

The Era of Individualized Medicine in Cancer

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Editorial

Treatment strategies mostly based on chemoradiotherapy are not efficient for a number of cancer patients. Moreover, targeted therapy has been shown to confer benefits, in some cancer types, for only a subset of patients. Therefore, there is a consensus among scientists and the medical community that the molecular information of a particular tumor is necessary to support clinical decisions even if considering the limited list of drugs available. Despite the advances in the development of targeted and immunotherapies, improvement of response also rely on interpretation of tumor profile. Furthermore, the use of off-label drugs arises as an opportunity of treatment when molecular characteristics of a certain tumor point out at a described molecular target even when this target is not well established for that particular cancer.

Currently, we have knowledge of many aspects of the patient and tumor that may relate to a successful response to treatment such as genetic variability, immune system, microbiota, metabolism and many others. However, only after the improvement of DNA sequencing technology and its cost reduction, the information of genetic alterations has dramatically increased and made possible the analysis of patients' samples. It is noteworthy that the pan cancer characterization performed by The Cancer Genome Atlas (TCGA) [1] has brought us a more detailed molecular profile of many cancer types and has improved diagnostic and clinical research areas.

Still, the efficiency of precision medicine in clinical decision is controversial. Many scientific studies and molecular information-based services use formalin-fixed paraffin-embedded (FFPE) tissue samples due the vast availability of such material, mostly derived from pathological archives. However, nucleic acid derived from these samples are difficult to extract, are often fragmented and usually covalently linked to proteins and other nucleic acids. Several issues impact significantly on the FFPE derived nucleic acid sample quality: fixation delay, how the fixation process was performed and the conditions and period in which the sample has been stored [2]. Some of the drawbacks resulting from the analysis of such poor material can be circumvented by specific methodological conduct, such as changing the deparaffinisation procedure, optimizing the extraction of the nucleic acid and by treating the resulting DNA with the enzyme Uracil-N Glycosylase (UNG) which prevents equivocal calling of C>T mutations in DNA sequencing. Even so, it is not possible to totally exclude the extent of artifacts in FFPE samples. Often these samples are used indiscriminately, without prior analysis of its quality, leading to false results and consequent misconduct by the physician. Hereafter the use of fresh frozen material is preferred to molecular analysis since it better represents the picture of the original biological tissue.

Another important issue is the tumor heterogeneity that is not limited to differences between different individuals (interpatient heterogeneity) but also occurs within a single tumor (intratumoral heterogeneity). As evidenced by TCGA analysis, some tumors are characterized by high mutational rates hence leading to a high degree of molecular heterogeneity [1].

Tumors constitute a dynamic cell population and subclones may arise during its development. Many studies have demonstrated that clonal heterogeneity can vary over time affected by multiple factors that comprise, for example, drug treatment and the emergence of new driver mutations. Thereby this scenario can represent a great challenge for cancer treatment, particularly when the diagnosis is based on a single tissue sample of a primary site.

Tissue biopsies are invasive and costly and, although tumor heterogeneity can be observed within a single sample, sometimes it may only be evident among different tumor regions or between primary and metastatic sites. Considering the dynamic nature of cancers, biopsies taken in a single time point may not reproduce the current status of the tumor. To overcome these issues, liquid biopsy emerged as a rapid, cost-effective and noninvasive method to assess tumor genetic characteristics at different time points during the course of disease. Tumor cells constantly release DNA fragments into the circulation and the use of circulating tumor DNA (ctDNA) may help to acquire genetic follow-up data.

Although there has been a huge increase in the availability of genetic and genomic information of tumors in the last decade, diagnostics are based on the subjective perspective of pathological immunohistochemical analysis, performed in samples in which quality is not even accessed. Today, there is more than enough molecular information to better classify tumors and, consequently, direct a more effective treatment for each patient if sample quality, heterogeneity and time of choice for molecular characterization and/or assessment are taken into account.

References

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