Genomic Characterization of CNS Metastases: Implications for Precision Medicine

Priscilla K. Brastianos, MD
Massachusetts General Hospital Cancer Center, Harvard Medical School

INTRODUCTION

Brain metastases are a frequent and devastating complication of cancer that represent an unmet clinical need. Autopsies have reported up to 25% of cancer patients will develop brain metastases, mostly derived from lung and breast cancer and melanoma. With improved systemic agents and long life expectancy for patients, the incidence of brain metastases is rising. Patients will often develop progressive brain metastases in the setting of extracranial disease that is adequately controlled with existing chemotherapies or targeted therapies. Historically, it has been unclear if this clinical divergence is due to inadequate systemic therapeutic penetration of the blood-brain barrier or different genetic drivers in the brain metastases. Our understanding of how metastases genetically evolve from the primary tumors continues to be limited.

Several theories of metastases development and evolution have been proposed, with different implications for management. The clonal theory of cancer evolution states that, starting from a single normal cell, across molecular time, multiple rounds of mutation and expansion occur. The end result of this process is a tree-like growth consisting of multiple related cancer subclones. Eventually individual clones break off and give rise to metastasis, which then undergo further evolution. The historical model of metastasis formation is that metastases are descended from a single cancer clone. Another possibility involves multiple related subclones contributing to metastasis formation. More recently, data from mouse models has supported a more complex self-seeding process, whereby cells derived from distant metastases can reseed their primary tumors.

Recently, several deep-sequencing studies have explored the genomic differences between different metastatic sites within the same patient to understand the evolution of the metastatic process. These studies of small numbers of patients have confirmed clonal evolution, with organ-specific branches and with significant intratumoral heterogeneity, specifically regional heterogeneity, within the primary tumor. A recent study of multiple non-CNS metastases in patients with prostate cancer (N=10) showed metastasis-to-metastasis seeding and self-seeding. Additional recent data from targeted sequencing and array comparative genomic hybridization studies suggest a mechanistic role for PI3K pathway activation in brain metastases.

EVOLUTIONARY PROCESSES WITHIN BRAIN METASTASES

Building on previous studies of metastasis growth and evolution, researchers at MGH, together with an international team of researchers, sought to further understand the evolutionary processes within brain metastases using next-generation sequencing technologies. The specific study goals were to elucidate the evolutionary patterns leading to brain metastases; identify whether brain metastases harbor clinically significant genetic differences compared to their primary tumors; determine the extent to which clinically significant mutations are shared among regionally, anatomically, and temporally distinct brain metastasis sites; and determine whether lymph nodes or extracranial metastases are genetically similar to brain metastases and might serve as their proxy for clinical decision-making.

To achieve these objectives, the research team performed whole-exome sequencing in 104 matched primary tumor biopsies, brain metastases, and normal tissue, including 20 patients with regionally, temporally, and anatomically separated brain metastasis sites; regional lymph nodes; and distal extracranial metastases. In addition, an integrative analysis of copy number alterations and somatic mutations was performed to estimate the clonal and subclonal architecture of the primary tumor and all paired metastatic sites for each patient. Each subclone was annotated with clinically actionable genetic alterations to better understand the molecular drivers in brain metastases.
Branched Evolution
DNA sequencing can be used to quantify the relative abundance of the variants present in the cancer-tissue cells. The computational method termed ABSOLUTE uses Bayesian statistical models to estimate a cancer cell fraction (CCF) for each mutation, which is the percent of cancer cells that have that mutation. For instance, mutations with a CCF of 1 are present in 100% of cells, meaning that they are clonal mutations in that biopsy sample. Mutations that have a CCF value of <1 affect only portion of cancer cells. These subclonal mutations occur later in evolution.

Using CCF values, researchers performed a phylogenetic reconstruction of an esophageal carcinoma sample that metastasized to the brain. Results support branched evolution, whereby the brain metastases and primary tumors shared a common ancestor, yet both the primary tumor and brain metastasis continued to evolve independently. The analysis showed a cluster of 261 mutations representing the most recent common ancestor of the primary tumor and metastasis. However, the metastasis was characterized by continued evolution, with a clonal cluster of 45 mutations in the metastasis tissue sample and a subclonal cluster of 21 mutations that were not present in the primary tumor. Subclonal mutations in the metastases were novel mutations in the metastasis that occurred after the brain metastasis developed. Further evolution within the primary tumor was also observed, with a new subclonal cluster of 18 mutations and a clonal population of 14 mutations that were absent in the metastasis sample. Therefore, the primary tumor and metastasis are best described as related or evolutionarily siblings.

Clinically Actionable Drug Targets

To identify ‘clinically actionable’ drug targets, the mutations were compared to the TARGET (Tumor Alterations Relevant for Genomics-Driven Therapy) database of of genes with diagnostic, prognostic, and therapeutic implications for cancer patients. The analysis confirmed that brain metastases are genetically distinct from their primary tumor biopsy. In total, 53% of the brain metastasis samples had clinically actionable targets that were not detected in the primary biopsy. In particular, 51% of brain metastasis samples harbored alterations predicting therapeutic sensitivity to a CDK inhibitor, including CDK4/6 amplifications and loss of CDKN2A. In addition, 43% of cases harbored alterations predicting sensitivity to a PI3K/PIK3CA and PIK3R1mutations and PTEN loss. The PI3K/AKT/mTOR pathway mutations were particularly common in patients with primary breast cancer (43%), lung adenocarcinoma (41%), and renal cell carcinoma (50%). Additional mutations predicting sensitivity to HER2/EGFR inhibitors and MAPK pathway inhibitors were also observed. Additional study findings showed that tissue from regional lymph nodes, extracranial metastases, and additional primary tumor biopsy sites were highly divergent from brain metastases. Therefore, a precision oncology approach based on genetic characterization of biopsies of primary tumors, regional lymph nodes, and distal extracranial sites will often be suboptimal for identification of therapeutic targets from which brain metastasis patients might benefit. In contrast, regionally, temporally, and anatomically separated brain metastasis sites were genetically homogeneous.

Summary

Patients with non-CNS cancer will often develop progressive brain metastases even when the primary tumor appears adequately controlled with existing chemotherapies or targeted therapies. Historically, this clinical divergence has been ascribed to inadequate systemic therapeutic penetration of the blood-brain barrier. However, recent research suggests that additional potentially oncogenic alterations may be present in brain metastases, and might contribute to this divergence of therapeutic response in some of these cases. In addition, brain metastases harbor clinically actionable genetic alterations that are distinct from the primary tumor, suggesting novel opportunities for the future treatment of metastatic brain disease.

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