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The Role of PI3K/AKT Signalling Pathway in Cancer Stem Cells: Emerging Therapeutic Targets and Resistance Mechanisms

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ABSTRACT

Cancer stem cells (CSCs) are an insignificant, however enormous population of tumor cells that display capacities of self-renewal, differentiation, and tumor initiation, consequently being the core feature in cancer progression, recurrence, and drug resistance. The phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) is one of the most critical signalling cascades regulating CSCs and controlling their stemness, survival, evasion of the immune system under stressful conditions, as well as metabolic reprogramming. This review provides an overview of the morphological features and functional aspects of the PI3K/AKT immune cascade and pathway, and how it essentially connects with both upstream and downstream effectors in CSC biology. The cross-communication of PI3K/AKT with other pathways, e.g., Wnt, Notch, and Hedgehog, is elaborated to emphasize the redundancy of the networks facilitating CSC maintenance and drug resistance. Additionally, we provide an in-depth scrutiny of the processes through which PI3K/AKT signalling leads to CSC resistance to chemotherapy, radiotherapy, and targeted therapy, as well as their plasticity, metastasis, and immune escape mechanisms. Current and future therapeutic approaches targeting the PI3K/AKT axis, such as small molecule inhibitors, combination therapy, and drug delivery nanotechnology, are also discussed. Finally, we present clinical issues and prospects for improving CSC-based therapy by using PI3K/AKT blockade to eliminate resistance and induce protracted, long-lasting cancer remission.

INTRODUCTION

Cancer stem cells (CSCs) are a particular subpopulation in the heterogeneous tumor mass with the ability of self-renewal, differentiation, and tumorigenic potential. These stem-like cells are highly similar to normal stem cells, yet they possess dysregulated signalling mechanisms that make them resistant to conventional treatments, allowing them to survive cytotoxic therapies and repopulate the tumor [1]. CSCs have been increasingly shown to play an important role in the initiation, development, metastasis, and recurrence of numerous malignancies, thus representing an important therapeutic target in contemporary oncology. The survival and function of CSCs post-treatment is emerging as a major cause of therapeutic resistance and disease recurrence, hence the urgent need to understand the molecular mechanisms that regulate CSC survival and function [2]. Among the various

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signalling cascades involved in CSC biology, the phosphoinositide 3-kinase/protein kinase B (PI3K/AKT) signalling cascade stands out as one of the most critical. It regulates essential cellular processes such as proliferation, apoptosis, metabolism, and survival [3]. Aberrant elevation of PI3K/AKT signalling is characteristic of many cancers and has been linked to oncogenic transformation, tumor progression, and poor clinical outcomes. This is largely due to the pivotal role PI3K/AKT plays in sustaining the stem-like phenotype of CSCs, which contributes to resistance against chemotherapy and radiotherapy, epithelial-mesenchymal transition (EMT), and immune evasion. These findings suggest that the PI3K/AKT pathway is not only central to general tumor biology but also has a unique role in promoting CSC-associated pathological behaviours [4]. Due to this strong association between PI3K/AKT signalling and CSC maintenance, it has emerged as a highly attractive therapeutic target. In-depth understanding of its molecular interactions with CSC regulatory networks is essential for developing more effective and lasting cancer treatments. Despite recent advances, challenges such as pathway redundancy, compensatory mechanisms, and the toxicity of targeted inhibitors still hinder clinical translation [5]. The study discusses the mechanistic role of this pathway in CSC-mediated therapeutic resistance and relapse [6]. Furthermore, the study highlights promising therapeutic strategies targeting PI3K/AKT, identifies existing gaps in clinical application, and outlines future directions to improve CSC-targeted therapies. By dissecting this essential signalling cascade, we hope to contribute to ongoing efforts to enhance the effectiveness of cancer treatment through the targeted elimination of CSCs [7].

This study aims to provide a detailed examination of the PI3K/AKT signalling pathway in the regulation and maintenance of CSCs across various tumor types.

Fundamental Constituents of the PI3K/AKT Pathway

The PI3K/AKT signalling pathway is a cascade of tightly regulated proteins that orchestrate key cellular processes, including growth, proliferation, and survival. The principal molecule initiating this cascade is Class I phosphoinositide 3-kinase (PI3K), a heterodimer composed of a catalytic subunit, p110 isoforms (α, β, δ, or γ) and a regulatory subunit (p85 or p101). Among these, p110α and p110β are ubiquitously expressed and frequently mutated or overexpressed in solid tumors, whereas p110δ and p110γ are predominantly found in leukocytes and are often implicated in immune-related malignancies. Upon activation, PI3K phosphorylates phosphatidylinositol-4,5-bisphosphate (PIP2), converting it into phosphatidylinositol-3,4,5-trisphosphate (PIP3), a key secondary messenger that recruits AKT to the cell membrane for activation [8]. Protein kinase B (AKT) exists in three isoforms: AKT1, AKT2, and AKT3, which share high sequence similarity but differ in function depending on tissue type and cancer context. Full activation of AKT requires phosphorylation at two critical residues: threonine 308 by phosphoinositide-dependent kinase-1 (PDK1) and serine 473 by the mechanistic target of rapamycin complex 2 (mTORC2) [9]. Once activated, AKT transmits signals downstream by phosphorylating a wide range of substrates involved in metabolism, apoptosis, and cell cycle regulation. Phosphatase and tensin homolog (PTEN) functions as a tumor suppressor by dephosphorylating PIP3 back to PIP2, thereby negatively regulating the PI3K/AKT pathway. Loss or mutation of PTEN is a frequent oncogenic event in multiple malignancies. Another key downstream component is the mechanistic target of rapamycin (mTOR), a serine/threonine kinase that exists in two distinct complexes: mTORC1 and mTORC2. These complexes regulate protein synthesis, cellular growth, and cytoskeletal organization, positioning mTOR as a critical effector of AKT signalling [10].

Upstream Controllers and Activation Machinery

External stimuli usually initiate the PI3K/AKT pathway by binding the pathway to membrane-bound receptors. EGFR, HER2, FGFR, and PDGFR are among the most characterized upstream activators, the so-called receptor tyrosine kinases (RTKs). When ligated, these receptors become auto-phosphorylated on tyrosine residues, forming binding sites on PI3K through the SH2 domain of its regulatory subunit. Equally, G-protein-coupled receptors (GPCRs) and integrins may activate PI3K directly, as well as using an adaptor protein such as IRS-1/2 and GAB1. These upstream cues lead to catalytic conversion of PIP2 into PIP3 in the inner leaflet of the plasma membrane to localize AKT and PDK1 at the membrane [1]. Basic anchoring of AKT in the plasma membrane promotes its phosphorylation and complete activation. PDK1 activates AKT by phosphorylation of the threonine residue (Thr308) and mTORC2 activates AKT by phosphorylation of the serine residue (Ser473), a two-step process being critical in its full activation. This controlled activation is highly temporally conditional and spatially restricted to downstream signal transduction. Interestingly, PI3K signal amplification could also be through oncogenic mutations, amplification, or loss-of-function mutation in some regulatory domains such as PTEN, which is often missing or down-regulated in many cancers [2].

Downstream Effectors and Cellular Functions

Phosphorylation Once turned on, AKT targets a wide variety of downstream proteins, affecting numerous cellular processes that can increase tumor formation and growth. mTORC1 is a key downstream effector that controls

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the growth of cells and protein synthesis by phosphorylating S6 kinase (S6K) and 4E-binding protein 1 (4E-BP1), which are important controllers of mRNA translation. This causes improved anabolic conditions and biomass gain, which promotes uncontrolled cell growth in cancer [3]. The forkhead box O (FOXO) collection of transcription factors is another important category of targets. Phosphorylation of FOXO proteins by AKT leads to nuclear expulsion and inactivation of the protein, repressing the activation of the genes dealing with apoptosis, cell cycle arrest, and oxidative stress response [4]. On the same note, glycogen synthase kinase 3 beta (GSK3B) gets phosphorylated by AKT to be inhibited in a way that advances cell phase and boosts the transcription of 8-catenin, a feature that is involved in epithelial-mesenchymal transition and stemness. AKT also inactivates the pro-apoptotic protein BAD through phosphorylation and stimulates MDM2, resulting in the degradation of the tumor suppressor p53, and all these inhibit intrinsic apoptotic pathways [5]. A combination of these downstream effects also gives cancer cells an augmented rate of proliferation, liability to cell death, metabolic reconfiguration, and immune evasion consequences. Within the framework of the cancer stem cells, the above-mentioned outputs mediate the maintenance of the stem cell phenotype through self-renewal, pluripotency and conventional therapy resistance, making the PI3K/AKT pathway the master regulator of oncogenic signalling [6].

Characterization and Major Identifiers of CSCs in Cancers

Cancer stem cells (CSCs) are a subset of cancer cells which exhibit, like normal stem cells, stem-like characteristics, such as the ability to self-renew and differentiate into a heterogeneous population of tumor cells. Like normal tissue stem cells, CSCs are conceptually presumed to be at the top of a cellular hierarchy in tumors and able to initiate and perpetuate tumorigenesis. The first cases of their detection were in acute myeloid leukaemia (AML) and then in solid tumors of breast, brain, colon, prostate, pancreatic and liver cancer [7]. Specific surface markers have been able to aid in the identification and isolation of CSCs, but this is tissue and tumor-type-dependent. As an example, the CD44high/CD24low and ALDH1 positivity is a standard universal in the breast cancer CSC, and the CD133 and nestin are universal markers in glioblastoma. In colorectal cancer, CD44, CD166 and Lgr5 have been used to describe CSCs; in hepatocellular carcinoma, they utilize CD133 and EpCAM. These markers are frequently functionally involved in the regulation of stemness, signalling patterns and engagement of the tumor environment [8] (Table 1).

Table 1: Key CSC Markers and Their Expression in Various Cancer Types

Cancer Type	Common CSC Markers	Marker Frequency (%)*	References
Breast Cancer	CD44^high/CD 24^low, ALDH1	CD44^high: 15-30%, ALDH1: 20-40%	[1]
Glioblastoma	CD133, Nestin	CD133: 10-25%	[2]
Colorectal Cancer	CD44, Lgr5, Cd166	CD44: 12-28%, Lgr5: 15-35%	[3]
Pancreatic Cancer	CD133, CXCR4	CD133: 7-20%	[4]
Hepatocellular Carcinoma	CD133, EpCAM	CD133: 10-25%	[5]

Biological Properties: Self-Renewal, Differentiation and Quiescence

The distinct characteristics of CSCs are self-renewal, the capacity to generate daughter cells with the characteristics of stem cells, and differentiation, the capacity that causes the generation of daughter cells with distinctive phenotypes [9]. The process of self-renewal is highly governed by both intrinsic and extrinsic signals that are controlled by both intrinsic transcription factors (e.g., NANOG, SOX2 and OCT4) and extrinsic signalling pathways (Notch: Wnt/beta-catenin, Hedgehog, and PI3K/AKT). The presence of these networks also preserves the stem-like state as well as eliminates early differentiation. Moreover, CSCs tend to be in quiescence or grow at low rates, and this aspect enables them to avoid the chemotherapeutic drugs, which are usually effective in destroying fast-growing cells [10]. This dormancy is not limited to being only a survival strategy, but a long-term maintenance of tumor as well as a delay of relapse. Moreover, CSCs are capable of rapid transformation between quiescence and proliferative phenotypes upon environmental stimuli, making them hard to attack therapeutically. Plasticity supplies CSCs with the ability to adjust to various micro-environmental conditions, be resistant to the cytotoxic stress, and support the re-formation of the tumor despite punishing treatment protocols [11].

Therapy Resistance, Recurrence, and Metastasis of CSCs Cells

Among the most clinically relevant peculiarities of CSCs, the first thing to be mentioned here is their high resistance to classic cancer treatment methods such as chemotherapy, radiotherapy, and targeted medications. Such resistance can be due to a variety of mechanisms, which include: an augmented repair capacity of DNA damage, up-regulation of drug efflux transporters (ABCG2 and ABCB1), an induction of anti-apoptotic signalling and a heightened expression of reactive oxygen species (ROS) scavengers. Further, interaction with constituents of the tumor microenvironment, such as hypoxic niches, cancer-associated fibroblasts, as well as immune suppressive cells, protects CSCs against therapeutic insult. Such defence mechanisms enable CSCs to evade treatment,

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causing minimal residual cancer and tumor relapse [12]. CSCs also play major roles in causing metastasis. By the acquisition of higher motility and invasive capacity through epithelial-to-mesenchymal transitions (EMT), a process frequently controlled by PI3K/AKT and other signalling pathways as well, CSCs develop the capacity to be more migratory and invasive. Such migratory CSCs have the capacity of spreading to far-away organs, becoming quiescent and afterwards reviving to develop the metastatic lesions. In clinical trials, increased expression of CSC markers is associated with poor survival, a greater chance of recurrence, and a lower survival rate in different cancers. CSCs, therefore, do not just constitute a mechanistic connection to therapeutic failure but also form a major barrier in attaining long-term cancer remission [13].

Maintaining CSC and Self-Renewal

The PI3K/AKT signalling pathway is the key to maintaining the stemness and survival of cancer stem cells (CSCs). The PI3K/AKT pathway combines external signals with internal transcriptional negative signalling to adjust the essential stem cell attributes, which include self-renewal, growth, and metabolic reprogramming. The phosphorylation of pro-apoptotic agents like BAD and transcription factors FOXO occurs when AKT is activated, and existing cell death and survival are inhibited and enhanced accordingly [1]. On top of that, AKT-induced activation of mTOR promotes anabolic growth as well as protein synthesis, which is fundamental in sustaining the high functional requirements of CSCs. In CSCs, PI3K/AKT signalling also enhances the expression of pluripotency-related transcription factors NANOG, SOX2, and OCT4, which also help in maintaining the undifferentiated tumor-initiating phenotype. Blocking the PI3K/AKT axis was found to decrease tumor sphere formation, clonogenic potential and expression of CSC markers in a variety of cancer cells, attesting to its central importance in CSC modulation [14].

EMT and Phenotypic Plasticity Advertisement

Epithelial dysregulated multipotent stem cells, an example of one of the mechanisms by which PI3K/AKT enhances CSC enrichment, is the induction of epithelial-to-mesenchymal transition (EMT), a biological process during which epithelial cells lose their polarity and adhesive property and gain the mesenchymal and migratory qualities. EMT is strongly linked to the development of stem-like characteristics, and the process is often induced in CSCs when they undergo metastasis as well as therapeutic resistance [15]. The PI3K/AKT pathway also plays a role in EMT through the activation of transcription factors (Snail, Slug, Twist, and ZEB1), the expression of which downregulates E-cadherin levels and activates the remodeling of the cytoskeleton. Such a transition not only enhances invasion and metastasis but also strengthens the plasticity of cancer cells such that non-CSCs can transition to a CSC-like state during stressful conditions [16]. Moreover, AKT promotes the stability of β-catenin by inhibiting GSK3β, a Wnt inhibitor, to facilitate the translocation of nuclear β-catenin into transcription of EMT-related genes. The plasticity of tumors is supported by the ability to promote the convergence of EMT and CSC phenotypes mediated by the PI3K/AKT signalling to enable them to adapt to hostile microenvironments and resist treatment [15].

Crosstalk among Other Stemness-Related Pathways

The PI3K/AKT pathway does not work independently but is highly involved in combining with other important signalling pathways implicated in regulating CSCs, like the Wnt/ 9912-catenin, Notch, as well as the Hedgehog pathway [17]. The PI3K/AKT pathway in the Wnt signalling pathway helps stabilize and translocate into the nucleus the β-catenin, thereby increasing the transcription of Wnt target genes relating to stemness. The cleavage and activity of the Notch intracellular domains in the Notch pathway are known to have PI3K/AKT signalling, regulating downstream gene expression in the Notch pathway, regulating cell fate and stem cell renewal. Likewise, PI3K/AKT signalling is vulnerable to stimulation by the Hedgehog pathway either indirectly through Smoothened or directly through cross-regulatory points, mTOR and GLI transcription factors. This widespread crosstalk forms a strong, highly redundant network responsible for helping CSC maintain, survive and acquire therapeutic resistance, which makes it difficult to target any individual pathway alone. It is a possibility that a more efficient approach to destroying CSC populations can be found by targeting the areas of convergence with such signalling cascades [18].

PI3K/AKT4.4 -CSC Interactions Type-Specific Cancer Evidence

Regulation of CSC through the PI3K/AKT signalling pathway has been reported in various malignancies. PI3K/AKT hyperactivity in breast cancer (which in many instances is associated with PIK3CA mutation or PTEN loss) is associated with higher levels of ALDH1+ CSCs and resistance to endocrine drugs, including tamoxifen. Blocking of PI3K in these models decreases mammosphere formation and chemotherapeutic sensitivity to CSCs. Patients with glioblastoma have AKT constitutively activated in CD133+ CSCs, and this leads to temozolomide and radiation resistance. Prevention of AKT in these cells decreases the tumorigenicity and induces apoptosis [19]. CSCs in colorectal cancer positive for CD44 and Lgr5 also depend on the PI3K/AKT pathway for their proliferation and survival. In this case, Wnt antagonists in combination with PI3K inhibitors have demonstrated the potential in the decrease of tumor reoccurrence and metastasizing. In pancreatic cancer and prostate

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malignancy, as well, faulty PI3K/AKT signalling helps shield CSCs in low-oxygen or reduced feed conditions, and leads to metastasy and drug resistance (Figure 1) [20].

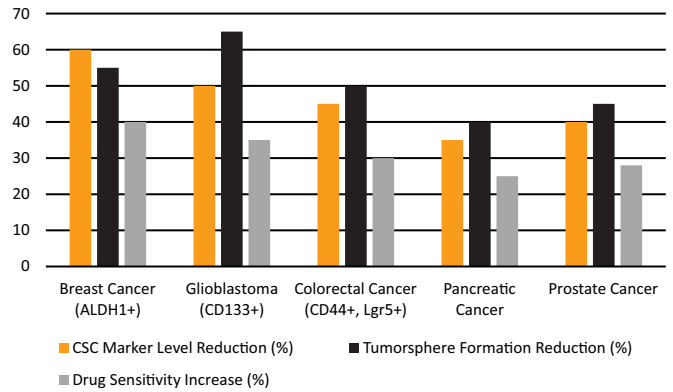

Figure 1: Effect of PI3K/AKT Inhibition on CSC Characteristics Across Cancer Types

Therapeutic Targeting of the PI3K/AKT Signalling in CSCs

Due to therapeutic resistance, targeting the PI3K/AKT signalling pathway has emerged as a promising strategy for eliminating cancer stem cells (CSCs) and overcoming resistance. Multiple inhibitor classes have been developed and are currently undergoing clinical or early-stage testing, each designed to disrupt different components of the pathway. Pan-PI3K inhibitors, including buparlisib (BKM120) and pictilisib (GDC-0941), inhibit all Class I PI3Ks to provide broad-spectrum suppression of the pathway. The study illustrates the distribution of inhibitors. These inhibitors have demonstrated efficacy in reducing CSC populations and tumor formation in various cancer models (Figure 2). However, their clinical application is often limited by toxicity resulting from systemic PI3K inhibition in normal tissues.

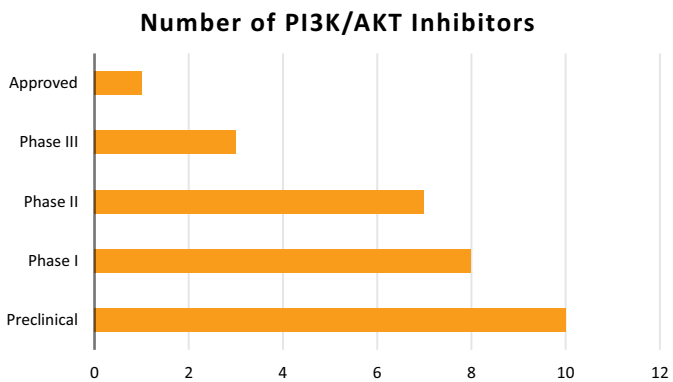

Figure 2: Distribution of Inhibitors by Clinical Trial Phase

Combination Therapy of CSCs and Bulk Tumor Cells

Deficiencies in eradicating tumor with monotherapy alone are common and are well known through the concept of pathway redundancy and compensation. As a result, combination therapy has been an appealing method of attacking CSCs and the majority of the tumor cells and cells that make up the bulk of the tumor. As an example, cytotoxic resistance of CSC is overcome in combination with PI3K/ AKT inhibitors and chemotherapy minimizing tumor recurrence. Likewise, combining PI3K/AKT inhibition with other anti-CSC pathways (e.g. Wnt, Notch or Hedgehog) has produced synergistic antitumor activity in preclinical models [21]. Furthermore, there has been a potential for the use of PI3K/AKT pathway inhibitors with immune checkpoint inhibitors (e.g. anti-PD-1/PD-L1 antibodies) to overcome the CSC-mediated immune evasion. The strategies are directed towards affecting the tumor microenvironment that is immunosuppressive, to induce strong anti-tumor immune responses. More efficacies with reduced resistance may further be achieved with personalized combination regimens that are based on tumor genomic and proteomic profiling [22].

Nanotechnology-Based Drug Delivery System and Nano-based Approaches

Improvements to drug delivery methods have allowed a more effective abrogation of the PI3K/AKT inhibitors to CSCs, reducing overall systemic toxicity. Liposomes, polymeric nanoparticles, and dendrimers are nanoparticle-based delivery systems that enable the encapsulation of PI3K/AKT inhibitors, resulting in minimal drug release, increased bioavailability, and enhanced tumor penetration [23]. These nano-carriers may be modified with ligands or antibodies that bind to surface markers expressed selectively on CSCs (e.g., CD44, CD133), and therefore, can be targeted to CSCs, leaving normal stem cells unharmed. Delivery of this type enhances the therapeutic index and off-target effects. In addition, co-packaging of PI3K/AKT inhibitors with chemotherapeutics or siRNAs against complementary pathways would also create a flexible system to administer a combination therapy. Into this category fall also recent developments involving stimuli-responsive nanoparticles which liberate their load in response to tumor micro-environmental factors, e.g. pH, enzymes, or redox conditions. Such intelligent delivery systems increase the concentration of drugs in CSCs micro-niches and bridge the physical barriers by the tumor stroma [24].

Clinical Challenges and Future Directions

Although it has made significant breakthroughs in the treatment of cancers through inhibition of the PI3K/AKT signalling pathway, there are still clinical issues that curtail therapeutic efficacy and expand clinical use of such drugs. The major limitation is systemic toxicity related to pathway inhibition, since PI3K/AKT signalling is involved in many normal bodily functions, including glucose metabolism, immune system regulation, and vascular homeostasis [25]. This mostly leads to undesirable side effects such as hyperglycemia, rash, gastrointestinal disturbances, and immunosuppression, which limit dosing and patient

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compliance. In addition, cancer cells often respond by initiating compensatory feedback signals after inhibiting PI3K/AKT and end up restoring either the upstream receptor tyrosine kinases or activating alternative survival pathways. Hence, developing resistance to drugs. Heterogeneity in tumors also adds to the problem of treatment, since cancer and cancer stem cell (CSC) subsets can utilize various signalling pathways to escape therapy. As a result, monotherapies against the pathway do not tend to produce long-lasting responses. Because of this, patient stratification and real-time monitoring of the effectiveness of the therapy have demanded the development of robust biomarkers in order to tailor patient outcomes [26]. Although molecular changes like PIK3CA mutations and PTEN loss are associated with increased activity of the pathway, they are not sufficient to forecast clinical benefit, which stresses the importance of dynamic biomarkers that take into account the activity of the pathway and the burden of CSCs. Resistance may be overcome and more effective cancer control achieved by the combination of targeted inhibitors to PI3K/AKT signalling together with other biologically relevant pathways known to be co-activated or microenvironmental substances that currently remain untargeted [27].

CONCLUSION

Combining PI3K/AKT inhibitors with immunotherapy is a potential approach that would address tumor immune evasion, offering a solution to treatment durability. Pathway inhibition has preclinical evidence of modestly decreasing immunosuppressive molecules such as PD-L1 and reshaping the tumor microenvironment to drive immune-activating biology, which would render both CSCs and bulk tumor cells more vulnerable to immune destruction. The use of PI3K/AKT inhibitors in combination with immune checkpoint blockade is under ongoing clinical trials, but the best regimens and selection criteria of patients are still awaited. Moving on, precision oncology strategies integrating in-depth molecular characterization and a new generation of computational methods have the promise to make the therapy more individualized depending on the tumor or CSC characteristics. The future direction of PI3K/AKT-targeted therapies is therefore the smooth interconnection between molecular diagnostics, targeted inhibition, and immune modulation, resulting in durable, individual patient-specific therapy outcomes.

Authors Contribution

Conceptualization: KA
Methodology: ZN[2]
Formal analysis: ZN[2]
Writing review and editing: KA, HI, ZA, ZN[1], AA, HMFA, FJ, ZN[2]
All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

All the authors declare no conflict of interest.

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REFERENCES

[1] Rascio F, Spadaccino F, Rocchetti MT, Castellano G, Stallone G, Netti GS *et al.* The Pathogenic Role of PI3K/AKT Pathway in Cancer Onset and Drug Resistance: An Updated Review. Cancers. 2021 Aug; 13(16): 3949. doi: 10.3390/cancers13163949.

[2] Xue C, Li G, Lu J, Li L. Crosstalk Between Circrnas and the PI3K/AKT Signaling Pathway in Cancer Progression. Signal Transduction and Targeted Therapy.2021 Nov; 6(1): 400. doi: 10.1038/s41392-021-00788-w.

[3] Su J, Song Y, Zhu Z, Huang X, Fan J, Qiao J *et al.* Cell–cell Communication: New Insights and Clinical Implications. Signal Transduction and Targeted Therapy.2024 Aug; 9(1): 196. doi: 10.1038/s41392-024-01888-z.

[4] Ahmad MZ, Ahmad J, Alasmary MY, Abdel-Wahab BA, Warsi MH, Haque A *et al.* Emerging Advances in Cationic Liposomal Cancer Nanovaccines: Opportunities and Challenges. Immunotherapy. 2021 Apr; 13(6): 491-507. doi: 10.2217/imt-2020-0258.

[5] Cai T, Liu H, Zhang S, Hu J, Zhang L. Delivery of Nano-vaccine Towards Lymphoid Organs: Recent Strategies in Enhancing Cancer Immunotherapy. Journal of Nano-biotechnology.2021 Nov;19(1):389. doi: 10.1186/s12951-021-01146-2.

[6] Emery J, Butow P, Lai-Kwon J, Nekhlyudov L, Rynderman M, Jefford M. Management of Common Clinical Problems Experienced by Survivors of Cancer. The Lancet. 2022 Apr; 399(10334): 1537-50. doi: 10.1016/S0140-6736(22)00242-2.

[7] Hervieu C, Christou N, Battu S, Mathonnet M. The Role of Cancer Stem Cells in Colorectal Cancer: From the Basics to Novel Clinical Trials. Cancers.2021Mar; 13(5): 1092. doi: 10.3390/cancers13051092.

[8] Lim JR, Mouawad J, Gorton OK, Bubb WA, Kwan AH. Cancer Stem Cell Characteristics and Their Potential as Therapeutic Targets. Medical Oncology.2021Jul; 38(7): 76. doi: 10.1007/s12032-021-01524-8.

[9] Da Silva PP, Da Silva FA, Rodrigues CA, Souza LP, de Lima EM, Pereira MH *et al.* Geographical Information System and Spatial–Temporal Statistics for Monitoring Infectious Agents in Hospital: A Model Using Klebsiella Pneumoniae Complex. Antimicrobial

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DOI: https://doi.org/10.54393/fbt.v5i3.180

Resistance and Infection Control.2021Jun;10(1):92. doi: 10.1186/s13756-021-00944-5.

[10] Kranz LM, Diken M, Haas H, Kreiter S, Loquai C, Reuter KC *et al.* Systemic RNA Delivery to Dendritic Cells Exploits Antiviral Defence for Cancer Immunotherapy .Nature.2016Jun;534(7607):396-401.doi:10.1038 /nature 18300.

[11] Tasnim N, De la Vega L, Anil Kumar S, Abelseth L, Alonzo M, Amereh M *et al.* 3D Bioprinting Stem Cell Derived Tissues. Cellular and Molecular Bio-engineering.2018Aug;11(4):219-40.doi:10.1007/s1 2195-018-0530-2.

[12] Ali N, Hanif N, Khan HA, Waseem MA, Saeed A, Zakir S *et al.* Deep Learning and Artificial Intelligence for Drug Discovery, Application, Challenge, and Future Perspectives. Discover Applied Sciences.2025May; 7(6): 533. doi: 10.1007/s42452-025-06991-6.

[13] Naveed M, Ali A, Aziz T, Ali N, Rehman HM, Khan AA *et al.* Computational Design of a Glycosylated Multi-Epitope Vaccine Against Hasv-1 And Hasv-2 Astrovirus for Acute Gastroenteritis. Scientific Reports.2025 Apr; 15(1): 13954. doi: 10.1038/s41598-025-96989-2.

[14] Di Fiore R, Suleiman S, Drago-Ferrante R, Subbannayya Y, Pentimalli F, Giordano A *et al.* Cancer Stem Cells and Their Possible Implications in Cervical Cancer: A Short Review. International Journal of Molecular Sciences.2022 May; 23(9): 5167. doi: 10.33 90/ijms23095167.

[15] Muller L, Fauvet F, Chassot C, Angileri F, Coutant A, Dégletagne C *et al*. EMT-Driven Plasticity Prospectively Increases Cell–Cell Variability to Promote Therapeutic Adaptation in Breast Cancer. Cancer Cell International.2025Feb;25(1):32.doi: 10.1186/s12935-025-03637-w.

[16] Brown MS, Abdollahi B, Wilkins OM, Lu H, Chakraborty P, Ognjenovic NB *et al.* Phenotypic Heterogeneity Driven by Plasticity of the Intermediate EMT State Governs Disease Progression and Metastasis in Breast Cancer. Science Advances.2022Aug;8(31): eabj8002. doi: 10.1126/sciadv.abj8002.

[17] Fulford LG, Reis-Filho JS, Ryder K, Jones C, Gillett CE, Hanby A *et al.* Basal-Like Grade III Invasive Ductal Carcinoma of the Breast: Patterns of Metastasis and Long-Term Survival. Breast Cancer Research.2007 Jan; 9(1): R4. doi: 10.1186/bcr1636.

[18] Gurunathan S, Thangaraj P, Wang L, Cao Q, Kim JH. Nanovaccines: An Effective Therapeutic Approach for Cancer Therapy. Biomedicine and Pharma-cotherapy.2024Jan;170:115992.doi:10.1016/j. biopha.2023.115992.

[19] Ganesan K, Du B, Chen J. Effects and Mechanisms of Dietary Bioactive Compounds on Breast Cancer Prevention. Pharmacological Research. 2022 Apr; 178: 105974. doi: 10.1016/j.phrs.2021.105974.

[20] Gao L, Meng F, Yang Z, Lafuente-Merchan M, Fernández LM, Cao Y *et al.* Nano-Drug Delivery System for the Treatment of Multidrug-Resistant Breast Cancer: Current Status and Future Perspectives. Biomedicine and Pharmacotherapy. 2024Oct;179:117327.doi:10.1016/j.biopha.2024.1173 27.

[21] Wang T, Narayanaswamy R, Ren H, Torchilin VP. Combination Therapy Targeting Both Cancer Stem-Like Cells and Bulk Tumor Cells for Improved Efficacy of Breast Cancer Treatment. Cancer Biology and Therapy.2016 Jun; 17(6): 698-707. doi: 10.1080/ 153 84 047.2016.1190488.

[22] Montazersaheb P, Pishgahzadeh E, Jahani VB, Farahzadi R, Montazersaheb S. Magnetic Nanoparticle-Based Hyperthermia: A Prospect in Cancer Stem Cell Tracking and Therapy. Life Sciences.2023Jun;323:121714.doi:10.1016/j.lfs .2023.121714.

[23] Chen H, Cheng H, Liang X, Cai S, Liu G. Immunosuppression Reversal Nanovaccines Substituting Dendritic Cells for Personalized Cancer Immunotherapy. Frontiers in Immunology.2022Jun; 13: 934259. doi: 10.3389/fimmu.2022.934259.

[24] Ahmad A, Imran M, Sharma N. Precision Nanotoxicology in Drug Development: Current Trends and Challenges in Safety and Toxicity Implications of Customized Multifunctional Nanocarriers for Drug-Delivery Applications. Pharmaceutics.2022 Nov; 14(11): 2463. doi: 10.3390 /pharmaceutics14112463.

[25] He Y, Sun MM, Zhang GG, Yang J, Chen KS, Xu WW et al. Targeting PI3K/Akt Signal Transduction for Cancer Therapy. Signal Transduction and Targeted Therapy. 2021 Dec; 6(1): 425. doi: 10.1038/s41392-021-00828-5.

[26] Peng Y, Wang Y, Zhou C, Mei W, Zeng C. PI3K/Akt/mTOR Pathway and Its Role in Cancer Therapeutics: Are We Making Headway? Frontiers in Oncology.2022Mar;12:819128.doi:10.3389/fonc.2022 .819128.

[27] Yang J, Nie J, Ma X, Wei Y, Peng Y, Wei X. Targeting PI3K in Cancer: Mechanisms and Advances in Clinical Trials. Molecular Cancer.2019 Feb; 18(1): 26. doi: 10.11 86/s12943-019-0954-x.

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