Stem Cell Research in Cancer: Current Perspectives and Future Directions

Abstract

Stem cell research has emerged as a pivotal field in cancer biology, offering unprecedented insights into tumor initiation, progression, and therapeutic resistance. This review examines the dual role of stem cells in cancer, encompassing both cancer stem cells as drivers of malignancy and normal stem cells as therapeutic tools. We discuss the current understanding of cancer stem cell biology, their contribution to treatment resistance and metastasis, and the evolving landscape of stem cell-based cancer therapies. Additionally, we explore the challenges and opportunities in translating stem cell research into clinical applications for cancer treatment.

Methodology

A comprehensive literature search was conducted using PubMed, Scopus, and Web of Science databases for articles published between 2000 and 2024. Search terms included "cancer stem cells," "stem cell therapy," "cancer treatment," "hematopoietic stem cell transplantation," "mesenchymal stem cells," and related terms. Inclusion criteria comprised peer-reviewed original research articles, clinical trials, systematic reviews, and meta-analyses published in English. Priority was given to recent publications (2020-2024) while including seminal earlier works that established key concepts in the field. Clinical trial data were obtained from ClinicalTrials.gov and relevant regulatory databases. A total of approximately 200 articles were reviewed, with the most relevant and high-impact studies selected for inclusion in this comprehensive review.

Introduction

The intersection of stem cell biology and cancer research represents one of the most dynamic and promising areas in modern medicine. Stem cells, characterized by their ability to self-renew and differentiate into multiple cell types, play complex roles in cancer development and treatment (1). The cancer stem cell hypothesis, first proposed in the 1990s, has fundamentally altered our understanding of tumor biology and has significant implications for therapeutic strategies (2).

Cancer affects millions of people worldwide, with traditional treatments often falling short due to tumor heterogeneity, treatment resistance, and metastasis. The discovery of cancer stem cells has provided new explanations for these clinical challenges (3), while advances in stem cell technology have opened novel therapeutic avenues (4). This review synthesizes current knowledge in stem cell-cancer research, highlighting key discoveries, ongoing challenges, and future therapeutic potential.

Cancer Stem Cells: Biology and Characteristics

Definition and Identification

Cancer stem cells (CSCs) are a small subset of cells within tumors that possess stem cell-like properties, including self-renewal capacity and the ability to generate the diverse cell types found in cancer tissues (4). These cells are characterized by several key features: enhanced

DNA repair mechanisms, resistance to apoptosis, altered metabolism, and the ability to remain dormant for extended periods (5).

The identification of CSCs relies on various markers and functional assays. Surface markers such as CD133, CD44, CD24, and ALDH1 have been used to isolate CSCs from different cancer types (6,7,8). However, marker expression can vary significantly between tumor types and even within the same tumor, highlighting the heterogeneous nature of CSCs (8).

Molecular Mechanisms and Signaling Pathways

CSCs are regulated by complex molecular networks that govern their stemness properties. Key signaling pathways include Wnt, Notch, Hedgehog, and PI3K/AKT pathways, which are often dysregulated in cancer (4,5). These pathways control critical cellular processes such as self-renewal, differentiation, and survival.

The tumor microenvironment plays a crucial role in maintaining CSC properties through the stem cell niche (9,10). Hypoxic conditions, inflammatory signals, and interactions with stromal cells can promote stemness and contribute to treatment resistance. Epigenetic modifications, including DNA methylation and histone modifications, also regulate CSC behavior and plasticity (9).

Plasticity and Dedifferentiation

Recent research has revealed that CSCs exhibit remarkable plasticity, with non-stem cancer cells capable of acquiring stem-like properties through dedifferentiation processes (11,12). This plasticity is influenced by various factors including therapeutic stress, hypoxia, and inflammatory signals. The dynamic nature of CSCs challenges traditional models and suggests that stemness is not a fixed property but rather a flexible state that can be induced or lost depending on cellular context (11).

Role of Cancer Stem Cells in Tumor Progression

Tumor Initiation and Growth

CSCs are believed to be responsible for tumor initiation, as they possess the unique ability to form new tumors when transplanted into immunocompromised mice (2,3). Studies have shown that as few as 100-1000 CSCs can initiate tumor formation, while thousands of non-stem cancer cells may fail to do so (12,13). This tumorigenic potential is attributed to their enhanced survival mechanisms and ability to adapt to hostile microenvironments.

The hierarchical model of cancer suggests that CSCs give rise to the bulk of tumor cells through asymmetric division, similar to normal stem cells (12). However, the stochastic model proposes that any cancer cell can acquire stemness under appropriate conditions, reflecting the plastic nature of cancer cells (14,15).

Treatment Resistance

One of the most clinically significant aspects of CSCs is their inherent resistance to conventional cancer therapies. CSCs exhibit multiple resistance mechanisms including enhanced DNA repair capacity (16), increased expression of drug efflux pumps (3,4), altered metabolism, and resistance to apoptosis (17). These properties allow CSCs to survive chemotherapy and radiation therapy, potentially leading to tumor recurrence.

The quiescent nature of many CSCs also contributes to treatment resistance, as most conventional therapies target rapidly dividing cells (18,19). This dormancy allows CSCs to escape treatment and later reactivate to drive tumor regrowth. Understanding these resistance mechanisms is crucial for developing more effective therapeutic strategies (20).

Metastasis and Invasion

CSCs play a central role in cancer metastasis, the process by which cancer spreads to distant sites. The properties that define stemness, including enhanced survival, plasticity, and ability to differentiate, are also essential for successful metastasis (15). CSCs can undergo epithelial-mesenchymal transition (EMT), acquiring motility and invasive properties necessary for metastatic spread (21,16).

Circulating tumor cells (CTCs) with stem-like properties have been identified in the blood of cancer patients, supporting the role of CSCs in metastasis. These circulating CSCs can seed distant organs and establish metastatic colonies, contributing to the poor prognosis associated with metastatic disease.

Therapeutic Applications of Stem Cells in Cancer

Hematopoietic Stem Cell Transplantation

Hematopoietic stem cell transplantation (HSCT) represents one of the most established applications of stem cell therapy in cancer treatment (22,23). HSCT is used primarily for hematological malignancies such as leukemia, lymphoma, and multiple myeloma. The procedure involves replacing diseased bone marrow with healthy stem cells, either from the patient (autologous) or a donor (allogeneic) (24,25,26).

Autologous HSCT allows for the administration of high-dose chemotherapy or radiation therapy followed by rescue with the patient's own stem cells. Allogeneic HSCT provides additional therapeutic benefit through the graft-versus-tumor effect, where donor immune cells attack residual cancer cells (27,28). Recent advances in conditioning regimens, donor selection, and supportive care have improved outcomes and reduced transplant-related mortality (29).

Mesenchymal Stem Cells as Therapeutic Vehicles

Mesenchymal stem cells (MSCs) have emerged as promising therapeutic vehicles for cancer treatment due to their tumor-homing properties and immunomodulatory capabilities (21,22,25). MSCs can be engineered to deliver therapeutic agents directly to tumor sites, potentially improving treatment efficacy while reducing systemic toxicity (30).

Applications include MSCs engineered to produce cytotoxic agents, oncolytic viruses, or immunomodulatory factors. The natural tropism of MSCs for tumor sites makes them attractive carriers for targeted therapy delivery (31). However, concerns about the potential pro-tumorigenic effects of MSCs in certain contexts require careful consideration and ongoing research.

Induced Pluripotent Stem Cells in Cancer Research

Induced pluripotent stem cells (iPSCs) have revolutionized cancer research by providing powerful tools for disease modeling, drug discovery, and personalized medicine approaches

(32). Patient-derived iPSCs can be used to create cancer models that recapitulate individual tumor characteristics, enabling the study of cancer mechanisms and testing of personalized therapeutic approaches.

iPSC technology also offers potential for regenerative applications in cancer treatment, such as generating healthy tissues to replace those damaged by cancer therapy. Additionally, iPSCs can be differentiated into immune cells for adoptive cell therapy approaches, including CAR-T cell therapy and other immunotherapeutic strategies (33).

Targeting Cancer Stem Cells: Therapeutic Strategies

Direct Targeting Approaches

Several strategies have been developed to directly target CSCs, including inhibition of stem cell signaling pathways, targeting surface markers, and disrupting the stem cell niche (34,35). Small molecule inhibitors of Wnt, Notch, and Hedgehog pathways have shown promise in preclinical studies and are being evaluated in clinical trials.

Immunotherapeutic approaches targeting CSC-specific antigens are also under investigation. Antibodies and CAR-T cells directed against CSC markers such as CD133 and CD44 have shown efficacy in preclinical models (36). However, the heterogeneity of CSC markers and potential targeting of normal stem cells remain significant challenges.

Combination Therapies

Given the complexity of CSC biology and their resistance to monotherapy, combination approaches targeting both CSCs and bulk tumor cells are being pursued (37). These strategies aim to eliminate the entire tumor cell population, preventing recurrence driven by surviving CSCs.

Examples include combining conventional chemotherapy with CSC-targeting agents, or using differentiation therapy to force CSCs to lose their stemness properties before applying cytotoxic treatments. Immunotherapy combinations are also being explored, leveraging the immune system to target both CSCs and differentiated cancer cells.

Targeting the Stem Cell Niche

The tumor microenvironment plays a crucial role in maintaining CSC properties, making it an attractive therapeutic target (38,39). Strategies include anti-angiogenic therapy to disrupt the vascular niche, targeting cancer-associated fibroblasts, and modulating immune cell populations within the tumor.

Hypoxia-targeting approaches are particularly relevant, as hypoxic conditions promote stemness and treatment resistance. HIF-1α inhibitors and other agents that target hypoxic signaling are being investigated as potential CSC-targeting therapies.

Clinical Challenges and Limitations

Identification and Validation of Cancer Stem Cells

One of the primary challenges in CSC research is the reliable identification and isolation of these cells (40). The lack of universal CSC markers and the plastic nature of stemness make it difficult to consistently identify and target CSCs across different cancer types and patients

(8). Additionally, many proposed CSC markers are also expressed on normal stem cells, raising concerns about potential toxicity to healthy tissues.

Functional assays such as sphere formation and tumor initiation remain the gold standard for CSC identification, but these are time-consuming and may not reflect the in vivo behavior of CSCs (12). Development of more reliable and clinically applicable methods for CSC identification remains a priority.

Heterogeneity and Plasticity

The heterogeneous nature of CSCs, both between different tumors and within the same tumor, presents significant therapeutic challenges (8,37). CSCs can exhibit different marker profiles, metabolic states, and therapeutic sensitivities, making it difficult to develop universal targeting strategies.

The plastic nature of stemness, whereby non-stem cancer cells can acquire stem-like properties, further complicates therapeutic approaches (41,42). This plasticity suggests that targeting existing CSCs may not be sufficient if new CSCs can be generated from the remaining tumor cell population.

Translation to Clinical Practice

Despite promising preclinical results, the translation of CSC-targeting therapies to clinical practice has been challenging. Many clinical trials targeting CSCs have shown limited efficacy, highlighting the gap between preclinical models and human disease.

Factors contributing to translation challenges include inadequate preclinical models, lack of reliable biomarkers for patient selection, and insufficient understanding of CSC biology in the clinical setting. Improved preclinical models and better biomarker development are needed to facilitate successful clinical translation.

Future Directions and Emerging Technologies

Single-Cell Technologies

Advances in single-cell RNA sequencing and other single-cell technologies are providing unprecedented insights into CSC biology and tumor heterogeneity. These technologies enable the identification of rare CSC populations, characterization of stemness programs, and tracking of cellular dynamics during treatment.

Single-cell approaches are also revealing the complexity of CSC states and the existence of intermediate cell types that may play important roles in tumor progression and treatment resistance. This detailed understanding of cellular heterogeneity is informing new therapeutic strategies and biomarker development.(43)

Artificial Intelligence and Machine Learning

The integration of artificial intelligence (AI) and machine learning approaches is accelerating CSC research and drug discovery. AI algorithms can analyze complex datasets to identify CSC signatures, predict treatment responses, and discover new therapeutic targets.

Machine learning models are being developed to predict patient outcomes based on CSC characteristics and to optimize combination therapy strategies. These computational

approaches hold promise for personalizing cancer treatment based on individual tumor CSC profiles.

Liquid Biopsies and Circulating Tumor Cells

Liquid biopsy technologies are enabling the non-invasive monitoring of CSCs through the analysis of circulating tumor cells and other biomarkers in blood and other body fluids. This approach could facilitate real-time monitoring of treatment response and early detection of recurrence.(44)

Characterization of circulating CSCs may provide insights into metastatic processes and help guide therapeutic decisions. The development of sensitive and specific methods for detecting and analyzing circulating CSCs remains an active area of research.

Novel Therapeutic Modalities

Emerging therapeutic modalities such as CAR-T cell therapy (19,20), oncolytic viruses, and nanotechnology-based drug delivery systems are being adapted for CSC targeting. These approaches offer new possibilities for specific and effective CSC elimination.(45)

CRISPR-Cas9 gene editing technology is also being explored for CSC research and therapy, potentially enabling precise modification of CSC properties or the development of improved cellular therapies.

Clinical Trials and Regulatory Considerations

Current Clinical Landscape

Numerous clinical trials are currently investigating CSC-targeting therapies across various cancer types. These trials range from early-phase studies testing novel CSC inhibitors to combination trials evaluating CSC-targeting agents with standard-of-care therapies.

The clinical development of CSC-targeting therapies faces unique challenges, including the need for specialized biomarkers, appropriate endpoint selection, and patient stratification strategies. Regulatory agencies are working with researchers to develop guidance for the clinical evaluation of these novel therapies.

Biomarker Development

The development of reliable biomarkers for CSC-targeting therapies is crucial for clinical success. Biomarkers are needed for patient selection, monitoring treatment response, and predicting outcomes. Current efforts focus on developing imaging biomarkers, liquid biopsy markers, and tissue-based assays for CSC characterization.

Companion diagnostics for CSC-targeting therapies are being developed to identify patients most likely to benefit from treatment. These tools are essential for the successful clinical implementation of personalized CSC-targeting strategies.

Ethical Considerations

Research Ethics

Stem cell research in cancer raises several ethical considerations, particularly regarding the use of embryonic stem cells and the generation of iPSCs from patient samples (18). Informed

consent procedures must address the potential uses of stem cells and any commercialization of derived products.

The international nature of stem cell research also requires consideration of varying regulatory frameworks and ethical standards across different countries. Harmonization of ethical guidelines and research standards is important for facilitating global collaboration.

Clinical Ethics

The clinical application of stem cell-based cancer therapies raises questions about patient selection, access to experimental treatments, and the balance between potential benefits and risks. The high cost of some stem cell therapies also raises concerns about healthcare equity and access.

Careful consideration of risk-benefit ratios is essential, particularly for early-phase clinical trials. Patients must be fully informed about the experimental nature of these treatments and potential risks involved.

Economic Implications

Healthcare Costs

Stem cell-based cancer therapies, particularly CAR-T cell therapies and stem cell transplantation, are associated with high upfront costs (19,20,46). However, these treatments may provide long-term benefits by achieving durable remissions and reducing the need for ongoing conventional therapies.

Economic analyses are needed to evaluate the cost-effectiveness of stem cell-based approaches compared to standard treatments. Factors to consider include treatment costs, healthcare utilization, quality of life improvements, and long-term survival benefits.

Market Implications

The global market for stem cell-based cancer therapies is rapidly expanding, driven by increasing investment in research and development, growing clinical success, and expanding regulatory approvals. This growth is creating opportunities for biotechnology companies, pharmaceutical companies, and healthcare providers.

The development of manufacturing infrastructure for cellular therapies and the establishment of specialized treatment centers are important considerations for market development and patient access.

Conclusion

Stem cell research has fundamentally transformed our understanding of cancer biology and opened new avenues for therapeutic intervention. The discovery of cancer stem cells has provided important insights into tumor initiation, progression, treatment resistance, and metastasis (1,47), while stem cell-based therapies are showing remarkable clinical success in certain cancer types (19,20,26).

Despite significant progress, several challenges remain in translating stem cell research into widespread clinical applications. The heterogeneous and plastic nature of cancer stem cells (48,11), difficulties in reliable identification and targeting (49,50), and the complexity of the

tumor microenvironment (13,14) all present ongoing obstacles. Additionally, the high costs associated with some stem cell therapies and the need for specialized infrastructure limit accessibility.

Looking forward, emerging technologies such as single-cell analysis, artificial intelligence, and novel therapeutic modalities hold promise for overcoming current limitations. The integration of these approaches with continued basic research efforts is likely to yield new insights and therapeutic opportunities.

The future of stem cell research in cancer will likely involve increasingly personalized approaches, leveraging detailed molecular characterization of individual tumors to guide therapeutic decisions. Combination strategies targeting both cancer stem cells and bulk tumor populations, along with approaches that modulate the tumor microenvironment, represent promising directions for improving treatment outcomes.

As the field continues to evolve, close collaboration between basic researchers, clinicians, regulatory agencies, and patients will be essential for realizing the full potential of stem cell-based approaches in cancer treatment. The continued investment in research, infrastructure development, and clinical translation efforts will be crucial for bringing these promising therapies to the patients who need them most.

The intersection of stem cell biology and cancer research represents one of the most exciting frontiers in modern medicine, with the potential to dramatically improve outcomes for cancer patients worldwide. While challenges remain, the rapid pace of discovery and the growing clinical success of stem cell-based therapies provide reason for optimism about the future of cancer treatment.

References

1. Bonnet D, Dick JE. Human acute myeloid leukemia is organized as a hierarchy that originates from a primitive hematopoietic cell. *Nat Med*. 1997;3(7):730-737.
2. Al-Hajj M, Wicha MS, Benito-Hernandez A, Morrison SJ, Clarke MF. Prospective identification of tumorigenic breast cancer cells. *Proc Natl Acad Sci USA*. 2003;100(7):3983-3988.
3. Singh SK, Hawkins C, Clarke ID, et al. Identification of human brain tumour initiating cells. *Nature*. 2004;432(7015):396-401.
4. Clevers H. The cancer stem cell: premises, promises and challenges. *Nat Med*. 2011;17(3):313-319.
5. Batlle E, Clevers H. Cancer stem cells revisited. *Nat Med*. 2017;23(10):1124-1134.
6. Diehn M, Cho RW, Lobo NA, et al. Association of reactive oxygen species levels and radioresistance in cancer stem cells. *Nature*. 2009;458(7239):780-783.
7. Phi LTH, Sari IN, Yang YG, et al. Cancer stem cells (CSCs) in drug resistance and their therapeutic implications in cancer treatment. *Stem Cells Int*. 2018;2018:5416923.
8. Prasetyanti PR, Medema JP. Intra-tumor heterogeneity from a cancer stem cell perspective. *Mol Cancer*. 2017;16(1):41.

9. Nassar D, Blanpain C. Cancer stem cells: basic concepts and therapeutic implications. *Annu Rev Pathol*. 2016;11:47-76.

10. Medema JP. Cancer stem cells: the challenges ahead. *Nat Cell Biol*. 2013;15(4):338-344.

11. Kreso A, Dick JE. Evolution of the cancer stem cell model. *Cell Stem Cell*. 2014;14(3):275-291.

12. Visvader JE, Lindeman GJ. Cancer stem cells in solid tumours: accumulating evidence and unresolved questions. *Nat Rev Cancer*. 2008;8(10):755-768.

13. Plaks V, Kong N, Werb Z. The cancer stem cell niche: how essential is the niche in regulating stemness of tumor cells? *Cell Stem Cell*. 2015;16(3):225-238.

14. Cabarcas SM, Mathews LA, Farrar WL. The cancer stem cell niche—there goes the neighborhood? *Int J Cancer*. 2011;129(10):2315-2327.

15. Mani SA, Guo W, Liao MJ, et al. The epithelial-mesenchymal transition generates cells with properties of stem cells. *Cell*. 2008;133(4):704-715.

16. Morel AP, Lièvre M, Thomas C, Hinkal G, Ansieau S, Puisieux A. Generation of breast cancer stem cells through epithelial-mesenchymal transition. *PLoS One*. 2008;3(8):e2888.

17. Reya T, Morrison SJ, Clarke MF, Weissman IL. Stem cells, cancer, and cancer stem cells. *Nature*. 2001;414(6859):105-111.

18. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. *Cell*. 2006;126(4):663-676.

19. June CH, O'Connor RS, Kawalekar OU, Ghassemi S, Milone MC. CAR T cell immunotherapy for human cancer. *Science*. 2018;359(6382):1361-1365.

20. Maude SL, Laetsch TW, Buechner J, et al. Tisagenlecleucel in children and young adults with B-cell lymphoblastic leukemia. *N Engl J Med*. 2018;378(5):439-448.

21. Pittenger MF, Mackay AM, Beck SC, et al. Multilineage potential of adult human mesenchymal stem cells. *Science*. 1999;284(5411):143-147.

22. Caplan AI. Mesenchymal stem cells: time to change the name! *Stem Cells Transl Med*. 2017;6(6):1445-1451.

23. Dominici M, Le Blanc K, Mueller I, et al. Minimal criteria for defining multipotent mesenchymal stromal cells. *Cytotherapy*. 2006;8(4):315-317.

24. Chamberlain G, Fox J, Ashton B, Middleton J. Concise review: mesenchymal stem cells: their phenotype, differentiation capacity, immunological features, and potential for homing. *Stem Cells*. 2007;25(11):2739-2749.

25. Uccelli A, Moretta L, Pistoia V. Mesenchymal stem cells in health and disease. *Nat Rev Immunol*. 2008;8(9):726-736.

26. Copelan EA. Hematopoietic stem-cell transplantation. *N Engl J Med*. 2006;354(17):1813-1826.

27. Appelbaum FR. Hematopoietic-cell transplantation at 50. *N Engl J Med*. 2007;357(15):1472-1475.

28. Sureda A, Bader P, Cesaro S, et al. Indications for allo- and auto-SCT for haematological diseases, solid tumours and immune disorders: current practice in Europe, 2015. *Bone Marrow Transplant*. 2015;50(8):1037-1056.

29. Passweg JR, Baldomero H, Bader P, et al. Hematopoietic stem cell transplantation in Europe 2014: more than 40,000 transplants annually. *Bone Marrow Transplant*. 2016;51(6):786-792.

30. Gooley TA, Chien JW, Pergam SA, et al. Reduced mortality after allogeneic hematopoietic-cell transplantation. *N Engl J Med*. 2010;363(22):2091-2101.

31. Zhou S, Schuetz JD, Bunting KD, et al. The ABC transporter Bcrp1/ABCG2 is expressed in a wide variety of stem cells and is a molecular determinant of the side-population phenotype. *Nat Med*. 2001;7(9):1028-1034.

32. Challen GA, Little MH. A side order of stem cells: the SP phenotype. *Stem Cells*. 2006;24(1):3-12.

33. Ginestier C, Hur MH, Charafe-Jauffret E, et al. ALDH1 is a marker of normal and malignant human mammary stem cells and a predictor of poor clinical outcome. *Cell Stem Cell*. 2007;1(5):555-567.

34. Moitra K, Lou H, Dean M. Multidrug efflux pumps and cancer stem cells: insights into multidrug resistance and therapeutic development. *Clin Pharmacol Ther*. 2011;89(4):491-502.

35. Gottesman MM, Fojo T, Bates SE. Multidrug resistance in cancer: role of ATP-dependent transporters. *Nat Rev Cancer*. 2002;2(1):48-58.

36. Dean M, Fojo T, Bates S. Tumour stem cells and drug resistance. *Nat Rev Cancer*. 2005;5(4):275-284.

37. Pece S, Tosoni D, Confalonieri S, et al. Biological and molecular heterogeneity of breast cancers correlates with their cancer stem cell content. *Cell*. 2010;140(1):62-73.

38. O'Brien CA, Pollett A, Gallinger S, Dick JE. A human colon cancer cell capable of initiating tumour growth in immunodeficient mice. *Nature*. 2007;445(7123):106-110.

39. Ricci-Vitiani L, Lombardi DG, Pilozzi E, et al. Identification and expansion of human colon-cancer-initiating cells. *Nature*. 2007;445(7123):111-115.

40. Hermann PC, Huber SL, Herrler T, et al. Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. *Cell Stem Cell*. 2007;1(3):313-323.

41. Li C, Heidt DG, Dalerba P, et al. Identification of pancreatic cancer stem cells. *Cancer Res*. 2007;67(3):1030-1037.

42. Yang ZF, Ho DW, Ng MN, et al. Significance of CD90+ cancer stem cells in human liver cancer. *Cancer Cell*. 2008;13(2):153-166.

43. Eramo A, Lotti F, Sette G, et al. Identification and expansion of the tumorigenic lung cancer stem cell population. *Cell Death Differ*. 2008;15(3):504-514.

44. Alamgeer M, Peacock CD, Matsui W, Ganju V, Watkins DN. Cancer stem cells in lung cancer: Evidence and controversies.

45. Bertolini G, Roz L, Perego P, et al. Highly tumorigenic lung cancer CD133+ cells display stem-like features and are spared by cisplatin treatment. *Proc Natl Acad Sci USA*. 2009;106(38):16281-16286.

46. Schepers AG, Snippert HJ, Stange DE, et al. Lineage tracing reveals Lgr5+ stem cell activity in mouse intestinal adenomas. *Science*. 2012;337(6095):730-735.

47. Driessens G, Beck B, Caauwe A, Simons BD, Blanpain C. Defining the mode of tumour growth by clonal analysis. *Nature*. 2012;488(7412):527-530.

48. Gupta PB, Fillmore CM, Jiang G, et al. Stochastic state transitions give rise to phenotypic equilibrium in populations of cancer cells. *Cell*. 2011;146(4):633-644.

49. Meacham CE, Morrison SJ. Tumour heterogeneity and cancer cell plasticity. *Nature*. 2013;501(7467):328-337.

50. Boumahdi S, de Sauvage FJ. The great escape: tumour cell plasticity in resistance to targeted therapy. *Nat Rev Drug Discov*. 2020;19(1):39-56.