Targeting Mitochondria in Kidney Diseases

Subjects: Biochemistry & Molecular Biology

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Kidney function highly depends on mitochondria, organelles that regulate different metabolic pathways. Mitochondria-altered function and structure are present during acute kidney injury (AKI) and chronic kidney disease (CKD).

mitochondrial alterations kidney diseases mitochondria targeting therapy

1. Introduction

Kidneys are among the most energy-demanding organs due to their filtration and reabsorption functions. In particular, the proximal tubular segment of the nephron consumes large amounts of energy in the form of adenosine triphosphate (ATP) provided by oxidative phosphorylation, a metabolic process performed in the mitochondria [1].

In addition to their energy-producing function, mitochondria also exert other metabolic processes such as glutaminolysis, the catabolism of branched-chain amino acids, fatty acid beta-oxidation, nucleotide biosynthesis, heme metabolism, redox balance, the management of metabolic by-products, cellular death regulation, calcium homeostasis, etc. [2][3].

Acute kidney injury (AKI) is characterized by an abrupt reduction in kidney function due to pre-renal, renal, and post-renal causes such as the reduction of blood supply, nephrotoxins, and obstruction, respectively [4]. On the other hand, chronic kidney disease (CKD) is characterized by the progressive and irreversible loss of kidney function and structure for more than three months and may be a consequence of other conditions such as diabetes, hypertension, or aging [5].

AKI and CKD are related to each other since the presence of one could predispose the development of the other [6][7][8]. In addition to their complicated pathophysiology, several mitochondrial alterations have been reported in both pathologies, contributing to their progression.

In different experimental AKI models, mitochondrial morphological alterations are prevalent in tubular segments, showing fragmentation, swelling, and the loss of cristae; moreover, functionality is also compromised, with reduced electron transport chain (ETC) activity, a loss of membrane potential, and increased reactive oxygen species (ROS) production as a consequence [9][10][11][12][13][14][15]. Interestingly, these alterations also persist during AKI to CKD progression [16][17][18]. Similarly, in established CKD, mitochondrial alterations are present, showing low

membrane potential and consequently reduced ETC activity and overproduction of ROS [19][20][21]; on the other hand, morphological alterations such as mitochondrial fragmentation have been noticed, especially in podocytes [21][22][23][24].

ROS overproduction is present in AKI and CKD, representing a therapeutic target since their abrogation reduces tissue damage and improves kidney function [25][26][27][28][29][30][31][32][33][34]. ROS are well-known inducers of the inflammatory response through the activation of the transcription factor nuclear factor kappa B (NF-kB) [35]; moreover, mitochondria-derived ROS are activators of the NLR family pyrin domain containing 3 (NLRP3) inflammasome/interleukin (IL)-1β axis [36][37], which has been reported to promote kidney injury [38]. The specific blocking of mitochondria-derived ROS also reduces kidney damage and improves kidney function [15][23].

Hence, specific mitochondrial targeting in order to block excessive ROS production and restore some mitochondrial functions could be a suitable complementary therapeutic strategy for kidney diseases.

Mitochondria targeting strategies include the use of small molecules, peptides, nanocarriers, and mitochondrial transplantation (**Figure 1**).

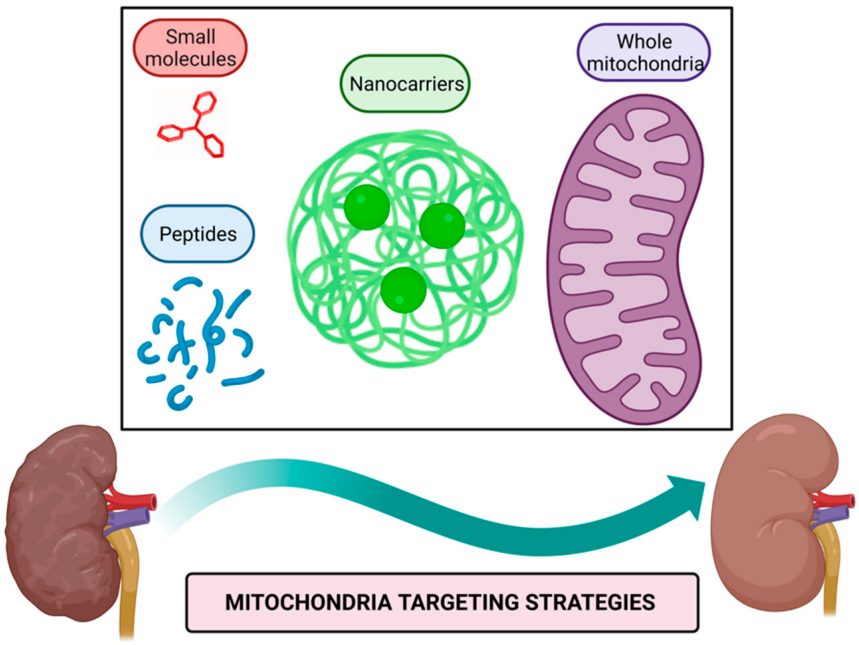

Figure 1. Mitochondria targeting strategies. Small molecules, peptides, nanocarriers, and whole mitochondria transplantation represent therapeutic strategies targeted to mitochondria to alleviate their dysfunction in kidney diseases. Figure created with BioRender.com.

Mitochondria targeting compounds include lipophilic cationic small molecules and peptides that can be used alone or conjugated with other bioactive molecules [39][40]; additionally, nanocarriers of drugs harboring signals that direct them to mitochondria or even whole mitochondria transferred to target tissue could be used to alleviate mitochondrial dysfunction [41][42].

2. Mitochondria Targeting Peptides

Peptides as therapeutics have emerged recently and show several advantages over other molecules, such as their chemical synthesis, selectivity, and minimal side effects. These could be used alone or conjugated with another bioactive compound [43][44].

Nowadays, the peptide peginesatide, an antagonist of the erythropoietin receptor, is used to treat CKD-associated anemia in humans [45]. Hence, other experimental approaches focused on mitochondria have been explored; for example, using a peptide to block the interaction of nucleophosmin with Bcl-2-associated X protein (Bax) inhibits apoptotic cell death; thus, resulting in decreased renal damage caused by ischemia [46] and suggesting that mitochondria targeting peptides could also be a potential therapy for kidney diseases.

Therapeutic peptides are classified as cell-targeting peptides (CTP) if they are directed specifically to a receptor or as cell-penetrating peptides (CPP) if they pass the plasma membrane to reach the cytoplasm [43][44]. Mitochondria targeting peptides require CPP characteristics to enter cells, and to reach mitochondria requires CTP characteristics harboring a mitochondria targeting sequence (MTS) or possessing cationic charges.

2.1. MTS-Containing Peptides

Mitochondrial proteome mainly is constituted by nuclear-encoded proteins that once synthesized possess an MTS to reach mitochondria through the recognition by the mitochondrial TOM complex eliciting the integration to mitochondrial membranes. The conserved pattern residues on MTS are φχχφφ, where φ represents an aromatic or hydrophobic residue, whereas χ represents any kind of residue, for example, the pattern LSRLL; additionally, MTS acquires an alpha-helix conformation that facilitates the insertion to the mitochondrial outer membrane. Once inside, MTS is degraded by mitochondrial processing proteinases (MPP) [3][47][48]. Considering those mentioned above, synthetic MTS-containing peptides have been developed and used as carriers of other compounds to facilitate their delivery into mitochondria to exert biological functions. The construct of a CPP with an MTS improves cellular and mitochondrial uptake [49], as has been demonstrated in vitro with peptides conjugated with DNase, human metallothionein 1A (hMT1A), and manganese-porphyrin [50][51][52]. Moreover, the cell-penetrating artificial mitochondria targeting peptide (CAMP)-hMT1A conjugate has been tested in a Parkinson's disease model in rats and demonstrated to restore tyrosine hydroxylase levels in striatum and substantia nigra resulting in improved motor coordination when it is administrated intracerebrally [51]; similarly, using a recombinant MTS-containing mitochondrial transcription factor A (TFAM) IV injected in mice also improves motor coordination, although it could be by the increase in complex I of the ETC [53]. MTS-containing TFAM has also been proven in a septic shock model, increasing animal survival and, in healthy mice, increasing the brain and muscle complex I level of the ETC [53][54].

Although for kidney diseases, there are no reports of the use of MTS-containing peptides, the conjugation of these with antioxidant molecules such as the mentioned metallothionein and manganese–porphyrin could have promising results, since both molecules have been reported to reduce renal damage in aristocholic acid-induced CKD and

I/R-induced AKI, respectively [55][56]. Moreover, recombinant MTS-containing TFAM could also help maintain mitochondrial DNA and increase complex I levels in kidney tubular epithelial cells.

One advantage of MTS-containing peptides over other molecules that target mitochondria is that cationic charges are expendable to enter mitochondria; hence, their insertion mechanism is independent of mitochondrial membrane potential.

2.2. Cationic Mitochondrial Penetrating Peptides

Positive charges and alpha-helix structures are basal characteristics of these peptides, and they differ from each other due to other structural features.

CAPH peptides possess the ability to enter the cell through endocytosis and reach mitochondria due to enriched proline residues in their structures, such as P11LRR and P14LRR peptides [57][58]; moreover, the addition of a dimethyl tyrosine (Dmt) residue to P11LRR structure exert antioxidant functions demonstrated in vitro [57][58].

As mentioned above, oxidative stress is a hallmark of kidney diseases, in which mitochondria are the primary sources of ROS [59]. Ergo, the use CAPH-Dmt has excellent potential to explore in AKI and CKD models.

The plant derivate roseltide rT1 is a cationic cysteine-rich peptide recognized by the TOM complex in an MTS-independent way; interestingly, roseltide rT1 by itself can bind ATP synthase and enhance ATP production in different cell lines [60]. During AKI and CKD, ATP production is compromised, as demonstrated in experimental models [11][16][17][18][26][31][61][62], and for this reason, roseltide rT1 by itself without conjugation with another bioactive compound could be helpful in the treatment of kidney disease.

Hexapeptides with delocalized lipophilic cations contain the modified residue cyclohexyl alanine in their structure to bring hydrophobicity and facilitate cellular uptake; positive charge residues such as lysine and arginine also are incorporated. In addition to these characteristics, cationic moieties of pyridyl salts in alanine residues bring mitochondrial selectivity [63]. Although these peptides are not proven in any disease model, it seems to have great potential as a drug delivery system to mitochondria. As described above, non-peptidic cationic molecules are a comprehensive system to target mitochondria due to the charge affinity.

Peptoids resemble backbone peptide structures but are resistant to proteolysis due to structural modifications, in which side chains are attached to the nitrogen atom instead of the alpha carbon [64]. These peptoids also require the lipophilic, cationic, and alpha-helix structure characteristics to enter the cell and mitochondria [65]. Although peptoids conjugated with any kind of drugs are not assessed in any disease models in animals, they represent a vast field to explore in kidney diseases, in which the conjugation with molecules that require more stability, such as transcription factors, bioactive lipids, or proteins involved in mitochondrial dynamics.

SS peptides are aromatic and cationic tetrapeptides able to enter mitochondria and, if they possess a tyrosine or Dmt residue in their structure, also function as antioxidants themselves. SS-01 and SS-20 that lack tyrosine or Dmt

residues can enter mitochondria but lack antioxidant activity, whereas SS-02 and SS-31, which possess any of those two residues, enter mitochondria and are potent antioxidants.

Among SS peptides, SS-31 (also known as MTP-131, Bendavia, and elamipretide) has gained great attention for the potent antioxidant activity and safety demonstrated in experimental models; in fact, SS-31 has been proved in clinical trials for human mitochondrial myopathies, Barth syndrome, cardiovascular diseases, and renal arterial stenosis [66][67][68][69][70].

In AKI, SS-31 IP administration reduces structural and functional damage induced by cisplatin in mice; moreover, it decreases oxidative damage and NLPR3-derived IL-1β synthesis [71]. Similarly, in I/R-induced AKI in rats, SS-31 subcutaneous administration reaches a high concentration in kidneys and reduces epithelial and endothelial damage; at the subcellular level, it avoids mitochondrial swelling, maintains cristae structure by its binding with cardiolipin, and recover ATP levels [72][73][74]. SS-31 peptide has been modified with CPP characteristics or encapsulated in nanopolyplexes to increase its cellular uptake and mitochondrial accumulation, thus resulting in enhanced antioxidant capacity demonstrated in vitro [75][76]. Moreover, the efficiency of SS-31 encapsulated in nanopolyplexes has been demonstrated in lipopolysaccharide (LPS)-induced AKI model in mice, showing better results than SS-31 alone [76]. Although cisplatin, I/R, and LPS-induced AKI SS-31 have demonstrated promising results, for other models such as aristocholic acid (AA) and adriamycin-induced AKI, there are controversial results [77] that could be explained by the specific physiopathology induced by these compounds or even by their chemical interaction with SS-31. It is known that AKI predisposes to CKD development; as has been reported in CKD development induced I/R, in which the treatment with SS-31 for six weeks and started four weeks after ischemic injury reduces the structural damage of kidneys, fibrotic damage, and mitochondrial swelling; surprisingly, this protective effect persists even nine months after I/R induction [78].

On the other hand, during diabetic nephropathy, the IP or subcutaneous administration of SS-31for at least four weeks of SS-31 does not affect glycemic levels; however, it improves kidney function, preserves podocyte structure, diminishes inflammatory and fibrotic markers, and reduces oxidative stress [79][80][81][82][83][84].

SS-02 and SS-20 peptides in conjugation with deferoxamine have also been demonstrated to possess mitochondrial antioxidant properties in vitro [85], suggesting their potential use.

A summary of proven and not proven mitochondria targeting peptides in kidney disease models is shown in **Figure 2**.

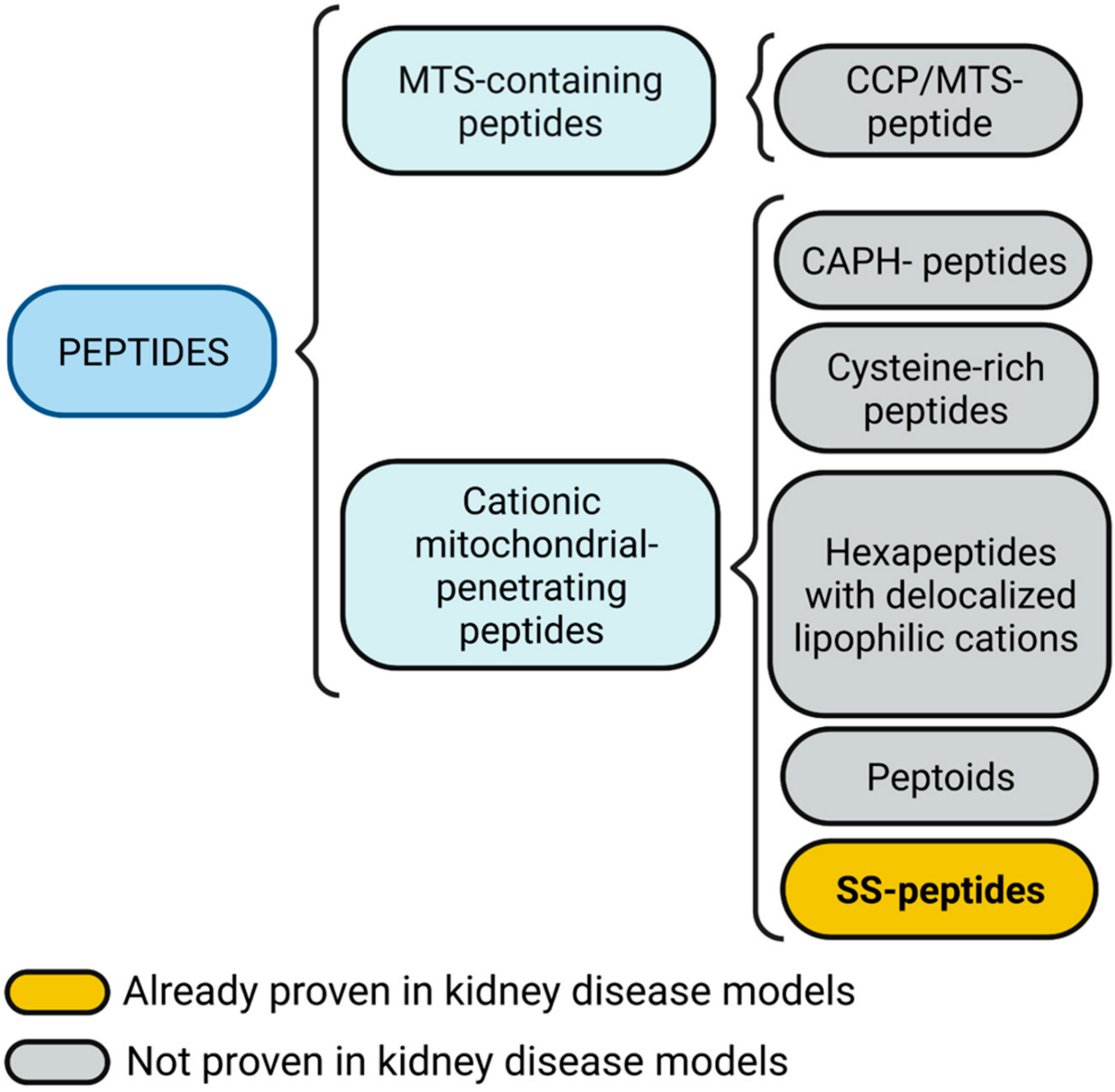

Figure 2. Mitochondria targeting peptides. Mitochondria targeting sequence (MTS)-containing peptides also could include a cell-penetrating peptide (CPP) feature. Cationic mitochondrial penetrating peptides could be subdivided into cationic amphiphilic polyproline helix (CAPH) peptides, cysteine-rich peptides, and hexapeptides with delocalized lipophilic cations, peptoids, and Szeto-Schiller (SS) peptides. Figure created with BioRender.com.

3. Mitochondrial Replacement

Mitochondrial replacement, also known as mitochondrial transplantation, is a novel experimental therapeutic strategy to transfer healthy mitochondria to the target tissue to recover mitochondrial function (**Figure 3**). This strategy has already been used in pediatric patients after cardiogenic shock, in which mitochondria isolated from their muscles are directly injected into the myocardium, demonstrating that patients with mitochondrial transplantation do not suffer short adverse effects and show fewer cardiovascular events several months after the intervention [86][87].

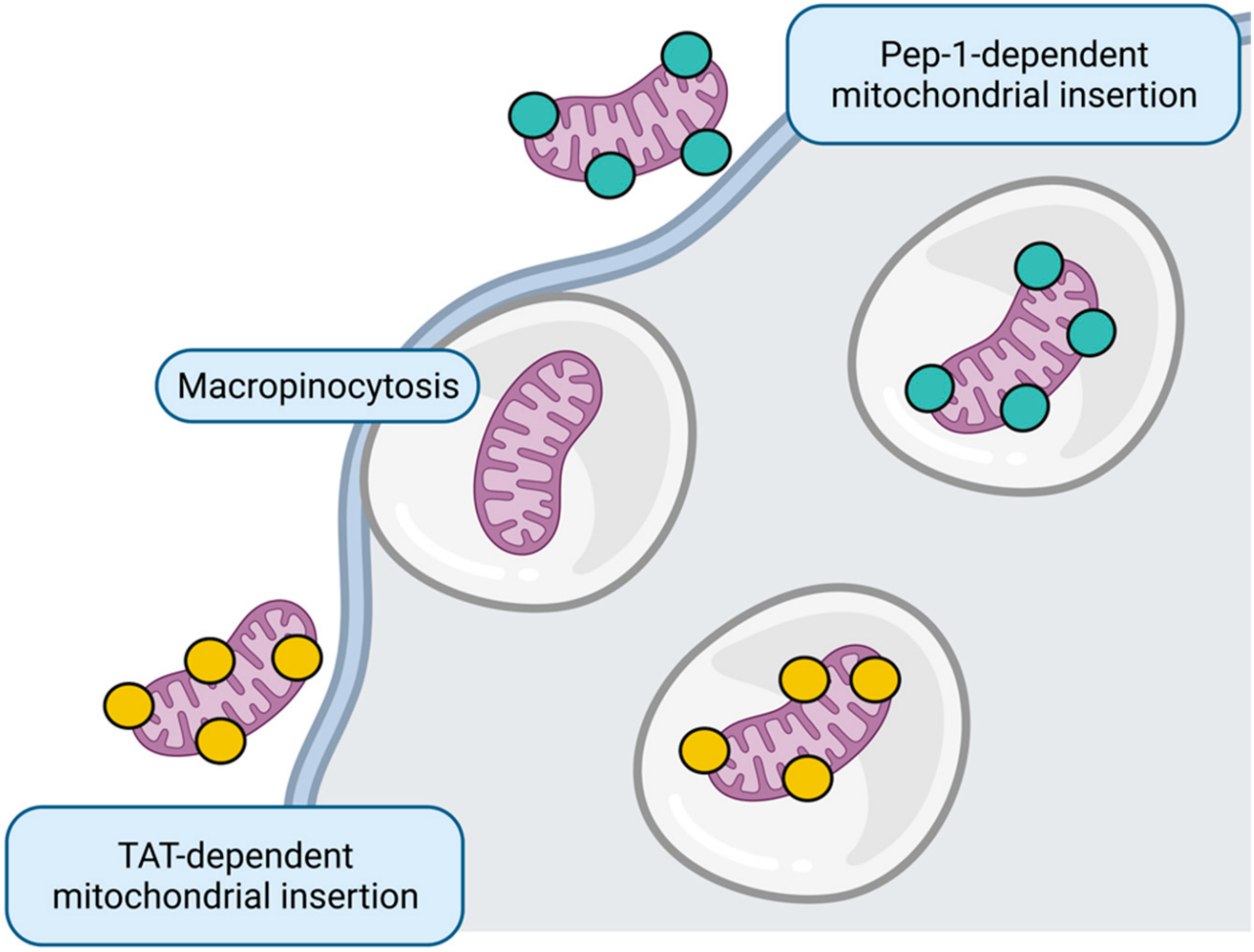

Figure 3. Mitochondrial replacement. Whole healthy mitochondria insertion to target cell could occur through micropinocytosis or directed through Pep-1 and transactivator of transcription (TAT) peptides. Figure created with BioRender.com.

Only AKI models have explored the effect of mitochondrial replacement. In the doxorubicin-induced AKI model, the transplantation of mesenchymal stem cell (MSC)-derived mitochondria to the renal subcapsular region results in improved kidney function and increased antioxidant enzyme levels; however, although tubular regeneration was increased, tubular dilation persists [88]. Similarly, in I/R-induced AKI in rats and pigs, the intra-arterial administration of muscle-derived mitochondria improves renal function in the first 24 to 48 h [89][90] and even promotes proliferation of renal cells [89] and reduces inflammation [90]. However, for CKD, mitochondrial replacement remains unexplored.

Although the primary mechanism described for internalization of transferred mitochondria to the tissue is micropinocytosis [91], some strategies that improve the uptake in vitro include mitochondria harboring CPP, such as Pep-1 [92][93][94] and transactivators of transcription (TAT) peptides [95].

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