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 myopathies, encephalopathies, can be associated with renal diseases which rare in adults and more frequently in children in whom are frequently unsuspected and underestimated. Their prevalence in the general population is also underestimated and may be as high as 1-2,000 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 divided in 4 principal components: the External Mitochondrial Membrane (EMM), the Internal Mitochondrial Membrane (IMM), the Intermediate Mitochondrial Space (IMS) and the matrix localized in the inside (organelle 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 most important codify 22 transference RNA, 2 Ribosomal RNA and 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 Mitochondrial DNA is more expose to damage secondary to the oxygen 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 possibility of mitochondrial mutation is increased and it results in several troublesome diseases 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.

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Human DNA was initially identified at the end of the 1860s by the Swiss chemist Friedrich Miescher [4] and later two outstanding scientists, the Russian biochemist Pliebus-Levene and Erwin Chargaff conducted a series of research that revealed additional details of the DNA molecule. Levene was the first to describe the order of the three components of a simple nucleotide (folate, sugar, and base) and also was the first one to discover that the sugar in RNA was Ribose and in DNA was Desoxiribose [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, which allowed Watson and Crick to deduce the structure of DNA in 1954 [6] without the help of the X-Ray diffraction photography it would have been very difficult for Watson and Crick to have attained their discovery [6]. DNA has been totally sequenced recently by Vant-ery colts [7] it is localized in the nucleus and organized in structures denominated chromosomes; there are 46 chromosomes organized in 23 pairs, 22 of them are called autosomes and one pair are sex chromosomes: XX in the case of females and XY in the case of males [8] this is in reality the human DNA (hDNA) which contains our complete genetic code and contains 3.3 billion of bases pairs, the letters that encode the message for the synthesis of specific proteins and, codifies approximately 100,000 genes [9].

About 1,500 millions of years ago a pro-eukarioteamitochondri-al 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 remnants of this bacterial endosymbiosis are known as the Mitochondrion, they are of monophilycocirigen [10] and appeared both in aerobic and in anaerobic bacteria [11]. In the eukariotic organisms the Mitochondrion evolve into different organelles like the mitochondrias, the hydrogenosomes and the mitosomas [12] that diverge among them in a very important ways, because one of the outstanding function of the mitochondria is the ATP synthesis dependent on the oxidative phosphorylation that has not been observed in the rest of the organelles derived from the mitochondrion. Therefore the hydrogenosomes uptakes ADP from the surrounding medium and excrete equimolar quantities of ATP. ATP synthesis in this organel is done by the phosphorylation at the sustrate level through the catalytic conversion of Succinil-Coenzyme A to Succinate by the enzyme succinate-thiolokinase [13]. In the mitosomas ATP is synthetized trough the phosphorylation at the sustrate level but inside the cytosol without a direct involvement of the mitosomas [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 organelles derived from the mitochondrion. Therefore the hydrogenosomes uptake ADP from the surrounding medium and excrete equimolar quantities of ATP. ATP synthesis in this organel is done by the phosphorylation at the sustrate level through the catalytic conversion of Succinil-Coenzyme A to Succinate by the enzyme succinate-thiolokinase [13]. In the mitosomas ATP is synthetized trough the phosphorylation at the sustrate level but inside the cytosol without a direct involvement of the mitosomas [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 organelles derived from the mitochondrion. Theseorganeles do share among them ATP dependant chauffon molecules (Cpm60) 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 sulphataed 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 establishment and maintenance of the original mitochondrial endosymbiosis. Among these proteins one that is highlight is nominated Rli-1 [16] with universal distribution in eukariote organisms an in the organelles derived from the mitochondrion and it is involve in the maturating of both the ribosomal DNA and transference RNA and therefore it is of outstanding 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 organelle that it requires more than 37 genetic products for its function; in fact 850 polipetides codify by hDNA are required for its function, approximately 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 Mitochondrial Membrane (IMM), the Intermediate Mitochondrial Space (IMS) and the matrix localized in the inside (organelectoplasm) [2].

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

Instead of the nuclear DNA where there exists only one pair of chromosomes in each cell, there are thousands copies of mitochondrial DNA and approximately 5 copies per mitochondria. The division of the mitochondria and the replication of mitochondrial DNA take place independently of the cell cycle. After the cell division the mitochondrias and its DNAm are randomly 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 lineage cells; that is why the fibroblasts contain a few hundreds of mitochondrias while the neurons can contain thousands and the cardiomiocytes tens thousands of mitochondrias, 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 lineages [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 precision the genetic line to whom we belong for hundreds of thousands of generations prior to us and by this way give us information about our original hominid ancestors. In the majority of cases, the mitochondrial DNA copies are identical among each other condition called homoplasia. During the cellular division, the mitochondrias are inherited randomly to the daughter cells (19).

The Kidney is a highly vascularized organ because it recieves 25% of the cardiac output per minute, approximately 125 ml/min which 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 primarily in the proximal tubule and excrete less than 1%, lets say if the kidney reabsorb 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 Sodium (FENa), if FENA is greater than 1% (252 mmol) it would indicate acute renal failure. To accomplish the reabsorption of this valuable filtered elements the kidney counts with different methods for reabsorp- tion among them; there is the paracellular transport that takes place in the adjacent portions of the cells in the tight junctions; and there is also the transcellular transport, although some of these mechanisms involve a facilitated transport though a concentration gradient and an advantageous pH gradient, the majority requires an active transpor- ter 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 organelles produces severe hydro-electrolytic alterations.

Mutations on mitochondrial DNA with neuromuscular clinical presentation are well known and recognized among them is the ME- LAS syndrome with mitochondrial encephalopathy, lactic acidosis and cerebrovascular stroke; the MERRF syndrome with myoclonic epilepsy with red twisted fibers; the medula and pancreas Pearson syndrome and the Kearns-Sayre syndrome, the Leber hereditary optic neuritis and the Leber plus syndrome in which 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 fatal neurodegenerative disease with subcortical brain lesions [21]. Renal diseases can occur in these four syndromes, they show up as nephrotic syndrome and, patients with a puntualmutation in m3243A>G manifest as Fanconi syndrome in the mitochondrial Pearson and Kearns-Sayre syndromes.

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

Clinical expression of mitochondrial renal cystopathies:

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

2. Glomerulopathies: 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, hyperphosphahemia, hypocalcemia, hyperkalemia, and anemia, hyponatremia of variable degree, hyperparathyroidism and anemia.

The vast majority of patients with renal findings have extra-renal symptoms like muscular findings as myopathies, muscle pain, my- clonus; and also show ocular findings like diplopia, palpebral ptosis, restrictions of ocular movements, pigmentary retinophaty, also course with several neurological findings like psicomotor delay development, seizures, sensomotoral deafness, optic atrophy, myclonus, pheriph- ericneurophyt, dementia and also show cerebrovascular findings and cardiac findings as blockage of different degrees, disritmias, hypertrophic concentric cardiomyopathy. Also the endocrine glands may be involved showing as diabetes mellitus, hypoparathyroidism and growth hormone deficiency [23].

The pediatricians and pediatric nephrologist have to be aware of these class of diseases, new discovered of seven defects in the biosynthesis of coenzymes Q10 in three of these COQ2, PDQS2 and COQ6 have an association with a prominent renal phenotype and show up as a corticosteroid resistant nephritic syndrome with variable association with multisystemic findings as neurosensorial deafness, epilepsy, ataxia and syndromes alike cerebrovascular events. Many progress to End Stage Renal Diseases and require renal replacement function procedures like dialysis 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 helpful the familiar background, in the particular patient the presence of multisystemic disease affecting 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 corticoresistent nephrotic syndrome, Fanconi syndrome, poliuria with incapacity to concentrate the urine and the presence of tubulo-intersticial findings in the renal biopsy and or focal segmental sclerosis and the finding in the epitheliun of the renal proximal tubules evidence of mitochondrial dismorphogenesis or its presence in the muscle biopsy help to establish the diagnosis. Up to date more than a 100 mitochondrial diseases hereditary in a mendelian way are known, those who affect primarily the kidney appear on table 1 [25].

**Treatment**

Unfortunately currently there are not specific therapy for the mitochondrialcitoatopathies, 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 exahercation. 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 phoshorilation and prevent by this way mitochondrial citopathiesexhacerbations and the aparence of acute liver failure, these include:

a. Prevention: Prevent the use of common use medication that interfere with the respiratory chain and can cause acute liver failure like valproic acid and barbiturates, prevent the use of comon antibitics that can alter mitochondrial protein synthesis like tetrycyclines and cloranfenicol; also prevent the use of biguanides and steroids.

b. Infections and extemated exercise should be avoid because they can excacerbate the lactic acidosis that has to be treated with a low infusion 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 improiving the neurological symptons can have a beneficia effect in the prognostic of renal function. Proton acceptors, Carnitine and Vitamin C are partially effective though there effects are minimal. Use of Citrate solution, potassium, phosphorous, Vitamin-D and fluids may be required for patients with renal tubulopathies 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 mitochondrialtransportassembling their internal membrane increasing their concentrations in this compartment and due to the absence of AcylCoAasnythethasa for large chain free fatty acids they can not be directed to the β oxidative pathway which results in and increased Lipid Peroxidation 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 appropriate dosages [28].

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

f. Thiazolinediones: Is a PPARγ useful in patients with acquired mitochondrial dysfunction due to its anti-inflammatory properties and other immunological 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 macrophages through the inhibition of macrophge Migration Protein-1 (MP-1), with all theses effects they reduce inflammation and fibrosis and at the renal level they stimulate the Nephrin gene expression a protein crucial in the renal filter that prevents proteinuria and consequently the progression of renal disease [29].

g. Sirtruins and Resveratrol:A new strategy that has demonstrated 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 Sirtruns family in particular Sirtrun-1 act as desacetylation enzymes of

<table>
<thead>
<tr>
<th>Molecular defects</th>
<th>Gen(es)</th>
<th>Renal Afection</th>
<th>Other Clinical Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Maintainace of</td>
<td>RRM2B, DGUPK, TK2</td>
<td>Proximal Tubulopathy</td>
<td>s. of Mitochondrial DNA depletion</td>
</tr>
<tr>
<td>DNA</td>
<td>SUCLA2, MPV17</td>
<td>3 principal phenotypes: hepato-cerebral,nephropathy andencephalomyopathic</td>
<td>Pulmonary hypertension</td>
</tr>
<tr>
<td>Translation</td>
<td>SARS2</td>
<td>Tubulo-intersticial salt lesser disease and with Hypomagnesemia</td>
<td></td>
</tr>
<tr>
<td>Mitochondrial</td>
<td>MRPS22</td>
<td>Tubulopathy</td>
<td>HypertrophicCardiomyopathy and Encephalopathy</td>
</tr>
<tr>
<td>Ribosomes</td>
<td>TF5M</td>
<td>Tubulopathy</td>
<td>Intrauterine growth delay, hepatic failure and Hipotonicity</td>
</tr>
<tr>
<td>Assembly of Complex</td>
<td>NDUFAF2</td>
<td>Renal Tubular Acidosis</td>
<td>Leih Syndrome</td>
</tr>
<tr>
<td>Assembly of Complex</td>
<td>BCSIL</td>
<td>Proximal Tubulopathy,Encephalopathy and Hapetic failure</td>
<td>Leih Syndrome</td>
</tr>
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<td>Assembly of Complex</td>
<td>COX10, SURF 1</td>
<td>Renal Tubulopathy and distal tubular Acidosis(SURF 1)</td>
<td>HipertrophicCardiomyopathy</td>
</tr>
<tr>
<td>Assembly of Complex</td>
<td>TEMEM70</td>
<td>Proximal Tubulopathy</td>
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<tr>
<td>Co-Enzyme Q10</td>
<td>PDSS2, COQ2, COQ6, COQ9</td>
<td>RSNS, Tubulopathy</td>
<td>Seizures, Ataxia, neurosensorial deafness, multisystemic disease</td>
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**Table 1:** Molecular Mechanisms responsible of the appearance of Mitochondrial Renal Diseases codify in the cellular nucleus [22].

Histones and other proteins regulators of the DNA transcription including HIF-2α, COX2, PGC-α, Smad3, Smad7, the tumoral-suppressor p53, FOXO3, FOXO4, Nkx3.1 and induce Nitric Oxide Synthesis (NOS), all of them are related with the biogenesis and the mitochondrial function, besides they reduce the oxidative stress, fibrosis and apoptosis [31]. The reseveratrol founded in the red grapes and strawberries, cranberries, blueberries, raspberries and red wines (wich is an inductor of Sirtrin-1) improves the mitochondrial function and the lipid concentrations, keep and maintain the PGC-1α, protecting at the renal level the integrity of the podocytes and therefore the renal filter. Other new Sirtruin-1 agonist have been described like the mononucleotide precursor of NAD+ or the riboside that increase metabolism [32].

Genetic Therapy

- Genetic therapy focus to the mitochondrial DNA is directed to correct genetic defects by directly remapping 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.
- 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 mitocandria 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 majority 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 muscle, the kidney and the endocrine system, although most 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 genetic therapy and the epigenomic medicine using different deacetylation and metylation enzymes and using MitomiRs offer new hope for their therapy.

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