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INTRA-PATIENT STRUCTURAL AND FUNCTIONAL GENOME HETEROGENEITY AND DEREGULATED TRANSCRIPTIONAL NETWORKS SHAPE CANCER PRECISION MEDICINE

Dimitrios Roukos
University of Ioannina, Greece

Background: The greatest current and future challenge is how to translate the revolution in biomedical research with next-generation sequencing (NGS) technologies and new methods exploring regulatory networks into clinical oncology. This strategy is the most rational approach to overcome unmet needs of therapeutic resistance, recurrence and death.

Methods: Valid published data, usually in top journals, on genome analysis of clinical samples were reviewed. Genomic studies are distinguished in two classes. Conventional, static single-biopsy analyses with whole-exome sequencing (WES), whole-genome sequencing (WGS) and RNA-sequencing (RNA-seq) can reveal structural and functional coding and noncoding mutational landscape. On the other hand, breakthrough genome studies applying NGS systems can evaluate genomic clonal evolution in time and space. Identification of intratumor heterogeneity (ITH) with multi-regional NGS (MR-NGS) before and after systemic therapy, as well as the detection of circulating genomic subclones (cGSs) with serial circulating cell-free DNA followed by NGS (cfDNA-NGS), could overcome intrinsic and acquired therapeutic resistance and, possibly, disease relapse.

Results: Large-scale NGS analyses of a single biopsy have already identified valid novel cancer driver genes, molecular classifications, druggable mutations and functional-noncoding regulatory alterations. Breakthrough analyses of multiple tumoral and liquid biopsies at different time points have demonstrated extensive ITH and different genomic characteristics after systemic treatment. Serial cfDNA-NGS has provided the opportunity for patient monitoring and early prediction of recurrence before clinical diagnosis.

Interpretation: I will present two future strategic targets. First, the innovative design of clinico-genomic trials to validate the promising published data on molecular classifications and novel druggable mutations. Moreover, ITH and serial cGSs offer the capacity to predict therapeutic response and guide decision-making on effective treatment with available and novel targeted drugs. Moreover, repeated cGS detection over the disease course could be used not only for patient monitoring but also for early targeting of resistant circulating subclones, aiming to prevent recurrence. These patient-centric genomic trials shape the roadmap of cancer precision medicine. Second, in a long-term horizon, identification of functional non-coding alterations in transcription factor binding sites represents the basis of understanding, predicting and targeting of dynamic transcriptional networks with innovative agents. Ultimately, intra-patient heterogeneity, including all structural and functional coding and non-coding alterations, will lead to comprehensive clinical precision oncology.

droukos@uoi.gr