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Research Article

Mitochondrial DNA Mutations and its Role in the Genesis of Renal Diseases an Update

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Abstract

The errors in the Mitochondrial DNA affects tissues that require highly dependent of energy to work properly like the Brain, the Heart, the Muscle and the Kidneys, the defects in the genesis of ATP affects this tissues sometimes involving more than one organ, therefore myophaties, encephalophaties, can be associated with renal diseaseswich rare in adults and more frequently in children in whom arefrequently unsuspected and underestimated. Their prevavalence in the general population is also underestimated and may be as high as 1-2:10,000 live births.

Keywords: Mitochondrial DNA mutations; Genesis of renal diseases

Introduction

The Mitochondrial DNA is localized in the cytosol within the mitochondrias; it was completed sequenced in 1981 [1]. Mitochondria are diveded in 4 principal components: the External Mitochondrial Membrane (EMM), the Internal Mitochondrial Membrane (IMM), the Intermediate Mitochondiral Space (IMS) and the matrix localized in the inside (organele cytoplasm) [2]. The mitochondrial DNA is circular and constituted by two bands, one heavy and one light (Figure 1), contains about 16 569 nucleotides that codify for 37 genes, the must important codify 22 transference RNA, 2 Ribosomal RNA andmiust important 13 polipetides that are part of multiple subunits of enzymatic complexes that area involved in the Respiratory Chain, among them 7 subunits are codify for Complex I, 1 sub-unit for Complex III, 3 subunits for complex IV and 2 subunits for Complex V all of them participate in the Oxidative Phosphorilation and in Tricarboxilic acid cycle: Krebs cycle [3] figure 2.As Mithocondrial DNA is more expose to damage secondary to the oxigen radicals produced during the oxidative phosphorylations and because its mechanism for protection are more rudimentary and less effective than those pertinent to de nuclear DNA, the possiblility of mithochondrial mutationsis increased and it results in several troublesome diseses that involves mainly those organs with high energy requirements. In this paper, we focus on the known Mitochondrial DNA mutation that can be the origen of renal diseases.

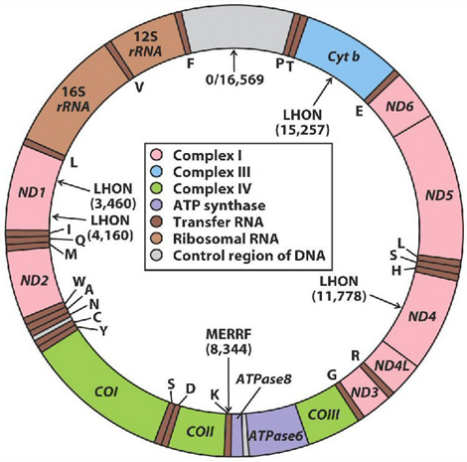

Figure 1: Mitochondrial DNA, showing its circular structure, constituted by two strands the outer a heavy and the inner a light strand, shows regions encoding for cytochrome b (Cyt B) and various subunits ofNADH-coenzyme Q reductase (ND), cytochrome c oxidase (COX), ATPasa, and ribosomal RNAs (rRNA) indicated.

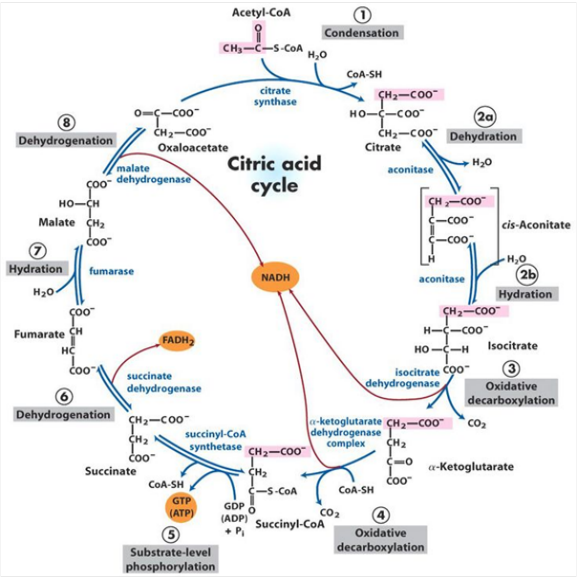

Figure 2: Krebbs cycle or tricarboxylic acid cycle.

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Human DNA was initially identified at the end of the 1860s by the swiss Chemistry Friederich-Miescher [4] and later two outstanding scientists, the rusian biochemistry PhiebusLevene and Erwin Chargaff conducted a series of reserch that revealed aditional details of the DNA molecule, Levene was the first to describe the order of the three components of a simple nucleotide (fosfate, sugar and base) and also was the first one to discover that the sugar in RNA was Ribosa and in DNA was Desoxiribosa [5], later the studies of Linus Pauling and Maurice Wilkins contributed but the later researcher due to a personal dispute with Professor Rosalind Franklin and without her permission in 1953 took the photography of the DNA molecule taken with X-Ray diffraction by her, and gave them to Watson, the photography of the DNA showed with clarity the helicoidal structure of the molecule, wich allowed Watson and Crick to deduce the structure of DNA in 1954 [6] without the help of theX-Ray diffraction photographies it would have been very difficult for Watson and Crick to have attained their discovery [6]. DNA has been totally sequenced recently by Vanter y cols [7] it is localized in the nucleous and orginized in structures denominated chromosoms; there are 46 chromosoms organized in 23 pairs, 22 of them are called autosoms and one pair are de sexual chromosoms: XX in the case of females and XY in the case of males [8] this is in reallity the real Human DNA (HDNA) wich contains our complete genetic code and contains 3.3 billions of bases pairs, the letters that encode the message for the sinthesis of specific proteins and, codifies aproximately 100,000 genes [9].

About 1,500 millions of years ago a pro-eukarioteamitochondrial cell [10] engulfed an anaerobic alfa-proto-bacteria member of the sub-division of Rickettsias, a group of intracellular bacteria probably an Archezoaprimitiva, this interaction resulted in a symbiotic relation for both; the remanents of this bacterial endosymbiosis are known as the Mitochondrion, they are of monophylicorigen [10] and appeared both in aerobic and in anaerobic bacterias [11]. In the eukariotic organisms the Mithochondrion evolve into different organels like the mitochondrias, the hidrogenosoms and the mitososms [12] that diverge among them in a very important ways, because one of the outstandig function of the mitochondria is the ATP synthesis dependent on the oxidative phosphorylation that has not been observed in the rest of the organeles derived from the mitochondrion. Therefore the hidrogenosoms uptakes ADP from the sourounding medium and excrete equimolar quantities of ATP. ATP synthesis in this organels is done by the phosphorylation at the sustrate level through the catalytic convertion of Succinil-Coenzyme A to Succinate by the enzyme succinate-thiokinase [13]. In the mitosoms ATP is synthetized trough the phosphorilation at the sustrate level but inside the cytosol without a direct involvement of the mitososms [14], because of these differences it can be concluded that the energetic metabolism is not the unifying fact among the mitochondria and the rest of organeles derived from the mitochondrion. Theseorganeles do share among them ATP dependant chaperon molecules (Cpn60) and/or mitochondrial heat shock proteins like mtSP70, as well as ATP/ADP transporters, but what it seems to be in reality the unifying line among them are the iron sulphataded proteins (FES). This FES [15] have important function in the electron transference during the enzymatic catalysis and in the metabolic regulation, moreover this proteins have an universal distribution in proeukariote and eukariote organisms and the current evidences suggest that these proteins have a central role for the establisment and maintenance of the original mitochondrial endosymbiosis. Among these proteins one that is highligth is nominated Rli-1 [16] with universal distribution in eukariote organisms an in the organeles derived from the mitochondrion and it is involve in the maturation of both the ribosomal RNA and transference RNA and therefore it is of outsanding importance.

The nuclear DNA controls the transcription activity of the mitochondrial DNA trough regulator proteins like the Mitochondrial Transcriptional Factor (MTFA) dependant of nuclear DNA. It is clear that the mitochondria is a so complex organele that it requires more than 37 genetic products for its function; in fact 850 polipetides codify by hDNA are required for its function, aproximately 75 are structural components of the respiratory complex and at least another 20 are required to maintain their structure and function. Mitochondria are diveded in 4 principal components: the External Mitochondrial Membrane (EMM), the Internal Mitochondrail Membrane (IMM), the Intermediate Mitochondiral Space (IMS) and the matrix localized in the inside (organelecytoplasm) [2].

The five complexes of the respiratory chain/system OXPHOS are: complex I (NADH ubiquinonaoxireductase), complex II (Succinate-ubquinonaoxireductase), complex III (Ubiquinol-cytochrome c oxidoreductase), complex IV (cytochrome c oxidase) and complex V (ATP sinthase) are localized in the IMM, there are also two electron transporters: the ubicuinona localized in the IMM and the cytochrome C in the EMM [17]. Beside that the Mitochondrial DNA works subjet under a double genetic control (nuclear and mitocondrial) there are another unique four findings for the behaivor of this organele that are important to know and comprehend to understand the mitochondrial functions.

Instead of the nuclear DNA where there exists only one pair of chromosoms in each cell, there are thousands copies of mitochonrial DNA and aproximately 5 copies per mitochondia. The división of the mitochondria and the replication of mitochondrial DNA take place independently of the cell cycle. After the cell división the mitochondrias and its DNAm are randomely distributed among the daughter´s cells (mitotic segregation).

The number of organels among the different cells is variable and depends primarily on the energetic requirements of that linage cells; that is why the fibroblasts contain a few hundreds of mitochondrias while the neurons can contain thousands and the cardiomiocytes ten thousands of mtochondrias, this shows that mitochondrias do not follow a genetic mendelian pattern but in fact they obey laws according with the genetic-energetic requirements of the specific cell lineage [18]. The mitochondrial DNA is inherited to the human offspring exclusively by the maternal line [19] due to the fact that the Father´s mitochondrias are present in the flagelous of the spermatozoids and once the spermatozoid penetrates the ovule it loses its flagelous and with it their mitochondrias (Figure 3). This fact allows establishing with great precisión the genetic line to whom we belong for hundreds or thousands of generations prior to us and by this way give us information about or must remotorigens. In the mayority of cases, the mitochondrial DNA copies are identical among each other condition called homoplasmia. During the celular division, the mitochondrias are inherited randomly to the daughter cells (19).

The Kidney is a highly vascularized organ because it recives 25% of the cardiac output per minute, aproximately 125 ml/min wich equals to a volume of filtered blood of 180 liters per day. Taking into account that the adult bloodvolume is about 6 liters, it filters that amount about 30 times a day. With this high flow you can understand

that the kidney filtrates a great variety of substances, some toxic to the body but others not that require to be recovered from the urine by different mechanisms; an example is the sodium, we know that its normal serum concentration is around 140 mmol/l, so during a day an amount of 25 200 mmol/day are filtered, but the kidney reabsorbs 99% in their different segments and primaraly in the proximal tubule and excrete less tan 1%, lets say if the kidney reabsorbs 99.4% (24,948 mmol of sodium) the losses will equal 0.6% or 151.2 mmol, that amount excreted is called the Fractional Excretion of S'odium (FENA), if FENA is greater than 1 %(252 mmol) it would indicate acute renal failure. To acomplish the reabsortion of this valuable filtered elements the kidney counts with different methods for reabsortion among them; there is the paracellular transport that takes place in the adyacent portions of the cells in the tight junctions; and there is also the tanscellular transport, altough some of these mechanisms involve a facilitated transport trough a concentration gradient and an advantageous pH gradient, the mayority requires an active trasporter with ATP consumption, for these reasons the epithelium of the renal tubules in its luminal side include a great number of mitochondrias to provide the required energy (Figure 4). Therefore the reduction or dysfunction of this organeles produces severe hydro-electrolytic alterations.

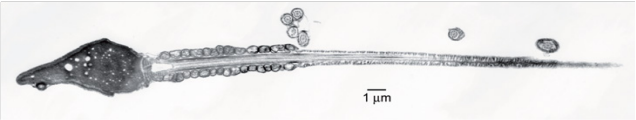

Figure 3: Human spermatozoid seen by electronic microscopy aprox. 45µm of longines showing its mitochondrias in the flagelus [20].

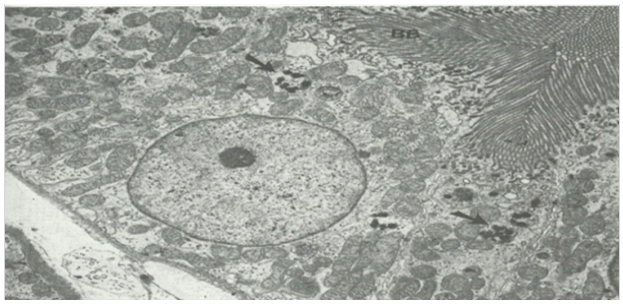

Figure 4: Electronic micrography of the renal proximal tubule where the brush border shows an elevated number of mitochondrias in this ephitelium magnification x 7,800 from the book "Diseases of the Kidney and Urinary tract" Robert W. Schrier, ed. 7th, ed. Lippincott Williams and Wilkins, 2001.

Mutations on mitochondrial DNA with neruromuscular clinical presentation are well known and recognized among them is the MELAS syndrome with mitochondrial encephalopathy, lactic acidosis and cerebrovascular stroke; the MERRF síndrome with myoclonic epilepsy with red twisted fibers; the medula and pancreas Pearson syndrome and the Kearn-Sayre syndrome, the Leber hereditary optic neuritis and the Leber plus syndrome in wich there is also degeneration of the basal ganglia and dystonia with a variety of parkinsonism that do respond with Levodopa treatment. The Leigh syndrome is a mortal neurodegenerative disease with subcortical brain lesions [21]. Renal diseases can ocurrer in these four syndromes, they show up as nephrotic syndrome and, patients with a puntualmutation in m3243A>G manifiest as Fanconi syndrome in the mitochondrial Pearson and Kearns-Sayre syndromes.

The presence of multisystemic diseases in childhood should suggest the exitance of mitochondrial defects especially if they are associated with metabolic acidosis and renal tubular defects. One has to recall that the renal tubulo-intersticial disease with poliuria and hyposthenuria are a very common manifestation of mitochondrial diseases affecting the proximal renal tubule. More than a hundread of mitochondrial diseases inherited with mendelian character have beeen reported, many of them are associated with nephropaties [22].

Clinical expression of mitochondrial renal cytophaties:

1. Tubulophaties: In the renal proximal tubule is where thake place more than the 90% of reabsortion of the necessary elements for the body that are filtrated trough the glomeruli and this activity requires must of the time to spend energy (ATP) what explains the elevated number of mitochondrias at this level.

Proximal Tubulophaties:

a. Toni Debré Fanconi syndome: With glucosuria, aminoaciduria, phosphaturia proteinuria, uricosuria and kaluresis.
b. Proximal Tubular Acidosis: With Bicarbonaturia and hypercalciuria.
c. Tubulointersticialnephrophaty: With hypostenuria, poliuria, hypernatriuresis and nicturia
d. Bartter syndrome: With metabolic alcalosis, hypokalemia, hiperreninemia, and hyperaldosteronism without arterial hypertension.

2. Glomerulophaties: Nephrotic syndrome with Focal Semental Sclerosis resistant to corticosteroids therapy.

3. End Stage Renal disease, with elvation of serum creatinine over 1.3 mg/dl, BUN elevation, hyperphospahemia, hypocalcemia, hyperkalemia, and anemia, hyponatremia of variable degree, hyperparathyroidsm and anemia.

The vast mayority of patients with renal findings have extra-renal symptoms like muscular findings as myophaties, muscle pain, myclonus; and also show ocular findings like diplopía, palpebral ptosis, restrictions of ocular movments, pigmentary retinophaty, also course with several neurological findings like psicomotor delay development, seizures, neurosensorial deafness, optic atrophy, myclonus, pheriphericneurophaty, dementia and also show cerebro-vascular events and cardiac findings as blokage of different degrees, disrritmias, hypertrohic concentric cardiomiopathy. Also the endocrine glands may be involved showing as diabetes mellitus, hypoparathyroidsm and growth hormone deficiency [23].

The pediatricians and pediatric pephrologist have to be aware of these class of diseases, new discovered of seven defects in the biosynthesis of coenzyme Q10 in three of these COQ2, PDSS2 and COQ6 have an association with a prominent renal phenotype and show up as a corticosteroid resistant nephrotic syndrome with variable association with multisystemic findings as neurosensorial deafness, epilepsy, ataxia and syndromes alike cerebro vascular events. Many progress to End Stage Renal Diseases and require renal replacement function procedures like dyalisis either Hemo or peritoneal or Kidney transplantation, nevertheless as it has been pointed out by several researchers that the presymptomatic therapy with Coenzima Q10 in high dosages

can prevent the progression of the renal disease and save of the neurological symptoms [24].

To establish the diagnosis of mitochondrial mutations it is very helpfull the familiar background, in the particular patient the presence of multisystemic disease afecting other organs highly aerobics: brain, liver, muscle, the presence of metabolic acidosis with elevation of lactate and piruvate help to establish the diagnosis but these alterations are not always present. In the kidney the presence of corticoresistant nephrotic syndrome, Fanconi syndrome, poliuria with incapacity to concentrate the urine and the presence of túbulo-intersticial findings in the renal biopsy and or focal segmental sclerosis and the finding in the ephitelium of the renal proximal tubule evuidence of mitochondrial dismorphogenesis or its presence in the muscle biopsy help to establish the diagnosis. Up to date more than a 100 mitochondrial diseases heredited in a mendelian way are known, those who affect primarialy the kidney appear on table 1 [25].

Treatment

Unfortunaly currently there are not specific therapy for the mitochondrialscitopathies, in general the therapy is palliative and symptomatic, although there are starting to emerge new options to limit de damage and the progression of these diseases as well new general mesurements to prevent their exhacerbation. In a not far future we will see a change because it has been started the use of proteins and trasporters of biological active molecules to stimulate at the mitochondrial level the synthesis of antioxidants and blockers of mitochondrial apoptosis programs [26].

The Therapy consists of the following mesurament.

General Mesuraments

To prevent disturbances in the oxidative phosphorilation and prevent by this way mitochondrial citopathiesexhacerbations and the aperance of acute liver failure, these include:

a. Prevention: Prevent the use of commonly use medication that interfiere with the respiratory chain and can cause acute liver failure like valproic acid and barbiturates, prevent the use of comon antibiotics that can alter mitochondrial protein synthesis like tetracyclines and cloranfenicol; also prevent the use of biguanaides and steroids.

b. Infections and extenuated excercise should be avoid because they can excacerbate the lactic acidosis that has to be treated with a low infusión of sodium bicarbonate and good hydration.

c. Suplementation: In cases of Complex III deficiency it can improve with Vitamin K3 suplements (40-60 mg/day) and Coenzyme Q10(80-300mg/day) both show that is early use besides improving the neurological symptoms can have a beneficial effect in the prognostic of renal function. Proton aceptors, Carnitine and Vitamin C are partially effective though there effects are minimal. Use of Citrate solution, potasium, phosphorous, Vitamin-D and fluids may be required for patients with renal tubulophaties with poliuria, renal tubular-acidosis and Fanconi syndrome that produce those deficiencies [27].

d. Dislipidemia when severe has to be controled because high blood concentrations of free fatty acids can enter the cell and the mitocondriastraspassing their internal membrane incresing their concentrations in this compartament and due to the absence of AcylCoAsyntethasa for large chain free fatty acids they can not be directed to the β oxidative pathway which results in and increased Lipid Perioxidation with lipotoxicity and damage to the mitochondrias, here the treatment besides diet with reduction in the content of mono and polyinsaturated fats has to include PPARγ agonists using any of them in the appropiate dosages [28].

e. Antioxidantes: Like omega-3 plolyinsaturated fats, the N-acetilcisteine and alopurinol.

f. Thiazolinedions: Is a PPARγ useful in patients with adquiredmitocondrial dysfunction due to its anti-inflamatories properties and other inmunological effects known currently, they inhibit the production of Tumor necrosis factor alfa, as well as the Nuclear Factor kappa Beta, they also inhibit the attraction and migration of macrophges through the inhibition of macrophge Migration Protein-1 (MP-1), with all thes effects they reduce inflamation and fibrosis and at the renal level they stimulate the Nephrin gene expression a protein crucial in the renal filter that prevents proteinuria and consequentely the progression of renal disease [29].

g. Sirtruins and Resveratrol:A new strategy that has demostrated to prolong life span in all the animal species is the caloric restriction [30] but is a complicated task to get to the target and can produce proteins and vitamins deficiencies; on the other hand the Sirtruins family in particular Sirtruin-1 act as desacetylation enzymes of

Molecular defects	Gen(es)	Renal Afection	Other Clinical Findings
Maintainace of	RRM2B, DGUPK, TK2	Proximal Tubulopathy	s. of Mitochondrial DNA depletion
Mitochondrial DNA	SUCLA2, MPV17	3 principal phenotypes: hepato-cerebralmyopathic andencéfalomyopathic	
TranslationMitochondrial(aminoacylation)	SARS2	Tubulointerstiscial salt looser disease and with Hypomagnesemia	Pulmonary hypertension
Mitochondrial Ribosomas	MRPS22	Tubulopathy	HypertrophicCardiomiopathy and Encephalopathy
TranslationMitochondrial (elongation)	TFSM	Tubulopathy	Intrauterine growth delay, hepatic failure and Hipotonicity
Assembly of Complex I	NDUFAF2	Renal Tubular Acidosis	Leigh Syndrome
Assembley of Complex III	BCSIL	Proximal TubulophatyEncephalopahtyand Hepatic failure	
Assambley of Complex IV	COX10, SURF 1	Renal Tubulopathy and distal tubular Acidosis(SURF 1)	Leigh Syndrome
Assambley of Complex V	TMEM70	Proximal Tubulopathy	HypertrophicCardiomiopathy
Co-Enzyme Q10	PDSS2, COQ2,COQ6, COQ9	RSNS, Tubulopathy	Seizures, Ataxia, neurosensorialdeafeness, multisystemic disease

Table 1: Molecular Mechanisms responsable of the appearence of Mitochondrial Renal Diseases codify in the celular nucleus [22].

Histones and other proteins regulators of the DNA transcription including HIF-2α COX2, PGC-α, Smad3, Smad7, the tumural-supressor p53, FOXO3, FOXO4, NK-κβ and induce Nitric Oxide Synthesis (NOS), all of them are related with the biogénesis and the mitochondrial function, besides they reduce the oxidative stress, fibrosis and apoptosis [31]. The resveratrol founded in the red grapes and strawberries, cranberries, blueberries, raspberries and red wines (wich is an inductor of Sirtruin-1) improves the mitochondrial function and the lipid concentrations, keep and mantain the PGC-1α, protecting at the renl level the integrity of the podocytes and therefore the renal filter. Other new Sirtruin-1 agonist have been described like the mononuclide precursor of NAD+ or the riboside that incresase metabolism [32].

Genetic Therapy

a. Genetic therpy focus to the mitocondrial DNA is directed to correct genetic defects by directly remplazing the affected gene or for the reparation of a point mutation are still in a very early satge but they are a promissory research avenue.

b. MicroRNAs (miRNAs) are small endogens RNAs non-codify but that can interfere with the translation or stability of specific translations that regulte the expression or repression of some genes [33], they have been localized in the mitocondria and for that reason are known as MitomiRs [34].

Conclusion

A great advance has taken place in recent years in the knowladge of mitochondrial citopathies, the mayority are due to nuclear DNA mutations and a minority to mitochondrial DNA mutations, is well known that these diseases affect organs with high energy demands like the brain, the heart, the muscleskeletic, the kidneyand the endocrine system, altough must of them have multisystemic and catastrophic symptoms and start early in the first year of life other are not so severe and the early diagnosis and therapy can improve their clinical conditions and prevent the progression of the damage in the affected organs, moreover in the future the genic therapy and the epigenomic medicine using different deacetylation and metylation enzymes and using MitomiRs offer new hope for their therapy.

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