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HIGHLIGHT

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Genomic evolution of cancer metastasis under therapeutic pressure

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In the era of precision medicine, the selection of cancer treatment relies increasingly on the identification of genomic alterations; however, it is not yet clear how frequently genomic profiling should be performed over the disease course of a patient with metastatic cancer. A large-scale study investigates the genomic evolution of cancer metastases under therapeutic pressure and finds that the actionable genome has remained relatively stable. The findings support the sufficiency of a single biopsy of cancer metastasis for therapeutic decision-making (Figure 1A).[1]

Cancer is a disease of the genome, and its development is an evolutionary process driven by advantageous mutations and clonal expansions. Extended use of comprehensive genomic profiling has identified a plethora of oncogenic drivers, unveiling genetically driven tumor dependencies and vulnerabilities, for which targeted therapies have been approved or in the drug development pipeline. For individual patients, a single biopsy is typically performed for molecular analysis to guide the selection of personalized cancer medicine approaches. However, whether this is sufficient remains speculative. According to previous genomic analyses in multiple types of metastatic cancer, the genetic heterogeneity observed in metastases was lower than their primary counterpart, and distinct metastatic lesions resembled each other genetically within individual patients. Furthermore, the vast majority of driver mutations are shared by all treatment-naïve metastases, suggesting that single biopsies and sequencing of metastases are sufficient for the design of therapeutic regimen.[2] Nevertheless, some anticancer therapies have been demonstrated to cause specific mutational signatures. Therefore, to optimize patient's care and clinical cost-effectiveness, it is essential to identify the therapeutic-associated dynamic shifts in the clonal composition of the lesions in the disease progression. van de Haar et al.,[1] therefore, set out to investigate the impact of the therapeutic pressure on the actionable cancer genome, providing the basis for rational decisions in the frequency of genomic analysis over the treatment course of the disease.

In total, the authors performed whole-genome sequencing for 481 biopsies, which were successively

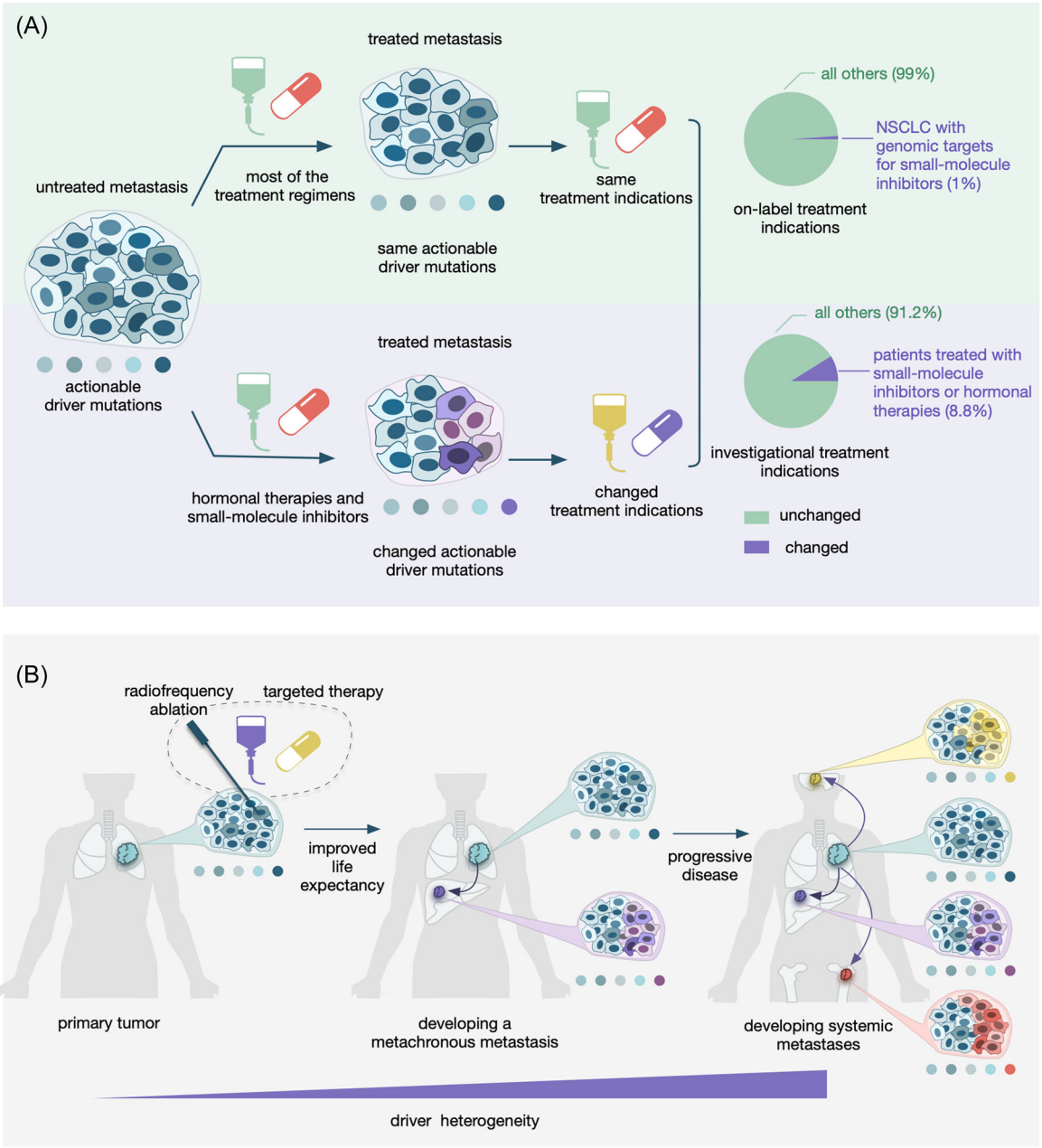

FIGURE 1 Genomic evolution of cancer metastasis under therapeutic pressure. (A) The actionable genome of cancer metastases remains remarkably stable under therapeutic pressures; genomic analysis of 481 biopsies from 231 metastatic cancer patients whose tumors were repeatedly sampled showed that there was limited heterogeneity of actionable genome over the treatment course. In 99% of cases, the on-label treatment indications remained unchanged during the course of the disease, while only 1% changed and were related to NSCLC with genomic targets for small-molecule inhibitors. Furthermore, the follow-up biopsies could not provide novel investigational treatment opportunities compared to the first genomic analysis in 91.2% of patients. For patients who are treated with small-molecule inhibitors or hormonal therapies, more frequent genomic alterations were observed. Thus, in the majority of clinical scenarios, genomic analysis of single biopsies is sufficient to maximize treatment opportunities. (B) Several clinical scenarios which could lead to additional driver mutations in metastases; as the prognosis of patients with advanced metastatic cancer improved, the selective pressure on tumor clones from novel therapeutic interventions (such as targeted therapies and radiofrequency), metachronous metastases ensuing from extended time windows, and clonal selection in different target organs during systemic metastases may cause novel driver mutations. Further studies are needed in these situations. NSCLC, non-small-cell lung cancer

sampled during the treatment course of 231 metastatic cancer patients, and such genomic data were analyzed by pairwise comparisons within individual patients. With the median biopsy intervals being 6.4 months, all major treatment options of multimodality therapy were covered, including chemotherapy, small-molecule inhibitor, monoclonal antibody, hormonal therapy, immune-checkpoint blockade, and radiotherapy. When it comes to genome-wide alterations, there was a remarkable rise in the number of somatic mutations from all different classes during treatment. By contrast, the number remained relatively unchanged over time when focusing exclusively on driver mutations. In total, 1132 out of the 1318 driver mutations were shared by the paired biopsies.

Notably, while some driver mutations merely represent a reflection of treatment effectiveness, some clinically actionable gene alterations may affect therapeutic responses and therefore need to be determined and considered in terms of therapeutic decision-making. To investigate the potential clinical effect of actionable mutations over the course of metastatic disease, the authors determined the stability of actionable genome by analyzing genomic biomarkers for standard-of-care (SOC) and clinical trial enrollment (investigational) treatments indications. For genomic biomarkers that can lead to SOC treatment indications, the first and successive biopsies were entirely consistent with each other. Likewise, the first biopsy yielded all the biomarkers for investigational treatment options in most patients. This observation suggested that the actionable genome of metastatic cancer remained exceptionally constant throughout the treatment course. Together with the previous finding in untreated metastases that driver gene heterogeneity is minimal, these results highlighted the limited genomic heterogeneity of both untreated and treated metastases.[2] Therefore, in the majority of clinical scenarios, genomic analysis of single biopsies, as currently performed in routine practice, is sufficient to offer essential information for evaluating treatment opportunities at any time point during the course of metastatic disease.

In addition, it is worth noting that in a small minority of cases, actionable genomic heterogeneity was also observed, where a single genomic analysis was inadequate to guide therapeutic decision-making. Specifically, within 12 patients with non-small-cell lung cancer harboring SOC genomic biomarkers for small-molecule inhibitors, three cases developed discordant genomic targets under therapeutic pressure compared with the first biopsy. Indeed, this population accounted for all three cases where the follow-up biopsies identified different SOC genomic treatment indications. Another particular scenario is relevant to the use of small-molecule inhibitors and hormonal therapies, both of which induced molecular alterations of the genes encoding the drug target in approximately 20% of the patients. Especially when the genes therapeutically targeted already carried genomic mutations before the administration of small-molecule inhibitors, this proportion significantly rose to 46%. Indeed, the heterogeneity of actionable genomic alterations ensuing from targeted therapies of solid cancer has been previously documented, for example, anti-estimated glomerular filtration rate treatment has been well known to trigger the emergence of RAS pathway mutations.[3]

Yet, the results from this study should be interpreted with caution. Of note, the median biopsy interval was only 6.4 months, which may misrepresent the actual situation in clinical practice. As multimodality treatment has demonstrated striking efficacy in patients with advanced-stage cancer, the resulting prolonged survival has led to a progressively complex situation, given that (1) exposure of a wide range of novel therapeutic approaches owing to improved life expectancies, for instance, targeted therapies, radiofrequency ablation, and immune therapy; (2) the occurrence of metachronous metastases ensuing from the increased time window; (3) clonal selection of different target organs in the case of systemic metastases could all result in the selection of subclonal cell populations with additional driver mutations[4] (Figure 1B). Moreover, the pattern of genomic evolution may also differ according to the different treatment received. Targeted therapies, such as small-molecule inhibitors, may merely give rise to genomic alterations related to the drug targets. While in the context of immunotherapies, the altered immune microenvironment could reciprocally impact the evolving tumors. As such, the evolution of tumors during anti-PD-1 therapy may be far more nuanced and changes in mutational load may vary depending on the response to treatment. New mutations can be found in postablation patient samples, however, whether and how the therapy per se modulates the mutational landscape of tumor remains largely unknown.[5] Therefore, how often genomic profiling should be performed in these situations still require further investigations.

Tumors are heterogeneous in nature and subject to selection pressures not only by organ microenvironments during metastases but also by different therapeutic strategies. For many years, the issue has been whether biopsy of a single lesion at one time point during treatment could provide a complete picture of tumor genetics that could be relied upon to guide therapeutic decision-making. Herein, the study of van de Haar et al.[1] provided a comprehensive landscape of the genomic evolution of metastatic cancer under different therapeutic pressures and justified the sufficiency of a single genomic analysis of a metastatic biopsy for optimal patient care. Furthermore, this study also elaborated the previous theory that targeted therapy can

impose selective evolutionary pressures on cancer cells, driving the occurrence of on-target genomic evolution and leading to acquired resistance to such regimens. The possibility of acquiring novel driver mutations in several clinical scenarios suggests the need for longitudinal genomic monitoring. Meanwhile, noninvasive approaches such as circulating tumor DNA profiling may be exploited to track clonal evolution dynamically in clinical practice.[3]

AUTHOR CONTRIBUTIONS

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CONFLICTS OF INTEREST

The authors declare no conflicts of interest.

DATA AVAILABILITY STATEMENT

Not applicable.

ETHICS STATEMENT

Not applicable.

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