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Mini Review Open Access

Circulating Cell-Free Mitochondrial DNA as Biomarker of Cardiovascular risk: New Challenges of Old Findings

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Abstract

Circulating cell-free mitochondrial DNA has been found in healthy subjects and patients with neoplasia, trauma, infections, and stroke, as well as cardiovascular (CV), autoimmune, metabolic and rheumatic diseases. The main triggers of deriving of cell-free mitochondrial DNA are various clinical conditions associated with cell death, necrosis, and activation of cells following antigen stimulation, inflammatory cytokine effect. Currently cell-free mitochondrial DNA is discussed a critical activator of inflammation and the innate immune system that may link mitochondrial dysfunction, cell death and target organ damage. The epidemiological evidence indicates that elevated circulating cell-free mitochondrial DNA is associated with the initiation and development of CV and metabolic diseases, while diagnostic and predictive value of this biomarker among non-cancer individuals is not fully understood. The mini review is summarized evidences regarding the biological role of circulating cell-free mitochondrial DNA and hypothesized the indication for clinical use of circulating DNA as diagnostic and predictive biomarkers among patients with CV risk.

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

Introduction

Cardiovascular (CV) disease remains a major cause of mortality and morbidity worldwide, a widely spread illness worldwide and associated with increasing mortality within last decades [1]. Therefore, the high burden of CV and metabolic risk factors in different countries may have been affected the increased incidences of death in subjects prior to documentation of CV disease. In this context, it is needed to extend the exploration of novel biological markers that are reflected various faces of pathogenesis of CV and metabolic diseases.

The phenomenon of existence of circulating nucleic acids referred as both DNA and RNA have been found in healthy subjects and patients with various diseases, including neoplasia, trauma, infections, stroke, as well as cardiovascular (CV), autoimmune (systemic lupus erythematous, systemic vasculitis), metabolic (diabetes mellitus, hyperthyroidism) and rheumatic diseases (rheumatoid arthritis) [2].

The principal mechanisms of bloodstream deriving of nucleic acids and their cellular origin found in healthy individuals are still not completely known [3]. It has suggested that free nucleic acids could be derived in the circulation from apoptotic or necrotic cells reflecting cell death due to various reasons [4]. Therefore, the nucleic acids are secreted actively in the bloodstream as component of micro vesicles resulting in activation of cells following stimulation with lipopolysaccharide or several antigens [5]. Indeed, cell-free DNA is released from apoptotic cells as nucleosomes from both healthy and diseased tissue that includes tumor cells as well as microbial nucleic acids from systemic infections [6]. Moreover, active cellular release of newly synthesized DNA has been suggested from activated cells [7]. Thus, there is evidence that both DNA and RNA may consist in two transferred forms, i.e. cell-free and micro vesicle-derived forms [8, 9]. Probably there are different biological functions exerted by circulating cell-free DNA and DNA derived with extracellular vesicles including exosomes and shedding micro vesicles [10]. Therefore, nuclear and mitochondrial DNA not only distinguishes nature and origin, but they may mediate different metabolic effects on target cells [10]. The mini review is summarized evidences regarding the biological role of circulating cell-free mitochondria originated DNA and hypothesized the indication for clinical use of soluble form of circulating cell-free mitochondrial DNA as diagnostic and predictive biomarkers among 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 and long segments [11]. The spontaneously released mitochondrial DNA fraction has been shown to be present in both actively dividing and non-dividing forms; associated with DNA-dependent RNA or DNA polymerase; and to have a lower molecular weight than the typical genetic mitochondrial DNA fractions [12]. Interestingly, lower molecular weight mitochondrial DNA fraction might term metabolic DNA and represent the precursor to the formation of the spontaneously released DNA fraction.

Thus, there is evidence that some populations of cell-free mitochondrial DNA might be released spontaneously. In contrast, the main triggers of deriving of cell-free mitochondrial DNA are various clinical conditions associated with cell death, necrosis, and activation of cells following antigen stimulation, inflammatory cytokine effect [13]. All these processes require macrophages / lymphocytes and may be hormonally mediated [14,15]. Macrophages play an important role in the generation of extracellular mitochondrial DNA from dead and dying cells, with the effect dependent on how the cell died [16].

The actual concept regarding biological role of cell-free

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mitochondrial DNA affects an ability of DNA fragments to impair a mitochondrial functionality and thereby to induce membrane cell dysintegrity [17]. In contrast of nuclear originated cell-free DNA, DNA liberated from mitochondria is a critical activator of inflammation and the innate immune system, it is accepted that elevated circulating level of cell-free DNA could link mitochondrial dysfunction, cell death and target organ damage in patients with wide spectrum diseases including CV and metabolic diseases [18,19]. Indeed, cell-free mitochondrial DNA could promote endothelial dysfunction and inflammatory effect on the vascular system through the activation of the toll-like receptor 9 that is widely expressed in different types of cells (e.g., T- and B-lymphocytes, mononuclears, epithelial and endothelial cells) and plays a pivotal role in the pathogenesis of malignancy, CV, rheumatic, metabolic, and autoimmune diseases [17-21]. Thus, development of micro- and macro-vascular complications might be related to cell-free mitochondrial DNA release from activated and apoptotic / necrotic cells due to various causes, not always related to neoplasm progression.

The role of cell free mitochondrial DNA in patients with CV and metabolic diseases

The epidemiological evidence indicates that alterations of mitochondrial DNA, including mutations and abnormal content of mitochondrial DNA, are associated with the initiation and development of CV and metabolic diseases. There is an association between leukocyte mitochondrial DNA content and a risk of coronary artery disease (CAD) [22]. Recent study has been shown that circulating cell-free mitochondrial DNA fragments were found the trigger of early endothelial dysfunction in the pre-diabetic patients at high CV risk [17]. Liu et al. [23] reported that circulating cell-free mitochondrial DNA was sufficiently higher in diabetics with CAD compared to those without CAD. Nevertheless, there was a significant correlation between cell-free mitochondrial DNA level and C-reactive protein concentration. Recent study has revealed that circulating cell-free DNA and their mitochondrial fragment might be used as indicators of cell death and tissue damage in percutaneous coronary artery intervention [24]. Therefore, cell-free DNA fragments are discussed a useful biomarker reflected cellular damage induced by exposure to chronic low-dose radiation within diagnostic procedures.

Analyses of data obtained from two prospective observational cohort studies of the intensive care unit patients (the Brigham and Women's Hospital Registry of Critical Illness and Molecular Epidemiology of Acute Respiratory Distress Syndrome) has shown that elevated cell-free mitochondrial DNA levels were associated with mortality and that an inclusion of this biomarker may improve a risk prediction in medical intensive care unit patients [25]. However, lack of results obtained from large clinical trials limits very well an interpretation of similar data. Taking into consideration that individualizing in the medical care is an important component of treatment strategy, use of biomarkers that could improve contemporary risk prediction scores appears to be attractive.

Overall, cell-free mitochondrial DNA is currently suggested an important challenge in diagnosis and prognostic evaluation of acute coronary syndrome, myocardial infarction, in prediction of CV disease, pulmonary thromboembolism, in non-invasive early detection of atherosclerosis and understanding its pathological mechanism *in vivo*, in assessing various issues of treatment for atherosclerosis [26-29]. Although cell-free mitochondrial DNA may be routinely used to accurately diagnose cancers, whether they could help to stratify non-cancer patients at CV risk is not clear. Nevertheless, over the last decade implementation of cell-free mitochondrial DNA measurement into clinical settings is hampered by technical problems with assay specificity and sensitivity that requires more investigations to easily understand the role of this biomarker in CV risk stratification on dysmetabolic states.

Conclusion

Soluble form of cell-free mitochondrial DNA is found a useful biomarker of cell death and non-specific tissue injury. However, in non-cancer individuals the diagnostic and predictive role of this biomarker is not fully understood. Probably, elevated levels of cell-free mitochondrial DNA could be used a diagnostic tool for early stage screening among subjects with suspected CV and metabolic diseases. Prospective studies with a larger cohort of non-cancer patients in various CV and metabolic diseases are required to precisely define the clinical importance of elevated cell-free mitochondrial DNA levels amount for diagnosing and predicting values.

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