

## An inside view on liquid biopsies

The first detection of nucleic acids in peripheral blood of healthy individuals and diseased patients by Mendel and Métais in 1948 marked the beginning of modern molecular biology. Now, 70 years later, investigations on liquid biopsies have become one of the hottest topics in biology. They are directed to their use as clinical assays and aim at developing non-invasive diagnostic, prognostic, treatment monitoring and follow-up tests. A specific feature of liquid biopsies is that they can overcome the interference of tumor heterogeneity and reflect the general information of primary tumor and metastasis. Since they provide a more representative characterization of cancer than a single tissue biopsy, they have attracted increasing interest in their analysis, characterization and possible clinical applications. Numerous technical platforms, of which the most popular analytical strategies are introduced here, are used to exploit liquid biopsies. The current issue focuses on the clinical relevance of liquid biopsies with a particular emphasis on the methodology and shortcomings of the analysis of circulating cell-free DNA, microRNAs (miRNAs), long non-coding RNAs (lncRNAs), microvesicles and circulating tumor cells (CTCs) in blood plasma or serum of cancer patients.

Regarding the analysis of cell-free tumor DNA, its detection is quite challenged due to the large excess of wild-type DNA present in the human blood circulation. Therefore, tumor-specific factors and highly sensitive methods are required for their analysis. At the genetic level, chromosomal rearrangements, copy number changes and mutations can be identified by whole genome or exome sequencing. At epigenetic level, various techniques are used for detection DNA methylated markers and posttranslational modifications of histone proteins. Since in pathological states, the size of cell-free DNA varies from DNA released under healthy physiological conditions, size-based separation methods have been established to enrich cell-free DNA from pathological sources.

Since the introduction of the term “exosomal shuttle”, 10 years ago, the characterization of microvesicles, such as exosomes, has attracted increasing interest in the scientific community. Exosomes are crucial regulators of many physiological and pathological processes, and extensively secreted into the blood circulation of cancer patients. As their cargo reflects the state of the parent cell, exosome analysis may provide valuable information on pathological processes. In particular, the fractionation of tumor-derived exosomes from normal wild-type exosomes, along with the profiling of their contents are expected to facilitate early detection of tumor, prediction of prognosis and monitoring therapy response in cancer. In this respect, exosome preparation and purification is an important criterion that allows the extraction of miRNAs and lncRNAs from the exosomes and additionally, investigations on the mechanistic function of these exosomal ncRNAs and their crosstalk between the cells.

In respect to CTCs, their levels in human blood are much lower than those of exosomes. Besides their enumeration, phenotypical and molecular characterization of CTCs has gained attention to identify and validate new markers intended to get implemented in targeted therapies. Genetic, epigenetic and transcriptomic approaches at single CTC level have been established able to identify new therapeutic targets and to deliver deeper insights into tumor heterogeneity. All these methods, introduced here, demand standardization of the pre-analytical handling of blood samples to establish future guidelines for routine clinical applications.

To recap, written by an international team of renowned experts from Austria, Canada, China, England, France, Germany, Russia, Slovenia, Turkey and USA, the current issue provides an overview on technologies using liquid biopsies and shows their importance as non-invasive, blood-based markers and their potential applications in medicine. The issue does not claim to be an exhaustive study, but highlights most general concepts of liquid biopsies. It begins with an introduction by Peter B. Gahan, one of the true pioneers on the research field of liquid biopsy. He is an Emeritus Professor of Cell Biology at King's College, London, UK and a Fellow of Society of Biology. He has authored and edited several books on circulating nucleic acids in plasma and Serum (CNAPS) and published over 250 scientific articles. Since the 1970s, he has studied circulating nucleic acids together with Maurice Stroun and Philip Anker who first provided evidence of the existence of disease-specific circulating nucleic acids and developed techniques for their characterization in plasma and serum and thus, put the foundation leading to the current investigations. The current issue is dedicated to Maurice Stroun who died at the age of 91 in September, last year. His indomitable pioneering spirit and his remarkable studies will be connected with CNAPS for ever.

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