

Cancer Heterogeneity and Biomarkers

Editorial

Athanasios Michas^{1*}, Evangelos Karamitrousis²,
Nikolaos Tsoukalas³, Michalis Lontos¹

¹Department of Clinical Therapeutics, National and Kapodistrian
University of Athens, Alexandra Hospital, Greece

²Department of Medical Oncology, Aristotle University of Thessaloniki,
Papageorgiou General hospital, Thessaloniki, Greece

³Department of Oncology, 401 General Military Hospital, Athens, Greece

Cancer is a disease directly linked with alterations in human genome and epigenome. The recent technological advances have significantly enhanced our knowledge regarding the various mechanisms of carcinogenesis and led to the development of effective targeted therapies. This knowledge makes clearly necessary and essential to identify biomarkers that guide and determine treatment decisions as well as prognosis of patients within the framework of precision medicine.

The heterogeneity of cancer is complex and arises from a variety of molecular mechanisms leading to the development of malignant phenotype. Two theoretical models are proposed regarding the development of heterogeneity. The first theory assumes that within every tumor, only a small cellular population has the ability to 'self-renew' and differentiate with malignant potential (cancer stem cells)^[1]. Heterogeneity mainly results from genetic changes in these progenitor cells and the evolutionary advantage that a cellular subpopulation of them will inevitably exhibit. The second theory is that of clonal evolution. According to this model, the tumor arises from an initial mutated cell, which accumulates different mutations, giving rise to different cell subpopulations (clones). Some of these mutations provide an evolutionary advantage to the cells carrying them against others (driver mutations), making this specific cellular subpopulation the dominant clone^[2].

Neoplastic heterogeneity is complex, and we can reasonably claim that each patient's cancer is unique. Initially, neoplasms of the same origin (e.g., lung, stomach) in different people, with similar morphological characteristics, may develop from different mutations (inter-tumor heterogeneity). At the same time, within each patient, cancer cells differ among themselves, as

do cells of metastases from those of the primary tumor (intra-tumor heterogeneity). Moreover, characteristics of cancer cells change over time, due to either the inevitable gradual accumulation of mutations or the natural selection process imposed by the treatment, which 'shapes' tumors and facilitates dominance of clones resistant to therapy^[3].

Under this perspective, continuous knowledge of tumor's molecular characteristics that could guide targeted treatment selection is of utmost importance. Biomarker, as defined by the Food and Drug Administration (FDA), is a measurable indicator that has the potential to be useful and accurate across the entire disease process of carcinogenesis. Biomarker that serve as indicators of response to treatment or patients' outcome are very useful in everyday clinical practice. They may include germline or somatic genetic variants, epigenetic signatures, transcriptional changes, and proteomic signatures. At least two characteristics are indispensable for the clinical application of a biomarker: (a) the existence of an easily adopted analytical method to define its occurrence and (b) the validation of its prognostic or predictive utility through clinical data^[4].

Currently, cancer heterogeneity has been successfully tackled in some neoplasms. Non-small-cell lung cancer is an excellent paradigm since all patients with non-squamous disease are subjected to extensive molecular analysis through next-generation sequencing as well as immunohistochemical determination of PD-L1 expression. This facilitates the recognition of subgroups of patients with specific molecular characteristics that informs for prognosis as well as appropriate targeted therapy selection. These developments have also led to the approval of specific drugs with tumor agnostic

* E-mail: athmixas@yahoo.gr

indications, meaning that treatment selection is no longer organ defined (e.g., breast cancer) but based on the molecular characteristic of each tumor independent of its anatomical origin (e.g., microsatellite instability-high tumors).

Despite recent advances, there is a long way ahead in order to achieve generalizability of precision medicine

in oncology. Recognition of not-frequent molecular mechanisms of carcinogenesis and monitoring of the temporal clonal evolution of tumors are currently areas of great scientific interest. Liquid biopsies, multi-omics analyses, and artificial intelligence algorithms are anticipated that they will soon transform the therapeutic field in the cancer treatment.

References

- [1] Shweta Bisht, Manisha Nigam, Shyam S. Kunjwal, Plygun Sergey, Abhay Prakash Mishra, Javad Sharifi-Rad. Cancer Stem Cells: From an Insight into the Basics to Recent Advances and Therapeutic Targeting. *Stem cells International*. 2022, Vol. 2022, 9653244.
- [2] Mel Greaves, Carlo C. Maley. CLONAL EVOLUTION IN CANCER. *NATURE*. 2012, Vol. 481, 7381.
- [3] Koulouris A, Tsagkaris C, Mountzios G. Heterogeneity in Clonal Evolution of Non small-cell Lung Cancer: Implications for Therapy. *Forum Clin Oncol*. 2023; 14 (1): 1-12.
- [4] Elisha Servorip Targain, Ashok Chauhan, Diptajit Paul*, Shailley Arora Sehgal, Abhishek Soni, Paramjeet Kaur. Assessment of Neutrophil-to-Lymphocyte Ratio as A Prognostic Marker in Locally Advanced Head and Neck Cancer Treated with Concomitant Chemoradiation. *Forum Clin Oncol*. 2023; 14 (1): 1-8.