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Introductory Chapter: Liquid Biopsy — A Promising Technology of the Future

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<http://dx.doi.org/10.5772/intechopen.86918>

1. Introduction

Liquid biopsy represents a spectrum of technologies for the molecular analysis of blood and other biological liquids (e.g. urine, saliva or others) in order to detect cell-free/tumour nucleic acids, exosomes, microRNAs, tumour-educated platelets and circulating or free-floating tumour or foetal cells, depending on the clinical context. In contrast to classic tumour markers, e.g. prostate-specific antigen (PSA) or carcinoembryonic antigen (CEA), liquid biopsy is distinguished by high specificity as it provides genomic, proteomic and cellular characteristics of the disease. The anticipated outstanding reliability of these tests has been reflected in the term itself: “liquid biopsy” is expected to be at least as informative as tissue biopsy, used as the gold standard in certain diagnostic fields, especially in oncology.

The advantages of liquid biopsy include non-invasive approach which is patient-friendly, associated with remarkably low possibility of complications and technically feasible even in patients who are in serious general status or affected by tumour or metastases that are not easily accessible by conventional tissue biopsy. The clinically simple application allows the repeated use of liquid biopsy resulting in real-time follow-up for the disease course. The testing is fast and exact as definite molecular markers are sought for. Generally, liquid biopsy is a much awaited tool to overcome the limitations set by tumour heterogeneity upon conventional tissue biopsy representing only a small part of the whole tumour [1]. However, some technological modifications of liquid biopsy in certain patients can be subjected to the same restrictions regarding heterogeneity. A characteristic example would be the assessment of circulating tumour cells (CTCs) in patients with low burden of malignant cells in the blood. For instance, the diagnostic threshold of

already confirmed cancer, ctDNA can identify either minimal residual disease after surgery with curative intent or tumour relapse. Similarly, the response to treatment can be monitored. Molecular alterations can be assessed to select personalised treatment.

In addition to the diagnostic, prognostic and predictive role in oncology, cfDNA analysis might be useful in other medical situations. Thus, circulating cell-free DNA can be derived from transplanted organs or from the foetus during pregnancy, serving as an early manifestation of graft rejection or reflecting genetic features on the foetus, respectively. In addition, cfDNA levels can be valuable also as a nonspecific biomarker of tissue damage in critical care medicine and related clinical situations, e.g. sepsis, haemodialysis and others [4].

4. Circulating microRNAs

MicroRNAs (miRNAs) are small, evolutionary conserved, single-stranded, non-coding RNA molecules (approximately 22 nucleotides in length) that bind target mRNA to regulate gene expression [11, 12] at the posttranscriptional level [13]. These molecules act as large-scale molecular switches. MicroRNAs are involved in different physiological and pathological events, including apoptosis, cell proliferation and differentiation; therefore, it is not surprising to see miRNAs participating in carcinogenesis as either tumour suppressors [14, 15] or oncogenes [16]. The cardinal tumour features include cell proliferation, invasion and metastasis as well as activated angiogenesis. miRNAs regulate all the steps. In addition, up- or down regulation of certain miRNAs is associated with the biological potential of cancer, e.g. proliferation, invasivity and epithelial-mesenchymal transition or grade. miRNAs can be assessed either in tissues or in biological liquids, in the last case becoming a target for liquid biopsy.

Again, the diagnostic and regulatory roles of miRNAs are not limited to oncology. Women who develop pre-eclampsia and spontaneous preterm birth are characterised by specific exosomal miRNA profile at early gestation. Considering the interplay between exosomal secretion, oxygen tension and endothelial proliferation, aberrant exosomal signalling by placental cells is suggested to have a pathogenetic role in pregnancy complications [17].

5. Exosomes

Exosomes represent a class of extracellular vesicles mediating intercellular communication. They consist of lipid bilayer, transmembrane and non-membrane proteins and single- and/or double-stranded DNA and RNAs, including microRNAs. A fraction of exosomal proteins are ubiquitous, while others are characteristic for specific cells or tissues.

Exosomes are collected for liquid biopsy analysis by different technological approaches, including methods targeting physical (size, density, sedimentation) or antigenic properties. After the tumour-derived exosomes have been isolated and identified, exosomal protein expression and genetic profile by exosomal RNAs or DNAs or exosomal miRNA signature can be tested. In addition to cancer-produced exosomes, those originating from immune cells also can be detected and evaluated [5].

6. Tumour-educated platelets

Platelets are known to participate not only in blood clotting but also in inflammatory and immune processes, e.g. communicating with lymphocytes or regulating cellular transmigration through blood vessel's wall. In malignant tumours, platelets are involved in neoangiogenesis, induction of epithelial-mesenchymal transformation and metastatic spread of tumour cells, protecting them from the immune system. Contacting with tumour cells, platelets can uptake clinically relevant, tumour-specific biomarkers, as demonstrated in the models of glioblastoma, non-small cell lung cancer or prostate cancer. Such platelets are described as tumour-educated platelets, potentially representing diagnostic or therapeutic targets, as well as a clue to further theoretical investigations of carcinogenesis [18].

7. Conclusions

In conclusion, liquid biopsy represents molecular analysis of biological liquids in order to detect cell-free/tumour nucleic acids, exosomes and/or microRNAs, tumour-educated platelets and circulating or free-floating tumour or foetal cells. These technologies have several advantages including high specificity, non-invasive approach and possibility of repeated use to ensure real-time follow-up of the patient. However, liquid biopsy currently is not a routine laboratory test in clinical practice yet. Major developments are expected in the nearest years, including progress in technologies, software and quality control systems as well as diagnosis-based research to substantiate many promising clinical applications.

Acknowledgements

Our work has been supported by Riga Stradins University, Riga, Latvia; grant N.21-1/1/2019-4.

Conflict of interest

Editors have no conflicts of interest.

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