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Review

DNA damage in non-communicable diseases: A clinical and epidemiological perspective

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ABSTRACT

Non-communicable diseases (NCDs) are a leading cause of death and disability, representing 63% of the total death number worldwide. A characteristic phenotype of these diseases is the accelerated aging, which is the result of phenomena such as accumulated DNA damage, telomere capping loss and subcellular irreversible/nonrepaired oxidative damage. DNA damage, mostly oxidative, plays a key role in the development of most common NCDs. The present review will gather some of the most relevant knowledge concerning the presence of DNA damage in NCDs focusing on cardiovascular diseases, diabetes, chronic obstructive pulmonary disease, and neurodegenerative disorders, and discussing a selection of papers from the most informative literature. The challenge of comorbidity and the potential offered by new systems approaches for introducing these biomarkers into the clinical decision process will be discussed. Systems Medicine platforms represent the most suitable approach to personalized medicine, enabling to identify new patterns in the pathogenesis, diagnosis and prognosis of chronic diseases.
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1. Introduction

According to the updated revised version of World Health Organization (WHO) on *Global Action Plan for the prevention and control of noncommunicable diseases 2013–2020*, non-communicable diseases (NCDs) are a leading cause of death and disability worldwide. NCDs are responsible for up to 36 millions of deaths (63% of the total death number) out of 57 millions of total deaths [1]. By definition, NCDs are non-*transmissible* diseases with long duration and slow progression, divided into four major disease clusters: cardiovascular, cancers, chronic pulmonary, and diabetes. NCDs may accelerate aging, causing both socio-economic and healthcare problems and influencing the burden of morbidity and mortality in the world. Human aging largely varies among individuals, as a

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result of accumulated DNA damage in cells and organs [2], loss of telomere capping protecting the chromosomal ends from fusion and loss of the material [3], and irreversible/nonrepaired oxidative damage in subcellular structures, due to free radical-based oxidation, unbalance in antioxidant/oxidant status and insufficient DNA repair.

In a homeostatic system, DNA damage is balanced by DNA repair. Whenever damage prevails over repair, the ultimate outcome would be the cell cycle arrest. Failure in the checkpoint mechanisms which ensure DNA integrity before allowing replication and cell division may cause DNA damage accumulation that in turn may lead to apoptosis, senescence, or genome mutation [4]. DNA damage and oxidative damage are present in all NCDs, and extensive evidence support the role of oxidative (accumulated) damage in the development of chronic diseases [5–7].

Accumulation of oxidative species starts when repair mechanisms fail to work properly, due to an unfavorable genetic background (such as in the case of single nucleotide polymorphisms), epigenetic events, or because of the amount of unrepaired damage. Oxidative damage has endogenous causes, due to cellular aerobic respiration (*e.g.* mitochondrial transport and many reactions of oxidation, also in endoplasmic reticulum, peroxisomes, lysosomes, *etc.*) and in addition, overproduction and accumulation of reactive oxygen species (ROS), nitrogen species, reactive aldehyde species, transition metal intermediates and advanced glycation end (AGE) products, induce damage to cellular macromolecules [8–10] influencing membrane lipids (such as lipid peroxidation), proteins, and particularly DNA. Several kind of damages are generated by this process, including base damage (purine and pyrimidine), adducts, single-strand breaks (SSB), double-strand breaks (DSB), DNA-DNA or DNA-protein cross links [11,12]. Oxidative damage may be caused also by exposure to environmental factors like cigarette smoke, asbestos, coal, diesel, chromium, drugs, radiation, silica nanoparticles. Unresolved and accumulated oxidative species can induce an inflammatory response, contributing to additional level of (oxidative) damage, influencing gene regulation and inducing cells to activate senescence or apoptotic phase [11,12]. Mostly affected is the mitochondrial DNA, in which oxidative damage results in acidification of cytoplasm and releasing of cytochrome *c*, leading to activation of apoptotic signals. From the four main DNA bases, guanine has the lowest oxidative potential, consequently the formation of modified base such as 8-oxo-7,8-dihydro-2′-deoxyguanosine (8-oxodGuo or 8-OHdG) is the most frequently measured effect of DNA damage [11,12], although there are other possible modifications such as 2-hydroxy adenine, FAPy-adenine (4,6-diamino-5-(formylamino)-pyrimidine or 4,6-diamino-5-formamidopyrimidine or 4,6-diamino-5-N-formamidopyrimidine), 8-oxoadenine, 5-hydroxycytosine, cytosine glycol and thymine glycol.

Assuming that mechanisms of DNA damage and repair are similar in different tissues [5,6], peripheral lymphocytes can serve as an excellent marker because of their half-life and their presence in all body districts [13,14]. DNA damage in lymphocytes is usually measured by standard cytogenetic tests such as Comet assay, cytochalasin B blocked micronucleus assay (CBMN), sister chromatid exchange assay (SCE), chromosomal aberration assay (CA), and telomere length assay (TL). These biomarkers have shown good correlation with other markers of oxidative stress and can represent a good substitute for measuring both the level of oxidative stress and early genetic damage on a faster and more efficient way [15–17]. Primary DNA damage as SSB and DSB, alkali-labile sites converted to DNA strand breaks due to the alkaline conditions of the method, oxidative DNA damage (with the use of FPG (formamidopyrimidine DNA-glycosylase)/Endo III (endonuclease III) enzymes) can be detected and measured by Comet assay [18], while chromosomal damage can be detected with CA (evaluation of chromatid or chromosome type breaks, dicentric chromosome, acentric chromosome, *etc.*), CBMN (micronuclei-consequence of chromosome breaks or chromosome loss during cell division, nucleoplasmic bridges-chromosome rearrangements and nuclear buds-DNA amplification) [19,20] and SCE (allows detection of the number of symmetrical exchange of DNA replication products between sisters chromatids at a given locus) [21]. TL assay is a marker of senescence and genomic stability/instability [22] and it has been shown that shorter telomeres are represented in the NCDs and connected also with inflammatory process in the patients [23–25].

Inflammatory molecules and accumulation of DNA damage in NCDs may be associated to a number of clinical features, such as severity, exacerbations, and co-morbidity. These parameters are also affected by life-style, socio-economic and psychological status of individuals, and evidence is available about the interaction between genetic background and environmental exposures in the pathogenesis of these events. A comprehensive evaluation of NCDs phenotypes should take into account all these data, together with the molecular underpinning (*e.g.*, omics data), for a more effective management of NCDs.

An innovative approach which allows addressing the complexity of NCDs providing a tool to model individuals' clinical features and molecular background is the use of Systems Medicine models (SM). SM regards each biological organism as "a network of interconnected and mutually dependent components that constitute a unified whole" [26]. Disease is viewed by SM as a dynamic alteration of genetic, epigenetic and metabolic networks that is primed by the interaction between inner molecular components and environmental factors [27,28]. This approach allows to use early biological effects biomarkers, especially of DNA damage and genomic instability, in combination with clinical features, to identify treatment strategies to be developed on new-personalized-criteria.

The present review will gather some of the most relevant knowledge concerning the presence of DNA damage in most common NCDs, such as cardiovascular, metabolic, respiratory and neurodegenerative disorders, discussing a selection of papers from the most informative literature.

The challenge of comorbidity and the potential for introducing these biomarkers into the clinical decision process will be discussed.

2. DNA damage in lymphocytes of cardiovascular patients

Cardiovascular disease (CVD) is the primary cause of mortality (80% for adults that are 65 or more years old) worldwide [29]. Cardiovascular failure may result from different pathways, including changes in the elasticity of large artery; higher blood pressure; alteration of heart rate, and several other conditions [30,31]. There are evidences that oxidative stress promotes endothelial dysfunction, atherosclerosis and progressive and inflammatory disease of the arterial wall leading to acute and chronic cardiovascular events [32].

The extent of DNA damage in circulation lymphocytes have prognostic values in patients with CVD [33,34], and can serve as potential target for therapeutic strategies, especially in the early management and prevention of the disease. The use of the Comet assay [35], and CBMN showed a significant increase and positive correlation of DNA damage with the incidence [36] and severity of CVD [36]. Significantly higher MN frequency was found in the CVDs patients when compared to controls [37], and shorter survival with higher MN frequency, especially in the upper tertile with 2.2-fold increased risk of developing adverse cardiac events [33]. CA showed higher frequencies in lymphocytes of CVD patients although they

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