Is osteoarthritis a mitochondrial disease? What is the evidence

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Abstract

Propose of review. To summarize the evidence that suggests that osteoarthritis (OA) is a mitochondrial disease.

Recent findings. Mitochondrial dysfunction together with mtDNA damage could contribute to cartilage degradation via several processes such as: (1) increased apoptosis; (2) decreased autophagy; (3) enhanced inflammatory response; (4) telomere shortening and increased senescence chondrocytes; (5) decreased mitochondrial biogenesis and mitophagy; (6) increased cartilage catabolism; (7) increased mitochondrial fusion leading to further reactive oxygen species production; and (8) impaired metabolic flexibility

Summary. Mitochondria play an important role in some events involved in the pathogenesis of OA, such as energy production, the generation of reactive oxygen and nitrogen species, apoptosis, authophagy, senescence and inflammation. The regulation of these processes in the cartilage is at least partially controlled by retrograde regulation from mitochondria and mitochondrial genetic variation. Retrograde regulation through mitochondrial haplogroups exerts a signaling control over the nuclear epigenome, which leads to the modulation of nuclear genes, cellular functions and development of OA. All these data suggest that OA could be considered a mitochondrial disease as well as other complex chronic disease as cancer, cardiovascular and neurologic diseases.

Keywords

Apoptosis, cartilage, mitochondria, mtDNA, osteoarthritis

INTRODUCTION

Articular cartilage has traditionally been classified as highly glycolytic tissue that derives its energy from anaerobic glucose metabolism, for this reason, the role of mitochondria in the pathogenesis of osteoarthritis (OA) has not been studied in detail until last decade [1]. OA has been recently defined as a chronic progressive disorder that involves movable joints and is characterized by cell stress and extracellular matrix degradation initiated by micro- and macro-injuries, that activate maladaptive repair responses, including proinflammatory pathways of innate immunity. The disease is first manifested as a molecular derangement (*abnormal tissue metabolism*) followed by anatomic and/or physiologic derangements (characterized by cartilage degradation, bone remodeling, osteophyte formation, joint inflammation, and loss of normal joint function) [2]. According to this definition, mitocondria could be involved in the OA pathogenesis because mitochondrial Oxidative Phosphorylation System (OXPHOS) account for up to 25% of total ATP production in articular cartilage, and an even higher percentage in situations that there are high tissue energy demands [3,4*,5]. In addition, OA chondrocytes show defective glycolysis, which makes them further reliant on OXPHOS. Furthermore, mitochondria are involved in other important multiple cell functions described in articular chondrocytes, such as heat regulation, calcium homeostasis, biogenesis and assembly of iron-sulfur proteins, control of apoptosis, reactive oxygen species (ROS) production, cell survival and proliferation, production of metabolites and coordination of metabolic pathway. This implies that mitochondrial dysfunction can have many and various

deleterious effects on chondrocytes function associated with cartilage degradation. In this review, we have summarized the evidence that suggests that mitochondria play a role in the pathogenesis of OA [6,7].

IN VITRO STUDIES CONFIRM MITOCHONDRIAL DYSFUNCTION IN OSTEOARTHRITIS

Disordered mitochondrial function contributes to the pathogenesis of complex diseases not classically considered to involve mitochondria, including cancer [8–10], cardiovascular disease [11–13] and neuro-degenerative diseases [14–16]. There is over-whelming evidence that defective mitochondrial function is also a contributing element to rheumatic diseases including the OA [3,6,17**,18].

Analyses of mitochondrial function in human OA chondrocytes have revealed decreased activity of the mitochondrial respiratory complexes II and III, as well as increased mitochondrial mass, compared with that in human healthy chondrocytes [19]. In addition, the apoptotic mitochondrial pathway has been implicated in the apoptosis of OA chondrocytes [20,21]. The inhibition of complexes III and V has been shown to increase the OA chondrocyte inflammatory response, including the production of pro-inflammatory cytokines and metalloproteinases, mediated by enhanced production of ROS [22–24]. Mitochondrial dysfunction has also been associated with a significant downregulation of superoxide dismutase 2 (SOD2) [25], one of the major mitochondrial antioxidant proteins, whose levels are also diminished in the superficial layers of end-stage OA cartilage [26,27].

As mitochondrial metabolism is an important source of ROS, the production of excessive amounts of these reactive molecules, attributed to mitochondrial dysfunction, has been implicated in the development of ageing-related OA [28], in compromising chondrocyte function [29,30] and in causing mtDNA damage and reducing the capacity for mtDNA repair [31]. Mitochondrial dysfunction and mtDNA damage have also the capacity to promote abnormalities in human articular chondrocytes that contribute to cartilage degradation in OA. Among these abnormalities, impaired anabolic and growth responses of human chondrocytes, excessive apoptosis, defect in autophagy, reduced telomere length, enhanced cellular senescence and inflammatory responses are particularly important [22,29,32].

More recently mitochondrial dynamics, including fission, fusion, mitophagy, turnover and plasticity, facilitate a metabolic shift either into a glycolytic phenotype or into an OXPHOS phenotype, depending on the cellular demand, have been implicated in OA [33,34**]. Mitophagy consists of the elimination of depolarized and damaged mitochondria and the activation of this process protects against mitochondrial dysfunction, prevents ROS production and improves chondrocyte survival under pathological conditions [35,36]. Mitochondrial biogenesis is deficient in human OA chondrocytes, leading the chondrocyte to adopt procatabolic responses [37].

Metabolic flexibility is also associated with mitochondria dysfunction due to their role in the last steps of both glucose and fatty acid (FA) metabolism [38,39]. OA is associated with a high accumulation of lipids in cartilage [40,41] and ectopic FA accumulation likely leads to lipotoxicity and contributes to the cellular

dysfunction [42]. In transmitochondrial cybrids, OA mitochondria showed less flexibility than OA-free mitochondria [43*].

Collectively, these abnormal processes have tremendous deleterious effects on cartilage biology and chondrocytes function. Mitochondrial dysfunction together with mtDNA damage could contribute to cartilage degradation via several processes such as: 1) increased apoptosis; 2) decreased autophagy; 3) enhanced inflammatory response; 4) telomere shortening and increased senescence chondrocytes; 5) decreased mitochondrial biogenesis and mitophagy; 6) increased cartilage catabolism; 7) increased mitochondrial fusion leading to further ROS production; and 8) impaired metabolic flexibility. When these changes cannot be managed by the repair and the antioxidant systems, the homeostatic system fails, and mitochondrial dysfunction is perpetuated, leading to progressive cartilage destruction and, eventually, to joint malfunction (Table 1) [21,36,44– 49,50**,51*].

CLINICAL DATA ASSOCIATES MITOCHONDRIAL GENETIC VARIATIONS WITH OSTEOARTHRITIS

Mitochondria contain their own genetic material (mtDNA) enclosed in a single circular chromosome. MtDNA codes for 13 essential genes that are critical for mitochondrial energy metabolism. Evolutionary changes in mtDNA coincided with the major human geographical transitions to facilitate human adaptation to different regional environments. These variants are called mtDNA haplogroups and they are defined by the presence of a particular set of single nucleotide polymorphisms in the mtDNA sequence in coding and noncoding regions that

were shaped by natural selection as humans migrated into colder climates [52,53]. Among individuals of Caucasian ancestry, 95% of the population belongs to one of the following haplogroups: H, I, J, T, U, K, V, HV , W or X. There is data that showed the relation between mtDNA haplogroups and the energy production, showing differences in their OXPHOS coupling efficiency [52,54,55]. An increasing number of studies showed associations between some of the mtDNA haplogroups and human longevity as well as with some multifactorial diseases such as Alzheimer Disease, type 2 Diabetes Mellitus, Obesity [56,57*,58,59] and also with OA. In terms of radiographic OA prevalence, European mtDNA haplogroup J and cluster JT have been significantly correlated with a decreased risk in a Spanish cohort [60,61]. The mtDNA haplogroup T has been associated with a lower risk of knee OA in a population from the United Kingdom [62]. Asian mtDNA haplogroup B has also seemed to be a protective factor against knee OA in a population from China and Korea [63,64,65*]. In contrast, the arcOGEN consortium did not find associations between mtDNA variants and the symptomatic knee OA prevalence [66]. Some points must be clarified to explain this discordant result; control samples used in arcOGEN study are population-based controls with only symptomatic information and without radiographic data. It is important highlight that up to 50% of patients without joint symptoms may have radiographic changes related to OA [67], therefore the selection of adequate healthy controls is crucial to draw consistent conclusions in case-control studies; this point could be one of the causes by which one study performed by the arcOGEN consortium also failed to replicate previous associations such as GDF5, or MCF2L [68] gene polymorphisms.

In addition to the prevalence, the progression and incidence of radiographic knee OA have been also associated with mtDNA haplogroups. A meta-analysis including data from three independent cohorts Prospective Cohort of Osteoarthritis from A Coruña (PROCOAC), Osteoarthritis Initiative (OAI), and Cohort Hip and Cohort Knee (CHECK) confirmed the association of the haplogroup T and the mtDNA cluster JT with a lower risk of radiographic knee OA progression over time [69]. A replication study and meta-analysis of 3217 subjects showed that the mtDNA haplogroup J is significantly associated with a lower rate of incident knee OA over an eight-year period [70] (Table 2).

OA-protective haplogroup J has been significantly associated with lower serum levels of catabolic type II collagen biomarkers, stromelysin-1 (MMP-3) and collagenase 3 (MMP-13) and nitric oxide, in contrast to haplogroup H carriers, which showed significantly higher levels [30,49,61,74–76]. In terms of imaging biomarkers, a longitudinal study including 255 participants from the OAI cohort that developed incident knee OA at 48 months revealed that patients with mtDNA haplogroup J were less likely to develop large bone marrow lesions (BMLs) in the tibiofemoral compartment of the knee than those with mtDNA haplogroup H [77]. Based on these findings, haplogroups J/T and H could represent two different OA phenotypes, leading to the consideration of these mtDNA haplogroups as complementary genetic biomarkers of the disease [76].

POTENTIAL MECHANISMS TO EXPLAIN THE ASSOCIATION OF MtDNA HAPLOGROUPS AND OSTEOARTHRITIS

As reflected in the two previous sections, mitochondrial dysfunction but also mitochondrial genetic polymorphisms, specifically the MtDNA haplogroups, have been shown to have influence on the prevalence, severity, incidence, and progression of the disease. To understand potential mechanism to explain this association it is important to keep in mind that a bi-directional communication exists between the nucleus and mitochondria with the aim of maintaining cellular homeostasis and regulating adaptation to a broad range of stressors [78,79]. Mitochondria are controlled by the nucleus by means of an ‘anterograde regulation’, and mitochondria (mtDNA variation) maintain partial regulatory signaling control over the nucleus through a ‘retrograde regulation’, which leads to the modification of cellular metabolism and function by activating the expression of nuclear genes with the aim of protecting against mitochondrial dysfunction [80– 82] (Fig. 1).

In this context, DNA methylation is involved in the phenotypic modulation that articular chondrocytes undergo during the OA process [83– 85]. Cartilages harboring haplogroups H and J show a differential methylation pattern, regardless of diagnosis and demonstrates that apoptosis is enhanced in haplogroup H cartilage samples, together with an enrichment of overexpressed genes related to cell death. On the contrary, apoptosis appeared more repressed in haplogroup J cartilages. In addition, compared with H cartilages, samples with haplogroup J also showed a significant enrichment of hypomethylated CpGs of genes related to developmental process, including those belonging to the homeobox family of

transcription factors, whereas haplogroup H cartilages showed an enrichment of genes related to metabolic processes [86*].

Transmitochondrial cybrids is a cell model with a defined and uniform nuclear background containing mitochondria from different sources. Using this cell model, functional experiments showed the existence of differences between haplogroups H and J. Cybrids harboring the haplogroup J showed higher mitochondrial respiration rate and glycolytic capacity, which is reflected in an decreased ATP generation, lower amounts of peroxynitrite and mitochondrial superoxide anion together with a lower rate of apoptosis under stress conditions as well as an increased ability to cope with oxidative stress. These J cybrids not only have a significantly lower rate of apoptosis under stress conditions, but also a lower expression of the pro-apoptotic gene BBC3, which induces apoptosis through mitochon- drial dysfunction [70].

Senescent chondrocytes accumulate in OA cartilage and are associated with a loss of tissue function. Replicative senescence at the cellular level is triggered when telomeres are excessively shortened. [21]. OA chondrocytes show shorter telomeres than those from healthy individuals which may be related to accelerated articular senescence and could contribute to the incidence and progression of OA [10]. Interestingly, individuals carrying the mtDNA haplogroup J exhibit a Peripherical Blood Leucocytes (PBL) telomere length longer than those non-J carriers [49]. In addition, the slower telomere decay in PBL is associated with a lower risk of incidence of knee OA over time. This slow telomere shortening is more significant in nonincident OA subjects carrying mtDNA cluster JT than those with cluster HV [50**]. An increased telomere loss rate in PBL may

reflect a systemic accelerated senescence phenotype which could be potentiated by the mitochondrial function, increasing the susceptibility of developing OA.

Some of these results described in human have been confirmed comparing the conplastic mice model (BL/6^{NZB}) (mice with a constant nuclear background but different mtDNA genomes) with the original strain (BL/6^{C57}). The level of divergence between the two strains is equivalent to that between human African and Eurasian mtDNAs. Comparative analysis of both mice strain showed profound differences in health longevity, behavior in terms of mitochondrial proteostasis, reactive oxygen generation, obesity, and insulin signaling as well as in cell-senescence-related parameters such as telomere shortening and mitochondrial dysfunction [87]. Most of the altered processes described are also associated with some chronic human diseases as OA. In agreement with this, analyses of the articular cartilage from the knee during the aging of these mice, revealed significant differences between them in terms of the expression of the autophagy-related protein microtubule-associated protein 1 light chain 3 (LC3) and extracellular matrix-degrading protein metallo-proteinase-13 (MMP-13) and beta-galactosidase, as well as significant differences in the Mankin score [88**]. Even more interesting were the results obtained in the surgical DMM OA model induced in both strains. The joints of BL/6^{NZB} mice that underwent surgery presented more cellularity together with a reduced OARSI histopathology score, subchondral bone, menisci and synovitis score compared to those of BL/6^{C57} mice. This was accompanied with higher autophagy and a lower apoptosis in the cartilage of BL/6^{NZB} mice that were operated. Therefore, this study demonstrates the functional impact of nonpathological variants of mtDNA on OA process using

a surgically induced OA model. Conplastic (BL/6^{NZB}) mice develop less severe OA compared to the BL/6^{C57} original strain [88**]. These findings support that the replacement of mtDNA reduces joint damage during aging and in OA surgery animal model.

CONCLUSION

Mitochondria play an important role in some events involved in the pathogenesis of OA, such as energy production, the generation of reactive oxygen and nitrogen species, apoptosis, autophagy, senescence and inflammation. The regulation of these processes in the cartilage is at least partially, controlled by retrograde regulation from mitochondria and mitochondrial genetic variation. Retrograde regulation through mitochondrial haplogroups exerts a signaling control over the nuclear epigenome, which leads to the modulation of nuclear genes, cellular functions and development of OA. All these data suggest that OA could be considered a mitochondrial disease as well as other complex chronic disease as cancer, cardiovascular and neurologic disease.

KEY POINTS

- There are evidence that defective mitochondrial function is also a contributing element to OA.
- Different mtDNA haplogroups have been associated with radiographic prevalence, incidence, and progression of OA in various prospective cohorts world- wide.
- Data from cellular experiments, animal models and clinical studies suggest that carrying mtDNA *cluster* J/T might confer some level of protection against OA compared to carrying mtDNA haplogroup H.
- These findings demonstrate that mitochondria and mtDNA could be OA biomarkers and critical targets for potential novel therapeutic approaches to treat OA.

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Table 2 is a modification of a table originally published in Frontiers Genetics, volume 10 in January 2020 by I.R.P. and coworkers.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

* of special interest

** of outstanding interest

1. Yang X, Chen W, Zhao X, *et al.* Pyruvate kinase M2 modulates the glycolysis of chondrocyte and extracellular matrix in osteoarthritis. DNA Cell Biol 2018; 37:271–277.
2. Kraus VB, Blanco FJ, Englund M, *et al.* Call for standardized definitions of osteoarthritis and risk stratification for clinical trials and clinical use. Osteoarthritis Cartilage 2015; 23:1233 –1241.
3. Blanco FJ, Rego I, Ruiz-Romero C. The role of mitochondria in osteoarthritis. Nat Rev Rheumatol 2011; 7:161–169.
4. Liu H, Li Z, Cao Y, *et al.* Effect of chondrocyte mitochondrial dysfunction on cartilage degeneration: a possible pathway for osteoarthritis pathology at the subcellular level. Mol Med Rep 2019; 20:3308 –3316.

* This study investigated the role of mitochondrial dysfunction in OA pathology. Results described here suggested that mitochondrial dysfunction may aggravate cartilage degradation in the pathogenesis of OA

5. Lane RS, Fu Y, Matsuzaki S, *et al.* Mitochondrial respiration and redox coupling in articular chondrocytes. Arthritis Res Ther 2015; 17:54–68.

6. Blanco FJ, Valdes AM, Rego-Perez I. Mitochondrial DNA variation and the pathogenesis of osteoarthritis phenotypes. Nat Rev Rheumatol 2018; 14:327–340.
7. Terkeltaub R, Johnson K, Murphy A, Ghosh S. Invited review: the mitochondrion in osteoarthritis. Mitochondrion 2002; 1:301–319.
8. Burke PJ. Mitochondria, bioenergetics and apoptosis in cancer. Trends Cancer 2017; 3:857–870.
9. Zong WX, Rabinowitz JD, White E. Mitochondria and cncer. Mol Cell 2016; 61:667–676.
10. Wallace DC. Mitochondria and cancer. Nat Rev Cancer 2012; 12:685–698.
11. Villar P, Breton B, Garcia-Pavia P, *et al.* Cardiac dysfunction in mitochondrial disease. Clinical and molecular features. Circ J 2013; 77:2799 –2806.
12. Fernández-Caggiano M, Barallobre-Barreiro J, Rego-Pérez I, *et al.* Mitochondrial DNA haplogroup H as a risk factor for idiopathic dilated cardiomyopathy in Spanish population. Mitochondrion 2013; 13:263–268.
13. Vásquez-Trincado C, García-Carvajal I, Pennanen C, *et al.* Mitochondrial dynamics, mitophagy and cardiovascular disease. J Physiol 2016;594:509– 525.
14. Macdonald R, Barnes K, Hastings C, Mortiboys H. Mitochondrial abnormalities in Parkinson's disease and Alzheimer's disease: can mitochondria be targeted therapeutically? Biochem Soc Trans 2018; 46:891–909.
15. Subramaniam SR, Chesselet MF. Mitochondrial dysfunction and oxidative stress in Parkinson's disease. Prog Neurobiol 2013; 106–107:17– 32.
16. Swerdlow RH. Mitochondria and mitochondrial cascades in Alzheimer's disease. J Alzheimers Dis 2018; 62:1403 –1416.
17. Vaamonde-García C, López-Armada MJ. Role of mitochondrial dysfunction on rheumatic diseases. Biochem Pharmacol 2019; 165:181 –195.

** Review describing the connection between rheumatic and musculoskeletal diseases with mitochondria alteration. Paper shows a growing amount of evidence emphasizes

the role of mitochondria in aging and inflammatory-related diseases, including rheumatic disorders.

18. Blanco FJ, June RK 2nd. Cartilage metabolism, mitochondria, and osteoarthritis. J Am Acad Orthop Surg 2020; 28:e242–e244.
19. Maneiro E, Martin MA, de Andres MC, *et al.* Mitochondrial respiratory activity is altered in osteoarthritic human articular chondrocytes. Arthritis Rheum 2003; 48:700– 708.
20. Kim HA, Blanco FJ. Cell death and apoptosis in ostearthritic cartilage. Current Drug Targets 2007; 8:333–345.
21. Hwang HS, Kim HA. Chondrocyte apoptosis in the pathogenesis of osteoarthritis. Int J Mol Sci 2015; 16:26035–26054.
22. Vaamonde-Garcia C, Riveiro-Naveira RR, Valcarcel-Ares MN, *et al.* Mitochondrial dysfunction increases inflammatory responsiveness to cytokines in normal human chondrocytes. Arthritis Rheum 2012; 64:2927 –2936.
23. Cillero-Pastor B, Carames B, Lires-Dean M, *et al.* Mitochondrial dysfunction activates cyclooxygenase 2 expression in cultured normal human chondrocytes. Arthritis Rheum 2008; 58:2409–2419.
24. Cillero-Pastor B, Rego-Perez I, Oreiro N, *et al.* Mitochondrial respiratory chain dysfunction modulates metalloproteases -1,-3 and -13 in human normal chondrocytes in culture. Bmc Musculoskelet Disord 2013; 14:235–245.
25. Gavriilidis C, Miwa S, von Zglinicki T, *et al.* Mitochondrial dysfunction in osteoarthritis is associated with down-regulation of superoxide dismutase 2. Arthritis Rheum 2013; 65:378–387.

26. Ruiz-Romero C, Calamia V, Mateos J, *et al.* Mitochondrial dysregulation of osteoarthritic human articular chondrocytes analyzed by proteomics: a decrease in mitochondrial superoxide dismutase points to a redox imbalance. Mol Cell Proteomics 2009; 8:172–189.
27. Scott JL, Gabrielides C, Davidson RK, *et al.* Superoxide dismutase down-regulation in osteoarthritis progression and end-stage disease. Ann Rheum Dis 2010; 69:1502–1510.
28. Collins JA, Wood ST, Nelson KJ, *et al.* Oxidative stress promotes peroxiredoxin hyperoxidation and attenuates pro-survival signaling in aging chondrocytes. J Biol Chem 2016; 291:6641–6654.
29. Blanco FJ, Lopez-Armada MJ, Maneiro E. Mitochondrial dysfunction in osteoarthritis. Mitochondrion 2004; 4:715–728.
30. Henrotin Y, Kurz B. Antioxidant to treat osteoarthritis: dream or reality? Current Drug Targets 2007; 8:347–357.
31. Grishko VI, Ho R, Wilson GL, Pearsall AWI. Diminished mitochondrial DNA integrity and repair capacity in OA chondrocytes. Osteoarthritis Cartilage 2009; 17:107–113.
32. Lotz M, Loeser RF. Effects of aging on articular cartilage homeostasis. Bone 2012; 51:241–248.
33. Naik PP, Birbrair A, Bhutia SK. Mitophagy-driven metabolic switch reprograms stem cell fate. Cell Mol Life Sci 2019; 76:27–43.
34. Blanco FJ, Fernandez-Moreno M. Mitochondrial biogenesis: a potential therapeutic target for osteoarthritis. Osteoarthritis Cartilage 2020; 28:1003–1006.

** Paper analysis how mitochondrial biogenesis and mainly mitochondrial fusion and reduced mitophagy, contribute to the metabolic disorder and inflammation that occurs during OA.

35. Lopez de Figueroa P, Lotz MK, Blanco FJ, Carames B. Autophagy activation and protection from mitochondrial dysfunction in human chondrocytes. Arthritis Rheumatol 2015; 67:966–976.
36. Ansari MY, Khan NM, Ahmad I, Haqqi TM. Parkin clearance of dysfunctional mitochondria regulates ROS levels and increases survival of human chondrocytes. Osteoarthritis Cartilage 2018; 26:1087 –1097.
37. Wang Y, Zhao X, Lotz M, *et al.* Mitochondrial biogenesis is impaired in osteoarthritis chondrocytes but reversible via peroxisome proliferator-activated receptor gamma coactivator 1alpha. Arthritis Rheumatol 2015; 67:2141 –2153.
38. Smith RL, Soeters MR, Wust RCI, Houtkooper RH. Metabolic flexibility as an adaptation to energy resources and requirements in health and disease. Endocr Rev 2018; 39:489–517.
39. Mobasheri A, Rayman MP, Gualillo O, *et al.* The role of metabolism in the pathogenesis of osteoarthritis. Nat Rev Rheumatol 2017; 13:302–311.
40. Cillero-Pastor B, Eijkel G, Kiss A, *et al.* Time-of-flight secondary ion mass spectrometry-based molecular distribution distinguishing healthy and osteoarthritic human cartilage. Anal Chem 2012; 84:8909 –8916.
41. Castro-Perez JM, Kamphorst J, DeGroot J, *et al.* Comprehensive LC-MS E lipidomic analysis using a shotgun approach and its application to biomarker detection and identification in osteoarthritis patients. J Proteome Res 2010; 9:2377–2389.
42. Nazli SA, Loeser RF, Chubinskaya S, *et al.* High fat-diet and saturated fatty acid palmitate inhibits IGF-1 function in chondrocytes. Osteoarthritis Carti- lage 2017; 25:1516 –1521.
43. Dalmao-Fernandez A, Lund J, Hermida-Gomez T, *et al.* Impaired metabolic flexibility in the osteoarthritis process: a study on transmitochondrial cybrids. Cells 2020; 9:809–824.

* The aim of the study was to examine the differences in glucose and Fatty Acids (FA) metabolism, especially with regards to metabolic flexibility, in cybrids from healthy (N) or OA donors. N cybrids had higher metabolic flexibility than OA cybrids. Indicating that cybrids from OA patients had mitochondrial impairments and reduced metabolic flexibility compared to N cybrids.

44. Musumeci G, Loreto C, Carnazza ML, Martinez G. Characterization of apoptosis in articular cartilage derived from the knee joints of patients with osteoarthritis. Knee Surg Sports Traumatol Arthrosc 2011; 19:307–313.
45. Musumeci G, Castrogiovanni P, Trovato FM, *et al.* Biomarkers of chondrocyte apoptosis and autophagy in osteoarthritis. Int J Mol Sci 2015; 16:20560– 20575.
46. Lotz M, Carames B. Autophagy: a new therapeutic target in cartilage injury and osteoarthritis. J Am Acad Orthop Surg 2012; 20:261–262.
47. Carames B, Olmer M, Kiosses WB, Lotz MK. The relationship of autophagy defects to cartilage damage during joint aging in a mouse model. Arthritis Rheumatol 2015; 67:1568 –1576.
48. Vinatier C, Dominguez E, Guicheux J, Carames B. Role of the inflammation-autophagy-senescence integrative network in osteoarthritis. Front Physiol 2018; 9:706.
49. Fernandez-Moreno M, Tamayo M, Soto-Hermida A, *et al.* mtDNA haplogroup J modulates telomere length and nitric oxide production. BMC Musculoskelet Disord 2011; 12:283–290.
50. Fajardo RG, Fariña FO, Rey AM, *et al.* Relationship between the dynamics of telomere loss in peripheral blood leukocytes from knee osteoarthritis patients and mitochondrial DNA haplogroups. J Rheumatol 2021; 48:1603–1607.

** Authors stablish the conclusion that an increased rate of telomere loss in PBLs may reflect a systemic accelerated senescence phenotype that could be potentiated by the mitochondrial function, increasing the susceptibility of developing knee OA.

51. Zheng L, Zhang Z, Sheng P, Mobasheri A. The role of metabolism in chondrocyte dysfunction and the progression of osteoarthritis. Ageing Res Rev 2021; 66:101249.

* Switching from oxidative phosphorylation to glycolysis is implicated in metabolic alterations that involve mitochondrial dysfunction, enhanced anaerobic glycolysis, and altered lipid and amino acid metabolism.

52. Ruiz-Pesini E, Mishmar D, Brandon M, *et al.* Effects of purifying and adaptive selection on regional variation in human mtDNA. Science 2004; 303:223 –226.

53. Torroni A, Huoponen K, Francalacci P, *et al.* Classification of European mtDNAs from an analysis of three European populations. Genetics 1996; 144:1835–1850.

54. Gomez-Duran A, Pacheu-Grau D, Lopez-Gallardo E, *et al.* Unmasking the causes of multifactorial disorders: OXPHOS differences between mitochondrial haplogroups. Hum Mol Genet 2010; 19:3343 –3353.

55. Kenney MC, Chwa M, Atilano SR, *et al.* Inherited mitochondrial DNA variants can affect complement, inflammation and apoptosis pathways: insights into mitochondrial-nuclear interactions. Hum Mol Genet 2014; 23:3537 –3551.

56. Wei W, Gomez-Duran A, Hudson G, Chinnery PF. Background sequence characteristics influence the occurrence and severity of disease-causing mtDNA mutations. PLoS Genet 2017; 13:e1007126.

57. Blanco FJ, June RK 2nd. Cartilage metabolism, mitochondria, and osteoarthritis. J Am Acad Orthop Surg 2020; 28:e242–e244.

* In this article the authors described that there is great clinical promise in further understanding the relevance of mt haplogroups in OA. Better understanding of the cellular mechanisms by which mt haplogroups affect OA pathogenesis may yield patient-specific drug targets. Also described a recent in vitro studies found that chondrocytes respond to compression with changes in central metabolites, particularly within the TCA

cycle. It remains unknown whether specific mtDNA haplogroups can promote or constrain chondrocyte driven cartilage repair and associated OA susceptibility.

58. Kozakiewicz P, Grzybowska-Szatkowska L, Ciesielka M, Rzymowska J. The role of mitochondria in carcinogenesis. Int J Mol Sci 2021; 22:.
59. Rego-Pérez I, Dura´n-Sotuela A, Ramos-Louro P, Blanco FJ. Mitochondrial genetics and epigenetics in osteoarthritis. Front Genet 2019; 10:1335.
60. Rego-Perez I, Fernandez-Moreno M, Fernandez-Lopez C, *et al.* Mitochondrial DNA haplogroups: role in the prevalence and severity of knee osteoarthritis. Arthritis Rheum 2008; 58:2387 –2396.
61. Rego I, Fernández-Moreno M, Fernández-López C, *et al.* Role of European mitochondrial DNA haplogroups in the prevalence of hip osteoarthritis in Galicia, Northern Spain. Ann Rheum Dis 2010; 69:210–213.
62. Soto-Hermida A, Fernandez-Moreno M, Oreiro N, *et al.* Blanco FJ. mtDNA haplogroups and osteoarthritis in different geographic populations. Mitochondrion 2014; 15:18–23.
63. Fang H, Zhang F, Li F, *et al.* Mitochondrial DNA haplogroups modify the risk of osteoarthritis by altering mitochondrial function and intracellular mitochondrial signals. Biochim Biophys Acta 2016; 1862:829 –836.
64. Fang H, Liu X, Shen L, *et al.* Role of mtDNA haplogroups in the prevalence of knee osteoarthritis in a southern Chinese population. Int J Mol Sci 2014; 15:2646– 2659.
65. Koo BS, Song Y, Lee S, *et al.* Association of Asian mitochondrial DNA haplogroup B with new development of knee osteoarthritis in Koreans. Int J Rheum Dis 2019; 22:411–416.

* This paper shows assoiation between mtDNA haplogroup B and knee OA in Asiatic patients confirming the results reported in caucasian population and reinforcing the importance of mitochondria in OA

66. Hudson G, Panoutsopoulou K, Wilson I, *et al.* No evidence of an association between mitochondrial DNA variants and osteoarthritis in 7393 cases and 5122 controls. Ann Rheum Dis 2013; 72:136– 139.
67. Hannan MT, Felson DT, Pincus T. Analysis of the discordance between radiographic changes and knee pain in osteoarthritis of the knee. J Rheumatol 2000; 27:1513 – 1517.
68. Zeggini E, Panoutsopoulou K, Southam L, *et al.* Identification of new susceptibility loci for osteoarthritis (arcOGEN): a genome-wide association study. Lancet 2012; 380:815– 823.
69. Fernandez-Moreno M, Soto-Hermida A, Vazquez-Mosquera ME, *et al.* A replication study and meta-analysis of mitochondrial DNA variants in the radiographic progression of knee osteoarthritis. Rheumatology 2017; 56:263–270.
70. Fernandez-Moreno M, Soto-Hermida A, Vazquez-Mosquera ME, *et al.* Mitochondrial DNA haplogroups influence the risk of incident knee osteoarthritis in OAI and CHECK cohorts. A meta-analysis and functional study. Ann Rheum Dis 2017; 76:1114 –1122.
71. Shen JM, Feng L, Feng C. Role of mtDNA haplogroups in the prevalence of osteoarthritis in different geographic populations: a meta-analysis. PLoS One 2014; 9:e108896.
72. Soto-Hermida A, Fernandez-Moreno M, Oreiro N, *et al.* Mitochondrial DNA (mtDNA) haplogroups influence the progression of knee osteoarthritis. Data from the Osteoarthritis Initiative (OAI). PLoS One 2014; 9:e112735.
73. Soto-Hermida A, Fernandez-Moreno M, Pertega-Diaz S, *et al.* Mitochondrial DNA haplogroups modulate the radiographic progression of Spanish patients with osteoarthritis. Rheumatol Int 2015; 35:337–344.

74. Rego-Pérez I, Fernández-Moreno M, Deberg M, *et al.* Mitochondrial DNA haplogroups modulate the serum levels of biomarkers in patients with osteoarthritis. Ann Rheum Dis 2010; 69:910–917.
75. Rego-Perez I, Fernandez-Moreno M, Deberg M, *et al.* Mitochondrial DNA haplogroups and serum levels of proteolytic enzymes in patients with osteoarthritis. Ann Rheum Dis 2011; 70:646–652.
76. Fernandez-Moreno M, Soto-Hermida A, Oreiro N, *et al.* Mitochondrial haplogroups define two phenotypes of osteoarthritis. Front Physiol 2012; 3:129.
77. Rego-Pérez I, Blanco FJ, Roemer FW, *et al.* Mitochondrial DNA haplogroups associated with MRI-detected structural damage in early knee osteoarthritis. Osteoarthritis Cartilage 2018; 26:1562 –1569.
78. Quiró s PM, Mottis A, Auwerx J. Mitonuclear communication in homeostasis and stress. Nat Rev Mol Cell Biol 2016; 17:213–226.
79. Wallace DC. Genetics: Mitochondrial DNA in evolution and disease. Nature 2016; 535:498– 500.
80. Jazwinski SM. The retrograde response: when mitochondrial quality control is not enough. Biochim Biophys Acta 2013; 1833:400–409.
81. Horan MP, Cooper DN. The emergence of the mitochondrial genome as a partial regulator of nuclear function is providing new insights into the genetic mechanisms underlying age-related complex disease. Hum Genet 2014; 133:435 –458.
82. Matilainen O, Quirós PM, Auwerx J, *et al.* Crosstalk in homeostasis and stress. Trends Cell Biol 2017; 27:453–463.

83. Fernández-Tajes J, Soto-Hermida A, Vázquez-Mosquera ME, *et al.* Genome-wide DNA methylation analysis of articular chondrocytes reveals a cluster of osteoarthritic patients. Ann Rheum Dis 2014; 73:668–677.
84. Roach HI, Aigner T. DNA methylation in osteoarthritic chondrocytes: a new molecular target. Osteoarthritis Cartilage 2007; 15:128–137.
85. Rushton MD, Reynard LN, Barter MJ, *et al.* Characterization of the cartilage DNA methylome in knee and hip osteoarthritis. Arthritis Rheumatol 2014; 66:2450 –2460.
86. Cortés-Pereira E, Fernández-Tajes J, Fernández-Moreno M, *et al.* Differential association of mitochondrial DNA haplogroups J and H with the methylation status of articular cartilage: potential role in apoptosis and metabolic and developmental processes. Arthritis Rheumatol 2019; 71:1191 –1200.

* The objective of this article was analyzed the influence of mitochondrial genome variation on the DNA methylome of articular cartilage. The authors stablished as conclusion that Mitochondrial DNA variation differentially associates with the methylation status of articular cartilage by acting on key mechanisms involved in osteoarthritis, such as apoptosis and metabolic and developmental processes.

87. Latorre-Pellicer A, Moreno-Loshuertos R, Lechuga-Vieco AV, *et al.* Mitochondrial and nuclear DNA matching shapes metabolism and healthy ageing. Nature 2016; 535:561 –565.
88. Scotece M, Rego-Pérez I, Lechuga-Vieco AV, *et al.* Mitochondrial DNA impact on joint damaged process in a conplastic mouse model after being surgically induced with osteoarthritis. Sci Rep 2021; 11:9112 –9124.

** The study demonstrates the functional impact of nonpathological variants of mtDNA on OA process. Conplastic (BL/6(NZB) mice develop less severe OA compared to original strain. These findings suggeswt that mitochondria and mtDNA could be critical targets for potential novel therapeutic approaches to treat osteoarthritis.

Table 1. Abnormal mitochondrial processes with deleterious effects on cartilage biology and chondrocyte function

Mitochondrial dysfunction contributes to cartilage degradation via several processes	References
Increased apoptosis	[21,44,45]
Decreased autophagy	[35,46,47]
Enhanced inflammatory response	[48]
Telomere shortening and increased senescence chondrocytes	[49,50**]
Decreased mitochondrial biogenesis and mitophagy	[36,37]
Increased cartilage catabolism	[39,51*]
Increased mitochondrial fusion leading to further ROS production	[36]
Impaired metabolic flexibility	[38,39,43*]

ROS, reactive oxygen species.

Table 2. Published associations of mtDNA variants with specific radiographic OA-related features

Study cohort	Population	Haplogroup	OR (95% CI) *P*-value/ effect on the biomarker	Reference
OA prevalence				
Spanish	457 OA cases, 262 controls	J	OR=0.460 (0.282–0.748) *P*=0.002	[60]
		JT	OR=0.564 (0.384–0.828) *P*=0.005	
Spanish	550 OA cases, 505 controls	J	OR=0.519 (0.271–0.994) *P*=0.048	[61]
UK	453 OA cases, 280 controls	T	OR=0.574 (0.350–0.939) *P*=0.027	[62]
UK	7846 OA cases, 5402 controls	J	OR=1.190 (0.720–1.950) ns[b]	[66]
Meta-analysis	2557 OA cases, 1339 controls	J	OR=0.570 (0.460–0.710) *P*<0.0001	[71]
	2478 OA cases, 1173 controls	JT	OR=0.700 (0.580–0.840) *P*=0.0002	
Chinese	187 OA cases, 420 controls	G	OR=3.834 (1.139–12.908) *P*=0.003	[64]
		B	OR=0.503 (0.283–0.893) *P*=0.019	
OA progression				
OAI	891 knee OA cases	T	HR=0.499 (0.261–0.819) *P*<0.05	[72]
Spanish	281 knee OA cases	JT[a]	HR=0.584 (0.354–0.964) *P*=0.036	[73]
CHECK	431 knee OA cases	T	HR=0.645 (0.419–0.978) *P*<0.05	[69]
		JT	HR=0.707 (0.501–0.965) *P*<0.05	
Meta-analysis	1603 knee OA cases	T	HR=0.612 (0.454–0.824) *P*=0.001	[69]
		JT	HR=0.765 (0.624–0.938) *P*=0.009	
OA incidence				
OAI	2579 subjects	J	HR=0.680 (0.470–0.968) *P*<0.05	[70]
CHECK	635 subjects	J	HR=0.728 (0.469–0.998) *P*<0.05	[70]
Meta-analysis	3214 subjects	J	HR=0.702 (0.541–0.912) *P*=0.008	[70]
Korean	438 subjects	B	RR=2.389 (1.315–4.342) *P*=0.004	[65*]

CHECK, Cohort Hip and Cohort Knee; HR, hazard ratio; mtDNA, mitochondrial DNA; ns, nonsignificant; OA, osteoarthritis; OAI, Osteoarthritis Initiative; OR, odds ratio; RR, risk ratio; UK, United Kingdom.

[a]When compared with mtDNA cluster KU.

[b]Diagnosis of symptomatic OA.