss-induced perturbation of haematopoiesis and leukaemogenesis. Nat. Commun. 2015;6:8501.
51. Fumarola C, Bonelli MA, Petronini PG, Alfieri RR. Targeting PI3K/AKT/mTOR pathway in non small cell lung cancer. Biochem. Pharmacol. 2014;90: 197–207.
52. Dey N, De P, Leyland-Jones B. PI3K-AKT-mTOR inhibitors in breast cancers: From tumor cell signaling to clinical trials. Pharmacol. Ther. 2017;175:91–106.
53. Offermann A, et al. MED15 overexpression in prostate cancer arises during androgen deprivation therapy via PI3K/mTOR signaling. Oncotarget. 2017;8:7964–7976.
54. Giulino-Roth L, et al. Inhibition of Hsp90 suppresses PI3K/AKT/mTOR signaling and has antitumor activity in Burkitt lymphoma. Mol. Cancer Therapeutics. 2017;16:1779–1790.
55. Zaidi AH, et al. PI3K/mTOR dual inhibitor, LY3023414, demonstrates potent antitumor efficacy against esophageal adenocarcinoma in a rat model. Ann. Surg. 2017;266:91–98.
56. Karki R, Malireddi RKS, Zhu Q, Kanneganti TD. NLRC3 regulates cellular proliferation and apoptosis to attenuate the development of colorectal cancer. Cell Cycle. 2017;16:1243–1251.
57. Molina JR, Sun Y, Protopopova M, Gera S, Bandi M, Bristow C, McAfoos T, Morlacchi P, Ackroyd J, Agip AA, et al. An inhibitor of oxidative phosphorylation exploits cancer vulnerability. Nat. Med. 2018;24:1036–1046.
DOI: 10.1038/s41591-018-0052-4
58. La T, Chen S, Guo T, Zhao XH, Teng L, Li D, Carnell M, Zhang YY, Feng YC, Cole N, et al. Visualization of endogenous p27 and Ki67 reveals the importance of a c-Myc-driven metabolic switch in promoting survival of quiescent cancer cells. Theranostics. 2021;11:9605–9622.
DOI: 10.7150/thno.63763
59. Senkowski W, Zhang X, Olofsson MH, Isacson R, Hoglund U, Gustafsson M, Nygren P, Linder S, Larsson R, Fryknas M. Three-dimensional cell culture-based screening identifies the anthelmintic drug nitazoxanide as a candidate for treatment of colorectal Cancer. Mol. Cancer Ther. 2015;14:1504–1516.
DOI: 10.1158/1535-7163.MCT-14-0792

60. Senkowski W, Jarvius M, Rubin J, Lengqvist J, Gustafsson MG, Nygren P, Kultima K, Larsson R, Fryknas M. Large-scale gene expression profiling platform for identification of context-dependent drug responses in multicellular tumor spheroids. Cell Chem. Biol. 2016;23:1428–1438.
DOI: 10.1016/j.chembiol.2016.09.013

61. Ortmayr K, Zampieri M. Sorting-free metabolic profiling uncovers the vulnerability of fatty acid beta-oxidation in *In vitro* quiescence models. Mol. Syst. Biol. 2022;18:e10716.
DOI: 10.15252/msb.202110716

62. Zhang X, Fryknas M, Hernlund E, Fayad W, De Milito A, Olofsson MH, Gogvadze V, Dang L, Pahlman S, Schughart LA, et al. Induction of mitochondrial dysfunction as a strategy for targeting tumour cells in metabolically compromised microenvironments. Nat. Commun. 2014;5: 3295.
DOI: 10.1038/ncomms4295

63. Altieri D.C. Mitochondria in cancer: Clean windmills or stressed tinkerers? Trends Cell Biol; 2022.
DOI: 10.1016/j.tcb.2022.08.001. in press

64. Missiroli S, Perrone M, Genovese I, Pinton P, Giorgi C. Cancer metabolism and mitochondria: Finding novel mechanisms to fight tumours. eBioMedicine. 2020;59:102943.
DOI: 10.1016/j.ebiom.2020.102943

65. Steinmetz J, Senkowski W, Lengqvist J, Rubin J, Ossipova E, Herman S, Larsson R, Jakobsson PJ, Fryknas M, Kultima K. Descriptive proteome analysis to investigate context-dependent treatment responses to oxphos inhibition in colon carcinoma cells grown as monolayer and multicellular tumor spheroids. ACS Omega. 2020;5:17242–17254.
DOI: 10.1021/acsomega.0c01419

66. Rehman SK, Haynes J, Collignon E, Brown KR, Wang Y, Nixon AML, Bruce JP, Wintersinger JA, Singh Mer A, Lo EBL, et al. Colorectal cancer cells enter a diapause-like DTP state to survive chemotherapy. Cell. 2021;184:226–242.e21.
DOI: 10.1016/j.cell.2020.11.018

67. Feng J, Xi Z, Jiang X, Li Y, Nik Nabil WN, Liu M, Song Z, Chen X, Zhou H, Dong Q, et al. Saikosaponin A enhances Docetaxel efficacy by selectively inducing death of dormant prostate cancer cells through excessive autophagy. Cancer Lett. 2022;554:216011.
DOI: 10.1016/j.canlet.2022.216011

68. Lindberg M.F., Meijer L. Dual-specificity, tyrosine phosphorylation-regulated kinases (dyrks) and cdc2-like kinases (CLKS) in human disease, an overview. Int. J. Mol. Sci. 2021;22:6047.
DOI: 10.3390/ijms22116047

69. Hu J, Nakhla H, Friedman E. Transient arrest in a quiescent state allows ovarian cancer cells to survive suboptimal growth conditions and is mediated by both Mirk/dyrk1b and p130/RB2. Int. J. Cancer. 2011;129:307–318.
DOI: 10.1002/ijc.25692

70. Kettle JG, Ballard P, Bardelle C, Cockerill M, Colclough N, Critchlow SE, Debreczeni J, Fairley G, Fillery S, Graham MA, et al. Discovery and optimization of a novel series of Dyrk1B kinase inhibitors to explore a MEK resistance hypothesis. J. Med. Chem. 2015;58:2834–2844.
DOI: 10.1021/acs.jmedchem.5b00098

71. Tang L, Wang Y, Strom A, Gustafsson JA, Guan X. Lapatinib induces p27(Kip1)-dependent G(1) arrest through both transcriptional and post-translational mechanisms. Cell Cycle. 2013;12:2665–2674.
DOI: 10.4161/cc.25728

72. Mercer SE, Ewton DZ, Deng X, Lim S, Mazur TR, Friedman E. Mirk/Dyrk1B mediates survival during the differentiation of C2C12 myoblasts. J. Biol. Chem. 2005;280:25788–25801.
DOI: 10.1074/jbc.M413594200

73. Deng X, Mercer SE, Shah S, Ewton DZ, Friedman E. The cyclin-dependent kinase inhibitor p27Kip1 is stabilized in G(0) by Mirk/dyrk1B kinase. J. Biol. Chem. 2004;279:22498–22504.
DOI: 10.1074/jbc.M400479200

74. Ashford AL, Oxley D, Kettle J, Hudson K, Guichard S, Cook SJ, Lochhead PA. A novel DYRK1B inhibitor AZ191 demonstrates that DYRK1B acts independently of GSK3beta to phosphorylate cyclin D1 at Thr(286), not Thr(288) Biochem. J. 2014;457:43–56.
DOI: 10.1042/BJ20130461

75. Sadasivam S, DeCaprio JA. The DREAM complex: Master coordinator of cell cycle-dependent gene expression. Nat. Rev. Cancer. 2013;13:585–595.
DOI: 10.1038/nrc3556

76. Deng X, Mercer SE, Sun CY, Friedman E. The normal function of the cancer kinase Mirk/dyrk1B is to reduce reactive oxygen species. Genes Cancer. 2014;5:22–30.
DOI: 10.18632/genesandcancer.1

77. Chang CC, Chiu CC, Liu PF, Wu CH, Tseng YC, Lee CH, Shu CW. Kinome-wide sirna screening identifies dyrk1b as a potential therapeutic target for triple-negative breast cancer cells. Cancers. 2021;13:5779.
DOI: 10.3390/cancers13225779

78. Chen Y, Wang S, He Z, Sun F, Huang Y, Ni Q, Wang H, Wang Y, Cheng C. Dyrk1B overexpression is associated with breast cancer growth and a poor prognosis. Hum. Pathol. 2017;66:48–58.
DOI: 10.1016/j.humpath.2017.02.033

79. Boni J, Rubio-Perez C, Lopez-Bigas N, Fillat C, De la Luna S. The DYRK family of kinases in cancer: Molecular functions and therapeutic opportunities. Cancers. 2020;12:2106.
DOI: 10.3390/cancers12082106

80. Becker W. A wake-up call to quiescent cancer cells-Potential use of DYRK1B inhibitors in cancer therapy. FEBS J. 2018;285:1203–1211.
DOI: 10.1111/febs.14347

81. Schmitt C, Kail D, Mariano M, Empting M, Weber N, Paul T, Hartmann RW, Engel M. Design and synthesis of a library of lead-like 2,4-bisheterocyclic substituted thiophenes as selective Dyrk/Clk inhibitors. Plos One. 2014;9:e87851.
DOI: 10.1371/journal.pone.0087851

82. Lee J, Galloway R, Grandjean G, Jacob J, Humphries J, Bartholomeusz C, Goodstal S, Lim B, Bartholomeusz G, Ueno NT, et al. Comprehensive two- and three-dimensional RNAI screening identifies pi3k inhibition as a complement to MEK inhibitor as703026 for combination treatment of triple-negative breast cancer. J. Cancer. 2015;6:1306–1319.
DOI: 10.7150/jca.13266

83. Garmendia I, Redin E, Montuenga LM, Calvo A. Yes1: A novel therapeutic target and biomarker in cancer. Mol. Cancer Ther. 2022;21:1371–1380.
DOI: 10.1158/1535-7163.MCT-21-0958

84. Touil Y, Igoudjil W, Corvaisier M, Dessein AF, Vandomme J, Monte D, Stechly L, Skrypek N, Langlois C, Grard G, et al. Colon cancer cells escape 5-FU chemotherapy-induced cell death by entering stemness and quiescence associated with the c-Yes/YAP axis. Clin. Cancer Res. 2014;20:837–846.
DOI: 10.1158/1078-0432.CCR-13-1854

85. Hamanaka N, Nakanishi Y, Mizuno T, Horiguchi-Takei K, Akiyama N, Tanimura H, Hasegawa M, Satoh Y, Tachibana Y, Fujii T, et al. Yes1 is a targetable oncogene in cancers harboring yes1 gene amplification. Cancer Res. 2019;79:5734–5745.
DOI: 10.1158/0008-5472.CAN-18-3376

86. 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;11:2736–2739.
DOI: 10.1111/1759-7714.13583

87. Fan PD, Narzisi G, Jayaprakash AD, Venturini E, Robine N, Smibert P, Germer S, Yu HA, Jordan EJ, Paik PK, 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:E6030–E6038.
DOI: 10.1073/pnas.1717782115

88. Corvaisier M, Bauzone M, Corfiotti F, Renaud F, El Amrani M, Monte D, Truant S, Leteurtre E, Formstecher P, Van Seuningen I, et al. Regulation of cellular quiescence by YAP/TAZ and Cyclin E1 in colon cancer cells: Implication in chemoresistance and cancer relapse. Oncotarget. 2016;7:56699–56712.
DOI: 10.18632/oncotarget.11057

89. Malladi S, Macalinao DG, Jin X, He L, Basnet H, Zou Y, De Stanchina E, Massague J. Metastatic Latency and Immune Evasion through Autocrine Inhibition of WNT. Cell. 2016;165:45–60.
DOI: 10.1016/j.cell.2016.02.025

90. Garris CS, Arlauckas SP, Kohler RH, Trefny MP, Garren S, Piot C, Engblom C, Pfirschke C, Siwicki M, Gungabeesoon J, et al. successful anti-PD-1 cancer

immunotherapy requires t cell-dendritic cell crosstalk involving the cytokines ifn-gamma and IL-12. Immunity. 2018;49:1148–1161.e7.
DOI: 10.1016/j.immuni.2018.09.024

91. Baldominos P, Barbera-Mourelle A, Barreiro O, Huang Y, Wight A, Cho JW, Zhao X, Estivill G, Adam I, Sanchez X, et al. Quiescent cancer cells resist T cell attack by forming an immunosuppressive niche. Cell. 2022;185:1694–1708.e19.
DOI: 10.1016/j.cell.2022.03.033

92. Lindell E, Zhong L, Zhang X. Quiescent cancer cells—a potential therapeutic target to overcome tumor resistance and relapse. International Journal of Molecular Sciences. 2023 Feb 13;24(4):3762.

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