Mitochondria as therapeutic targets in acute kidney injury

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Abstract: PURPOSE OF REVIEW: Mitochondria are complex intracellular organelles with a variety of important functions. The kidney tubule is densely packed with mitochondria, and mitochondrial dysfunction is thought to be central to the pathogenesis of acute kidney injury (AKI). Mitochondria therefore represent potential targets for novel therapeutic interventions in AKI. RECENT FINDINGS: Several mitochondrial targeted approaches have shown promise in recent preclinical studies of AKI, including measures to: reduce oxidative stress within mitochondria; prevent mitochondrial fission and activation of cell death pathways; enhance recycling of damaged mitochondria via autophagy and mitophagy; and accelerate mitochondrial biogenesis postinsult. SUMMARY: Recent studies show that it is now eminently feasible to pharmacologically manipulate various key aspects of mitochondrial biology in the kidney, and this has much potential for the future treatment of AKI. However, significant hurdles will have to be overcome in the translational pathway for these strategies to successfully migrate to the clinic.

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Summary
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Keywords
acute kidney injury, antioxidants, mitochondria, mitochondrial biogenesis, mitophagy

INTRODUCTION

The renal tubule, and in particular the proximal tubule, is densely packed with mitochondria, which exist primarily to generate sufficient quantities of ATP, via oxidative phosphorylation (OXPHOS), to power the huge amounts of solute transport performed every day in the kidney. The importance of mitochondria in the proximal tubule is illustrated by the fact that renal Fanconi syndrome is the most common kidney phenotype in children with genetic mitochondrial diseases [1,2]. Moreover, mitochondrial defects are implicated in the pathogenesis of a wide range of kidney diseases, including diabetic nephropathy and certain types of nephrotic syndrome [3]. However, most attention to date has focused on the role of mitochondria in acute kidney injury (AKI), in which all of the major causes in humans – ischemia-reperfusion injury (IRI), drug toxicity, and sepsis – are thought to induce mitochondrial damage in the proximal tubule.

AKI is associated with significant morbidity and mortality, and thus represents a major public health burden. The hitherto fruitless quest for effective treatments for AKI is now increasingly moving into the realm of the mitochondrion, driven by a potent cocktail of factors, including an explosion of new knowledge concerning basic mitochondrial biology, the increasing recognition of their importance in the pathogenesis, and the development of drugs that can specifically target mitochondria. In this article, the potential roles of some recently studied mitochondrial therapies in AKI will be discussed. Ultimately, the key question is, can any of these effectively prevent or reverse AKI in humans? Only time will tell, but some important issues to consider in the meantime will be discussed in the final section.

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KEY POINTS

- Mitochondria are complex dynamic organelles, and mitochondrial dysfunction is central to the pathogenesis of AKI.
- Several mitochondrial targeted therapies have recently been developed and tested in preclinical models of AKI.
- Mitochondrial-specific antioxidants and inhibitors of mitochondrial fission are protective, whereas stimulation of mitochondrial biogenesis can enhance recovery postinsult.
- The role of autophagy/mitophagy in AKI remains controversial, with conflicting results from different studies.

MITOCHONDRIA IN THE KIDNEY TUBULE

Mitochondria are complex organelles present in almost all eukaryote cells, and are instantly recognizable by their textbook appearance with a double membrane and numerous cristae formed by infoldings of the inner membrane. They are thought to be descended from a bacterial ancestor, and provide a huge evolutionary advantage for their host cells by virtue of the fact that they perform aerobic respiration, which generates significantly more ATP per fuel molecule than anaerobic processes. Put simply, without mitochondria the energy needs of the kidney could not be met. In addition, mitochondria have a range of other important functions, including biosynthesis of macromolecules and modulation of intracellular Ca^{2+} signals. Furthermore, they are probably a major source of reactive oxygen species (ROS) production and also have a key role in the activation of cell death pathways (apoptosis and necrosis). It follows from this that mitochondrial dysfunction can potentially be harmful to host cells in a number of different ways, many of which have yet to be fully elucidated [4].

Mitochondria are highly dynamic organelles, capable of moving, fusing, and dividing. Total mitochondrial mass is determined by the balance between the rate of breakdown and removal – via a dedicated form of autophagy termed mitophagy – and by the rate of generation of new organelles (mitochondrial biogenesis). It is becoming increasingly clear that disorders in mitochondrial dynamics, recycling, and biogenesis can all cause or worsen disease states in humans [5], leading to the concept that these processes could represent targets for therapeutic interventions.

MITOCHONDRIA IN ACUTE KIDNEY INJURY

For reasons that remain incompletely explained, the proximal tubule lacks the capacity to perform anaerobic glycolysis [6]. As such, it is exquisitely sensitive to aerobic insults, such as IRI, and cellular ATP levels plummet within seconds of oxygen deprivation [7]. Increasing evidence suggests that mitochondria are also damaged in septic AKI, but it remains unclear whether this is secondary to a lack of oxygen delivery (the classical paradigm) or rather direct toxicity induced by the inflammatory milieu, although opinion seems to coalescing more around the latter concept [8]. Mitochondria in the proximal tubule are also damaged by therapeutic drugs that frequently cause AKI, such as ifosfamide, cisplatin, tenofovir, and gentamicin [9]. Moreover, a very recent study suggests that elevated urinary mitochondrial DNA (mtDNA) predicts the development of AKI in humans undergoing cardiac surgery [10]. The realization that mitochondria play a central role in AKI has stimulated the search for new therapies that can target these complex and fascinating organelles.

MITOCHONDRIAL-TARGETED THERAPIES

The overall aims of mitochondrial-targeted therapies in AKI are essentially to achieve one of three things: to limit harm to mitochondria and minimize the downstream consequences for the cell; to enhance recycling of damaged mitochondria; or to accelerate recovery of normal mitochondrial mass and function postinsult. More specifically, they can currently be classified as targeting one of four distinct processes: mitochondrial ROS generation and oxidative stress; mitochondrial fission and activation of cell death pathways; mitochondrial breakdown via autophagy/mitophagy; and mitochondrial biogenesis. In the following sections, consideration will be given to the respective merits of each of these approaches. As this article is focused on strategies currently in vogue, older targets will not be discussed, such as inhibitors of the mitochondrial permeability transition pore, which have been covered in depth elsewhere [11].

Mitochondrial-targeted antioxidants

Mitochondria are thought to be a major intracellular source of ROS (produced as a byproduct of OXPHOS), and oxidative stress has been widely implicated in many disease processes. In fact, it now represents a considerable challenge to identify any where it has not. Conversely, clinical trials with nonspecific antioxidants have proven to be a major

disappointment. This apparent paradox naturally leads to two possible conclusions. First, ROS may not actually be as important as previously thought. Alternatively, more selectively targeted antioxidants might be required to achieve a therapeutic effect. The latter argument is supported by the emerging concept that nonmitochondrial ROS can have important physiological roles, such as the regulation of solute transport in the kidney [12]. Mitochondrial ROS production is thought to increase when normal OXPHOS is compromised (e.g. in IRI), so antioxidants targeted to mitochondria could be of benefit, to limit oxidative stress and damage specifically within these organelles.

Three classes of mitochondrial-targeted antioxidants have been developed in recent years – SS-peptides, MitoQ, and plastoquinone analogues (SkQ1/SkQR1) – all of which work on a similar principle. As lipophilic cations, they selectively accumulate into the mitochondrial matrix at very high concentrations, utilizing the voltage gradient across the mitochondrial inner membrane created by the OXPHOS complexes (the SS peptides may also interact with cardiolipin, a major constituent of the mitochondrial inner membrane [13]). All three classes of these agents have shown evidence of benefit in preclinical models of AKI and appear to have satisfactory safety profiles.

Discovered by serendipity [14], the SS peptides arguably show the greatest promise for AKI at present. In a series of studies in rodent models by Szeto *et al.* [13,15▪▪], it has been shown that two agents in this class (SS-20 and SS-31) offer significant protection in AKI because of IRI, with striking positive effects on mitochondrial morphology and function, cell polarity, and overall kidney function. SS-31 (marketed as Bendavia) has also shown evidence of benefit in a larger animal model (renovascular disease in pigs) [16], and the effects in human AKI are now being investigated. Meanwhile, MitoQ, an analogue of the OXPHOS component ubiquinone (CoQ10), has been studied in a multitude of different disease processes in different organs, including in humans [17]. Regarding the kidney, it has recently been shown to have beneficial effects in AKI induced by IRI [18] and cisplatin [19]. The plastoquinone analogues also seem to be protective in preclinical AKI models, including IRI, rhabdomyolysis, and gentamicin toxicity [20,21]. One potential limitation of all of these agents is that they have to be given before the insult, so their clinical usage would effectively be confined to scenarios where AKI is predictable. However, this is also the case for many other nonmitochondrial therapies currently in development. Moreover, the fact that such structurally heterogeneous compounds have all shown benefit in various models in different research groups suggests that targeting mitochondrial ROS production is a strategy worth pursuing (albeit with the caveats discussed in the final section).

Another recently identified method to lower mitochondrial ROS production involves the signaling molecule stanniocalcin-1 (STC1), which is highly expressed in the kidney [22]. STC1 is a stress protein that responds to stimuli such as hypoxia, and traffics to the mitochondrial membrane, where it increases the expression of uncoupling proteins, which, in turn, may reduce the rate of ROS production by the mitochondrial OXPHOS complexes (possibly by lowering the potential across the mitochondrial inner membrane, although this mechanism remains controversial). Transgenic overexpression of STC1 in mice provides protection against IRI-induced AKI [22], and a very recent follow up study has suggested that it may also activate AMP-activated kinase (AMPK) [23▪▪], a crucial metabolic sensor that regulates mitochondrial function (see the section below on mitochondrial biogenesis). Meanwhile, another study hot off the press has suggested that mitochonic acid, a derivative of the plant hormone indole-3-acetic acid, also lowers mitochondrial ROS production, and shows evidence of benefit in AKI because of IRI [24▪▪]. Mitochonic acid is thought to target the inner mitochondrial membrane protein mitofilin, and may also work by maintaining the normal structure of mitochondrial cristae and promoting ATP production.

Mitochondrial dynamics

Mitochondria are highly dynamic organelles, capable of fusing and dividing with each other, to exchange genetic and other information. Accordingly, mitochondria are increasingly viewed as existing within complex interconnected networks, rather than as isolated entities. In the last few years, several key players in mitochondrial fusion/fission have been identified, including the profusion proteins mitofusin 1 and 2 (MFN 1 and 2) and OPA1, and the profission protein DRP1 [25]. It has also become clear that genetic mutations in fission/fusion proteins can cause diseases in humans [5], and that mitochondrial fission is probably an important step in the release of proapoptotic factors, such as cytochrome *c*, from mitochondria into the cytosol [25]. There is, therefore, increasing interest in targeting mitochondrial dynamics pharmacologically in AKI.

In numerous previous studies, including from our own group, it has been demonstrated that normally elongated mitochondria in the proximal

tubule rapidly fragment in response to insults such as IRI and cisplatin (Fig. 1) [26]. In an elegant series of experiments, Brooks *et al*. [27] demonstrated in both cell and mouse models that DRP1 is rapidly recruited to fragmented mitochondria in the proximal tubule. They reported that inhibition of DRP1 activity, using either genetic or pharmacological approaches, was protective against mitochondrial fragmentation, initiation of apoptosis, and overall kidney damage. The DRP1 inhibitor used (Mdivi-1) has also now been shown to have beneficial effects in various other organ systems [28], and could represent a potential new therapy in human AKI.

Further evidence for the importance of mitochondrial dynamics was provided by a very recent study that investigated the role of the profusion protein MFN2 [29▪▪]. In this work, a mouse with a conditional knockout of MFN2 in renal tubules was used, as embryonic deficiency is lethal. As expected, mitochondria within the proximal tubules of these animals are punctate and fragmented, consistent with a greater tendency towards mitochondrial fission. However, contrary to expectations, the MFN2-deficient animals showed greater protection against IRI-induced AKI, compared to wild types. The explanation for this counter-intuitive result is not clear, but might relate to an increased capacity for tubular cell proliferation postinsult in the MFN2-deficient mice. These intriguing results further underline that mitochondrial dynamics are important in the pathogenesis of AKI, but also suggest that the relationship between mitochondrial morphology and outcome might not be so simple as previously thought.

Autophagy and mitophagy

Damaged mitochondria within cells are identified and removed by a process of selective autophagy termed mitophagy, whereby they are engulfed by auto-phagosomes, which then subsequently fuse with lysosomes, within which degradation of contents takes place. The turnover of mitochondria in the proximal tubule is thought to be quite high (estimated half-life of 2 weeks [30]), and inhibition of autophagy leads to the accumulation of damaged mitochondria and proximal tubule dysfunction [31]. Previous studies have shown that autophagy is activated in tubular cells in AKI, and pharmacological enhancement of this process could in theory minimize cellular stress and accelerate recovery. Support for this concept was provided by studies showing that genetic or pharmacological inhibition of autophagy worsened outcome in response to insults such as cisplatin and IRI, whereas activation with the mTOR inhibitor rapamycin was protective [31–33]. However, other studies have reported very different findings, and the role of autophagy in AKI thus remains hotly debated [34]. A full discussion of this topic is beyond the scope of this article, but plausible explanations for conflicting results include the dynamic nature of the autophagic process [35], cross-talk with cell death pathways, and a paucity of specific activators, inhibitors and markers of mitophagy [34]. Resolving these issues will

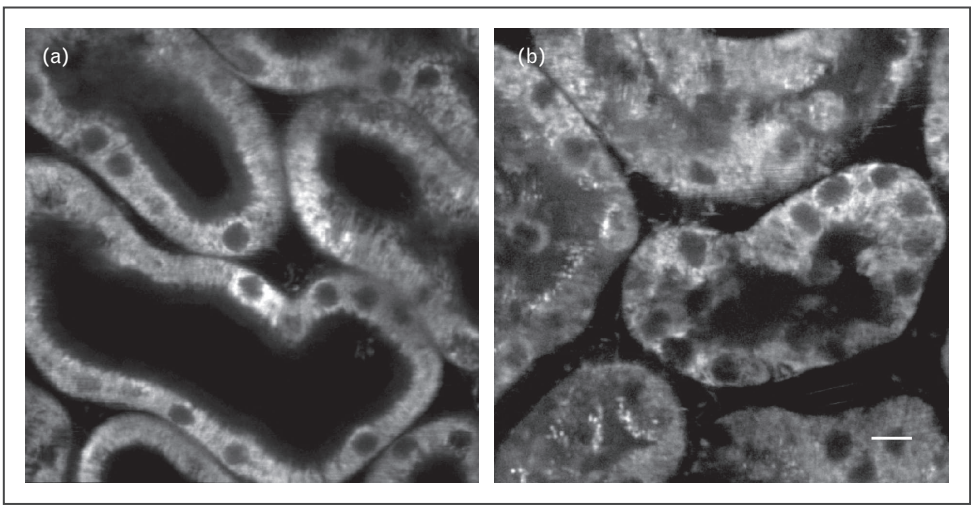

FIGURE 1. Mitochondrial damage in acute kidney injury. (a) Kidney proximal tubules contain a high density of mitochondria, which have a characteristic elongated appearance and basolateral distribution. (b) Example image acquired 48 h post cisplatin exposure, showing damaged and fragmented mitochondria in proximal tubules. Images were acquired in live anesthetized mice using intravital multiphoton microscopy and the fluorescent mitochondrial-specific probe tetramethylrhodamine methyl ester (TMRM). Scale bar = 10 μm.

therefore be necessary to enable the realistic evaluation of mitophagy as a target in AKI.

Mitochondrial biogenesis

AKI in humans is typically characterized by tubular cell damage rather than cell death [36]. Therefore, although some degree of cell proliferation and replenishment undoubtedly takes place, the principle component of recovery postinsult is probably the reestablishment of normal structure, function, and polarity in surviving proximal tubule cells. As part of this process, damaged mitochondria removed via mitophagy need to be replaced by newly generated organelles. Much has been learnt in the last few years concerning the key molecules that drive mitochondrial biogenesis within cells, and pharmacological enhancement of this process might accelerate recovery in AKI [37,38].

Peroxisome proliferator-activated receptor-γ coactivator-1α (PGC-1α) is a transcriptional coactivator that has been identified as a master regulator of mitochondrial biogenesis. The expression of PGC-1α in the kidney cortex has been shown to decline in parallel with renal function in a model of septic AKI, and then increase in the recovery phase, when mitochondrial biogenesis should be occurring [39]. Moreover, mice with a genetic defect of PGC-1α in the proximal tubule were more susceptible to injury, whereas in-vitro cell experiments suggest that overexpression of PGC-1α postinsult can enhance recovery [40]. Peroxisome proliferator-activated receptor-γ activators act upstream of PGC-1α and were previously used in the treatment of diabetes mellitus. Experimentally, these agents have shown beneficial effects in AKI because of insults including IRI, cisplatin and tenofovir [41–43]. However, they are no longer in widespread clinical usage because of adverse side effects. Another upstream activator of PGC-1α is AMPK, which acts as a crucial metabolic switch, effectively upregulating cellular metabolism in response to a fall in ATP level, and pharmacological activation of AMPK has been shown to be protective in AKI because of IRI [44]. Moreover, as mentioned earlier, very recent work suggests that the extracellular signaling protein STC1 also acts via the AMPK pathway [23▪▪].

Attention in the mitochondrial biogenesis field has also focused recently on sirtuins, which are protein deacetylases that have key roles in regulating cellular metabolism, mainly in response to changes in $NADH/NAD^+$ ratio. The sirtuin 1 (SIRT1) activator SRT1720 stimulates mitochondrial biogenesis via the PGC-1α pathway, and has been shown to enhance mitochondrial recovery and tubular function following IRI [45]. Meanwhile, very recent work suggests that SIRT3 (which is mainly localized in mitochondria) is downregulated in cisplatin-induced AKI, and that SIRT3-deficient mice are more susceptible to injury [46▪▪]. Upstream activation of AMPK conferred mitochondrial protection in wild-type but not SIRT3-deficient mice, suggesting that AMPK acts via SIRT3. There are currently no known specific activators of SIRT3, so the search is now on for such agents.

Finally, Schnellmann *et al.* have used unbiased high-throughput screening approaches to search for novel activators of mitochondrial biogenesis, and have identified the β_2-adrenergic receptor agonist formoterol as a promising candidate. In their most recent work, they have demonstrated that formoterol enhances the restoration of mitochondrial proteins and function in the kidney post-IRI, and also completely restores kidney function, suggesting that it could represent a promising new treatment for AKI [47▪▪].

CHALLENGES AHEAD

In the preceding sections, an attempt has been made to succinctly describe novel strategies currently being explored to target mitochondria in AKI (summarized in Fig. 2). In the final part, some consideration will be given to the challenges that lie ahead in migrating this exciting mass of preclinical data into effective treatments. First, some historical context is required; in the last few decades, the battlefield of AKI research has become strewn with the corpses of initially promising yet ultimately ineffective treatment strategies, the latest high-profile victim being ischemic preconditioning [48]. There are a variety of now widely recognized reasons for this, which have been covered in detail in other recent articles [49▪,50]. In summary, they include issues such as inadequacy of experimental models, publication bias, lack of appropriate biomarkers, preexisting comorbidities, and an overobsession with finding a single 'silver bullet' targeting a solitary pathway (rather than adopting a more sophisticated multilevel intervention strategy). Moreover, there may be significant species differences in how the kidney responds to insults; for example, a recent study has suggested that IRI induces much less severe structural changes in proximal tubule cells in humans than in rodents [51].

In addition to these general points, several issues specific to mitochondrial therapies require consideration. For example, in addition to a pathophysiological role in promoting oxidative stress, mitochondrial generated ROS might also have an important signaling role in providing feedback to the nucleus, and thus initiating an appropriate cell

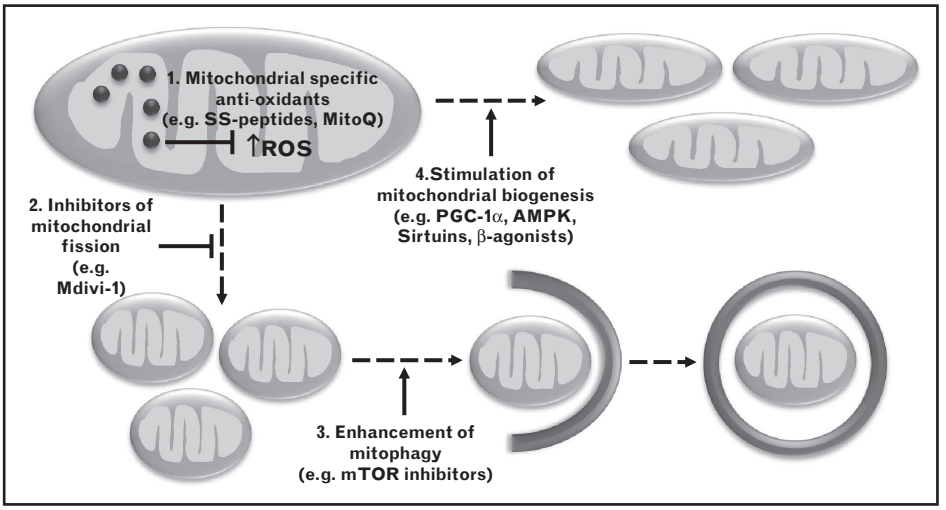

FIGURE 2. Summary diagram of current experimental strategies to target mitochondria in acute kidney injury. (1) Mitochondrial-specific antioxidants, such as SS-peptides and MitoQ, accumulate within the mitochondrial matrix and can limit the increase in reactive oxygen species (ROS) that is thought to occur in acute kidney injury (AKI), thus minimizing oxidative stress. (2) Inhibition of the pro-fission protein DRP-1 with Mdivi-1 can limit mitochondrial fragmentation and the subsequent activation of cell death pathways. (3) Damaged mitochondria are removed via mitophagy, whereby they are engulfed by auto-phagosomes, and enhancement of this process might be beneficial in AKI, but this remains controversial. (4) Stimulation of mitochondrial biogenesis by various methods can accelerate recovery post AKI. AMPK, AMP-activated kinase; PGC-1α, peroxisome proliferator-activated receptor-gamma coactivator-1 alpha.

stress response, including expression of transcription factors that regulate mitochondrial biogenesis [52]. Moreover, although antioxidants can be designed to accumulate within mitochondria, for most other drugs specifically targeting and accessing these organelles represents a huge pharmacological challenge. Furthermore, despite the fact that mitophagy could be a key component of the cellular response to AKI, it remains unclear whether we should be trying to help or hinder this process. Finally, although there are now several strategies available to enhance mitochondrial biogenesis postinsult, there are theoretical risks in doing so. For example, increased proliferation of damaged and incompletely recovered mitochondria might increase oxidative stress within cells.

Probably the biggest hindrance to date in mitochondrial medicine has been a lack of techniques to study key aspects of mitochondrial physiology in living animals. Accordingly, much of what mitochondria actually do in their native environment remains a mystery. For example, for all the *in vitro* studies implicating a role for ROS in kidney diseases, we have absolutely no idea how much ROS are actually produced in tubular cells *in vivo*. It could be argued, therefore, that we have no convincing rationale as yet to trial mitochondrial-targeted antioxidants in humans; highly effective in preclinical studies they may be, but then so was ischemic preconditioning. Serendipity aside, successful implementation of mitochondrial therapies to the kidney field will be ultimately be dependent on developing technologies that allow detailed and comprehensive real-time assessment of mitochondria *in vivo*, and how exactly these organelles are affected by disease causing insults and putative treatments.

CONCLUSION

Mitochondria are central to the pathogenesis of AKI, so when searching for new therapeutic targets it makes sense to focus on them. It is now demonstratively possible to manipulate various key aspects of mitochondrial physiology *in vivo* – including redox state, dynamics, recycling, and regeneration – and recent studies suggest that doing so could be beneficial in AKI. Additional gains might also be made by combining more than one of these strategies. However, many major hurdles lie ahead in the translational pathway, and overcoming these will require a critical and creative appraisal of what has gone wrong in the past in AKI research and what needs to change. To properly understand what happens to mitochondria in AKI, and which interventions are really effective, we may need to prioritize the development of better technology over performing more clinical trials. For the very definition of stupidity is to repeat the same thing over and again, yet somehow expect a different result.

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Conflicts of interest

There are no conflicts of interest.

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