Mitochondrial DNA in osteoarthritis disease

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Osteoarthritis (OA) is the most prevalent chronic joint disease, and we actually know that the activation of maladaptive responses to injury, including pro-inflammatory pathways, leads to the loss of normal joint function characterized by cartilage degradation, bone remodeling, osteophyte formation, and joint inflammation [1]. Recent insights into the epidemiology and impact of OA on patients have clearly established that OA is a severe disease of the whole joint as an organ, with large unmet medical needs.

OA has a complex etiology that comprises the combination of multiple factors, including gender, age, occupation, trauma, body mass index, and genetics. Approximately, between 30 and 65% of the risk of OA is genetically determined [2] with evidence accumulated from different genome-wide association studies (GWAS) [3]. Most of these studies focused on nuclear genetic variants; however, over the last decade, evidence has accumulated for an association between specific mitochondrial DNA (mtDNA) genetic variants, called haplogroups, and different OA-related features, including prevalence, progression, and incidence [4].

mtDNA haplogroups: definition and clinical associations

mtDNA haplogroups are the result of sequentially accumulating mutations along radiating maternal lineages as women migrated out of Africa to colonize the rest of the world, adapting their energy metabolism to different environments to allow our ancestors to adapt to colder climates. This resulted in the regional enrichment of specific mtDNA lineages, called haplogroups which, today, affect health and longevity due to the profound differences in both energy metabolism and mammalian biology that exist among them [5,6,7,8].

The meta-analysis presented by Zhao and co-workers confirms and reinforces the involvement of specific mtDNA variants in the prevalence and progression of OA. Specifically, variants within the mtDNA cluster TJ are not only under-represented in OA patients but also are less frequent in patients with higher progression rates; however, the impact comes mainly from variants J and T respectively [9]. mtDNA haplogroups J and T are considered "sister haplogroups" that share a set of uncoupling mtDNA polymorphisms [8] that make these two haplogroups biochemically different from other mtDNA variants, especially haplogroup H [10, 11]. Specifically, haplogroup J is the mtDNA lineage with the highest percentage of non-synonymous mutations [12]. These mitochondrial haplogroups have also been associated, as either protective or risk factors, with different human diseases.

Traditionally, haplogroup J has been associated as a risk factor for energy-deficiency diseases and protective for degenerative diseases [5]. Some common examples of these associations include the increased penetrance of complex I gene mutations associated with Leber's hereditary optic neuropathy (LHON) [13], increased susceptibility to multiple sclerosis [14], or worse profile of CD4+ recovery in HIV-infected patients [15]. On the contrary, this mitochondrial variant has been described as protective against different cardiomyopathies [16, 17], Parkinson disease [18], lower risk of knee OA incidence [19], or even increased longevity in different human populations [20]. Meanwhile, haplogroup T has been described as a risk factor for obesity [21], multiple sclerosis [22], or coronary artery disease and diabetic retinopathy [23] and protective against breast cancer in BRCA2 mutation carriers [24].

Despite all the above mentioned, there is an evidence about the lack of reproducibility in some mtDNA genetic association studies performed in complex traits or diseases. This can be due to different reasons, which are discussed below.

On the one hand, different critical reviews concluded that most of these studies did not monitor the possibility of population stratification in their cohorts, and even these studies would be statistically underpowered [25]. To solve this, the combined analysis of results from different studies through a meta-analysis can help to identify not only patterns of association but also sources of disagreement among the different studies [26]; thus, the number of false positives would be reduced, and also, an optimal statistical power to demonstrate a true association would be possible [27]. Taking this into account, the study of Zhao and co-workers reinforces the association of mtDNA haplogroups with the prevalence and progression of OA, especially at the level of haplogroups of mtDNA cluster TJ [9].

On the other hand, given the role of environmental selection on mtDNA haplogroup variation and that, therefore, mitochondria act as key sensors of environmental changes, it can be speculated that a specific mtDNA variant could be maladaptive in different environments with new lifestyles if these local environmental changes are too severe to be managed by a specific mtDNA haplogroup [7]. Based on this assumption, one could expect population-specific associations regarding the same disease or trait, as is the case of the association of mtDNA haplogroup J with increased longevity in different human populations [20].

Last but not least, and related to the previous, an interaction between nuclear DNA and mtDNA variants exists, and this interaction has important effects on cellular metabolism and physiology [7]. Probe of this are numerous examples that show how the mitochondrial background modifies the association of specific nuclear polymorphisms related, in a robust manner, to different human diseases such as Alzheimer, breast cancer, multiple sclerosis, or Parkinson [14, 24, 28,29,30]. Based on these findings, it could be possible that a specific mtDNA variant significantly associated with a disease in a population with a specific nuclear background lacks this association in the context of a different nuclear background.

Functional implications of mitochondrial variation

A series of functional studies, aimed to demonstrate the effect of the mitochondrial background on cellular metabolism and physiology, as well as on mammalian biology, were performed using transmitochondrial cybrids and conplastic mice.

Studies using transmitochondrial cybrids (cells with a defined and uniform nuclear background containing mitochondria from different sources) carrying haplogroups J or T pointed to a series of features related to the uncoupling nature of the mutations characteristic of these haplogroups [31], including lower oxygen consumption, lower ATP levels, diminished ROS production, and higher capacity to cope with oxidative stress and apoptosis [19, 32, 33]. During mitochondrial uncoupling, electron transport is uncoupled from energy production leading to a generation of heat instead of ATP, increasing the probability of energetic failure; in addition, a decrease of mitochondrial ROS would also be expected by increasing the oxidation of the electron transport chain, thus reducing oxidative damage and apoptosis [34]. This hypothesis would explain how the same haplogroup behaves as a risk factor for energy-deficiency diseases and protective against degenerative diseases and increased longevity [5, 35].

Regarding the use of conplastic mice (mice with constant nuclear background but different mtDNA genomes), a study by Latorre-Pellicer and co-workers, using two strains of conplastic mice, revealed profound differences in health longevity. The level of divergence between the two strains was equivalent to that between human Eurasian and African mtDNAs, and they observed a different behavior in terms of reactive oxygen species generation, mitochondrial proteostasis, obesity, mitochondrial dysfunction, insulin signaling, and telomere shortening [6]. In the field of OA, preliminary results using the same animal model revealed significant differences between the two strains in the Mankin score as well as in the expression levels of both autophagy-related protein microtubule-associated protein 1 light chain 3 (LC3) and extracellular matrix–degrading protein metalloproteinase-13 (MMP-13) [36].

The influence of the mitochondrial genome on cellular behavior has not only been demonstrated by using these two models (cellular and animal) but also in terms of the epigenetic regulation that the mitochondrial genome exerts on the nuclear genome. Thus, through a process called "retrograde regulation," mtDNA haplogroups are able to modulate the cell's nuclear DNA methylome and, as a consequence, lead to the modification of cellular metabolism and function by activating the expression of nuclear genes (Fig. 1) [37, 38]. Specifically, in the case of OA, it has been demonstrated that mtDNA haplogroups J and H differentially modulate the methylation status of articular cartilage by acting on key mechanisms involved in this disease, such as apoptosis as well as metabolic and developmental processes [39].
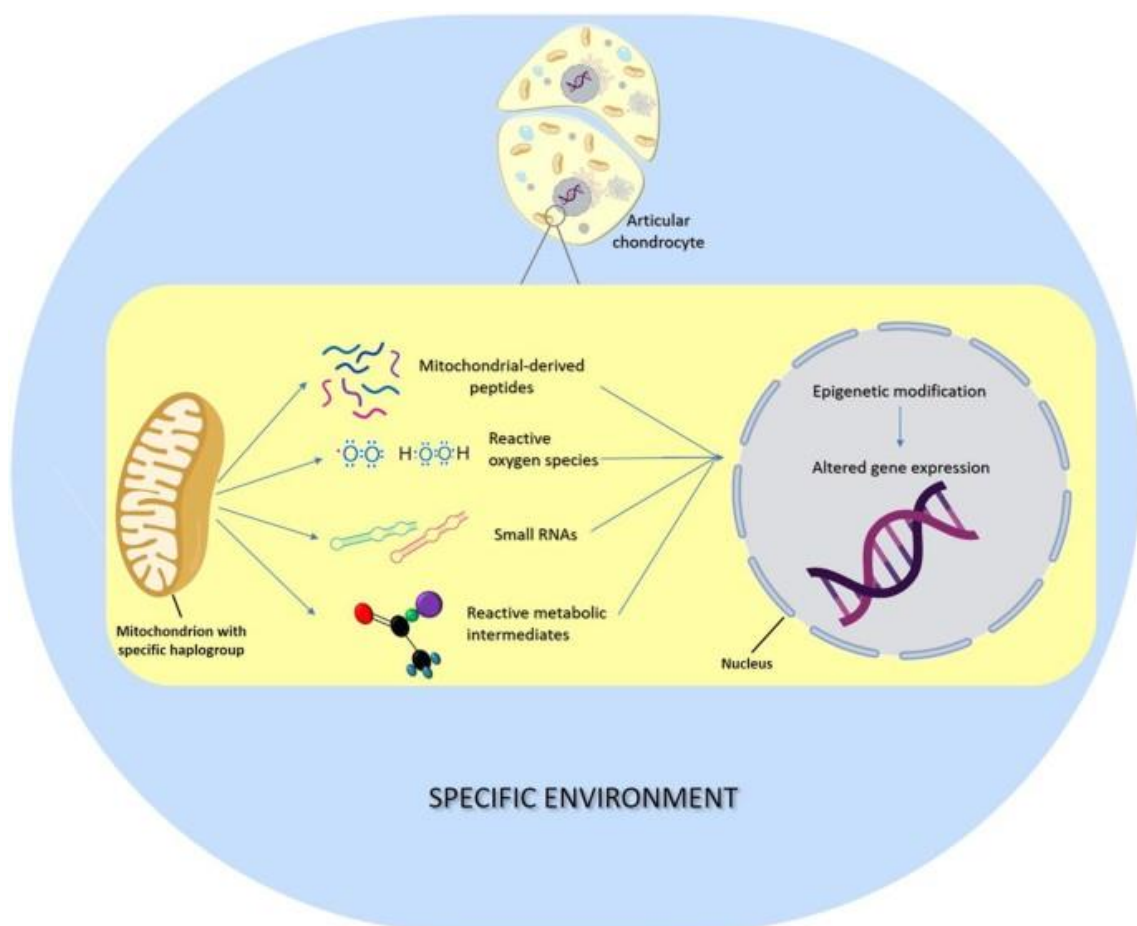

Fig. 1. Schematic view of the "retrograde regulation" by which specific mtDNA haplogroups modulate the gene expression of nuclear genes. In the context of a certain environment, mitochondrial genetic background alters mitochondrial behavior and, through different signal stimuli such as mitochondrial-derived peptides, reactive oxygen species, small RNAs, or reactive metabolic intermediates, leads to the modification of nuclear gene expression

Finally, in terms of therapeutic research, since the ultimate goal should be the restoration of normal mitochondrial function, others and we propose mitochondria as an attractive therapeutic target in OA. This could be achieved through different approaches such as (i) the activation of mitophagy, given its importance in preventing mitochondrial dysfunction [40]; (ii) the reestablishment of extracellular matrix homeostasis by suppressing mitochondrial oxidative damage [41]; (iii) the emulation of the physiological effects of OA-protective haplogroups and/or administering healthy isolated mitochondria into the osteoarthritic joint; and (iv) the activation of mitochondrial biogenesis [42].

Conclusion

In summary, the study of Zhao and co-workers [9] provides reinforced evidence for the involvement of the mitochondrial genome in the pathogenesis of OA. Even with the existence of complex interactions between nuclear and mitochondrial genomes, due to the large unmet medical needs, the results of this and other studies show the importance of considering mitochondria as an important therapeutic target in OA.

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Contributions

FJB and IRP contributed equally in the design and coordination of the study; both conceived the study and helped to draft the final version of the manuscript.

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