Mini Review

iMedPub Journals
http://www.imedpub.com/

Translational Biomedicine
ISSN 2172-0479

2016
Vol.7 No.2:68

DOI: 10.21767/2172-0479.100068

The Cell-Free Mitochondrial DNA: A Novel Biomarker of Cardiovascular Risk?

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Received: May 15, 2016; **Accepted:** May 25, 2016; **Published:** May 30, 2016

Citation: Berezin AE. The Cell-Free Mitochondrial DNA: A Novel Biomarker of Cardiovascular Risk? Transl Biomed. 2016, 7: 2.

Abstract

Circulating cell-free mitochondrial DNA could find in healthy subjects and patients with neoplasia, trauma, infections, stroke, autoimmune, metabolic and rheumatic diseases. The triggers of cell-free mitochondrial DNA secretion are various impacts, i.e. microbial antigen stimulation, inflammatory cytokine, active molecules. It is speculated that the cell-free mitochondrial DNA might be a critical activator of inflammation, coagulation and the innate immune system linking mitochondrial dysfunction, cell death and target organ injury. There is evidence regarding that the cell-free mitochondrial DNA levels may elevate in healthy individuals depending aging and in cancer and non-cancer subjects at risk of CV diseases, as well as in persons with established CH disease. The results of several studies have shown that elevated circulating cell-free mitochondrial DNA has associated with cardiovascular (CV) diseases, while diagnostic and predictive value of this biomarker in non-cancer individuals is not fully clear. The mini review is devoted the biological role, diagnostic and predictive value of cell-free mitochondrial DNA in patients at CV risk.

Keywords: Cardiovascular disease; Endothelial dysfunction; Cell-free mitochondrial DNA; Clinical outcomes; Prediction

Introduction

The advances in the treatment of cardiovascular (CV) disease over last decades have leaded to decrease mortality and disability due to CV events in the developed countries [1]. However, the increased prevalence of CV disease associates with high economic burden and medical care expenditures. Data of recent clinical trials have been shown the improvement of survival of the patients after CV events might predict with biological markers reflecting the several phases of the pathogenesis of CV disease. Current clinical guidelines presented by American College of Cardiology/American Heart Association and European Society of Cardiology are emphasized needing to use biomarkers toward risk stratification of individuals at higher risk of CV disease, patients with known CV disease, as well as target therapy of several diseases (e.g. heart failure). The accuracy and predictive value of widely used biomarkers (i.e. cardiac troponins, natriuretic peptides, galectin-3, soluble ST2) are sufficiently distinguished depending age, sex, metabolic co-morbidities, decreased kidney function. In this context, the discovery of novel biomarkers that might use to identify the individual CV risk is discussed widely.

Recent studies have revealed the increased concentration of nucleic acids defined as DNA (genomic DNA, mitochondrial DNA, viral DNA) and RNA (mRNA and microRNAs) in the circulation among patients with several diseases including CV and rheumatic diseases, diabetes, sepsis, infections [2,3]. Moreover, cell-free nucleic acids were measured in the circulation in healthy subjects and the concentration of the both cell-free DNA and RNA may depend on aging. Although the molecular mechanisms leading to release of nucleic acids from cells into circulation are yet not completely clear [4], it is suggested that apoptotic and/or necrotic cells could be defined as the main source of cell-free DNA and RNA [5]. Moreover, target cells may produce actively and secrete nucleic acid resulting in several triggers, such as microbial lipopolysaccharides/antigenes, tumor cells, inflammatory cytokines, active molecules [6-8], in two transferred forms, i.e. cell-free circulating fraction and microvesicle-derived fraction [9,10]. However, extracellular microvesicles may convey a small portion of the both DNA and RNA, whereas the majority of nucleic acids represent as free circulating form [11]. Because mitochondrial DNA are secreted by apoptotic and activated cells triggering CV risk factors [11-13], they have some theoretical advantages as CV biomarkers of genomic DNA released from necrotic cells and appear to be tumor biomarker. The mini review is devoted the biological role, diagnostic and predictive value of cell-free mitochondrial DNA in patients at CV risk.

Biological role of circulating cell-free mitochondrial DNA

Cell-free mitochondrial DNA appears to be found as double-stranded molecules, which are biologically fragmented into both short (lower than 1 Kb) and long (up to 21 kb) segments [14]. The spontaneously released mitochondrial DNA fraction has been shown to be present in both actively dividing and non-dividing forms. Moreover, secretion of mitochondrial DNA has associated with DNA-dependent RNA or DNA polymerase and may have a lower molecular weight than the typical

genetic mitochondrial DNA fractions [15]. Interestingly, lower molecular weight mitochondrial DNA fraction might term metabolic DNA and represent the precursor to the formation of the spontaneously released DNA fraction [16]. The active secretion of mitochondrial DNA fractions needs to involving of antigen-presenting cells (i.e. mononuclears/macrophages, lymphocytes, dendritic cells) and regulating by hormonal mechanisms [17-19]. In this context, cell-free mitochondrial DNA content in contrast miRNAs could reflect a severity of cardiac damage and probably might have a predictive value in humans with acute myocardial infarction [20-22].

The biological role of cell-free mitochondrial DNA and its fragments is controversial. The controversy relates an ability of DNA fragments to impair both mitochondrial function and membrane cells, as well as to induce tissue reparation [23]. Indeed, recent studies have shown cell-free mitochondrial DNA may not only activate inflammation, coagulation and immunity through the toll-like receptor (TLR)-3 and TLR-9, but induce cell death and tissue damage. Finally, cell-free mitochondrial DNA is directly involved in the pathogenesis of endothelial dysfunction and vasculopathies, which are discussed an important component of development of CV diseases, rheumatic and autoimmune disease, malignancy [24-26]. On the other hand, cell-free mitochondrial DNA might contribute to endogenous repair systems through regulation of mobbing and differentiation of progenitor cells [24].

The cell free mitochondrial DNA in CV diseases

The association between concentration of mitochondrial DNA and CV risk was found in the numerous recent studies [26-28]. It is supposed that circulating fragments of cell-free mitochondrial DNA could be a trigger of development of early endothelial dysfunction and tissue injury among individuals at higher CV risk [23,29], patients with acute myocardial infarction after percutaneous coronary artery intervention [30].

There are the results of two prospective observational cohort studies devoted the discovery of predictive role of elevated cell-free mitochondrial DNA levels in the intensive care unit patients (the Brigham and Women's Hospital Registry of Critical Illness and Molecular Epidemiology of Acute Respiratory Distress Syndrome) [31]. It has found a markedly association between circulating levels of mitochondrial DNA and in-hospital mortality. However, it is needed to note that there is no evidence of large clinical trials to extrapolate the data to patient population with known CV disease.

Additionally, elevated cell-free mitochondrial DNA levels could be important challenge in the risk stratification of the subjects with asymptomatic atherosclerosis, acute coronary syndrome, myocardial infarction, heart failure, pulmonary thromboembolism [32-36]. There is a large body of evidence regarding the molecular alterations of cell-free mitochondrial DNA and its relationship with tumor development and progression [3]. Indeed, most of the molecular alterations found in cell-free mitochondrial DNA circulating in plasma reflect the genetic and epigenetic changes found in primary tumors. In this context, it is important to define that long cell-free mitochondrial DNA fragments relate to necrosis phenomena, whereas shorter fragments are produced by physiological apoptosis phenomena and in aging [37]. Probably, so-called integrity index, based on the ratio between long and short cell-free mitochondrial DNA fragments, might useful in patients with cancers [38].

Interestingly the clinical use of cell-free mitochondrial DNA measurement is limited by several technical obstacles associated with undefined reproducibility of the serial measurement [39]. However, the single-measured cell-free mitochondrial DNA level has used with diagnostic value in persons suspected cancers [40,41]. Finally, the use of continuing biomarker monitoring of cell-free DNAs has been questioned. It relates to sufficient overlapping circulating levels of cell-free DNA in healthy individuals and patients with underlying diseases including tumor, CV disease, infections, and inflammation. The decreased levels of cell-free DNA were found in cancer survivors after completed surgical care or chemo/radiotherapy. Additionally, patients who exhibited high levels of cell-free DNA might have a high risk of relapse or are considered not responders to the treatment. Whether measurement of circulating variabilities of cell-free DNA could help to stratify non-cancer patients at CV risk is not clear, while the acute myocardial infarction patients after percutaneous coronary intervention/successful thrombolysis or cardiopulmonary resuscitation might demonstrate tendency to decrease of concentration [31,33,34,42]. Furthermore, there is a closely association between cell-free DNA with hospital mortality and organ dysfunction [43,44]. All these require more investigations to confirm the role of cell-free mitochondrial DNA in CV diseases.

Conclusion

Cell-free mitochondrial DNA levels may elevate in healthy individuals depending aging and in cancer and non-cancer subjects at risk of CV diseases, as well as in persons with established CH disease. The measurement of fragments of cell-free mitochondrial DNA may be use in routine clinical practice as a useful biomarker of non-specific tissue damage with higher predictive value in non-cancer individuals with CV diseases.

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