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Short Communication

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A Short Communication on Metastatic Cancer Stem Cells

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Abstract

Metastatic cancer remains the leading cause of cancer-related mortality and is increasingly associated with a subpopulation of cancer stem cells (CSCs). These cells exhibit self-renewal capacity, tumor initiation potential, and the ability to generate intratumoral heterogeneity. Emerging evidence suggests that metastatic dissemination and colonization may be driven by CSCs capable of surviving systemic spread and adapting to distant microenvironments. Although the CSC model provides a useful framework for explaining tumor recurrence and therapeutic resistance, its universality across cancer types remains debated. Key signaling pathways, including WNT/β-catenin, NOTCH, Hedgehog, BMI1, and EZH2, are implicated in CSC maintenance and metastatic behavior. In addition, epithelial–mesenchymal transition (EMT) and pre-metastatic niche formation further support the link between stemness and metastasis. Collectively, these findings suggest that CSCs play a critical role in tumor progression and represent promising therapeutic targets for preventing metastasis and improving cancer outcomes.

Keywords: Cell Clones, Tumor Cells, Metastatic Cancer Stem Cells, Hypothesis, Hematological Malignancies, Human Melanoma, Epithelial–Mesenchymal Transition, Melanocytes, Glial Cells

1. Introduction (Short communication)

The concept that metastases originate from a limited number of cell clones, representing only a minor fraction of disseminated tumor cells, has led to the hypothesis that metastatic outgrowth may be driven by a specialized subpopulation known as metastatic cancer stem cells (CSCs). This hypothesis has gained substantial attention in recent years and is supported by accumulating experimental evidence [1,2]. The cancer stem cell model proposes a hierarchical organization within tumors that closely resembles the architecture of normal tissues. At the apex of this hierarchy resides a population of CSCs characterized by their ability to undergo asymmetric division, thereby maintaining a self-renewing stem cell pool while generating rapidly proliferating progenitor cells. These progenitors subsequently differentiate into more mature tumor cells with limited proliferative capacity, ultimately constituting the bulk of the tumor mass.

A defining feature of CSCs is their long-term self-renewal capacity and sustained tumorigenic potential. Experimental evidence from serial transplantation assays demonstrates that CSC-enriched populations possess significantly greater tumor-initiating capacity compared with unselected tumor cell populations. CSCs were initially identified in hematological malignancies, such as acute myeloid leukemia, and have since been reported in a wide range of solid tumors, including melanoma, as well as breast, brain, prostate, pancreatic, and colorectal cancers [2,3]. Despite these findings, the cellular origin of CSCs remains a subject of debate. One prevailing theory suggests that CSCs arise from normal tissue stem cells that acquire oncogenic mutations while retaining their intrinsic self-renewal properties. Alternatively, accumulating evidence supports the notion that more differentiated progenitor or even mature tumor cells may undergo dedifferentiation following genetic or epigenetic alterations, thereby reacquiring stem cell-like properties [1,4-6].

The ability of CSCs to self-renew and generate heterogeneous tumor cell populations provides a compelling explanation for tumor recurrence following apparently successful treatment. Conventional therapies often eliminate the rapidly proliferating bulk tumor cells but fail to eradicate the more therapy-resistant CSC population, allowing tumors to re-emerge. Nevertheless, the CSC hypothesis remains controversial. Notably, studies by the Morrison group demonstrated that optimization of xenotransplantation conditions significantly increased the apparent frequency of tumor-initiating cells in human melanoma, suggesting that tumor-initiating capacity may not be restricted to a rare subpopulation

in all cancers [7,8]. These findings challenge the universality of the CSC model and indicate that its applicability may vary across tumor types.

With respect to metastasis, the relationship between CSCs and metastatic competence remains largely circumstantial and is predominantly supported by correlative evidence. However, the hypothesis that the rare cells capable of forming metastases correspond to CSCs is biologically appealing. Such cells would inherently possess the capacity to initiate secondary tumors that recapitulate the histological complexity and cellular heterogeneity of the primary lesion [9]. Importantly, both normal and cancer stem cells critically depend on specialized microenvironments, referred to as stem cell niches, which regulate their survival, self-renewal, and differentiation. In the context of metastasis, Kaplan et al. described the existence of pre-metastatic niches that are essential for metastatic colonization [10]. The requirement for disseminated tumor cells to remodel or establish a supportive niche at distant sites may explain the prolonged latency and frequent failure of metastatic outgrowth observed clinically [11].

Molecular evidence further supports a connection between CSCs and metastasis. Metastatic tumors often exhibit overexpression of stem cell-associated genes, including the polycomb group proteins EZH2 and BMI1, which are key regulators of stem cell maintenance and epigenetic silencing [12]. Both EZH2 and BMI1 are overexpressed in multiple metastatic cancer types and are associated with tumor progression, poor prognosis, and reduced patient survival [13-16]. Gene expression signatures linked to BMI1 and EZH2 have been shown to predict metastasis and unfavorable clinical outcomes. Moreover, studies by Chang, Weinberg, and colleagues identified embryonic stem cell-like gene expression modules in diverse tumor types, which strongly correlate with metastatic potential and poor survival [17-20].

Functional evidence also implicates CSCs in invasion and metastasis. Stem cell-like subpopulations isolated from lung cancer cell lines exhibit enhanced invasive capacity in vitro compared with non-stem cell-like counterparts. In pancreatic cancer, Hermann et al. identified a subset of CSCs expressing the chemokine receptor CXCR4 at the invasive front of tumors. While all pancreatic CSCs were capable of tumor formation in xenograft models, only the CXCR4-positive fraction exhibited metastatic behavior, highlighting functional heterogeneity within the CSC compartment. Similar observations have been reported in colorectal cancer, where tumor cells at the invasive front display nuclear β-catenin localization, a hallmark of intestinal stem cells [21,22]. Although stemness was not directly assessed in these studies, WNT/β-catenin signaling is well established as a regulator of stem cell maintenance and has been shown to promote migration and invasion in human mesenchymal stem cells [23].

Additional evidence linking stem cell-associated pathways to metastasis is provided by the morphogen NODAL, a key regulator of pluripotency in embryonic stem cells [24]. NODAL is aberrantly expressed in aggressive melanomas, where it contributes to the maintenance of a dedifferentiated, stem-like phenotype and is required for efficient tumor formation in vivo [25]. Furthermore, a growing body of evidence indicates a strong mechanistic link between CSCs and epithelial–mesenchymal transition (EMT). The Weinberg group demonstrated that induction of EMT through transcription factors such as Twist or Snail confers stem cell-like properties upon breast epithelial cells [26]. Conversely, normal and malignant mammary stem cells exhibit molecular and phenotypic features characteristic of EMT.

Notably, several signaling pathways that govern stem cell self-renewal, including WNT, Sonic Hedgehog, NOTCH, and bone morphogenetic protein (BMP) signaling, are also potent inducers of EMT [27,28]. During embryonic development, neural crest cells undergo EMT to migrate extensively before differentiating into diverse cell lineages, including neurons, glial cells, melanocytes, and connective tissue. This process is tightly regulated by transcription factors such as Snail and Twist, which are also implicated in cancer invasion and metastasis [27,29-31]. Understanding the extent to which these developmental programs are co-opted by CSCs during metastatic dissemination remains an important area of investigation.

2. Conclusion

Metastatic cancer stem cells represent a key driver of tumor dissemination, recurrence, and therapeutic resistance through their self-renewal capacity and adaptive plasticity. Although the universality of the CSC model remains debated, accumulating molecular and functional evidence supports their involvement in metastasis. Targeting CSC-associated pathways and the tumor microenvironment may offer promising strategies to improve long-term treatment outcomes [32].

References

1. Pardal, R., Clarke, M. F., & Morrison, S. J. (2003). Applying the principles of stem-cell biology to cancer. *Nature Reviews Cancer, 3*(12), 895-902.
2. Lobo, N. A., Shimono, Y., Qian, D., & Clarke, M. F. (2007). The biology of cancer stem cells. *Annu. Rev. Cell Dev. Biol., 23*(1), 675-699.
3. Hermann, P. C., Huber, S. L., Herrler, T., Aicher, A., Ellwart, J. W., Guba, M., ... & Heeschen, C. (2007). Distinct populations of cancer stem cells determine tumor growth and metastatic activity in human pancreatic cancer. *Cell stem cell, 1*(3), 313-323.
4. Bachoo, R. M., Maher, E. A., Ligon, K. L., Sharpless, N. E., Chan, S. S., You, M. J., ... & DePinho, R. A. (2002). Epidermal growth factor receptor and Ink4a/Arf: convergent mechanisms governing terminal differentiation and transformation along the neural stem cell to astrocyte axis. *Cancer cell, 1*(3), 269-277.
5. Fodde, R. (2009). The stem of cancer. *Cancer cell, 15*(2), 87-89.
6. Rapp, U. R., Ceteci, F., & Schreck, R. (2008). Oncogene-induced plasticity and cancer stem cells. *Cell cycle, 7*(1), 45-51.

7. Kelly, P. N., Dakic, A., Adams, J. M., Nutt, S. L., & Strasser, A. (2007). Tumor growth need not be driven by rare cancer stem cells. *Science, 317*(5836), 337-337.
8. Quintana, E., Shackleton, M., Sabel, M. S., Fullen, D. R., Johnson, T. M., & Morrison, S. J. (2008). Efficient tumour formation by single human melanoma cells. *Nature, 456*(7222), 593-598.
9. Brabletz, T., Jung, A., Spaderna, S., Hlubek, F., & Kirchner, T. (2005). Migrating cancer stem cells—an integrated concept of malignant tumour progression. *Nature Reviews Cancer, 5*(9), 744-749.
10. Kaplan, R. N., Riba, R. D., Zacharoulis, S., Bramley, A. H., Vincent, L., Costa, C., ... & Lyden, D. (2005). VEGFR1-positive haematopoietic bone marrow progenitors initiate the pre-metastatic niche. *Nature, 438*(7069), 820-827.
11. Li, F., Tiede, B., Massagué, J., & Kang, Y. (2007). Beyond tumorigenesis: cancer stem cells in metastasis. *Cell research, 17*(1), 3-14.
12. Valk-Lingbeek, M. E., Bruggeman, S. W., & van Lohuizen, M. (2004). Stem cells and cancer: the polycomb connection. *Cell, 118*(4), 409-418.
13. Berezovska, O. P., Glinskii, A. B., Yang, Z., Li, X., Hoffman, R. M., & Glinsky, G. V. (2006). Essential role for activation of the Polycomb group (PcG) protein chromatin silencing pathway in metastatic prostate cancer. *CELL CYCLE-LANDES BIOSCIENCE-, 5*(16), 1886.
14. Kim, J. H., Yoon, S. Y., Jeong, S. H., Kim, S. Y., Moon, S. K., Joo, J. H., ... & Kim, J. W. (2004). Overexpression of Bmi-1 oncoprotein correlates with axillary lymph node metastases in invasive ductal breast cancer. *The Breast, 13*(5), 383-388.
15. Kleer, C. G., Cao, Q., Varambally, S., Shen, R., Ota, I., Tomlins, S. A., ... & Chinnaiyan, A. M. (2003). EZH2 is a marker of aggressive breast cancer and promotes neoplastic transformation of breast epithelial cells. *Proceedings of the national academy of sciences, 100*(20), 11606-11611.
16. Varambally, S., Dhanasekaran, S. M., Zhou, M., Barrette, T. R., Kumar-Sinha, C., Sanda, M. G., ... & Chinnaiyan, A. M. (2002). The polycomb group protein EZH2 is involved in progression of prostate cancer. *Nature, 419*(6907), 624-629.
17. Glinsky, G. V., Berezovska, O., & Glinskii, A. B. (2005). Microarray analysis identifies a death-from-cancer signature predicting therapy failure in patients with multiple types of cancer. *The Journal of clinical investigation, 115*(6), 1503-1521.
18. Yu, J., Yu, J., Rhodes, D. R., Tomlins, S. A., Cao, X., Chen, G., ... & Chinnaiyan, A. M. (2007). A polycomb repression signature in metastatic prostate cancer predicts cancer outcome. *Cancer research, 67*(22), 10657-10663.
19. Ben-Porath, I., Thomson, M. W., Carey, V. J., Ge, R., Bell, G. W., Regev, A., & Weinberg, R. A. (2008). An embryonic stem cell–like gene expression signature in poorly differentiated aggressive human tumors. *Nature genetics, 40*(5), 499-507.
20. Wong, D. J., Liu, H., Ridky, T. W., Cassarino, D., Segal, E., & Chang, H. Y. (2008). Module map of stem cell genes guides creation of epithelial cancer stem cells. *Cell stem cell, 2*(4), 333-344.
21. Ho, M. M., Ng, A. V., Lam, S., & Hung, J. Y. (2007). Side population in human lung cancer cell lines and tumors is enriched with stem-like cancer cells. *Cancer research, 67*(10), 4827-4833.
22. Brabletz, T., Hlubek, F., Spaderna, S., Schmalhofer, O., Hiendlmeyer, E., Jung, A., & Kirchner, T. (2005). Invasion and metastasis in colorectal cancer: epithelial-mesenchymal transition, mesenchymal-epithelial transition, stem cells and β-catenin. *Cells tissues organs, 179*(1-2), 56-65.
23. Brabletz, T., Jung, A., Reu, S., Porzner, M., Hlubek, F., Kunz-Schughart, L. A., ... & Kirchner, T. (2001). Variable β-catenin expression in colorectal cancers indicates tumor progression driven by the tumor environment. *Proceedings of the National Academy of Sciences, 98*(18), 10356-10361.
24. Neth, P., Ciccarella, M., Egea, V., Hoelters, J., Jochum, M., & Ries, C. (2006). Wnt signaling regulates the invasion capacity of human mesenchymal stem cells. *Stem cells, 24*(8), 1892-1903.
25. Hendrix, M. J., Seftor, E. A., Seftor, R. E., Kasemeier-Kulesa, J., Kulesa, P. M., & Postovit, L. M. (2007). Reprogramming metastatic tumour cells with embryonic microenvironments. *Nature Reviews Cancer, 7*(4), 246-255.
26. Topczewska, J. M., Postovit, L. M., Margaryan, N. V., Sam, A., Hess, A. R., Wheaton, W. W., ... & Hendrix, M. J. (2006). Embryonic and tumorigenic pathways converge via Nodal signaling: role in melanoma aggressiveness. *Nature medicine, 12*(8), 925-932.
27. Mani, S. A., Guo, W., Liao, M. J., Eaton, E. N., Ayyanan, A., Zhou, A. Y., ... & Weinberg, R. A. (2008). The epithelial-mesenchymal transition generates cells with properties of stem cells. *Cell, 133*(4), 704-715.
28. Huber, M. A., Kraut, N., & Beug, H. (2005). Molecular requirements for epithelial–mesenchymal transition during tumor progression. *Current opinion in cell biology, 17*(5), 548-558.
29. Bailey, J. M., Singh, P. K., & Hollingsworth, M. A. (2007). Cancer metastasis facilitated by developmental pathways: Sonic hedgehog, Notch, and bone morphogenic proteins. *Journal of cellular biochemistry, 102*(4), 829-839.
30. Cheung, M., Chaboissier, M. C., Mynett, A., Hirst, E., Schedl, A., & Briscoe, J. (2005). The transcriptional control of trunk neural crest induction, survival, and delamination. *Developmental cell, 8*(2), 179-192.
31. Kuriyama, S., & Mayor, R. (2008). Molecular analysis of neural crest migration. *Philosophical Transactions of the Royal Society B: Biological Sciences, 363*(1495), 1349.
32. Tucker, R. P. (2004). Neural crest cells: a model for invasive behavior. *The international journal of biochemistry & cell biology, 36*(2), 173-177.