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Original Article

Mitochondria-Targeted Nanosystems: A New Strategy for the Treatment of Acute Kidney Injury

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Abstract:
Acute kidney injury (AKI) is a clinical syndrome of sudden or prolonged abrupt decline or loss of renal function with a high mortality rate.There are several common causes of AKI, such as diabetic nephropathy, renal ischaemia-reperfusion and haemolysis. The treatment of AKI with nanomedicines is an active area of research, with the advantages of good bioavailability and the ability to reduce the pharmacological toxicity of their drugs to other organs. Current studies have shown that mitochondria play an important role in the occurrence and development of AKI, and these mechanisms include the maintenance of structural and functional stability, and the mitochondrial quality control mechanism is in homeostasis. Therefore, the study of mitochondria-targeted functional nanosystems is a hot topic in current research. This review summarises the specific targets of mitochondria-targeted nanosystems constructed by researchers in the past 5 years in the treatment of acute kidney injury, and describes their major breakthroughs in the field of mitochondria targeting.

Keywords: Mitochondria-targeted, nanosystems, AKI

1. Introduction

The application of mitochondria-targeted nanosystems in the treatment of kidney diseases is a cutting-edge research area. As an important centre of energy metabolism within the cell, the stability of mitochondria structure and function is critical for cellular health. In renal diseases, especially AKI, mitochondrial dysfunction leads to inadequate energy supply and exacerbates cellular damage. Therefore, maintaining the stability of mitochondria and regulating their function have become key therapeutic strategies. Many studies have developed a variety of mitochondria-targeted nanosystems, which can efficiently deliver drugs or other therapeutic molecules directly to mitochondria to enhance therapeutic effects. These nanosystems achieve precise targeting of mitochondria through specific mitochondria-targeting ligands or drugs that specifically target mitochondria. This review focuses on the significant role of mitochondria-targeted nanosystems in protecting against acute kidney injury, in addition to describing the

specific mechanisms by how mitochondria-targeted nanosystems specifically target mitochondria.

2. Mitochondria-targeted Nanosystems for the Treatment of Acute Kidney Injury

As semi-autonomous organelles in the cell, mitochondria are responsible for many important functions, such as signalling, biosynthesis, regulation of oxidative stress, and energy metabolism. At this stage, the use of mitochondria as a target for the treatment of renal diseases mainly focuses on mitochondrial structure, function, and mitochondrial quality control. The structure of mitochondria refers to the membrane of mitochondria and the proteins on the membrane i.e. mitochondrial membrane permeability transition pore. Mitochondrial function, including energy metabolism, is regulated by Reactive Oxygen Species, (ROS) levels. Within the basic mitochondrial structure and function, the mitochondria's semi-autonomous nature allows it to be independently controlled, which is the mitochondrial quality control mechanism which includes kinetic homeostasis, mitochondrial autophagy, and mitochondrial biosynthesis. This subsection specifically summarises the numerous regulatory mechanisms of current mitochondria-targeted nanosystems and addresses their specific role in the treatment of acute kidney injury.

2.1 Structure of Mitochondria

Stable mitochondrial structure is the basis for maintaining the stability of other mitochondrial functions. In acute kidney injury, damage to the mitochondrial structure can lead to the inability of normal function, which in turn leads to more serious injury. Therefore, mitochondrial structural stability is the most important target of current research. In this regard, Zhao[1] proposed a mitochondria-targeted antioxidant Mito-2,2,6,6-tetramethylpiperidinyl-N-yloxy (TEMPO) (MT) self-assembled with aspartic acid-containing KLD (KLDD) to form a crosslinked nanofibrous hydrogel, and this nano-system reduced renal mitochondrial ROS (mtROS) production by decreasing the kidney injury molecule-1 (Kim-1) expression, pro-inflammatory factor expression levels were reduced to improve the structure of mitochondria, as well as its short half-life and significant in vivo side effects.

2.1.1 Inner and Outer Membrane of Mitochondria

The structure of mitochondria mainly refers to the inner and outer membranes of mitochondria, the integrity of which is the key to maintaining the structural stability of mitochondria. During AKI, the mitochondrial membrane in renal tubular epithelial cells is damaged by oxidative stress and the phospholipids on the membrane are destroyed, thus failing to maintain mitochondrial integrity.

Recent studies have identified SS-31 as a mitochondrial cardiolipin protector that specifically binds to cardiolipin in the inner mitochondrial membrane, protecting the mitochondrial structure and reducing apoptosis and oxidative stress[Error! Reference source not found.2]. To further improve the biodistribution efficacy and delivery efficiency of this nanosystem, Liu[4] designed pH-responsive renal-targeted nanopolysomes (NPs) to efficiently deliver SS-31. Both in vivo and ex vivo studies showed that that NPs exhibited higher antioxidant and anti-apoptotic effects compared to free SS-31 and their therapeutic effects were significantly better.

2.1.2 Mitochondrial Permeability Transition Pore

In addition to the membrane, mitochondrial proteins are also essential for controlling material transport and signalling. The mitochondrial membrane permeability transition pore (MPTP) is a nonspecific channel located between the inner and outer mitochondrial membranes, and its opening is closely related to the maintenance of a balance between mitochondrial function and cell

survival, with the degree of opening reflecting the dynamic changes in mitochondrial function[Error! Reference source not found.].The short-term and reversible opening protects cells from oxidative damage and allows Ca2+ ions to flow out of the mitochondrial matrix and cell signalling[57] .However, in AKI, MPTP can have a prolonged and irreversible opening that will lead to mitochondrial swelling, which in turn causes rupture of the outer mitochondrial membrane and release of substances such as cytochrome C, triggering apoptosis and necrosis[58.]

The molecular structure and composition of MPTP are not yet fully defined, but it is known to involve a variety of proteins, including adenine nucleotide translocase (ANT), voltage-dependent anion channel (VDAC), cyclophilin D (Cyp D), phosphate carrier (PiC), and the Bcl-2 family of proteins[9]. These molecules may be involved in either the structural composition or functional regulation of MPTP. During AKI, the integrity of the mitochondrial membrane is impaired and the abnormal opening of the MPTP is a key pathological process, especially in ischaemia-reperfusion injury (IRI), which is a major cause of AKI[8]Fig1 .

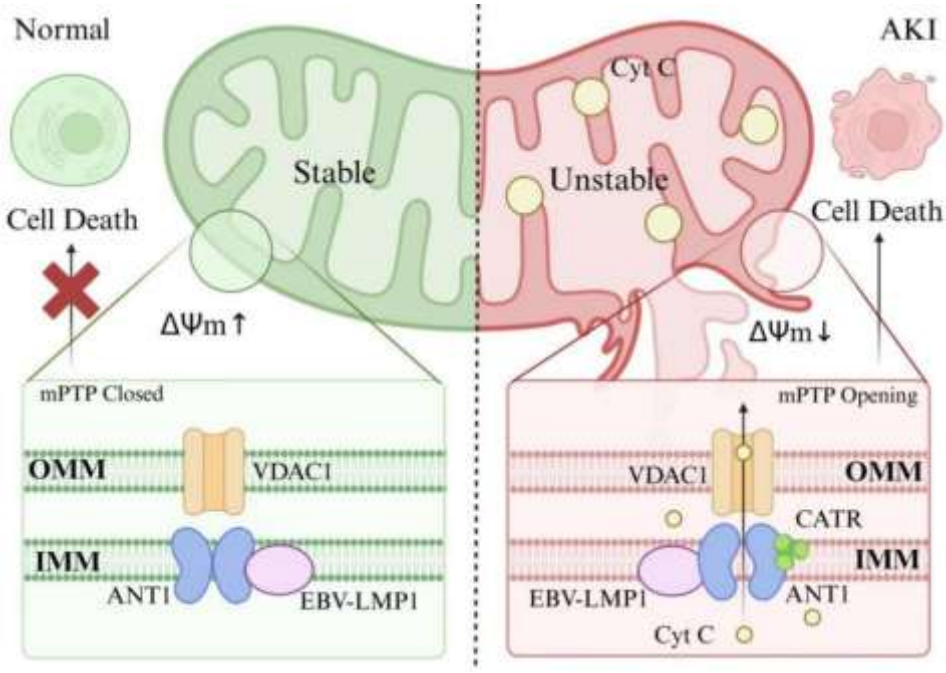

Fig1 The changes of MTPT in normal conditions and during AKI

Previous studies have shown that IR-induced AKI will result in major structural alterations in mitochondria, but that administration of drugs via bone marrow mononuclear fine (BMMC) restores the damage.Clara Rodrigues-Ferreira[10] specifically investigated the molecular mechanism in which is related to the opening of MPTP. By Ca2+ green fluorescence assay, it was found that IR inhibits the rapid accumulation of Ca2+ and induces the opening of the cyclosporin A-sensitive permeability transition pore (PTP), whereas BMMC induces the formation of a complex between ANT and VDAC, which facilitates the release of Ca2+, inhibits the opening of the PTP and thus prevents this change.

2.2 Functions of Mitochondria

The basic mitochondrial function is determined by the fact that mitochondria are the centre of energy metabolism in the cell, which includes the production of ATP required for life activities and the regulation of oxidative metabolism and mitochondrial Reactive Oxygen Species (ROS). A

balance needs to be maintained between the energy demands of the cell and the energy produced by the mitochondria to ensure proper cellular function.

The kidney is a high-energy-consuming organ, especially the renal tubular epithelial cells, which derive energy mainly from fatty acid β-oxidation by mitochondria. In AKI, impairment of basic mitochondrial function affects the energy supply to the cell thereby exacerbating the extent of the damage as well as affecting mitochondrial quality control[11]. It is therefore critical to target the levels of oxidative stress in the mitochondria - ROS levels and the processes and levels of ATP production by the mitochondria[12].

2.2.1 Regulation of ROS

ROS play an important role in mitochondria as a by-product of mitochondrial respiration and are strongly associated with acute kidney injury[13]. The occurrence of kidney injury leads to an exponential increase in mitochondrial ROS, which in turn results in more severe injury, and thus mitochondrial ROS are considered to be central to renal injury[14].

ROS include oxygen radicals [including superoxide anion radical (O^{2-}), hydroxyl radical (HO^{-})] as well as certain non-radicals, some of which are oxidising agents and some of which can be converted to hydrogen peroxide radicals [including hydrogen peroxide (H_2O_2), hypochlorous acid (HOCl)][15], whose main source is the mitochondria.Fig2

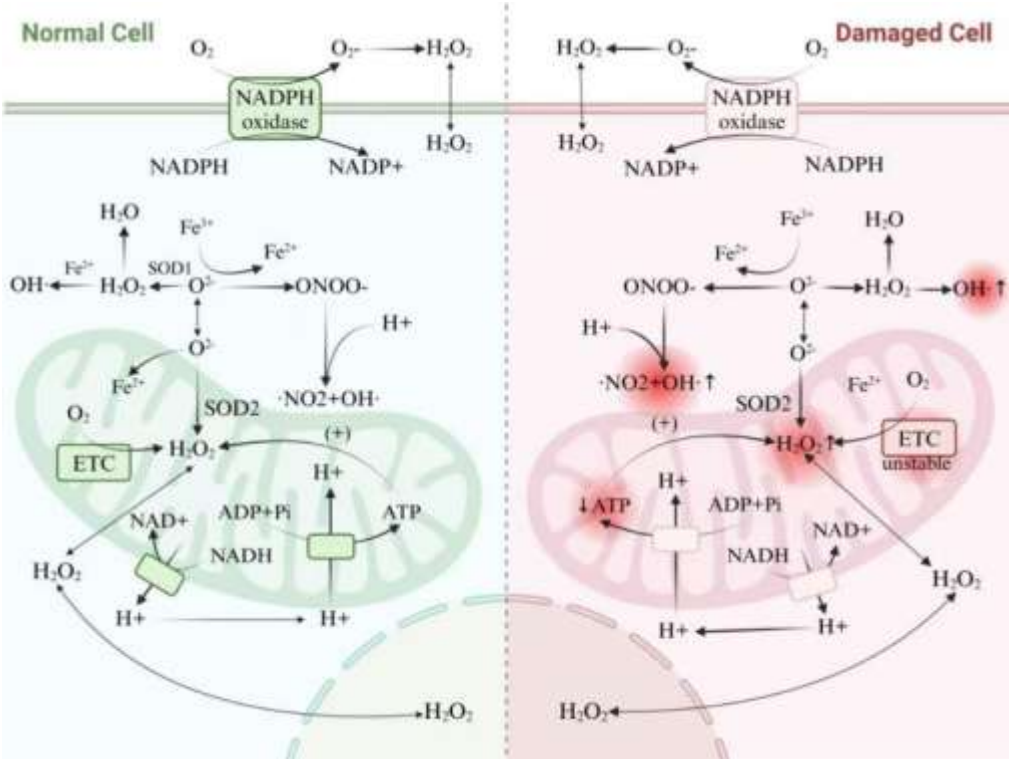

Fig 2 Elevated mtROS levels and reduced ATP levels in acute kidney injury

High levels of ROS in mitochondria lead to a state of high oxidative stress in cells, which in turn causes injury. In order to minimise the high oxidative stress levels in ischemia-reperfusion-induced acute kidney injury, Ran[16] constructed a DNA nanostructure with natural biocompatibility, good bioavailability and stability. This nanosystem consists of four single-stranded dna (ssdna) annealed to form tetrahedral framework nucleic acids (tFNAs) with a flavonoid component from the flowers of Typha angustifolia L., Typhaceae, known as ‘Pu huang’

in traditional Chinese medicine (TCM). Typhaneoside (Typ) is piggybacked into tFNA-Typ complex (TTC). Whereas Typ has good antioxidant effects[17][18] , the application of nanosystems greatly enhanced its relevant effects. In vitro, the system showed good mitochondrial targeting under confocal microscopy as well as good biocompatibility, significantly reducing apoptosis and mitochondrial ROS levels in acute kidney injury due to ischaemia-reperfusion. In addition, in vivo, the system has a dual targeting role, firstly, it has an excellent ability to target human renal proximal tubule cells (HK-2), which enables further reduction of renal injury, and secondly, this study confirms the good mitochondrial targeting of TTC, which plays a significant role in mitochondria to regulate ROS.

On the other hand, high level of ROS is also an important target, for example, Ceria nanoparticles have a strong ability to scavenge ROS, but Ceria nanoparticles do not selectively target mitochondria, and ultra-small Ceria nanoparticles have the disadvantage of being prone to agglomeration[19]. In order to overcome these drawbacks and to improve therapeutic efficacy, Yu [20] designed a ROS-responsive nanomedicine delivery system by modifying Ceria nanoparticles with triphenylphosphine (TCeria NPs) for mitochondrial targeting, and then coating and loading atorvastatin (Atv/PTP-TCeria NPs) with ROS-responsive organic polymers (mPEG-TK-PLGA), in order to construct a ROS-responsive nano-system for scavenging high levels of ROS f

2.2.2 Mitochondrial Energetics

The production of ROS in mitochondria is inevitably accompanied by the generation of adenosine triphosphate (ATP)[21]. Therefore, mitochondria are known as the ‘energy factories of the cell’ and play a central role in cellular metabolism, being responsible for the production of cellular ATP, supplying energy for normal cellular activities and maintaining the mitochondrial membrane potential (ΔΨm) stable[22]. During AKI, a large amount of energy is required by the cell due to various oxidative reactions. Ψm) is stable.55 During AKI, the cell requires a large amount of energy due to various oxidative reactions, and then there is an insufficient supply of ATP, which leads to the inability of the cell to carry out normal life activities that require energy supply. Therefore, ATP depletion in renal tubular cells plays a central role in the pathogenesis of renal diseases such as AKI.

Using a novel mouse strain that systematically expresses an ATP biosensor (an ATP synthase subunit and two fluorophores), Shinya Yamamoto[23] concluded that upon induction of ischemia, ATP levels in proximal tubule (PT) cells decreased to a nadir within minutes, whereas those in distal tubule (DT) cells gradually declined within 1 hour. After reperfusion, the rate of ATP recovery in PTs became slower with increasing ischaemic time. In contrast, ATP in DTs rebounded rapidly regardless of ischaemia duration. Therefore, stabilisation of ATP levels is an important avenue in the search for a treatment for AKI.

After it was known that Pannexin 1 (PANX1) channel transmembrane proteins can drive ATP release during I/R injury, Su[24] established a mouse model of renal I/R injury and a cellular hypoxia/reoxygenation (H/R) model, demonstrating that genetic deletion of PANX1 attenuates I/R injury by enhancing mitochondrial autophagy and decreasing ATP levels through affecting the ATP-P2Y-mTOR signalling pathway, thereby attenuating I/R injury. /R injury after renal tubular cell death, oxidative stress and mitochondrial damage. Zhao[25] further explored the application of nanomedicines in this pathway and established an artificial mitochondrial transfer pathway, which enhances the activity of the mitochondrial electron transport chain (ETC) and promotes the increase of ATP production by using endosomal-bound gold nanoparticles

(GNPs) as an effective electron transfer medium. This nanocarrier is bound to the inner mitochondrial membrane and has good mitochondrial targeting capabilities.

2.3 Mitochondrial Quality Control

In addition to mitochondrial structure and function, the semiautonomous nature of mitochondria is reflected in the ability of mitochondria to inherit and carry out certain life activities independently. This process involves an important intracellular mechanism, the mitochondrial quality control mechanism, which maintains mitochondrial homeostasis and function by monitoring mitochondrial quality and executing a series of protective procedures, including processes such as mitochondrial biogenesis, mitochondrial dynamics, mitochondrial protein hydrolysis, and mitochondrial autophagic degradation. In AKI, controlling other mitochondrial activities is also particularly important, and mitochondrial quality control is a major target for mitochondria-targeted nanosystems[26].

2.3.1 Mitochondrial Dynamics

Mitochondrial dynamics is a state of dynamic equilibrium in which mitochondria maintain their form, number and function through a continuous process of division and fusion. Its main processes include fusion and division of mitochondria. The fusion process is mainly regulated by proteins such as mitophilin 1 (MFN1), mitophilin 2 (MFN2), and optic atrophy 1 (OPA1)[27], while the division process is mainly regulated by mitochondrial dynamin 1 (Drp1) and its receptor proteins, Fis1, and Mff[28].AKI leads to mitochondrial fragmentation, i.e., overexpression of proteins subject to the division process of the mitochondria, and on the contrary, mitochondrial fusion proteins are reduced in expression. This paper summarises and summarises the progress of several mitochondria-targeted nanomedicines that will alleviate AKI by modulating mitochondrial dynamics.Fig3

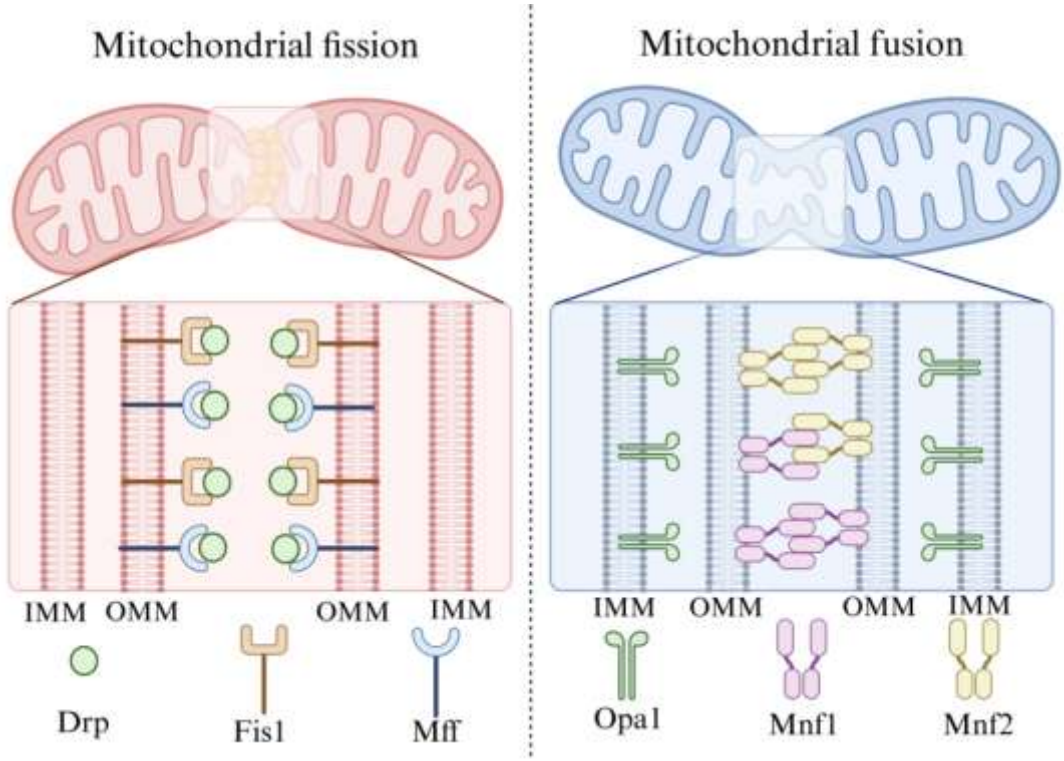

Fig3. Mitochondrial quality control mechanisms

Chronic renal failure leads to myocardial ischaemia-reperfusion injury[29].Wang[30] selected the extracts (Guanxinning injection, GXN) of Salvia miltiorrhiza (Danshen, DS) and Chuanxiong (Chuanxiong, CX), which are widely used in Chinese medicine for the prevention and treatment of myocardial ischemia and renal insufficiency, for the treatment of this injury, and which have antioxidant, anti-inflammatory and anti-ischemia-reperfusion injury properties. In the study, GXN and post-ischemic treatment (IPOC) were co-applied in the ischemic treatment of rats with chronic renal failure (CRF) and found to attenuate the injury by mediating the increase in the expression of mitochondrial fusion proteins MFN1 and OPA1. In addition, ramelteon was able to attenuate IRI-induced AKI by decreasing the expression of Drp1, Fis1, and Mff and increasing the expression of Mfn1 and Mfn2[31].

Diabetic kidney disease (DKD) also increases the risk of AKI, and the search for therapeutic approaches to treating renal injury caused by high glucose is also a focus of current research. In a study by Kristan H Cleveland[32] , formoterol was found to have an important role in the treatment of aberrant mitochondrial fission fusion in DKD, by restoring the activity of the mitochondrial fusion protein Mfn1 through a second Gβγ-dependent mechanism consisting of Raf/MEK1/2/ERK1/2/Mfn1, which facilitates mitochondrial biogenesis in response to the pathological changes caused by glucose elevation-induced pathological changes. SS31, a mitochondria-targeting peptide, not only plays a major role in maintaining mitochondrial structural and functional stability, but also protects against tubular mesenchymal injury in diabetic mice by reducing mitochondrial fragmentation through inhibition of Drp1 expression and increasing Mfn1 expression[33].

2.3.2 Mitochondrial Autophagy

In addition to mitochondrial division and fusion, mitochondrial autophagy occurs when mitochondria are damaged. Mitochondrial autophagy (mitophagy) is the maintenance of cellular and mitochondrial homeostasis by specifically encapsulating damaged or homeostatically dysregulated mitochondria and then degrading them to prevent cellular damage by damaged mitochondria[34]. Recent studies have shown that mitochondrial autophagy is highly active in acute kidney injury (AKI) caused by renal IRI and plays an important role in the progression of AKI and subsequent renal repair[3536].

Mitochondrial autophagy has been identified to be mediated by a total of four signal transduction pathways in two major categories[37]:the ubiquitin-dependent PTEN-inducible putative kinase (PINK) 1-PARK2 pathway6;the non-ubiquitin-dependent Bcl-2/adenoviral E1B 19 kD a-interacting protein 3 (BNIP3)/Nip-like protein-mediated pathway[39], FUN14 domain protein 1-mediated pathway, and the cardiolipin-mediated pathway6 . mediated pathway[37]. Fig4 Among them, Huang[38] used the first signalling pathway to construct a novel mitochondria-targeted nanosystem for inhibition, ultra-small tungsten-based nanodots (TWNDs), to reduce mitochondrial ROS and increase mitochondrial autophagy, and furthermore, detected its ROS level by flow assay, and detected its autophagy pathway by western blot. Detection of specific proteins of the mitochondrial autophagy pathway such as PARKIN to verify its therapeutic goodness in kidney injury as well as good mitochondrial targeting and biocompatibility.

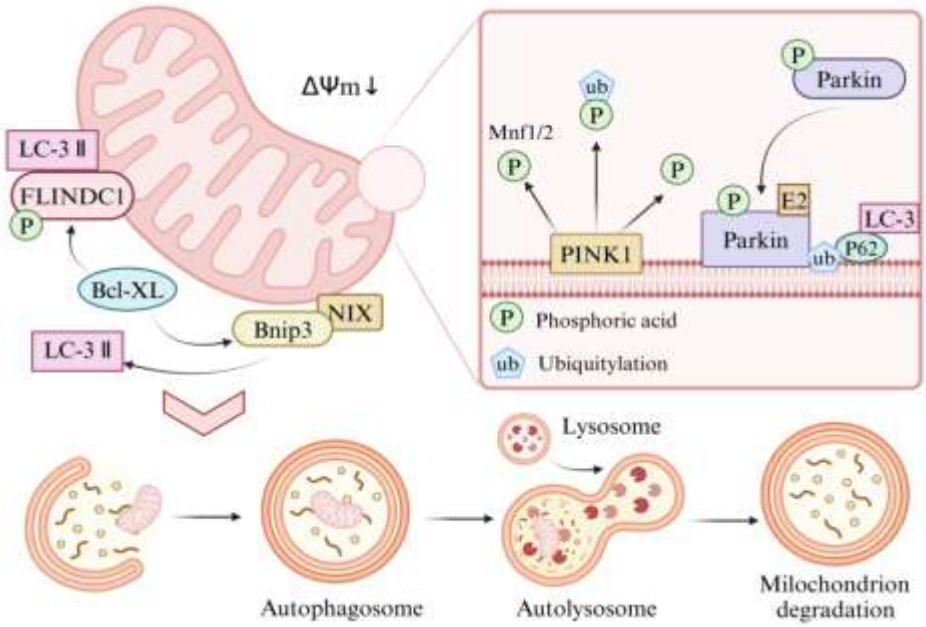

Fig4 The process related to mitochondrial autophagy

2.3.3 Mitochondrial Biogenesis

Mitochondrial biogenesis (MB) refers to the process of increasing the number and quality of mitochondria in a cell, which includes several aspects such as mitochondrial DNA (mtDNA) replication, mitochondrial protein synthesis, and assembly of mitochondrial components[26] .Mitochondrial biosynthesis is essential for maintaining cellular metabolic function and energy supply, and in In AKI, mitochondria are in a state of high oxidative stress and their related functions are inhibited, which is reflected in mtDNA damage and impaired protein synthesis in mitochondrial biosynthesis, etc. Therefore, maintaining the stability of mitochondrial biosynthesis can be regarded as one of the key targets for the treatment of AKI.

2.3.3.1 mtDNA

mtDNA is a special type of DNA present in mitochondria that is used to encode the mitochondria's own genome, such as a number of proteins and RNA molecules required for itself. During AKI-IRI mtROS cause mtDNA damage and inflammation, a process that further exacerbates AKI[40].At the same time, the replication and distribution mechanisms of mtDNA are crucial for maintaining mitochondrial quantitative and qualitative stability. In this regard, Yang[41] designed a nanoparticle-based synthetic mitochondrial transcriptional regulator (MitoScript) that targets the mtDNA light chain promoter region of MitoScript, leading to the downregulation of ND6 gene silencing, which in turn affects the cellular redox state. In addition, MitoScript has excellent colloidal stability, biocompatibility, cellular uptake rate, and mitochondrial targeting, and can be monitored in living cells using near-infrared fluorescence. In AKI mtDNA damage leads to a series of increased levels of oxidative stress. In their study of mesenchymal stem cell (MSC)-derived extracellular vesicles (MSC-EVs), Zhao[42] found an important role in stabilising mtDNA damage in acute kidney injury due to diabetic nephropathy, which relies on the mitochondrial transcription factor A (TFAM) pathway to regulate miRNA and protein expression to maintain mtDNA expression and transcriptional homeostasis.

In addition, mtDNA can be used as a therapeutic agent. Rúben Faria[43] For previous studies of peptides incorporating mitochondria-targeting

sequences (MTS), it was considered that plasmid DNA (pDNA) containing mitochondria-encoded NADH dehydrogenase 1 protein (ND1) and peptide complexes to form nanosystems with mitochondria-targeting that could be developed for application in gene therapy.

2.3.3.2 Mitochondrial Protein Synthesis

The mtDNA can independently encode certain proteins in the mitochondria, and these particular proteins also play an important role in stabilising mitochondrial biosynthesis. When AKI occurs and mitochondrial mtDNA is damaged, mRNA transcription is abnormal during transcription and protein synthesis is impeded.Fig5

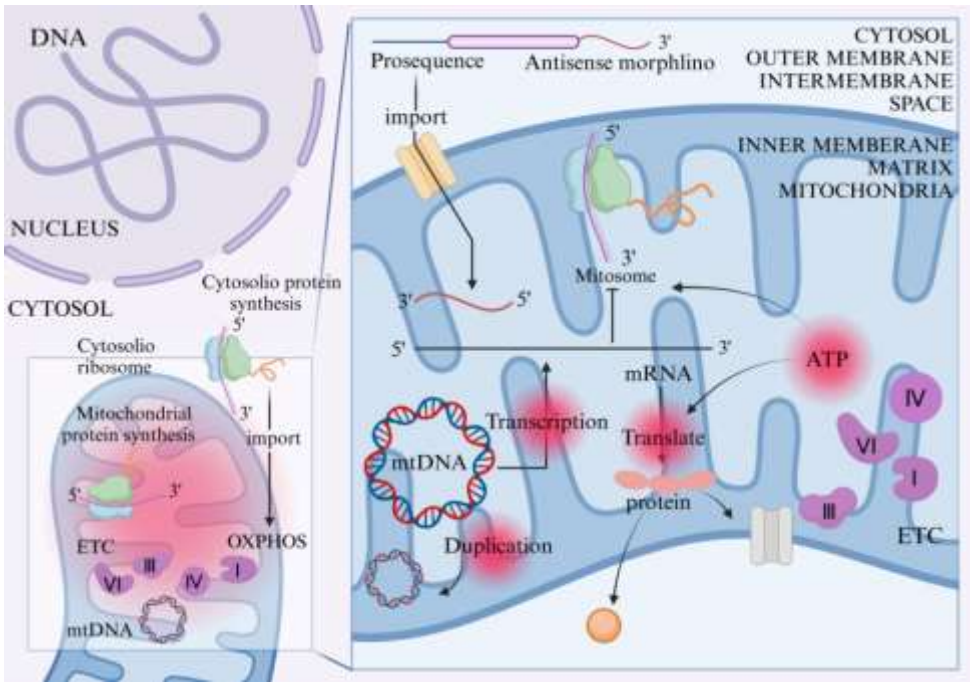

Fig5 Mitochondrial biosynthesis process

Currently, it is known that the β2-adrenergic receptor (AR) of formoterol stimulates mitochondrial biogenesis in renal proximal tubules and restores renal function[44]. However, formoterol has a number of cardiovascular side effects, which limit its use.Ernest [45] synthesised poly(ethylene glycol) methyl ether block-poly(propylene cross ester-co-glycolide) nanoparticles containing encapsulated formoterol by a modified single-emulsion solvent-evaporation technique. co-glycolide) nanoparticles (PLGA-PEG), which further led to an increase in the expression of peroxisome proliferator-activated receptor-γ coactivator 1α (PGC-1α), a major regulator of MB, as well as an increase in the expression of electron transport chain proteins, markers of MB.PGC-1α (peroxisome proliferator activated receptor-γ coactivator 1α) is a key transcriptional coactivator in the regulation of mitochondrial biosynthesis by activating multiple nuclear genes involved in mitochondrial DNA and protein synthesis.

3. Design and Construction of Mitochondria-Targeted Nanosystems

Nanosystems for mitochondrial targeting is a prospective strategy for the treatment of mitochondrial-related diseases such as AKI, which utilises nanosystems directly targeting mitochondria to load drugs or load mitochondria-targeted drugs onto nanosystems to increase bioavailability and concentration of drugs at the tumour site, and to reduce systemic toxicity and side-effects. In this subsection, we will look at nanomaterials and drugs with mitochondria-

targeting capabilities that have been investigated in the last few years.

3.1 Nanomaterials with Mitochondria-Targeting Functions and Their Modifications

Various types of nanocarriers have been developed, such as nanosystems based on small molecule drugs, liposomes, nanomicelles, mesoporous silica, dendritic polymers, charge-reversible nanocopolymers, lipid-shell-polymer hybrid nanoparticles, metal-organic skeletons and peptide-modified nanosystems. And many of these carriers are inherently mitochondria-targeted, such as TPP[46], which is inherently lipophilic and positively charged, which allows it to interact with the negatively charged membranes of the mitochondria and facilitate the uptake of the nanocarriers through the difference in the potential of the membranes. In addition the mitochondrial targeting ability of TPP is due to its recognition of mitochondria-specific markers such as mitochondrial localisation sequences (MLS) and specific receptors on the mitochondrial membrane.

Table1 Nanomaterials loaded with drugs with mitochondrial targeting function

Mitochondria-targeted nanosystems	Drugs	Acting cell types	Acting cell types	Animal models	References
Polymeric micelles（OPDEA-PDCA）	Dichloroacetic acid（DCA）	Poly[2-(N-oxide-N,N-diethylamino)ethyl methacrylate]（OPDEA）	K7M2	BALB/c mice inoculated with K7M2 tumour cells	47
Mito-FFa	fenofibric acid (FFa）	triphenylphosphonium(TPP）	4T1、MDA-MB-231、CT26、AML12、Raw264.7、BMDCs, Batf3-/- - cells from C57BL/6 mice	BALB/c mice inoculated with 4T1 tumour cells, C57BL/6 mice inoculated with MC38 tumour cells	48
TCeO2-TRA-FNL-gel	All-trans retinoic acid（TRA）	Triphenylphosphine (TPP)-modified cerium oxide (CeO2)	HaCat cell	MQ-induced psoriasis in BALB/c mice	49
PEP−TPP−mitochondrial compound	CSTSMLKAC (PEP)	Triphenylphosphine cation (TPP+)	AC16 cells, mouse primary cardiomyocytes, bEnd.3 cells	IR-injured C57BL /6J mice, Cox4i1-GFP mice	50
TOS-PDA-PEG-TPP	α-tocopheryl succinate（α-TOS）	TPP	A549、LLC	LLC Balb/c nude mice and Balb/c mice inoculated with LLC cells	51
PLA8k-PEG6k-TPP	PLA8k-PEG4k		HeLa、A549	BALB/c nude mice inoculated with HeLa/R tumour cells	52
TPP-ceria	Ceria NPs		SH-SY5Y	5XFAD	53

NPs				transgenic mouse	
（TPP-PPG@ICG）	NGO		MG63、MG63/Dox	mice inoculated with MG63/Dox tumour cells	54

3.2 Drugs with Mitochondria-Targeting Capabilities That Can Be Loaded Onto Nanomaterials

However, not all nanomaterials are mitochondria-targeted, so when we want to build a mitochondria-targeted nanosystem, we need to consider whether the loaded drug is mitochondria-targeted or not, and then make use of the relevant synthetic methods to enable the drug to be loaded onto the nanomaterial, and thus achieve the major breakthrough of improving drug utilisation and realising precision-targeted therapy at the same time.

For example, metal nanocarriers are widely used in nanosystems in current research and are involved in the treatment of a variety of diseases[55]. However, we also know that mitochondria do not have a wide range of specific uptake capabilities for any kind of metal. Therefore, when there is a need to construct metal nanocarriers with mitochondria-targeting functions, another route is needed. It is known that chrysin is a mitochondria-targeting agent capable of demonstrating multimodal therapeutic use in glioblastoma (GBM) treatment by severely affecting the IDH2 gene (isocitrate dehydrogenase) and its interaction with the multi-combic methyltransferase EZH1/2[56]. In a study by Babita Kaundal[57] , chrysin was loaded onto gold nanocarriers and combined with photodynamic therapy to together to improve the therapeutic effect on tumours.

Liposomes are also widely used in nanosystems, but they do not have mitochondrial targeting capabilities for better therapeutic effects. In this regard, Tan[58] used amphiphilic oxalamide-octane conjugate (SS) as a mitochondria-targeting molecule, which was bound to the surface of arsenic trioxide liposomes to increase the accumulation of the drug in the tumour cells by targeting the mitochondria, triggering the permeability of the outer mitochondrial membrane, and promoting the release of cytochrome C through the inhibition of Bcl-2, which led to the cascade of caspase 3, resulting in apoptosis of the tumour cells. Takao Tsujioka[59] encapsulated resveratrol (RES), a naturally occurring polyphenol compound with cardioprotective properties, in a multifunctional membrane-encapsulated nanodevice for targeting pancreatic β-cells (β-MEND) to form a new nanosystem, β-MEND (RES), which is not cytotoxic to H9c2 cells and can significantly activate the cells. H9c2 cells and significantly activates the maximum cellular respiratory capacity.

4. Discussion and Expectations

Kidneys are one of the vital organs in the body, not only responsible for filtering waste and excess water from the blood, but also maintaining electrolyte and acid-base balance in the body. The healthy state of the kidneys is vital for the proper functioning of the entire body. However, when the kidneys are acutely injured, this balance is disrupted, leading to a variety of complications that may be rapidly apparent in the short term or accumulate over time, with serious health consequences[5960]. Mitochondria, as the ‘energy factories’ within the cell, play a particularly critical role in the kidneys. They not only provide the necessary energy for the high energy-

consuming activities of the kidney, but also regulate cellular metabolism and participate in cellular signalling. These autonomous functions of mitochondria make them a target that cannot be ignored in the treatment of renal diseases[61]. Especially in AKI therapy, the structural integrity, functional status, autophagy mechanism, and biosynthetic processes of mitochondria have a direct impact on disease progression and recovery.

With the ongoing research, researchers have identified certain limitations of traditional pharmacological approaches in the treatment of AKI. To overcome these limitations, scientists have begun to explore novel therapeutic means. Nanosystems, due to their unique physicochemical properties and biocompatibility, are considered to have great potential in improving drug efficacy and reducing side effects. In particular, mitochondria-targeted nanosystems, which are capable of precisely delivering drugs to mitochondria and targeting specific mitochondrial life activities for modulation, can protect mitochondria while slowing down the damage of AKI.

Currently, research on mitochondria-targeted nanosystems is mainly focused on the laboratory stage, where scientists have explored their protective effects on multiple mitochondrial targets by constructing nanocarriers with specific targeting properties. Although these studies have made some progress, they are still a long way from clinical application. Future studies will need to further elucidate the specific mechanism of action of mitochondria-targeted nanosystems in AKI therapy, validate their safety and efficacy, and explore their potential for application in clinical therapy.

Statements & Declarations

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Competing Interests

The authors declare that they have no competing interests.

References

1. Zhao M, Zhou Y, Liu S, et al. Control release of mitochondria-targeted antioxidant by injectable self-assembling peptide hydrogel ameliorated persistent mitochondrial dysfunction and inflammation after acute kidney injury. Drug Deliv. 2018;25(1):546-554. doi:10.1080/10717544.2018.1440445
2. Reddy PH, Manczak M, Kandimalla R. Mitochondria-targeted small molecule SS31: a potential candidate for the treatment of Alzheimer's disease. Hum Mol Genet. 2017 Apr 15;26(8):1597. doi: 10.1093/hmg/ddx129. Erratum for: Hum Mol Genet. 2017 Apr 15; 26(8):1483-1496. doi: 10.1093/hmg/ddx052.
3. Supinski GS, Wang L, Schroder EA, Callahan LAP. SS31, a mitochondrially targeted antioxidant, prevents sepsis-induced reductions in diaphragm strength and endurance. J Appl Physiol (1985). 2020;128 (3):463-472. doi:10.1152/japplphysiol.00240. 2019
4. Liu D, Jin F, Shu G, et al. Enhanced efficiency of mitochondria-targeted peptide SS-31 for acute kidney injury by pH-responsive and AKI-kidney targeted nanopolyplexes. Biomaterials. 2019;211:57-67. doi:10.1016/j.biomaterials.2019.04.034

5. Patel P, Mendoza A, Robichaux DJ, Wang MC, Wehrens XHT, Karch J. Inhibition of the Anti-Apoptotic Bcl-2 Family by BH3 Mimetics Sensitize the Mitochondrial Permeability Transition Pore Through Bax and Bak. Front Cell Dev Biol. 2021 Dec 1;9: 765973. doi: 10.3389/fcell.2021.765973.
6. Endlicher R, Drahota Z, Štefková K, Červinková Z, Kučera O. The Mitochondrial Permeability Transition Pore-Current Knowledge of Its Structure, Function, and Regulation, and Optimized Methods for Evaluating Its Functional State. Cells. 2023; 12(9):1273. Published 2023 Apr 27. doi:10.3390/cells12091273
7. Robichaux DJ, Harata M, Murphy E, Karch J. Mitochondrial permeability transition pore-dependent necrosis. J Mol Cell Cardiol. 2023; 174:47-55. doi:10.1016/j.yjmcc.2022.11.003
8. Ji X, Chu L, Su D, et al. MRPL12-ANT3 interaction involves in acute kidney injury via regulating MPTP of tubular epithelial cells. iScience. 2023;26(5):106656. Published 2023 Apr 14. doi:10.1016/j.isci.2023.106656
9. Bonora M, Giorgi C, Pinton P. Molecular mechanisms and consequences of mitochondrial permeability transition. Nat Rev Mol Cell Biol. 2022;23(4):266-285. doi: 10.1038/s41580-021-00433-y
10. Rodrigues-Ferreira C, Lopes JA, Carneiro PF, Dos Santos Lessa C, Galina A, Vieyra A. Bone Marrow Mononuclear Cells Restore Normal Mitochondrial Ca2+ Handling and Ca2+-Induced Depolarization of the Internal Mitochondrial Membrane by Inhibiting the Permeability Transition Pore After Ischemia/ Reperfusion. Cell Transplant. 2022;31:963689 7221085883. doi:10.1177/096368972210858 83
11. Jiao H, Jiang D, Hu X, et al. Mitocytosis, a migrasome-mediated mitochondrial quality-control process. Cell. 2021;184(11):2896-2910.e13. doi:10.1016/j.cell.2021.04.027
12. Palma FR, Gantner BN, Sakiyama MJ, et al. ROS production by mitochondria: function or dysfunction?. Oncogene. 2024;43(5):295-303. doi:10.1038/s41388-023-02907-z
13. Su L, Zhang J, Gomez H, Kellum JA, Peng Z. Mitochondria ROS and mitophagy in acute kidney injury. Autophagy. 2023;19(2):401-414. doi:10.1080/15548627.2022.2084862
14. Martin JL, Gruszczyk AV, Beach TE, Murphy MP, Saeb-Parsy K. Mitochondrial mechanisms and therapeutics in ischaemia reperfusion injury. Pediatr Nephrol. 2019;34 (7): 1167-1174. doi:10.1007/s00467-018-3984-5
15. Kezic A, Spasojevic I, Lezaic V, Bajcetic M. Mitochondria-Targeted Antioxidants: Future Perspectives in Kidney Ischemia Reperfusion Injury. Oxid Med Cell Longev. 2016;2016: 2950503. doi:10.1155/2016/2950503
16. Yan R, Cui W, Ma W, Li J, Liu Z, Lin Y. Typhaneoside-Tetrahedral Framework Nucleic Acids System: Mitochondrial Recovery and Antioxidation for Acute Kidney Injury treatment. ACS Nano. 2023;17(9): 8767-8781. doi:10.1021/acsnano.3c02102
17. Chen, P.; Cao, Y.; Bao, B.; Zhang, L.; Ding, A. Antioxidant Capacity of Typha Angustifolia Extracts and Two Active Flavonoids. Pharm. Biol. 2017, 55 (1), 1283−1288.
18. Barboza, J. R.; Pereira, F. A. N.; Fernandes, R. A.; Vasconcelos, C. C.; Cartagenes, M.; Oliveira Lopes, A. J.; Melo, A. C.; Guimaraes, I. D. S.; Rocha, C. Q. D.; Ribeiro, M. N. S. Cytotoxicity and ProApoptotic, Antioxidant and Anti-Inflammatory Activities of Geopropolis Produced by the Stingless Bee Melipona Fasciculata Smith. Biology (Basel). 2020, 9 (9), 292.
19. Bao Q, Hu P, Xu Y, Cheng T, Wei C, Pan L, et al. Simultaneous Blood-Brain Barrier Crossing and Protection for Stroke Treatment Based on Edaravone-Loaded Ceria Nanoparticles. Acs Nano. 2018; 12: 6794-805.
20. Yu H, Jin F, Liu D, et al. ROS-responsive

nano-drug delivery system combining mitochondria-targeting ceria nanoparticles with atorvastatin for acute kidney injury. Theranostics. 2020;10(5):2342-2357. Published 2020 Jan 16. doi:10.7150/thno.403 95

21. Palma FR, Gantner BN, Sakiyama MJ, et al. ROS production by mitochondria: function or dysfunction?. Oncogene. 2024;43(5):295-303. doi:10.1038/s41388-023-02907-z
22. Yamamoto S, Yamamoto M, Nakamura J, et al. Spatiotemporal ATP Dynamics during AKI Predict Renal Prognosis. J Am Soc Nephrol. 2020;31(12):2855-2869. doi:10.1681/ASN.2020050580
23. Boyenle ID, Oyedele AK, Ogunlana AT, et al. Targeting the mitochondrial permeability transition pore for drug discovery: Challenges and opportunities. Mitochondrion. 2022;63:57-71. doi:10.1016/j.mito.2022.01.006
24. Jo Y, Woo JS, Lee AR, et al. Inner-Membrane-Bound Gold Nanoparticles as Efficient Electron Transfer Mediators for Enhanced Mitochondrial Electron Transport Chain Activity. Nano Lett. 2022;22(19):7927-7935. doi:10.1021/acs.nanolett.2c02957
25. Tang C, Cai J, Yin XM, Weinberg JM, Venkatachalam MA, Dong Z. Mitochondrial quality control in kidney injury and repair. Nat Rev Nephrol. 2021;17(5):299-318. doi:10.1038/s41581-020-00369-0
26. Gao S, Hu J. Mitochondrial Fusion: The Machineries In and Out. Trends Cell Biol. 2021;31(1):62-74. doi:10.1016/j.tcb.2020.09.008
27. Giacomello M, Pyakurel A, Glytsou C, Scorrano L. The cell biology of mitochondrial membrane dynamics. Nat Rev Mol Cell Biol. 2020;21(4):204-224. doi:10.1038/s41580-020-0210-7
28. Jankowski J, Floege J, Fliser D, Böhm M, Marx N. Cardiovascular Disease in Chronic Kidney Disease: Pathophysiological Insights and Therapeutic Options. Circulation. 2021;143(11):1157-1172. doi:10.1161/CIRCULATIONAHA.120.050686
29. Wang A, Zhang D, Liu J, et al. Guanxinning Injection Combined With Ischemic Postconditioning Attenuate Myocardial Ischemic Reperfusion Injury in Chronic Renal Failure Rats by Modulating Mitochondrial Dynamics. Front Cardiovasc Med. 2022;9:905254. Published 2022 May 30. doi:10.3389/fcvm.2022.905254
30. Chen P, Liu W, Wei Y. Ramelteon attenuates renal ischemia and reperfusion injury through reducing mitochondrial fission and fusion and inflammation. Transl Androl Urol. 2023;12(12):1859-1870. doi:10.21037/tau-23-543
31. Cleveland KH, Schnellmann RG. The β2-adrenergic receptor agonist formoterol restores mitochondrial homeostasis in glucose-induced renal proximal tubule injury through separate integrated pathways. Biochem Pharmacol. 2023;209:115436. doi:10.1016/j.bcp.2023.115436
32. Yang SK, Li AM, Han YC, et al. Mitochondria-Targeted Peptide SS31 Attenuates Renal Tubulointerstitial Injury via Inhibiting Mitochondrial Fission in Diabetic Mice. Oxid Med Cell Longev. 2019;2019:2346580. Published 2019 Jun 2. doi:10.1155/2019/2346580
33. Yang X, Zhang R, Nakahira K, Gu Z. Mitochondrial DNA Mutation, Diseases, and Nutrient-Regulated Mitophagy. Annu Rev Nutr. 2019;39:201-226. doi:10.1146/annurev-nutr-082018-124643
34. Wang Y, Cai J, Tang C, Dong Z. Mitophagy in Acute Kidney Injury and Kidney Repair. Cells. 2020;9(2):338. Published 2020 Feb 1. doi:10.3390/cells9020338
35. Choi ME. Autophagy in Kidney Disease. Annu Rev Physiol. 2020;82:297-322. doi:10.1146/annurev-physiol-021119-034658
36. Durcan TM, Fon EA. The three 'P's of mitophagy: PARKIN, PINK1, and post-translational modifications. Genes Dev. 201 5;29(10):989-999. doi:10.1101/gad.262758 .115

37. Qin S, Liu C, Chen Y, et al. Cobaltosic oxide-polyethylene glycol-triphenylphosphine nanoparticles ameliorate the acute-to-chronic kidney disease transition by inducing BNIP3-mediated mitophagy. Kidney Int. 2023;103 (5):903-916. doi:10.1016/j.kint.2023.01.025
38. Huang Q, Yang Y, Zhao T, et al. Passively-targeted mitochondrial tungsten-based nanodots for efficient acute kidney injury treatment. Bioact Mater. 2022;21:381-393. Published 2022 Sep 14. doi:10.1016/j. bioact mat.2022.08.022
39. Tang C, Cai J, Yin XM, Weinberg JM, Venkatachalam MA, Dong Z. Mitochondrial quality control in kidney injury and repair. Nat Rev Nephrol. 2021;17(5):299-318. doi: 10.1038/s41581-020-00369-0
40. Zhao M, Wang Y, Li L, et al. Mitochondrial ROS promote mitochondrial dysfunction and inflammation in ischemic acute kidney injury by disrupting TFAM-mediated mtDNA maintenance. Theranostics. 2021;11(4):1845-1863. Published 2021 Jan 1. doi:10.7150 /thno.50905
41. Yang L, Rathnam C, Hidaka T, et al. Nanoparticle-Based Artificial Mitochondrial DNA Transcription Regulator: MitoScript. Nano Lett. 2023;23(5):2046-2055. doi:10.102 1/acs.nanolett.2c03958
42. Zhao M, Liu S, Wang C, et al. Mesenchymal Stem Cell-Derived Extracellular Vesicles Attenuate Mitochondrial Damage and Inflammation by Stabilizing Mitochondrial DNA [published correction appears in ACS Nano. 2021 Dec 28;15(12):20692. doi: 10.10 21/acsnano.1c09895]. ACS Nano. 2021;15(1): 1519-1538. doi:10.1021/acsnano.0c08947
43. Faria R, Vivés E, Boisguerin P, Sousa A, Costa D. Development of Peptide-Based Nanoparticles for Mitochondrial Plasmid DNA Delivery. Polymers (Basel). 2021;13 (11):1836. Published 2021 Jun 1. doi:10.3390/ polym13111836
44. Jesinkey SR, Funk JA, Stallons LJ, et al. Formoterol restores mitochondrial and renal function after ischemia-reperfusion injury. J Am Soc Nephrol. 2014;25(6):1157-1162. doi: 10.1681/ASN.2013090952
45. Vallorz EL, Blohm-Mangone K, Schnellmann RG, Mansour HM. Formoterol PLGA-PEG Nanoparticles Induce Mitochondrial Biogenesis in Renal Proximal Tubules. AAPS J. 2021;23(4):88. Published 2021 Jun 24. doi:10.1208/s12248-021-00619-4
46. Mei Y, Qin X, Yang Z, et al. Engineered a dual-targeting HA-TPP/A nanoparticle for combination therapy against KRAS-TP53 co-mutation in gastrointestinal cancers. Bioact Mater. 2023;32:277-291. Published 2023 Oct 14. doi:10.1016/j.bioactmat.2023.10.003
47. Jin J, Yuan P, Yu W, et al. Mitochondria-Targeting Polymer Micelle of Dichloroacetate Induced Pyroptosis to Enhance Osteosarcoma Immunotherapy. ACS Nano. 2022;16(7):103 27-10340. doi:10.1021/acsnano.2c00192
48. Wang Y, Wang W, Gu R, et al. In Situ Vaccination with Mitochondria-Targeting Immunogenic Death Inducer Elicits CD8+ T Cell-Dependent Antitumor Immunity to Boost Tumor Immunotherapy. Adv Sci (Weinh). 2023;10(20):e2300286. doi:10.1002/advs.20 2300286
49. Wang W, Xu X, Song Y, et al. Nano transdermal system combining mitochondria-targeting cerium oxide nanoparticles with all-trans retinoic acid for psoriasis. Asian J Pharm Sci. 2023;18(5):100846. doi:10.1016/j.ajps. 2023.100846
50. Sun X, Chen H, Gao R, et al. Intravenous Transplantation of an Ischemic-specific Peptide-TPP-mitochondrial Compound Alleviates Myocardial Ischemic Reperfusion Injury. ACS Nano. Published online January 10, 2023. doi:10.1021/acsnano.2c05286
51. Meng Z, Wang B, Liu Y, et al. Mitochondria-targeting polydopamine-coated nanodrugs for effective photothermal- and chemo-synergistic therapies against lung cancer.

Regen Biomater. 2022;9:rbac051. Published 2022 Aug 1. doi:10.1093/rb/rbac051
52. Ren L, Xu P, Yao J, et al. Targeting the Mitochondria with Pseudo-Stealthy Nanotaxanes to Impair Mitochondrial Biogenesis for Effective Cancer Treatment. ACS Nano. 2022;16(7):10242-10259. doi:10. 1021/acsnano.1c08008
53. Kwon HJ, Cha MY, Kim D, et al. Mitochondria-Targeting Ceria Nanoparticles as Antioxidants for Alzheimer's Disease. ACS Nano. 2016;10(2):2860-2870. doi:10.1021/ acsnano.5b08045
54. Zeng WN, Yu QP, Wang D, et al. Mitochondria-targeting graphene oxide nanocomposites for fluorescence imaging-guided synergistic phototherapy of drug-resistant osteosarcoma. J Nanobiotechnology. 2021;19(1):79. Published 2021 Mar 19. doi: 10.1186/s12951-021-00831-6
55. Hu H, Xu Q, Mo Z, et al. New anti-cancer explorations based on metal ions. J Nanobiotechnology. 2022;20(1):457. Published 2022 Oct 23. doi:10.1186/s12951-022-01661-wHu H, Xu Q, Mo Z, et al. New anti-cancer explorations based on metal ions. J Nanobiotechnology. 2022;20(1):457. Published 2022 Oct 23. doi:10.1186/s12951-022-01661-w
56. Wu JJ, Zhang J, Xia CY, et al. Hypericin: A natural anthraquinone as promising therapeutic agent. Phytomedicine. 2023; 11 1:154654. doi:10.1016/j.phymed.2023.154654
57. Kaundal B, Karmakar S, Roy Choudhury S. Mitochondria-targeting nano therapy altering IDH2-mediated EZH2/EZH1 interaction as precise epigenetic regulation in glioblastoma. Biomater Sci. 2022;10(18):5301-5317. Published 2022 Sep 13. doi:10.1039/ d1bm 02006d
58. Tan X, Zhu X, Xu D, et al. A mitochondria-targeted nano-platform for pancreatic cancer therapy. Front Chem. 2022;10:951434. Published 2022 Sep 21. doi:10.3389/ fchem. 2022.951434
59. Lameire NH, Bagga A, Cruz D, et al. Acute kidney injury: an increasing global concern. Lancet. 2013;382(9887):170-179. doi:10.10 16/ S0140-6736(13)60647-9
60. Thomas ME, Blaine C, Dawnay A, et al. The definition of acute kidney injury and its use in practice. Kidney Int. 2015;87(1):62-73. doi: 10.1038/ki.2014.328
61. Maeda S, Sakai S, Takabatake Y, Yamamoto T, et al. MondoA and AKI and AKI-to-CKD Transition. J Am Soc Nephrol. 2024 May 31; 35(9):1164–82. doi: 10.1681/ASN.00000000 00000414.