

Circulating Nucleic Acids (CNAs) in a New Perspective

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Abstract

Circulating nucleic acids (CNAs), now a days have become the popular tools for non-invasive diagnosis and monitoring of the diseases, such as cancer, stroke, trauma, myocardial infarction, autoimmune disorders, and pregnancy-associated complications. Recently, attempts have been made to investigate the biological functions of the CNAs and also to elucidate their role in various malignancies. One of the important functions of CNAs is that these can behave as mobile genetic elements as function of their size and have ability to destabilize genome. This assumption has led to the investigation of CNAs degrading or neutralizing agents. These new developments have directed us to see CNAs in a new perspective in biological science.

Background

Circulating nucleic acids (CNAs) were first discovered in the plasma of healthy and sick individuals in 1948 [1]. However, this discovery did not spark any interest among scientific community at that time. It was only in 1960s, when research in this field was resumed and led to the discovery of high levels of circulating DNA in patients with systemic lupus erythematosus [2].

By definition, CNAs are segments of genomic, mitochondrial or viral DNA, RNA and microRNA (miRNA) found in the bloodstream [3]. Various mechanisms by which CNAs are proposed to be released into circulation include apoptosis and necrosis [4] or spontaneous release of nucleic acids from cells [5]. However, apoptosis or necrosis is the main phenomenon responsible for cell-free CNAs [4-7]. Circulating tumor cells (CTCs) have also been hypothesized to release CNAs in the bloodstream [8-13]. The CNAs originated from viruses, such as EBV, HPV and hepatitis B virus have also been found in plasma or serum of healthy individuals, and in cases of malignancies associated with viral infections [14-16].

CNAs are not only found in the animal kingdom, but in plants, and in the microbial world as well. CNAs in the form of

fragmented DNA and chromatin have a size range of between 100 bp-1000 bp, have a half-life of 10-15 minutes and are ultimately removed by the liver [17,18].

Over the past decade, a lot of studies have pooled the information indicating the diagnostic potential of these CNAs, particularly in cancer screening and monitoring of the efficacy of anticancer therapeutics [19].

Biological Functions of CNAs and its Implications

A lot of research has been done to investigate the diagnostic potential of CNAs till now. However, there is scarcity of investigations to understand pathophysiological functions of CNAs. Some intriguing reports in 1999, have suggested that, circulating DNA may be taken up by cells and result in evident gene expression [20,21]. Recently, it was reported that CNAs (DNA and chromatin fragments) isolated from blood of healthy volunteers and cancer patients are actively taken up by cells in culture leading to their rapid accumulation in cell nuclei and ultimately their association with cell chromosomes [22]. These intracellular CNAs activated the proteins of DDR and apoptotic pathways and triggered a DNA-damage-repair-response (DDR) with up-regulation of multiple pathways of DNA damage and repair, facilitating their integration into host cell genome. This work provides the first direct evidence that CNAs can behave like mobile genetic elements and change the expression levels of certain genes in otherwise healthy cells in vitro and in vivo, thereby promoting invasion and metastasis [23,24].

This new hypothesis could offer a fascinating mechanism of age-related mutagenesis. CNAs could be considered as a new, endogenous source of genome instability, contributing to the increased genome mosaicism with age [25]. There are evidences that CNAs becomes more frequent in the circulation due to increased vulnerability of aged and damaged cells to cell death [26,27]. In response, activation of the DDR could increase the genome instability significantly, contributing to age-related degenerative diseases, such as cancer and inflammation.

Recently, it has been reported that cellular entry and acquisition of biological properties of CNAs are functions of its

size [28]. Small fragments of DNA (300-3000 bp) of different origins for example, from cancerous and non-cancerous human cells, bacteria and plant, not only can indiscriminately enter into other cells across species and kingdom boundaries but can also integrate into their genomes and activate biological processes. Therefore, fragmented DNA that are generated following cell-death may act as mobile genetic elements and can have evolutionary implications by being involved in horizontal gene transfer.

CNAs Degrading Agents as New Possible Drugs

Enzymes DNase I and II, present in circulation are known to degrade DNA. However, low activity of DNase I and II have been detected when their inhibitors are secreted such as in malignant diseases, explaining why the elevated DNA levels in circulation are observed [29,30]. Since, CNAs released from dying cells can enter into healthy cells of the body to integrate into their genomes and induce DNA damage, apoptosis and inflammation in them, it can be hypothesized that toxicity of chemotherapy to a large extent, might be due to release of large quantities of CNAs from dying cells and also that caused by the drugs themselves. Mitra et al. suggested that chemotherapy toxicity caused by CNAs released from dying cells can be prevented by simultaneous treatment with CNAs neutralizing or degrading agents, such as anti-histone antibody complexed nanoparticles, DNase I and Resveratrol-Cu [31]. Many naturally occurring DNA cleaving agents can also be explored for their possible use in combating chemotherapy induced toxicity. The possibility of CNAs acting as mobile genetic elements and their consecutive role in genome instability and evolutionary processes will provide a new direction in drug discovery.

Conclusion

In cancer patients, chemotherapy originated CNAs from dying cells could cause genome destabilization. These side-effects of chemotherapy can be potentially prevented by CNAs neutralizing or degrading agents administered concurrently with chemotherapy. Successful translation of this approach may result in prevention of casualty resulting from chemotherapy. Thus, validated role of CNAs in genome instability and evolutionary processes may elucidate a potential treatment strategy for preventing age-related degenerative diseases.

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