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Editorial Open Access

Circulating Cell-Free Nucleic Acids as Potential Biomarkers for Noninvasive Diagnosis of Diseases in the Future

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The cell-free, nude and single- and double-helix structured Nucleic Acids (NAs) that are jointly circulating for reasons, such as necrosis, secretion and apoptosis (programmed cell death), and are obtained by the purification of plasma and serum samples in the circulatory system, are called circulating free NAs (ccfNA) [1-4]. The phenomenon of ccfNA (DNA, RNA, fetal DNA, fetal RNA, mitochondrial DNA and mitochondrial RNA) concentrations is of importance for many biomedical disciplines, including the fields of different cancers, autoimmune diseases, obstetric diseases, neurological diseases, mitochondrial diseases, exercise physiology, virus infections, prenatal diagnosis, etc. [4-13]. At the same time, ccfNA in the blood has been suggested as a potential biomarker under many conditions [2,3,10,14-21].

The presence of ccfNA in the human blood was first described in 1948 by Mandel and Metais. There was a great increase in the studies on this subject in the last 15 to 20 years, and results stating that ccfNAs might replace invasive diagnostic techniques were reported [4-6,12, 13,22-24]. Furthermore, Schwarzenbach et al. [23] added the following substantially true information to the literature: "Detecting ccfNA in plasma or serum could serve as a 'Liquid Biopsy', would be useful for numerous diagnostic applications and would avoid the need for tumour biopsies". The amount of ccfNA is influenced by clearance, degradation and physiological filtering events of the blood and lymphatic circulation. NAs are cleared from the blood by the liver and kidney and they have a variable half-life in the circulation, ranging from 15 minutes to several hours in cancer patients [14]. In addition, the nuclease activity in the blood can be one of the important factors for the turnover of ccfNAs.

One of the problems in the analysis and evaluation of ccfNA is the standardization of assays, such as isolation technologies, internal standards, assay conditions, specificity and sensitivity [25,14]. The variables are important and need to be standardized for consensus analysis and reporting [23,26]. It might be considered that these shortages may be eliminated soon, e.g. in about 5 years.

As a result of the studies on many cancer patient groups – primarily breast, advanced lung adenocarcinoma and colorectal – by using ccfDNAs, it was reported that important and useful results might be detected regarding the diagnosis of the disease, its degree, prognosis and the follow-up of its treatment [5-7,22,24-29]. Moreover, not only the amount of ccfNAs in the circulation, but also the fact that the screening of disease-specific gene mutations and the epigenetic analyses might be made, are seen [7,14]. The presence of a correlation between the ccfDNA amounts of the patients who had had a cardiac arrest and their postresuscitation survival rates was shown [13]. It was detected that one might have information about the ccfDNA levels and the degree and intensity of infections in virus-induced infections [9,14,30]. There are studies which report that both the diagnosis (e.g. Preeclampsia) and the prenatal diagnosis (e.g. Trisomies) of the fetal DNAs (ccffDNA) isolated from the maternal plasma, can be made in gynecology in a noninvasive way [9,15,30]. In this way, the risk of abortus of the fetus during both amniocentesis and Chorionic Villus Sampling (CVS) can also be eliminated. It was reported that novel and valuable information on autoimmune diseases and the mechanism of cancer formation, in particular might be provided by the help of experimental media to be formed, by means of exercise physiology [10].

It was reported that by studying both mtDNAs and mtRNAs of the mitochondria in the circulation and by making these analyses under standard conditions, noninvasive diagnostic tests might be performed for many diseases, particularly cancer [4,5,31,32].

Besides the quantification of ccfDNA, circulating RNAs are also detectable in the serum and plasma of patients. It is known that RNA which is released into the circulation is surprisingly stable, in spite of the fact that increased amounts of RNases circulate in the blood of cancer and different patients (Preeclampsia, cerebral attack, etc.) [23]. This implies that RNA may be protected from degradation by its packaging into exosomes, such as microparticles, microvesicles or multivesicles which are shed from cellular surfaces into the bloodstream [2,8,23]. The presence of RNAs in the circulation was reported approximately 12 years ago and particularly, as a result of studying microRNA's (miRNAs) in the last 5 years, it was demonstrated that significant data could be provided both in diagnosis and treatment, and after treatment [3,8,18,20]. This area is in need of universal standards to allow better comparisons and validations of specific blood microRNA's miRNAs [23,27,33]. With the standardization of these studies, both quantitative and qualitative analyses of all types of RNA (microRNA's (miRNAs), mitochondrial messenger RNAs (mtRNAs), etc.) in the circulation can be made under easier conditions.

In conclusion, within 5 to 10 years at the latest, the diagnosis and treatment of substantially different diseases and the follow-up of their treatment can be possible with the noninvasive method, by the help of the analysis of the free nucleic acids (DNAs, RNAs, mtDNAs, mtRNAs, fDNAs, fRNAs, etc.) in the circulation, and most of the diagnostic procedures requiring the invasive diagnosis can be performed under less risky conditions with noninvasive methods.

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