

Cancer Metastasis at a Glance: A Brief View of Breast Cancer Brain Metastasis

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INTRODUCTION

Cancer initiation and progression is a challenging scenario through developmental processes, which may be more complicated by occurrence of metastasis. Basically, diverse genetic alterations, including mutations, formation of truncated proteins and related pathways play key roles either in diagnosis or the most influential therapeutic purposes. These may lead to an applicable preventive package against metastatic events [1]. By considering the biological and clinical characteristics, it has been stated that “Adolescent and Young Adult (AYA)” cancer patients are diversely defined compared to patients of older age groups. In this regard, it was aimed to investigate exceptional metastatic AYA cancer patients at genomic level and by considering the capability of molecular alterations in drug innovation [2]. Interestingly, by considering type of malignancy, genetic diversity has been found amongst AYA group and other age groups. “Driving genetic alterations and their druggability” has been recognized in specific metastatic AYA cancer patients. It was emphasized that drivers and mediators of Epithelial–Mesenchymal Transition (EMT) are capable of maintaining epithelial properties, as observed for the surrounding normal epithelium. The accidental overexpression of Twist, Snail, and SIP1, as the regulators of EMT, in cancer cells lead to alterations in gene expression and cellular behavior. These regulators repress the expression of *E-cadherin* and trigger

expression of the EMT transcriptional program [3]. In addition, distant metastasis is a threatening event of malignant tumors with diverse processing manner in a variety of cancers. Genetic elements, evolutionary mechanisms, and metastatic cell targeting are challenging paradigms. Tumor progression through metastatic mode is believed to be a multistep process and is reflective of cancer cells’ migration from the initial tumor to the distant tissues [4-6]. Interestingly, recurrence in breast cancer may be traced within years or even decades and the circulated tumor cells harbor less alteration than the original tumors, which is reflective of an early event through tumor progression [7, 8]. However, the capability of cancer cells to invade far organs, does not necessarily lead to colonization of the target tissue(s). Therefore, programmed sequential events are responsible for metastasis and include local invasion, intravasation, survival in the circulation, extravasation, and colonization. The metastatic scenario is managed through biological, genetic and epigenetic events, occurrence of mutations, and required functional alterations [9]. However, the metastatic process requires more complicated events, even in mouse cancer models [10]. Besides, the progression of metastasis depends on the following steps, which are the key aspects for innovation of appropriate therapeutic programming:

- 1- Formation of an antagonistic tumor
 - 2- The circulation of cancer cells in the blood stream
 - 3-Departure of these cells to the target/distant organ(s)
 - 4- Facilitation by metastasis genes
 - 5- Further evolution in a specific malignancy
 - 6- Probable occurrence of relapse due to the dormancy of specific type of malignancy in certain target organs
 - 7- Distinctive colonization and infiltration in target organs
 - 8- The restriction item as “natural barrier” in metastatic process is required to be overcome by cancer cells
- Although much progress has been achieved by clinicians and scientists in the field of cancer, yet, metastasis is the most challenging event with many unmasked

facts. Therefore, the medical world faces the complex machinery of cancer initiation, progression, and therapy. By considering rapid progression in modern technologies, although the molecular- and cell biology-based research would lead to more appropriate diagnoses and target-based therapies, yet the divers personalized patterns, even in the same pedigree, is an alarm in cancer management.

THE GENES INVOLVED IN METASTATIC PROCESSES

There are genes, which facilitate transformation from carcinoma in situ to invasive carcinoma at primary tumor, and initiate a successful circulation from the primary tumor to blood stream and then to the target organ. Furthermore, the highlighted scenario for distant metastasis includes infiltration, dormancy, and colonization. The tumor initiators include 1) oncogenes, which are responsible for growth, survival, progenitor-like-state and genomic instability, including ERBB2, CTNNB1 (β -catenin), KRAS, PI3K, EGFR, and MYC; 2) tumor suppressor genes (APC, TP53, PTEN, BRCA1, and BRCA2); 3) metastatic progression factors to extravase and manage survival, such as PTGS2, EREG, MMP1, LOX, ANGPTL4, and CCL5; and 4) the genes responsible for colonization at specific organs (PTHRP, ILL11, CSF2RB (GM-CSF), IL6, and TNF α) [11].

METASTATIC EVENTS

The programming of metastases relies on the sequences of genes' activation and inactivation, which may lead to invasion of tissues within the cancer cells' territory, followed by metastatic event in target organ(s). The key required events for metastases include EMT, extracellular matrix degradation, bone marrow progenitor enrolment, and angiogenesis. Developmental programming is essential for EMT and is under control of key transcription factors, including TWiST1, SNAi1, and SNAi2 [12]. The metastatic cascade events are followed by the circulation of cancer cells, capable of passing through the capillary, reaching the distant organ and promoting infiltration of distant tissues. Besides, the expression of involved genes in metastases, and the characteristics of target organs play crucial roles in prediction of prognosis in different cancers. It is worth noting that by entry of circulated cells and infiltration process, the aggressive malignant cells are also capable of invading the neighboring tumor tissues as well. Invasion is a challenging event and different mechanisms are involved in the circulation process, including cellular motility and basement membrane degradation [13, 15]. Furthermore, RHOC, as a cytoskeletal modifier, plays a role in propagation of metastasis [15].

In fact, the circulating configurations play an import-

ant role in infiltration in the distant organ. Infiltration of the distant organ also requires an interaction between tumor cells and the basement membrane [16, 17]. Regarding the blood-brain barrier and astrocyte, a complicated process is involved in infiltration of circulating tumor cells into the parenchyma of brain, which requires to be unmasked [18, 19]. The blood-brain barrier, with its close-fitting layer of endothelial cells, is rather complicated. Consequently, the infiltration of circulating cancer cells in the brain parenchyma could require highly specialized functions, many of which require basic, complementary, and traditional insights. Furthermore, cancer therapy has an unexpected impact on the metastatic pattern via dormancy of Her2-neu positive breast cancer patients, who have been treated with Herceptin, and may lead to recurrence of a definite organ. In this regard, it has been shown that the occurrence of brain metastasis has also increased [19].

VIEWPOINTS

A successful metastasis relies on; 1) Barriers to metastatic infiltration that are found to be organ-specific; 2) The nature of capillary walls in target tissues; 3) Whether the cancer cells in primary tumor harbor the essential functional characteristics for a successful extravasation. These conditions are required for breast cancer cells, yet in the brain, the penetration of capillaries leads to a problematic infiltration, which is reflective of the brain barrier. However, the cancer cells by having the required functions, such as vascular factor and micro-environment signals of tumors, are allowed for extravasation [11]. The metastatic intermediaries may support either malignant progression at primary tumor level or facilitate infiltration ability in the target organ. In this regards, the expression of genes, including epi-regulin (EREG) and prostaglandin G/H synthase 2 (PTGS2), are required to endorse capillary association in specific tumors, such as breast. Therefore, the breast cancer cells will be authorized to pass the endothelial barriers [11]. "Bridging the gap in metastatic breast cancer" has been reported by Professor Marc Beishon presented at Advanced Breast Cancer (ABC) conference. The highlight points included the programs in survival of breast cancer patients and the examples of successful therapies. He has also focused on the requirements for the "ABC consensus guidelines" within healthcare systems. The selected topics and primary version of "consensus statements" are listed below [20]:

- 1- Performance of genetic counseling for "BRCA-associated disease in patients with triple negative or luminal metastatic breast cancer."
- 2- In patients with HER2+ and brain metastasis, as a sole target, and "stable extra-cranial disease", "systemic therapy" should not be altered.
- 3- The performance of next-generation sequencing is

not an evidence-based test, without any benefit for the cancer patients with metastatic tumors.

A review article on pathogenesis of Breast Cancer Metastasis to Brain (BCBM) was recently published [21]. As a beneficial outcome for cancer patients, tracing of predisposition to the occurrence of BCBM would lead to an early and appropriate diagnosis and management through the progression of cancer and occurrence of metastasis. These factors are demonstrated in Figure 1 [21]. Furthermore, numerous genes and signaling pathways have influential impact on BCBM. In this review, different pathways were explored and the early signaling pathway has been especially highlighted, as it governs the progression of metastasis. Therefore, the inhibition of these pathways may lead to remarkable therapeutic discovery. Therefore, the key elements of BCBM relies on the following facts, as have been addressed in the author's review in details [21]:

- 1- Involvement of different genes and signaling pathways.
- 2- Importance of Chemokine signaling as “a worthy biological support for the seed and soil theory”.
- 3- Cell migration as an essential machinery in metastasis through chemokines by promoting a sequence of events including angiogenesis, extravasation, proliferation, survival, and colonization.
- 4- Interaction between ErbB2 overexpression and VEGF expression in order to stimulate the proliferation and migration of primary tumor cells.
- 5- Successful target-based therapy considered as a great dream in BCBM and angiogenic-based therapy by anti-VEGF may initiate some hope in the cancer world

[22].

6- Other target-based factors include Poly-Adenosine Diphosphate Ribose Polymerase (PARP), HER2 tyrosine kinase, Insulin-like Growth Factor (IGF) or its binding protein (IGFBP) [23].

By considering other metastatic destination, the processes from breast to brain are also complicated, which has been broadly explored in a review by the authors [24]. It was proposed that the cascade manner in gene expression might play a role in transforming a benign breast neoplasm to an aggressive tumor, which may pave the way toward the metastasis to bone. However, the most important paradigm in BCBM management includes the following items:

- 1- Performing a reliable follow-up study of the patients effected by breast cancer.
- 2- An early detection of metastatic brain neoplasia.
- 3-Characterizing the molecular and cellular profiles in metastatic brain neoplasia.
- 4- Bridging genetics and cell biology to the metastatic tumor-initiation and progression.
- 5- Providing an influential therapy in cancer patients affected by BCBM.

As a brief direction, by considering the personalized cancer management and translational research, a multi-disciplinary approach is required for unmasking the most influential-, molecular- and cellular- alterations though the developmental processes in BCBM. Finally, the questions in cancer management for BCBM are 1) what was the global strategy in the past? 2) What is the current statue? And 3) Is there any harmonic research movements in the cancer world?

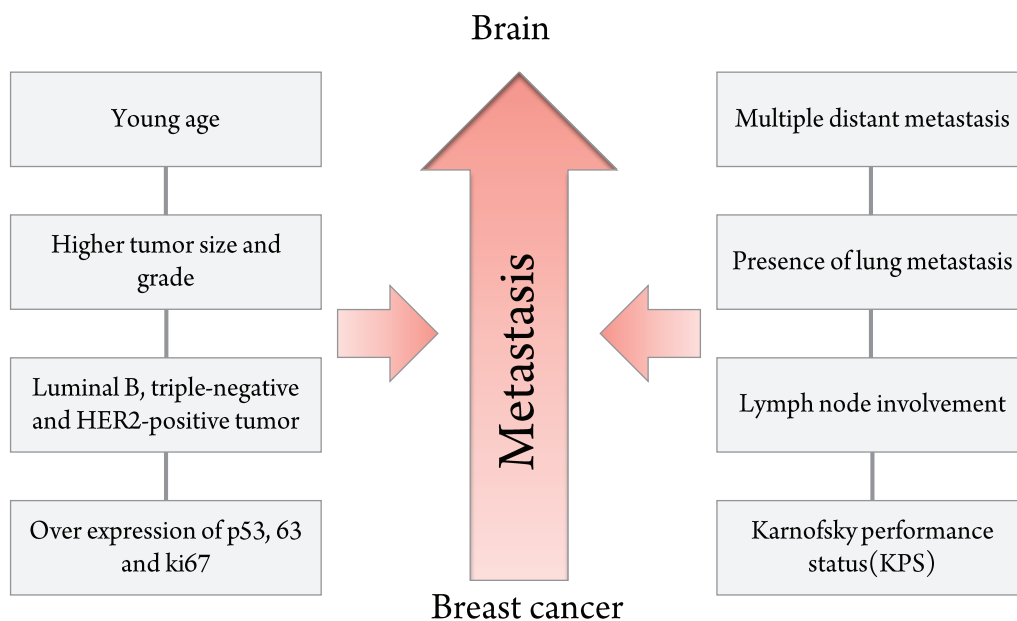


Figure 1: Predisposing Factors in the Occurrence of Breast Cancer Metastasis to Brain.

Identification of risk factors would provide accurate diagnosis and better management of patients.

[KPS: patient's ability to perform everyday tasks on a scale of 0 (dead) to 100, no symptom disease] [21].

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CONFLICT OF INTEREST

The author declared that there was no conflict of interests.

ETHICS APPROVAL

Not applicable.

REFERENCES

- Stratton MR, Campbell PJ, Futreal PA. The cancer genome. *Nature*. 2009;458(7239):719-24. DOI: [10.1038/nature07943](https://doi.org/10.1038/nature07943) PMID: [19360079](https://pubmed.ncbi.nlm.nih.gov/19360079/)
- Cha S, Lee J, Shin JY, Kim JY, Sim SH, Keam B, et al. Clinical application of genomic profiling to find druggable targets for adolescent and young adult (AYA) cancer patients with metastasis. *BMC Cancer*. 2016;16:170. DOI: [10.1186/s12885-016-2209-1](https://doi.org/10.1186/s12885-016-2209-1) PMID: [26925973](https://pubmed.ncbi.nlm.nih.gov/26925973/)
- Kang Y, Massague J. Epithelial-mesenchymal transitions: twist in development and metastasis. *Cell*. 2004;118(3):277-9. DOI: [10.1016/j.cell.2004.07.011](https://doi.org/10.1016/j.cell.2004.07.011) PMID: [15294153](https://pubmed.ncbi.nlm.nih.gov/15294153/)
- Christofori G. New signals from the invasive front. *Nature*. 2006;441(7092):444-50. DOI: [10.1038/nature04872](https://doi.org/10.1038/nature04872) PMID: [16724056](https://pubmed.ncbi.nlm.nih.gov/16724056/)
- Gupta GP, Massague J. Cancer metastasis: building a framework. *Cell*. 2006;127(4):679-95. DOI: [10.1016/j.cell.2006.11.001](https://doi.org/10.1016/j.cell.2006.11.001) PMID: [17110329](https://pubmed.ncbi.nlm.nih.gov/17110329/)
- Steeg PS. Tumor metastasis: mechanistic insights and clinical challenges. *Nat Med*. 2006;12(8):895-904. DOI: [10.1038/nm1469](https://doi.org/10.1038/nm1469) PMID: [16892035](https://pubmed.ncbi.nlm.nih.gov/16892035/)
- Schmidt-Kittler O, Ragg T, Daskalakis A, Granzow M, Ahr A, Blankenstein TJ, et al. From latent disseminated cells to overt metastasis: genetic analysis of systemic breast cancer progression. *Proc Natl Acad Sci U S A*. 2003;100(13):7737-42. DOI: [10.1073/pnas.1331931100](https://doi.org/10.1073/pnas.1331931100) PMID: [12808139](https://pubmed.ncbi.nlm.nih.gov/12808139/)
- Karrison TG, Ferguson DJ, Meier P. Dormancy of mammary carcinoma after mastectomy. *J Natl Cancer Inst*. 1999;91(1):80-5. PMID: [9890174](https://pubmed.ncbi.nlm.nih.gov/9890174/)
- Chambers AF, Groom AC, MacDonald IC. Dissemination and growth of cancer cells in metastatic sites. *Nat Rev Cancer*. 2002;2(8):563-72. DOI: [10.1038/nrc865](https://doi.org/10.1038/nrc865) PMID: [12154349](https://pubmed.ncbi.nlm.nih.gov/12154349/)
- Hanahan D, Weinberg RA. The hallmarks of cancer. *Cell*. 2000;100(1):57-70. DOI: [10.1016/s0092-8674\(00\)81683-9](https://doi.org/10.1016/s0092-8674(00)81683-9) PMID: [10647931](https://pubmed.ncbi.nlm.nih.gov/10647931/)
- Nguyen DX, Bos PD, Massague J. Metastasis: from dissemination to organ-specific colonization. *Nat Rev Cancer*. 2009;9(4):274-84. DOI: [10.1038/nrc2622](https://doi.org/10.1038/nrc2622) PMID: [19308067](https://pubmed.ncbi.nlm.nih.gov/19308067/)
- Yang J, Weinberg RA. Epithelial-mesenchymal transition: at the crossroads of development and tumor metastasis. *Dev Cell*. 2008;14(6):818-29. DOI: [10.1016/j.devcel.2008.05.009](https://doi.org/10.1016/j.devcel.2008.05.009) PMID: [18539112](https://pubmed.ncbi.nlm.nih.gov/18539112/)
- Kedrin D, van Rheenen J, Hernandez L, Condeelis J, Segall JE. Cell motility and cytoskeletal regulation in invasion and metastasis. *J Mammary Gland Biol Neoplasia*. 2007;12(2-3):143-52. DOI: [10.1007/s10911-007-9046-4](https://doi.org/10.1007/s10911-007-9046-4) PMID: [17557195](https://pubmed.ncbi.nlm.nih.gov/17557195/)
- Weber GF. Molecular mechanisms of metastasis. *Cancer Lett*. 2008;270(2):181-90. DOI: [10.1016/j.canlet.2008.04.030](https://doi.org/10.1016/j.canlet.2008.04.030) PMID: [18522865](https://pubmed.ncbi.nlm.nih.gov/18522865/)
- Clark EA, Golub TR, Lander ES, Hynes RO. Genomic analysis of metastasis reveals an essential role for RhoC. *Nature*. 2000;406(6795):532-5. DOI: [10.1038/35020106](https://doi.org/10.1038/35020106) PMID: [10952316](https://pubmed.ncbi.nlm.nih.gov/10952316/)
- Lalor PF, Lai WK, Curbishley SM, Shetty S, Adams DH. Human hepatic sinusoidal endothelial cells can be distinguished by expression of phenotypic markers related to their specialised functions in vivo. *World J Gastroenterol*. 2006;12(34):5429-39. PMID: [17006978](https://pubmed.ncbi.nlm.nih.gov/17006978/)
- Paku S, Dome B, Toth R, Timar J. Organ-specificity of the extravasation process: an ultrastructural study. *Clin Exp Metastasis*. 2000;18(6):481-92. DOI: [10.1023/a:1011858925376](https://doi.org/10.1023/a:1011858925376) PMID: [11592305](https://pubmed.ncbi.nlm.nih.gov/11592305/)
- Aragon-Ching JB, Zujewski JA. CNS metastasis: an old problem in a new guise. *Clin Cancer Res*. 2007;13(6):1644-7. DOI: [10.1158/1078-0432.CCR-07-0096](https://doi.org/10.1158/1078-0432.CCR-07-0096) PMID: [17363516](https://pubmed.ncbi.nlm.nih.gov/17363516/)
- Weil RJ, Palmieri DC, Bronder JL, Stark AM, Steeg PS. Breast cancer metastasis to the central nervous system. *Am J Pathol*. 2005;167(4):913-20. DOI: [10.1016/S0002-9440\(10\)61180-7](https://doi.org/10.1016/S0002-9440(10)61180-7) PMID: [16192626](https://pubmed.ncbi.nlm.nih.gov/16192626/)
- Marc Beishon. Bridging the gap in metastatic breast cancer 2016. Available from: www.cancerworld.org/pdf/S866_CW_70_Spotlight_ABC_New.pdf.
- Bahrani T, Mehdipour P. Pathogenesis of Breast Cancer Metastasis to Brain: a Comprehensive Approach to the Signaling Network. *Mol Neurobiol*. 2016;53(1):446-54. DOI: [10.1007/s12035-014-9023-z](https://doi.org/10.1007/s12035-014-9023-z) PMID: [25465242](https://pubmed.ncbi.nlm.nih.gov/25465242/)
- Soffiatti R, Trevisan E, Ruda R. Targeted therapy in brain metastasis. *Curr Opin Oncol*. 2012;24(6):679-86. DOI: [10.1097/CCO.0b013e3283571a1c](https://doi.org/10.1097/CCO.0b013e3283571a1c) PMID: [22820413](https://pubmed.ncbi.nlm.nih.gov/22820413/)
- Williams LA, Davis-Dusenbery BN, Eggen KC. SnapShot: directed differentiation of pluripotent stem cells. *Cell*. 2012;149(5):1174- e1. DOI: [10.1016/j.cell.2012.05.015](https://doi.org/10.1016/j.cell.2012.05.015) PMID: [22632979](https://pubmed.ncbi.nlm.nih.gov/22632979/)
- Fazilaty H, Mehdipour P. Genetics of breast cancer bone metastasis: a sequential multistep pattern. *Clin Exp Metastasis*. 2014;31(5):595-612. DOI: [10.1007/s10585-014-9642-9](https://doi.org/10.1007/s10585-014-9642-9) PMID: [24493024](https://pubmed.ncbi.nlm.nih.gov/24493024/)