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Review

HIVAN associated tubular pathology with reference to ER stress, mitochondrial changes, and autophagy

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A B S T R A C T

Human immunodeficiency virus associated nephropathy (HIVAN) is a unique form of a renal parenchymal disorder. This disease and its characteristics can be accredited to incorporation of DNA and mRNA of human immunodeficiency virus type 1 into the renal parenchymal cells. A proper understanding of the intricacies of HIVAN and the underlying mechanisms associated with renal function and disorders is vital for the potential development of a reliable treatment for HIVAN.

Specifically, the renal tubule segment of the kidney is characterized by its transport capabilities and its ability to reabsorb water and salts into the blood. However, the segment is also known for certain disorders, such as renal tubular epithelial cell infection and microcyst formation, which are also closely linked to HIVAN.

Furthermore, certain organelles, like the endoplasmic reticulum (ER), mitochondria, and lysosome, are vital for certain underlying mechanisms in kidney cells. A paradigm of the importance of said organelles can be seen in documented cases of HIVAN where the renal disorder results increased ER stress due to HIV viral propagation. This balance can be restored through the synthesis of secretory proteins, but, in return, the secretion requires more energy; therefore, there is a noticeable increase in mitochondrial stress. The increased ER changes and mitochondrial stress will greatly upregulate the process of autophagy, which involves the cell's lysosomes. In conjunction, we found that ER stress and mitochondrial changes are associated in the Tg26 animal model of HIVAN.

The aim of our review is to consolidate current knowledge of important mechanisms in HIVAN, specifically related to the renal tubules' association with ER stress, mitochondrial changes and autophagy. Although the specific regulatory mechanism detailing the cross-talk between the various organelles is unknown in HIVAN, the continued research in this field may potentially shed light on a possible improved treatment for HIVAN.

Introduction

The kidneys are responsible for extracting solutes from blood, filtering out wastes, and then excreting them in the form of urine. The types of fluids removed and filtered by the kidneys include but are not limited to salts, acids, and drugs. The kidneys are composed of millions of units called nephrons, each consisting of a renal tubule connected to glomeruli, tiny blood capillaries that filter out wastes from blood into the kidney tubules. Each nephron lies within the three regions of the kidney (see Fig. 1) - the outermost cortex, the medulla, and the innermost renal pelvis. In the cortex of the kidney lies the cortical nephron with short Loops of Henle, whereas the medulla contains the juxtamedullary nephron, which extends from the lower cortex into the medulla with long Loops of Henle; each type of nephron possesses similar tubules, but their location in the kidney differs. Lastly, in the innermost portion of the kidney, the collecting ducts collect the urine and transfer it to the renal pelvis, which then transfers it to the ureter (Ganong, 2003).

The kidney filtration process is honed by its renal tubular segments: the proximal convoluted tubule (PCT), Loop of Henle, and distal convoluted tubule (DCT). After solutes and wastes from the Bowman's capsule blood capillaries are filtered out, the PCT, Loop of Henle, and DCT all take various roles of reabsorption and secretion of solutes between the tubular and interstitial fluid. This transfer of solutes is aided by the tubules' extensive surface area and myriad of transport systems. Finally, before being expelled as urine, the tubular fluid is transferred to the collecting ducts where further water can be reabsorbed, depending on the levels of antidiuretic hormone (ADH) - a hormone responsible for inducing water reabsorption by binding to cell receptors in the collecting ducts (Mavani et al., 2015).

Human Immunodeficiency Virus (HIV) is an incurable virus that has been passed down from monkey to man 100 years ago. HIV attacks the body's immune system, specifically a type of white blood cell called CD4 cells (T cells), which is a vital component of the body's ability to fight off and recover from infections, which over time can lead to unique opportunistic infections or cancers, the signals for late stage HIV or

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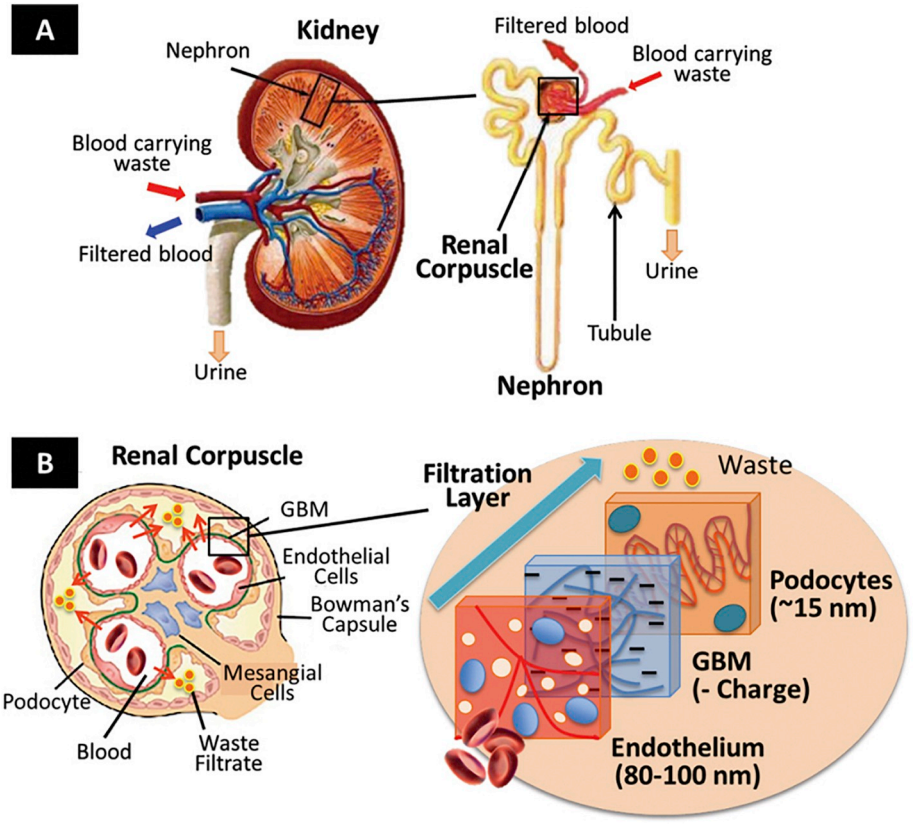

Fig. 1. The image above details the structure of the kidney. Part A displays the kidney's basic filtering units: nephrons. Part B shows the glomerulus and the three filtration layers that waste must pass through (Lee and et al., 2015)

Acquired Immunodeficiency Syndrome (AIDS) (Dahabieh et al., 2015). Currently, no effective cure exists for HIV, but with specific treatments it can be significantly controlled. Antiretroviral therapy (ART) is the medicine currently being used to treat HIV and it can potentially prolong the lives of HIV patients and prevent the transmission of HIV to others. ART has successfully increased the life expectancy of HIV infected adults, leading to a near-normal lifespan for many patients (Kariyanna et al., 2010; Nadkarni et al., 2014). Although said treatment has greatly benefitted the livelihood of many patients, scientific focus has shifted to the growing number of patients with perpetual HIV infection, which results in a mounting issue of comorbidities (Kariyanna et al., 2010; Nadkarni et al., 2014). These comorbidities originate from a variety of different organ systems each of which carry its own innate complexities and complications. This paper seeks to address possible complications associated with HIV and renal conditions.

The combination of kidney diseases being more prevalent in older patients and a plethora of elderly affected by HIV, results in many people suffering from comorbidities. Clinically, the combination of Chronic Kidney Disease (CKD) and HIV manifests as proteinuria and renal dysfunction. But, this phenomenon can also pathologically manifest as focal segmental glomerulosclerosis (FSGS), associated with other renal complications such as interstitial inflammation (Rao, 2001). These complications have been reported in nearly 10% of all HIV-infected patients in the United States (Naicker et al., 2015). Previously, CKD unfailingly progressed to end-stage renal disease (ESRD), which innately has a high mortality rate. Fortunately, with the introduction of ART, the risk of developing ESRD or other renal conditions was reduced by 60% (Naicker et al., 2015).

Similar to CKD, Acute Kidney Injury (AKI) is another extremely common renal complication amongst American patients. AKI is clinically shown through a drastic decline in Glomerular Filtration Rate (GFR), which is measured by an increase in serum creatinine or a decline in urine output (Kariyanna et al., 2010; Nadkarni et al., 2014). Furthermore, patients with pre-existing CKD are at a higher risk for AKI, which further implies that elderly patients are particularly susceptible to its development. This prediction is supported by the knowledge that AKI develops due to structural and functional deterioration of the kidney, which is also frequently associated with the aging process and the presence of comorbidities (Chao et al., 2014). Older patients with AKI are often linked with premature mortality or survivors are left with CKD, which can potentially progress to ESRD. As previously stated, AKI development is commonly compounded by the presence of comorbidities, which is frequent in HIV patients. According to a study by Christina M. Wyatt, AKI is three times more likely in HIV patients than that of the uninfected population (Wyatt et al., 2006). Contrary to CKD, AKI is very difficult to diagnose, clinically. However, severe cases of AKI may present with oliguria/anuria, anemia, uremic encephalopathy or edema (Kalim et al., 2008). Despite any prior evidence, AKI should always be experimentally confirmed through: variations in serum creatinine levels, urinalysis, or a renal biopsy. Unlike CKD, AKI is much harder to treat and does not respond well to ART treatment. For instance, the mortality rate of HIV patients affected with AKI undergoing ART treatment is still high at around 31% (Kalim et al., 2008). Typically, the response to AKI is either Hemodialysis, an increasingly common treatment, or renal transplant, which is difficult to obtain for HIV patients.

The combination of CKD, AKI and other less common renal conditions in HIV patients is commonly referred to as HIV-associated Nephropathy (HIVAN). HIVAN is a form of FSGS, specifically characterized by a collapse of the glomerular tufts and associated with tubulointerstitial lesions (Wyatt et al., 2006). Currently, HIVAN is the leading cause of ESRD in HIV affected patients. As previously stated, it manifests as azotemia, proteinuria and little to no edema in patients with HIV. Histologically, HIVAN is diagnosed by collapsing

glomerulopathy, microcystic tubular dilatation, interstitial inflammation and fibrosis (Wyatt et al., 2006).

Due to the aggressive nature of HIVAN, diagnosis was considered fatal because HIV was considered a contraindication for organ transplantation; therefore, patients commonly relied on dialysis as their only method of non-curable treatment. However, with the recent introduction of highly active antiretroviral therapy (HAART), the life expectancy of HIV patients suffering from renal issues has drastically increased to the point where kidney transplantation has emerged as a feasible option (Landin et al., 2010). A recent comprehensive review by Luis Landin of the Transplant Surgery Division of the University Hospital La Fe compared the data of HIVAN patients where the primary treatment was HAART. Amongst the 254 patients, 93% survived for 1-year and organ rejection was only diagnosed in 36% (Landin et al., 2010). Therefore, the ART era, specifically the introduction of HAART, has shed new light on HIVAN due to its ability to dramatically increase the lifespan of HIVAN patients, which in turn increases the importance of prompt diagnosis and proper care.

1. Renal Tubular Cells and their Functions

Proximal tubular epithelial cells (PTECs) are present in the PCT renal tubular segments, which are distinct cells that hold various morphological and physiological functions. These PTECs function to aid in transport of ultrafiltrate across the lumen. For example, the PTECs contain transport systems such as the sodium-glucose cotransporter 2 (SGLT2), which is expressed to reabsorb filtered glucose from the glomerular filtrate (Takesue et al., 2018). These epithelial cells in the PCT are capable of executing the functions of the PCT in recovery of fluid and secretion via their brush-border morphology. Specific to the PCT, the tubules' brush-border surface not only contains microvilli to enhance the surface area and facilitate exchange with the tubular fluid, but it also contains transporters, such as the Na^+ transporter, which is responsible for directly exchanging solutes and ions (Walmsley et al., 2010). Similar to the morphology of the PCT epithelial cells, the DCT contains cells with basolateral membranes, equipped with infoldings to facilitate transport of solutes in the tubular fluid (Subramanya and Ellison, 2014).

The first renal tubular segment that stems from the glomeruli, tiny blood capillaries, in the Bowman's capsule is the PCT (Pollak et al., 2014). The PCT is the site of the nephron where most solutes, including glucose, amino acids, phosphate, bicarbonate, and citrate are reabsorbed into the peritubular capillaries. What ensues after this major reabsorption is the secretion of drugs and their metabolites, later in the PCT (Zhuo and Li, 2013).

The component connecting the PCT and DCT is known as the Loop of Henle. Divided into three regions - thin descending loop, thin ascending loop, and thick ascending loop - the Loop of Henle functions to reabsorb water and transfer NaCl via Na^+/Cl^- transporter across the tubular membrane. In the thin descending loop, there is high permeability to water as it stems towards the renal medulla where there are high levels of interstitial solute concentration. In the thin ascending loop, permeability to water decreases and increases for ions, like Na^+ and Cl^- (Ganong, 2003). Lastly, in the thick ascending loop, Na^+, K^+, and Cl^- are all actively co-transported via the NKCC2 cotransporter; this cotransporter needs all three Na^+, K^+, and Cl^- ions to regulate the dependency of Na^+/Cl^- transport with the K^+ transport (Mount, 2014). Akin to the dysfunctions of the PCT the Loop of Henle can also manifest renal disorders.

The second tubular segment, which follows the ascending Loop of Henle is the distal convoluted tubule (DCT). The DCT primarily directs Na^+/Cl^- transport and the reabsorption of Ca^{2+} and Mg^{2+} across the epithelial membrane. In order to maintain urine pH, the DCT is also responsible for secreting protons and reabsorbing bicarbonate buffer (Subramanya and Ellison, 2014). As aforementioned, the renal tubules are capable of efficiently executing their roles not only due to their morphological layout, such as epithelial cells, but also due to their rich mitochondria (Zhuo and Li, 2013; Ralto and Parikh, 2016). This increased mitochondrial presence is intended to produce adenosine triphosphate (ATP), which provides energy for solute transport (Lee et al., 2014). Even though the renal tubular segments of the nephron consort extensively, there can still be many problems associated with them, as will be mentioned shortly. Such problems in the tubular segments can engender end stage renal disease (ESRD), a consequence of advanced chronic kidney disease or other kidney disorders, diabetes, and hypertension (Ghaderian and Beladi-Mousavi, 2014).

2. Renal Tubular Pathology in Different Renal Diseases

2.1. Renal tubular acidosis

Renal tubular acidosis (RTA) is a kidney disease that occurs due to the disturbance of bicarbonate reabsorption in the tubules or the inability of the tubules to properly excrete H^+ into the urine, thus causing increased blood acidity levels. RTA's presence is linked to the tubular segments' two regions: the PCT and DCT, each with a different characterizing factor (Yaxley and Pirrone, 2016). In the proximal tubule region, proximal RTA, also known as type 2 RTA, is characterized by the inability to properly reabsorb bicarbonate into the bloodstream. Without this buffer designed to deacidify blood, blood pH decreases and urine pH is usually more acidic (Curthoys and Moe, 2014). In the DCT, RTA is commonly referred to as type 1 RTA. At this distal site, the tubules are unable to properly secrete H^+ ions into the tubular fluid. In addition to causing this acidosis of the blood, the excretion of urine is very alkaline (Trepiccione et al., 2017). In some rare cases, type 1 RTA is associated with autoimmune diseases such as Sjögren's syndrome (Curthoys and Moe, 2014; Trepiccione et al., 2017). Individuals with Sjörgen's syndrome possess chronic inflammation in the tear and salivary glands, resulting in dry eyes and dry mouth, respectively. In addition to the inflammation, Sjörgen's can also manifest other renal disorders such as interstitial nephritis, which can lead to type 1 or distal RTA (Yaxley and Pirrone, 2016; Stefanski et al., 2017). The pathophysiology of these reabsorption disturbances in both the PCT and DCT is not extensively known; however, mechanical problems with respect to the solute transporters are evident to contribute to the pathogenesis of such dysfunctions (Karatzas et al., 2017). Additionally, with respect to the HIV virus, other literatures have speculated that antiretroviral drugs used to treat HIV patients may be a rare cause in generalized tubular dysfunction, which can ultimately lead to RTA and other renal failures (Isa and Daud, 2011). cART is the primary reason for the increased life-expectancy and drug nephrotoxicity of the HIV-infected population, leading to a greater prevalence of chronic kidney disease (CKD) (Naicker et al., 2015).

2.2. Acute tubular necrosis

Acute tubular necrosis (ATN) is a renal disorder characterized by the destruction and damage to the kidney tubules, which can commonly lead to renal failure. Often caused by ischemia, the lack of oxygen and blood flow to the kidney tubules, ATN can also be induced by tubular exposure to nephrotoxic drugs ("Pathophysiology review", 2010). Such drugs that impart nephrotoxic effects include analgesics, antimicrobials, and immunosuppressants (Popović et al., 2016). Specifically, for nephrotoxic ATN, since the kidney functions to concentrate toxins and wastes, creating an ultrafiltrate, this role also serves as a detriment to tubules by making them more vulnerable to toxic harm exposure. In addition to ischemia and nephrotoxicity, another factor in the onset of ATN is tubular obstruction. That is, individuals with excessive accumulation of immunoglobulins and uric acid crystals in the tubules may be at risk for ATN ("Pathophysiology review", 2010). Similar to the rare onset of renal tubular acidosis (RTA) induced by antiretroviral therapy for HIV patients, increased risk of ATN can also be

caused by antiretroviral medications, such as Pentamidin and Tenofovir (TDF), which target the proximal tubules (Li and Zhuang, 2013; Kalyesubula and Perazella, 2011).

2.3. HIVAN

Renal tubular epithelial cell infection and microcyst formation are characteristic histological features of HIVAN. Previously, it has been reported that the role of epithelial mesenchymal transition (EMT) is significant in the development of glomerular and tubular cell phenotypes in HIVAN (Ayasolla et al., 2015). Furthermore, it has been suggested that the HIV-1 gene transcript increases as tubules dilate and the epithelium becomes flattened and atrophic; however, the fate of the segments infected and the microcysts in HIVAN are not clearly understood (Ayasolla et al., 2015). A recent study by Kamesh R Ayasolla, et al. demonstrated that HIV, specifically HIVAN, may be contributing to tubular cell phenotype via lysophosphatidic acid (LPA) mediated downstream signaling. Furthermore, LPA and its receptors have been implicated in the tubular interstitial cell fibrosis (TIF) and cyst formation in autosomal dominant polycystic kidney disease (PKD). Therefore, there exists an association between HIV-induced tubular cell phenotype via NFkB activation in HIVAN where LPA is its contributing factor (Ayasolla et al., 2015). Additionally, it has been found that in end stage renal disease, renal enlargement may result from the presence of many tubular microcysts. Renal tubular pathology in HIVAN is also characterized by tubular degeneration and regeneration, atrophy, and impaired cytokinesis in tubular epithelial cells (Ayasolla et al., 2015).

The HIV virus itself also has posed concerns for renal tubular health, implicating that simply the virus may play a role in contributing to tubular pathology in HIVAN. In a study conducted examining the expression of HIV-1 in renal tubular epithelial cells, it was found that HIV-1 both activates an apoptotic pathway and induces G2/M arrest, possibly playing a role in tubular cell death in HIVAN (Vashistha et al., 2008). Another study has revealed that renal tubular epithelial cells may be one of the primary targets of HIV pathogenesis as they express the transgene HIV-1 highly. Increased proliferation, apoptosis, and dedifferentiation in the epithelial cell cycle all may contribute to disease pathology, especially in HIVAN (Barisoni et al., 2000).

3. Endoplasmic reticulum stress in renal diseases

The endoplasmic reticulum (ER) is an organelle that plays a huge role in a cell's translational and post-translational mechanisms. Some of the eclectic roles of the ER include synthesizing cholesterol, fats, proteins, protein folding/trafficking, and storing/releasing calcium when needed. All of the aforementioned roles are highly essential to the cell as it helps maintain homeostasis. However, with extracellular or intracellular stressors such as hypoxic conditions, energy deprivations, or mutations, the fine homeostasis maintained by the ER can easily be disrupted (Inagi, 2009). Consequences of a dysfunctional ER include misfolding of proteins and misfolded protein aggregations, which, if left untreated, can result in cellular apoptosis (Inagi, 2009). The importance of the ER and its role in protein synthesis, folding, and modification may explain the pathogenesis of several different diseases, one example being kidney disease.

Under stressful conditions, the ER increases its protein folding abilities by activating a response pathway known as the unfolded protein response (UPR). The UPR is essential to combating stress as it helps the cell halt protein translation as well as improve protein folding mechanisms via upregulating chaperone translation machinery (Cunard, 2015). UPR mainly works in three different pathways to accomplish its goals of alleviating ER stress: (1) the IRE1α, (2) PERK, and (3) ATF6 pathways (Cunard, 2015). The ATF6 and IRE1α pathways work by increasing ER chaperone gene transcription which in turn help with protein folding, and the PERK cascade works to halt protein translation (Cunard, 2015). Thus, the combination of these three pathways works synergistically to allow the ER to catch up with the misfolded proteins caused by stressors.

When tubular cells of the kidney are under stress for a prolonged duration of time, their adaptive UPR pathway is generally insufficient enough to attain homeostasis, thus the apoptotic pathway is activated to eliminate the cell (Inagi et al., 2014). The resulting tubular apoptosis thereby leads to the pathogenesis of CKD (Inagi et al., 2014). Previous literature has concluded that stressors such as proteinuria, glucose overload (hyperglycemia), oxidative stress, and nephrotoxins can trigger tubular cellular apoptosis via the apoptotic UPR pathway, which can ultimately result in tubular diseases due to ER stress (Inagi et al., 2014). In addition to the stressors described above, studies have also shown that aging can also change the effectiveness of the adaptive UPR pathway (Inagi et al., 2014). More specifically, it has been found that when aged tubular cells are exposed to proteinuria, their GRP78 (an ER chaperone protein) levels are highly suppressed whereas the apoptotic CHOP protein is greatly increased in the apoptotic UPR pathway (Inagi et al., 2014). However, the tubular cells are not the only cells affected by ER stress in the kidneys, Podocytes have an important function in the kidneys as they help with glomerular filtration, thus lots of glomerular diseases are related to podocyte injuries (Inagi et al., 2014). For example, current literature suggests that protein aggregation due to a dysfunctional ER in podocytes results in morphological and physiological damage of the cell, ultimately resulting in glomerular filtration failure and proteinuria (Inagi et al., 2014). Taken together, ER stress plays an important role in renal disease as it can affect different cells by activating the apoptotic UPR pathway under severe conditions to induce tubular cell apoptosis.

4. ER stress in HIVAN

While the ER stress plays a role in various kidney diseases and affects different types of renal cells, it remains unclear as to how it is involved in HIVAN. Previously, there is no sound evidence whether ER stress is involved in HIVAN. For this reason, we conducted research on the Tg26 mice (an animal model of HIVAN) to study the ER biochemical changes in HIVAN mice. Our data indicated a significant increase in expression of phospho-PERK as well as the corresponding PERK protein expression through immunohistochemical staining of glomeruli and western blot analysis, respectively (Bryant et al., 2018). Moreover, we also noticed a significant increase in the corresponding ATF4 levels, which further led to an increase in pro-apoptotic CHOP levels, promoting cell death (Bryant et al., 2018). These results taken together demonstrated the activation of the apoptotic UPR pathway due to severe ER stress and its implication in the pathogenesis of HIVAN.

5. Mitochondrial changes in renal diseases

While the ER plays an imperative role in a cell's translational and post-translational mechanism, the mitochondria is essential in its role in providing the energy necessary to carry said translational and metabolic processes. Primarily, this unique organelle produces ATP through oxidative phosphorylation. Structurally, the mitochondrion is a double membrane bound organelle with a complex matrix and cristae. Functionally, the membranes serve as a barrier by folding into cristae that separate the mitochondrial matrix and intermembrane space. This separation assists the organelle to uphold a proton concentration gradient that indirectly creates ATP. As an essential step in the process of eukaryotic evolution, the size of the mitochondrial chromosome was drastically reduced, and the behavior of mitochondria within eukaryotic cells radically changed. Recent advances have revealed how the organelle's behavior has evolved to allow the accurate transmission of its genome and to become responsive to the needs of the cell and its own dysfunction. The kidney is an organ that requires high amounts of energy. Thus, the high numbers of mitochondria present in the kidney is relatively unsurprising. Mitochondria constantly undergo changes by

processes known as fission and fusion. These processes are essential as they maintain structural integrity, and regulate internal organelle signaling such as metabolism and apoptosis (Che et al., 2014). Mitochondrial fusion proteins such as mitofusion 1 (Mfn1), mitofusion 2 (Mfn2), and optic atrophy 1 (Opa1), and fission proteins: fission protein 1 (Fis1) and dynamin related protein (Drp1) have recently been shown to be involved in renal pathology (Che et al., 2014). As previously stated, AKI presents itself in patients as a sudden halt in the ability to process waste material from blood. New research has found mitochondrial fission/fusion imbalance, in AKI, which has led to fragmentation of mitochondria in renal tubular cells (Che et al., 2014). More specifically, fusion is downregulated due to proapoptotic protein interaction with mfn1/mfn2, and fission is upregulated by Drp1. Overall, the fragmented organelle is now susceptible to Bax which induces permeabilization of the outer membrane, releasing cytochrome *c*, resulting in cell death via apoptosis (Che et al., 2014). Obstructive AKI due to kidney stones has been shown to in parallel relate to mitochondrial damage. Renal tubular studies indicated evidence of reactive oxygen species (ROS) production and apoptosis of mitochondria when challenged with oxalate, which was correlated with tubular atrophy in rodents (Eirin et al., 2017). Lastly, a study from Gall et al. created a mouse knockout model for the mfn2 gene (Zhan et al., 2013). In this study, the proximal tubular cells were isolated from the mice and revealed high mitochondrial fission as well as sensitivity to cytochrome *c* release and apoptosis under conditions of ATP depletion (Zhan et al., 2013). All in all, the characteristic changes of mitochondrial morphology, and thus its function, have been present in AKI and tubular cell death.

6. Mitochondrial changes in HIVAN

Given that mitochondrial dynamics change in kidney diseases, how could mitochondria be implicated, if at all, in HIVAN? Our recent in vivo studies on Tg26 mice, examined renal function and structural alterations, as well as mitochondrial function and morphology. To confirm HIVAN, kidney function was first evaluated by analyzing serum BUN, creatinine, and proteinuria. Our results showed evidence of kidney failure as indicated by significant increase in BUN, creatinine, and proteinuria levels in Tg26 mice compared to wild type (WT) mice (Bryant et al., 2018). As for the morphological analysis of the mitochondria, we found fragmented and reduced cristae membranes in the Tg26 mice, compared to the normal and organized membranes of the mitochondria in WT mice. Furthermore, mitochondria are important organelles in the modulation of ROS generation; it was found in the study that ROS is upregulated during HIVAN pathology due to inflammation and the accumulation of fragmented/damaged mitochondria (Bryant et al., 2018).

At the biochemical level, we analyzed several mitochondrial proteins; SIRT3's primary function is to regulate acylation of mitochondrial enzymes and thereby control energy output under stressful conditions. SIRT3 is known to carry out its functions via activation of PGC1α, a nuclear cofactor that coordinates the expression of nuclear-encoded mitochondrial genes, and citrate synthase, a mitochondrial enzyme, to increase and meet the energy demands of a cell. Given this information, our western blot results showed a significant decrease in SIRT3, citrate synthase, and PGC1α activity (Bryant et al., 2018). Oxidative stress also played a role in mitochondria, as we analyzed different antioxidant markers in the renal tissue of Tg26 and WT mice. With immunohistochemical staining and PCR analysis of Nrf-2 as well as HO-1, we found significant decrease in mRNA and protein levels in the glomeruli of renal tissue in TG mice suggesting high oxidative stress in renal tissue (Bryant et al., 2018). Moreover, apoptosis in TG mice was shown to increase significantly compared to WT mice as evident by increased BAX protein expression (Bryant et al., 2018). Lastly, mitochondrial fusion and fission mRNA levels: Mfn2, OPA1, Fis1, and Drp1 were analyzed by rtPCR and western blots with reported lower fusion mRNA/protein levels, but higher fission mRNA/protein levels in the Tg26 mice (Bryant et al., 2018). All in all, our results point towards a mitochondrial contribution in the pathology of HIVAN via fusion/fission imbalance, cellular apoptosis, oxidative stress, and energy depletion.

7. Autophagy in renal diseases

7.1. Autophagy

Research of autophagy is becoming increasingly popular as results show its vast involvement in the pathogenesis of a number of diseases and disorders, and methods to monitor autophagy are becoming more prominent (Havasi and Dong, 2016). Autophagy is a catabolic process composed of numerous cellular pathways, involving the cellular degradation and recycling of damaged and unnecessary cytoplasmic components in the lysosomal system to maintain cellular homeostasis (Schuck et al., 2014). Autophagy is classified into three main types: macroautophagy, microautophagy, and chaperone-mediated autophagy; the most widely understood is macroautophagy, which plays a key role in the functioning of neurons, especially in disease conditions (Levine et al., 2011; Kragh et al., 2012).

Macroautophagy can be divided into four major processes: nucleation, expansion, maturation, and degradation (Kesidou et al., 2013). During macroautophagy, the formation of double membrane autophagosomes undergoes intricate signaling pathways between various signaling proteins to fuse with lysosomes and release their contents. Then, these contents are degraded by lysosomal enzymes and are sent to the cytosol for reuse/recycle (Kesidou et al., 2013; Cai et al., 2016). Microautophagy is a much lesser known form of autophagy, but similar to macroautophagy, functions to degrade and recycle damaged cargo in the lysosomal machinery. During microautophagy, the lysosomal membrane receives the cytoplasmic contents through a process described as invagination, where the lysosome itself surrounds and directly engulfs the targeted cargo (Parzych and Klionsky, 2014).Chaperone-mediated autophagy (CMA), in contrast to macroautophagy and microautophagy, is an overall highly selective process where the lysosome is targeted by binding of the substrate to the heat shock-cognate protein of 70 Kda (hsc70). CMA initially targets the motif KFERQ, which is present in a multitude of proteins, through chaperone proteins, which work to transport the protein substrates to LAMP2A, where the cargo is degraded. After binding, the substrate interacts with LAMP2A at the surface of the lysosomes and translocated for degradation in the lysosomal lumen through the disassembly and assembly of LAMP2A. (Cuervo and Wong, 2014). Fig. 2 describes each type of autophagy in further detail (Parzych and Klionsky, 2014).

There are two major types of autophagy: bulk autophagy and selective autophagy. While bulk autophagy pertains to a wide range of cargo with no specific target, selective autophagy uses selective mechanisms in which a specific cargo is targeted (Ding and Yin, 2012). Mitophagy is a form of selective autophagy that involves the degradation and clearance of damaged mitochondria through specific proteins such as BNIP3L/NIX in the LC3-interacting region or the ligase PARK2 through the PINK1 kinase. Initiated by the phosphorylation of Atg32, mitophagy can be characterized by two steps: the activation of general autophagy and then the selective mechanism targeting mitochondria (Parzych and Klionsky, 2014; Ding and Yin, 2012).

7.2. Autophagy in kidney health and disease

Macroautophagy, hereinafter referred to as 'autophagy, plays various roles in the healthy kidney, including the glomerular, podocyte, and tubular cells, in order to maintain cellular homeostasis and function. In specificity to tubular cells, although autophagic function is relatively lower, deletion of the Atg5 gene resulted in deteriorative effects such as accumulation of incompetent mitochondria, apoptosis,

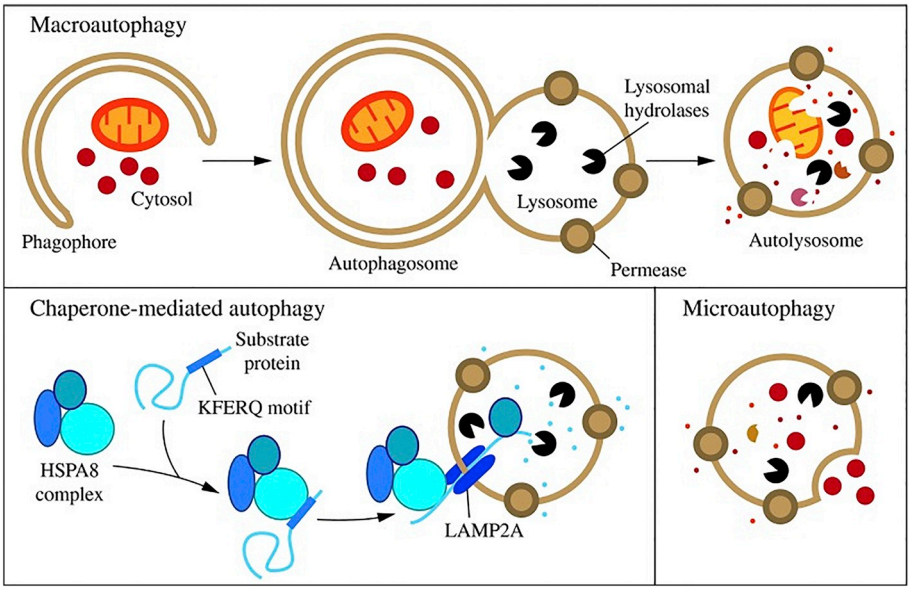

Fig. 2. The three types of autophagy in mammalian cells (Parzych and Klionsky, 2014).

hypertrophy, degeneration, and impairment in kidney function (Wang and Choi, 2014; Cybulsky, 2013). However, in the distal tubule and collecting duct, the deletion of the autophagy gene seemed to have no significant impact (Havasi and Dong, 2016). Overall, autophagy is an integral component to the maintenance of glomerular, podocyte, and tubular homeostasis and disruption of it leads to injury and disease. Although chaperone-mediated autophagy is often far less common than macroautophagy, it has been found that in the basal tubular cells of the kidney, CMA is activated in far greater levels. Class 1 PI-3 kinase signaling shows that in proximal tubular cells, which have relatively low glycolysis levels, Akt upregulates glycolysis activity while also inhibiting FoxO, resulting in decreased CMA activity (Franch, 2014). Despite this, CMA is still greatly active due to its upregulation through dietary lipids, activity of other proteolytic pathways, and oxidative stress. CMA is upregulated during inhibition of macroautophagy as well as inhibition of the ubiquitin-proteasome system; oxidative stress also promotes CMA through an increased presence of KFERQ substrate proteins (Cybulsky, 2013; Franch, 2014). Studies with cultured rat renal epithelial cells have provided insight on the contributory role of upregulated CMA to disease, as suppression of CMA resulted in an increase in PAX2, a protein vital to kidney development (Franch, 2014). This increased activity of CMA in kidney cells has great implications during kidney disease.

Several common kidney diseases have been discovered to have strong relations with autophagy, including diabetic nephropathy (DN) and AKI. An understanding of the role of autophagy in these kidney diseases gives further insight and implications in the potential roles of autophagy in other kidney disease including HIVAN. In the diabetic kidney, it has been determined that there is increased KFERQ signal motif in parallel with decreased LAMP2a in control kidneys of mice, potentially implicating that CMA regulation is important for ameliorating kidney disease. Furthermore, podocyte cells in mouse models of

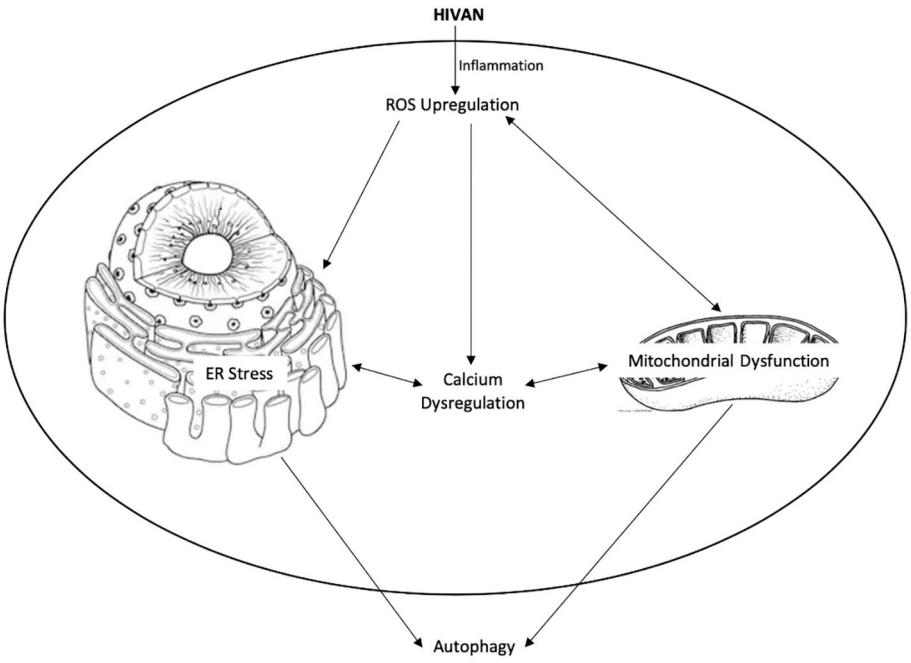

Fig. 3. A summary of the interplay between ER stress, mitochondrial changes, and autophagy in context to HIVAN pathology. During HIVAN, characteristic inflammation results in the upregulation of ROS which thereafter induces ER stress, calcium dysregulation, and mitochondrial dysfunction. This dysregulation of calcium further upregulates both the ER stress response and mitochondrial dysfunction. As a result, autophagy related signaling cascades are activated. Because of the inter-dependency between calcium dysregulation, ER stress, and mitochondrial function, disease pathology seems to persist, ultimately leading to excess levels of autophagy and thereby a clear disruption of cellular homeostasis.

diabetic nephropathy show enhanced mechanistic/mammalian target of rapamycin (mTOR) activity, and the administration of rapamycin in both type 1 and type 2 diabetes models mice resulted in the prevention of DN (Ding and Yin, 2012). This may be due to the altered nutritional state and differences in intracellular stress that is characteristic of diabetic nephropathy, as both are regulators of autophagy.

In AKI, a renoprotective role of autophagy was observed (Ding and Yin, 2012). Studies have found that the inhibition of autophagic activity promotes injury in a mouse model of AKI, as it initiates a shift to apoptosis (Cuervo and Wong, 2014). Similar results were observed in an ischemia reperfusion renal injury mouse model of AKI, as suppression of autophagy increased apoptosis in tubular cells (Cybulsky, 2013). Autophagy also helps to protect renal tubular cells against cyclosporine toxicity during AKI. Despite these positive roles of autophagy, many negative effects have also been found. In one study, suppressing autophagy through the overexpression of BCL2L1 resulted in ameliorated apoptosis, renal dysfunction, and ischemia (Huber et al., 2012; Yang et al., 2008). Tubular cell studies have also depicted that the ER stress induced autophagy targets damaged tubular cells; DAP-kinase KO mice show amelioration of injury due to reduced tubular cell autophagy (Huber et al., 2012; Gozuacik et al., 2008). Overall, studies have shown a duel role of autophagy in acute kidney injury; further research is needed to determine the precise interactions between autophagy and disease progression.

7.3. Autophagy in HIVAN

Although it still remains unclear the true effect of autophagy on the kidney, during health and disease, research has established that autophagy has a prominent role in the survival of kidney cells, including glomerular mesangial, renal tubular cells, and podocytes, during various kidney-related diseases. Since the last few years, research has also been focusing on the significance of autophagy in HIV and various HIV related conditions due to the vast role of autophagy in the immune system (Nardacci et al., 2017). Recent research also suggests that autophagic activity is also important in the pathogenesis of HIVAN.

As described above, mTOR pathways in various kidney diseases, including diabetic nephropathy, AKI, and polycystic kidney, are greatly activated and potentially play a contributory role to the progression of disease. Similarly, it has been shown in a study conducted by Kumar et al. that mTOR pathways are extensively active in the glomerular and tubular cells of HIVAN mice (Kumar et al., 2010). Podocytes in HIVAN mice also showed increased phosphorylation of mTOR and renal tissue. As glomerular and tubular lesions are primary characteristics of HIVAN disease, these findings suggest a contributory role of mTOR on HIVAN disease. Furthermore, the study investigated the effect of inducing rapamycin, a potent inhibitor of mTOR, on the pathogenesis of HIVAN. The results, as expected, showed less renal lesions, attenuated HIVAN phenotype, and reduced proteinuria, a common symptom of HIVAN that signifies impairment of kidney function (Kumar et al., 2010). Considering the relationship between mTOR and autophagy and the prominence of autophagy in other kidney disease, this suggests a relationship between reduced autophagic activity and the development of HIVAN. Additionally, oxidative stress is critically associated with the progression of HIVAN. A 2013 study demonstrated the down-regulatory role of mTOR signaling in the development of p53-induced oxidative kidney cell injury in HIVAN mice (Rai et al., 2013). The results of the study showed that inhibiting mTOR through rapamycin greatly ameliorated disease conditions by reducing sclerosis in glomeruli and tubular microcysts while also playing a protective role against podocyte apoptosis, which again suggests that HIVAN pathology is associated with reduced autophagic activity (Rai et al., 2013).

There is also a potential relationship between autophagy and the ApoL1 gene. HIVAN is characterized by dysregulation and dysfunction of podocytes and glomerular cells (Ray and Hu, 2011). In these types of cells, it has been found that autophagy is central to maintaining homeostasis and plays a protective role against glomerular injury, as Atg5 deficient mice were more prone to glomerular and renal disease (Hartleben et al., 2010). Another characteristic of HIVAN is the identification of the ApoL1 gene. Apol1 novel BH3-only pro-death protein that is often strongly correlated with autophagic and apoptotic activity, as it is homologous to the Bcl2 class of proteins; when overexpressed, ApoL1 induces autophagic cell death (Ray and Hu, 2011; Fine et al., 2012). In healthy kidney tubular epithelial cells, it is noted that ApoL1 is strongly expressed and is induced by cytokines such as tumor necrosis factor-alpha (TNF-a) and interferon-gamma (IFN-y), both of which are proinflammatory cytokines upregulated in HIV cells, suggesting that autophagy promotes disease through ApoL1. Furthermore, as ApoL1 is very involved with autophagic mechanisms, disruption of this gene through genetic variants and mutations potentially inducing cytotoxicity and kidney injury (Ray and Hu, 2011; Kruzel-Davila et al., 2017). Specifically, research has confirmed that the G1 and G2 mutation of the ApoL1 gene greatly increases susceptibility to HIVAN, although only present in the African American population (Kruzel-Davila et al., 2017). In general, ApoL1 variants have a critical role in contributing to the progression of kidney disease, including HIVAN, perhaps through inducing autophagy and autophagic cell death. However, further research has also opened implications towards more underlying factors which are yet to be known. For instance, a study amongst 76 HIVAN patients revealed that there were no significant clinical or pathological differences between patients with or without the ApoL1 gene (Atta et al., 2012). In the future, a greater understanding of the connection between autophagy and the ApoL1 gene may increase knowledge of the HIVAN pathogenesis.

The nef gene is also very involved in the pathogenesis of HIVAN. Numerous studies, including both in vitro and in vivo evidence, show that the nef gene is overexpressed in HIVAN, thus it plays a central role in the disease's progression. HIVAN is a result of the expression of viral genes in renal epithelial cells, nef being one of these. More specifically, the nef gene largely contributes to podocyte dysfunction. Various studies have exhibited that solely the nef gene is sufficient to induce podocyte de-dedifferentiation and glomerulosclerosis (Medapalli et al., 2011). Nef plays a significant role in dysregulating autophagic activity. It has been observed that expression of nef is directly correlated with an increase in specific autophagic marker proteins ATG8/LC3-II and p62. This data suggests that nef acts to halt the autophagic process by mimicking the mechanisms of autophagy inhibitor Bafilomycin A1 (Saribas et al., 2015). From this, it is reasonable to infer that the nef gene plays a vital role in the progression of HIVAN by downregulating autophagic activity, resulting in a disruption of homeostatic balance.

8. Interplay between ER, mitochondria and autophagy in renal diseases

Recently, it has been found that the dynamics and interactions between the mitochondria and ER actually alter as the cell receives specific signals (Rainbolt et al., 2014). In the earlier stages of ER stress, the interaction between a mitochondrion and ER increase, thereby promoting more calcium influx into the mitochondrion (Rainbolt et al., 2014). This in turn promotes metabolism via upregulation of the Krebs cycle, ultimately increasing oxidative phosphorylation activity to increase ATP output (Rainbolt et al., 2014). Overall, this sudden increase in energy helps promote the translation of stress-response proteins to combat ER stress. Conversely, prolonged exposure to stress decreases aerobic respiration, lowers ATP available, and builds calcium deposits in the mitochondrion as it gets depleted from the ER (Rainbolt et al., 2014). Such prolonged exposure to ER stress ultimately leads to the opening of mitochondrial permeability transition pore (MPTP) which increases the calcium influx to the mitochondria, and activates apoptosis. Parkin, a key protein responsible for mitophagy and regulation of mitochondrial dynamics, is an example of a link between mitochondrial-ER crosstalk (Senft and Ronai, 2015). During ER stress and ATF4

upregulation, Parkin gets activated by ATF4 which in turn helps regulate the calcium transfer between ER and the mitochondrion, ultimately controlling mitochondrial respiration and energetics during ER stress (Senft and Ronai, 2015). Adding on, mitochondrial fission/fusion proteins also link ER stress and mitochondrial function. For example, mitofusion 2 (mfn2) is a key fusion protein which, upon inactivation, results in mitochondrial calcium accumulation, and low respiration (Senft and Ronai, 2015). Moreover, while mitofusion 1 (mfn1) is a protein responsible primarily for regulating mitochondrial fusion, mfn2 is highly abundant in mitochondria-ER contact sites (MERC) present between the ER and mitochondria, where it helps to regulate ER and mitochondrial tethering ((Basso et al., 2018). Mitochondrial fusion proteins could rescue damaged mitochondria via facilitating interactions with ER to promote exchange of metabolites (Rainbolt et al., 2014). Moreover, mitochondrial fission can further help regain mitochondrial function by allowing cells to separate non-functional mitochondria from functional, allowing them to target mitochondria more effectively (Rainbolt et al., 2014). The above two functions that utilize mitochondrial quality control pathways are mediated by PERK (Rainbolt et al., 2014). Lastly, PERK signaling can also regulate mitochondrial function by upregulating the E3 ligase Parkin via downstream activation of ATF4 (Rainbolt et al., 2014). In doing so, the overexpression of Parkin increases the interaction between ER and mitochondria, promoting more calcium transfer and overall cell survival, as it helps promote ubiquitination for protein degradation, mitophagy, and maintain mitochondrial protein homeostasis (Rainbolt et al., 2014). Understanding the role of Parkin in promoting ubiquitination, a recent study done by Basso et al. discovered that in both cells deficient for parkin, and in Parkin mutant human fibroblast cells the interaction and tethering between the mitochondrion and ER is decreased (Basso et al., 2018). Moreover, Basso et al. hypothesized whether the role of ubiquitination of mfn2 plays a post translational role in promoting a mitochondria-ER interaction. Thus, they seeked to first identify sites of parkin-mediated ubiquitination on mfn2, and found that lysine 416 (K416) was the site in the HR1 domain of mfn2 (Basso et al., 2018). After that finding, Basso et al. created K416 mutants that were unable to be ubiquitinated, and found that the resulting mutant was also unable to create mitochondria-ER interactions. Adding on, this result also led to less mitochondrial uptake of calcium ions upon treatment (Basso et al., 2018). All in all, this supports previous literature regarding the role of Parkin in mediating ubiquitination on proteins, and Basso et al.'s study demonstrates the important role ubiquitination has on mitochondria-ER interactions.

Furthermore, there exists a strong relationship between the signaling pathways of autophagy and mitochondrial function. The interplay between autophagy and mitochondria has been traced to several mitophagy and nonselective autophagy proteins, holding potential implications in various diseases. Studies have demonstrated the extensive intiatory and mediatory role of ubiquitin ligase Parkin in the depolarization of mitochondria. This data has opened the door to new hypotheses regarding the role of autophagic dysfunction in Parkinson's Disease (Narendra et al., 2008). Such examples of data are a focus of increasing interest in myriad diseases. In the life cycle of mitochondria, autophagy targets depolarized mitochondria through fission, suggesting the effect of efficiency of fission on the rate of mitophagy. Parkin also aids in the development of Mfn1 and Mfn2 fusion pathways that work to maintain mitophagy effectiveness. Ultimately, the adaptation of mitochondria, in context of function and morphology, is essential to the proper carrying out of autophagy during nutrient starvation for mitochondria, highlighting the interplay. To maintain the homeostasis of mitochondria, it is important that autophagy does not interfere with healthy mitochondria. To ensure this during events of excess autophagy, fission GTpase Drp1 is phosphorylated by protein kinase A (PKA). This results in a favor in fusion activity than protectively elongates mitochondria and thus maintains ATP levels (Okamoto and Kondo-Okamoto, 2012). In fact, results were found within only one hour of induced nutrient starvation. In a study detailing the effect of significant autophagic gene Atg7 on the liver response to conditions of nutrient starvation, the important role of autophagy in the regulation of various cellular abnormalities including dysfunctional mitochondria (Okamoto and Kondo-Okamoto, 2012; Komatsu et al., 2005). Furthermore, deficiency in mitochondrial respiratory function hinders the induction of Atg8, again displaying mitochondria as a regulator for autophagy (Graef and Nunnari, 2011).

With the given information, strong connections can be made to associate signaling pathways of autophagy and mitochondrial function, which can be traced to certain mitophagy and nonselective autophagy proteins. The research has opened the door to new hypotheses regarding autophagic activity and its prevalent consequence of the UPR response during ER stress, which has potential implications in other diseases. The PERK pathway is the largest UPR branch in the regulation of autophagy and it achieves this by inhibiting mTOR through the translation of transcription factor ATF4, which then induces CHOP, resulting in autophagy upregulation. Knockout studies of ATG mice have shown that ATF6 and IRE1a branches of UPR also have similar effects on autophagy by displaying reduced autophagic signaling (Rashid et al., 2015). ER stress also induces the GSK3β-TIP60-ULK1 pathway, which then leads to the phosphorylation of TIP60. This in turn leads to the acetylation of ULK1 and enhanced CHOP expression, thus upregulating autophagic activity (Nie et al., 2016). Moreover, EIF2AK3, a translational initiation factor, is required due to the accumulation of misfolded protein, which can be treated with the induction of autophagy. The induction of autophagy is further controlled by the downstream UPR mediators of EIF2AK3 such as ATF4 and DDIT3. Another method to induce autophagy through EIF2AK3- and ATF4-DDIT3 pathways demands a hypoxic environment which ultimately involved regulation of MAP1LC3B and ATG5 proteins. Alternatively, during episodes of high ER stress, ERN1 induces autophagy via activating AMPK or through the dissociation of BENC1 from its binding with anti-apoptotic protein BCL2 via MAPK8-mediated phosphorylation of BCL2. Research also implies that factors downstream of ERN1, such as XBP1, also play an essential role in the negative feedback loop of ER stress-mediated autophagy. Proteolytic cleavages under ER stress can potentially upregulate DAPK1. The increased DAPK1 phosphorylates BECN1, which again leads to the dissociation of BCL1 from its negative regulator, thereby triggering autophagy (Rashid et al., 2015). Overall, the misfolded protein, a common feature in many neurodegenerative diseases, induces ER stress and, therefore, inhibits autophagy functionality. Overall, it is widely understood that ER stress is a potent inducer of autophagy in order to maintain cellular homeostasis.

9. Conclusion

While ART has effectively improved the lifespan of the HIV population, it has also left this population perpetually infected, resulting in comorbidities of myriad organs. This paper reviewed HIV-associated renal tubular pathology and the mechanistic interplay of subcellular disruptions, all of which is summarized in Fig. 3. Kidney cells have various organelles, including the endoplasmic reticulum (ER), mitochondria, lysosomes, and peroxisomes, that are maintained by homeostatic mechanisms dependent on cellular demands. When the ER capacity is insufficient, during cellular differentiation or HIV viral propagation, the ER stress response increases the expression of ER chaperons and ER-mediated degradation factors. This balance may be restored through increased synthesis of secretory or membrane bound proteins. On the other hand, the mitochondrial stress response upregulates mitochondrial chaperons and protease expression in the mitochondrial matrix and intermembrane space when unfolded proteins accumulate in the mitochondria. In turn, the lysosome stress response is activated during autophagy to increase the function of the lysosome by transcriptional induction of lysosomal genes. Research on this organelle interplay is extensive in other renal pathologies; however, the specific

pathological molecular mechanisms of the HIV stress response in kidney, specifically the ER, mitochondria and autophagy has been relatively unmarked despite their intricate interplay. Renal cells have all these organelles. However, their pathological molecular mechanisms associated with HIVAN remain unclear. In this context, research about the HIV stress response in kidney, specifically the ER, mitochondria and autophagy, has been relatively unmarked. It is difficult to pinpoint their similarities, differences, and cross-talk. Many studies have focused their attention on the connection between mitochondria and other organelles. From these findings it is concluded that these contacts are associated with various processes including trafficking, mitochondrial stress, ER stress, autophagy, apoptosis, and many other events. All of these functions are crucial in kidney cell fate following HIVAN, allowing us to conclude that ER stress, mitochondrial dysfunction, and autophagy dysregulation are associated with HIVAN and are involved in the perturbation of cellular homeostasis and function.

In our recent work, we have identified changes of mitochondrial biology and ER stress in the cortex of HIVAN Tg26 mice (Bryant et al., 2018). HIVAN inhibits the capacity of the kidney to counteract mitochondrial stress, maintain/recover mitochondrial function, and repair mitochondrial and cellular damage associated with HIVAN. While renal cells are highly mitochondrial energy-dependent, mitochondrial dysfunction will eventually lead to inhibition of renal function and renal cell damage. All of our findings indicate that cross talk between ER and mitochondria play a crucial role in HIVAN. However, studies on the role of ER, mitochondria and autophagy are still in their infancy, and many questions have to be addressed. A growing body of literature now connects the relationship between ER stress, mitochondrial changes and autophagy to calcium homeostasis. The foundation of this extra connection is based on the fact that calcium homeostasis plays an important role in the induction of autophagy and the regulation of mitochondrial dynamics; thereby, indirectly associating calcium homeostasis with ER stress (Kania et al., 2015). Therefore, research should begin placing a greater focus on these organelle relationships as more potential mechanisms to target ER stress during HIVAN pathology to develop a treatment for HIVAN.

Author's contribution

The authors above have made a valuable and/or intelligent contribution to the review and agreed jointly to approve it for publication.

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