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Autophagy as a novel therapeutic approach for MSC-based therapy in acute renal damage: a comprehensive review

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Abstract: A prevalent, dangerous medical illness with bad prognoses is acute kidney damage (AKI). A conserved multistep system called autophagy is important for numerous biological activities as well as illnesses. Recent research has shown that during AKI, proximal tubular cells undergo autophagy induction. Under some circumstances, autophagy has a pro-survival or pro-death function. Mesenchymal stem cells (MSCs) also provide therapeutic promise for the restoration of kidney damage. The current state of knowledge about the function of autophagy in AKI and MSC-based AKI therapy is compiled in this review. In order to prevent and treat acute renal damage, more research is anticipated.

Keywords: *MSCs; acute kidney injury; cisplatin; autophagy*

1.Introduction

AKI is a major health issue that affects people all over the world, and its prevalence is rising as a result of medication side effects or the consequences of other illnesses. AKI also causes chronic kidney disease, uremia, and hypertensive nephropathy to develop. (Shord, Thompson et al. 2006, Shi, McMillan et al. 2018, Landau, Guo et al. 2019).

Effective therapeutic options are limited, the mechanism of cisplatin-induced nephrotoxicity is complex, and early identification is difficult. While cisplatin is a potent chemotherapy treatment for a variety of solid tumors, its usage is limited by unfavorable side effects on healthy organs. Nephrotoxic drugs like cisplatin can harm the kidneys, leading to both acute kidney injury and chronic kidney disease.

Preclinical research has provided light on the intracellular stressors, such as DNA damage, mitochondrial disease, oxidative stress, and endoplasmic reticulum stress, that contribute to the cellular and molecular mechanisms of cisplatin nephrotoxicity. In the cause of cisplatin nephrotoxicity, stress responses such as autophagy, cell-cycle arrest, senescence, apoptosis, programmed necrosis, and inflammation play a significant role.

Further study is needed to understand how these pathways are integrated and to identify the cell type-specific roles of essential substances involved in regulated necrosis, inflammation, and epigenetic modifications in cisplatin nephrotoxicity. Several potential therapeutic targets for cisplatin nephrotoxicity have been identified. However, a careful assessment of how renoprotective measures affect the effectiveness of cisplatin treatment is required. A thorough knowledge of the intricate cellular and molecular mechanisms underlying cisplatin nephrotoxicity and genome-wide association studies will be made possible by more study using tumor-bearing animals, multi-omics, and genome-wide association studies. lead to the potential discovery of specific targets for protecting the kidney without reducing cisplatin's effectiveness as a chemotherapy agent (Tang, Livingston et al. 2023).

Interestingly Mesenchymal stem cells (MSCs) represent a novel therapeutic aid in regeneration and maintenance of the damaged organ. Among these cells is the breast milk derived mesenchymal (Br-MSCs) stem cells that displayed a several characters of the embryonic one without the threating of tumor or teratoma formation. Since these cells expressed several embryonic transcription factors that ensure a unique regenerative capabilities and plasticity

Autophagy is one of the cellular conserved mechanisms that modulates that cellular damage and conserving a tissue positive energy balance thus it so-called the cellular quality control system, which aid in recycling the damaged organelles therefore, it is considered one of the tissue regenerative mechanisms. However, the data regarding the interplay between MSCs and the autophagy process is scanty. Thus, the current review summarized the role of the autophagy process in modulating the cisplatin-induced AKI in referring to the crosstalk between this conserving mechanism and MSCs.

2. Pathophysiology and molecular mechanism behind Cisplatin-induced nephrotoxicity

Cisplatin is a very successful and clinically advanced anticancer medication that is used to treat a variety of solid cancers, including ovarian cancer, stomach cancer, and lung cancer. (Dasari and Tchounwou 2014). The main adverse consequence of taking cisplatin is nephrotoxicity, though. According to clinical studies, patients with acute kidney damage (AKI) who use cisplatin run a risk of nephrotoxicity that ranges between 20% and 35% of death. (Gonzalez-Vitale, Hayes et al. 1977, Pierson-Marchandise, Gras et al. 2017). Additionally, when using cisplatin, pediatric children also experience nephrotoxicity. (Barton, Pizer et al. 2018). Numerous cytotoxic pathways used by cisplatin to cause nephrotoxicity. In addition to causing DNA damage, cisplatin also activates apoptotic pathways, damages cells through oxidative stress and inflammation, and causes cytoplasmic organelle malfunction, especially in the endoplasmic reticulum and mitochondria. (Pabla and Dong 2008). There is currently no medication that can either prevent or treat cisplatin-induced nephrotoxicity. To guard against cisplatin-induced AKI, numerous high-efficacy and low-toxicity medications made from natural components have been created. Ginseng, curcumin, and pomegranate are a few examples of foods that have antioxidant and anti-inflammatory properties. They may also help to prevent oxidative stress by increasing

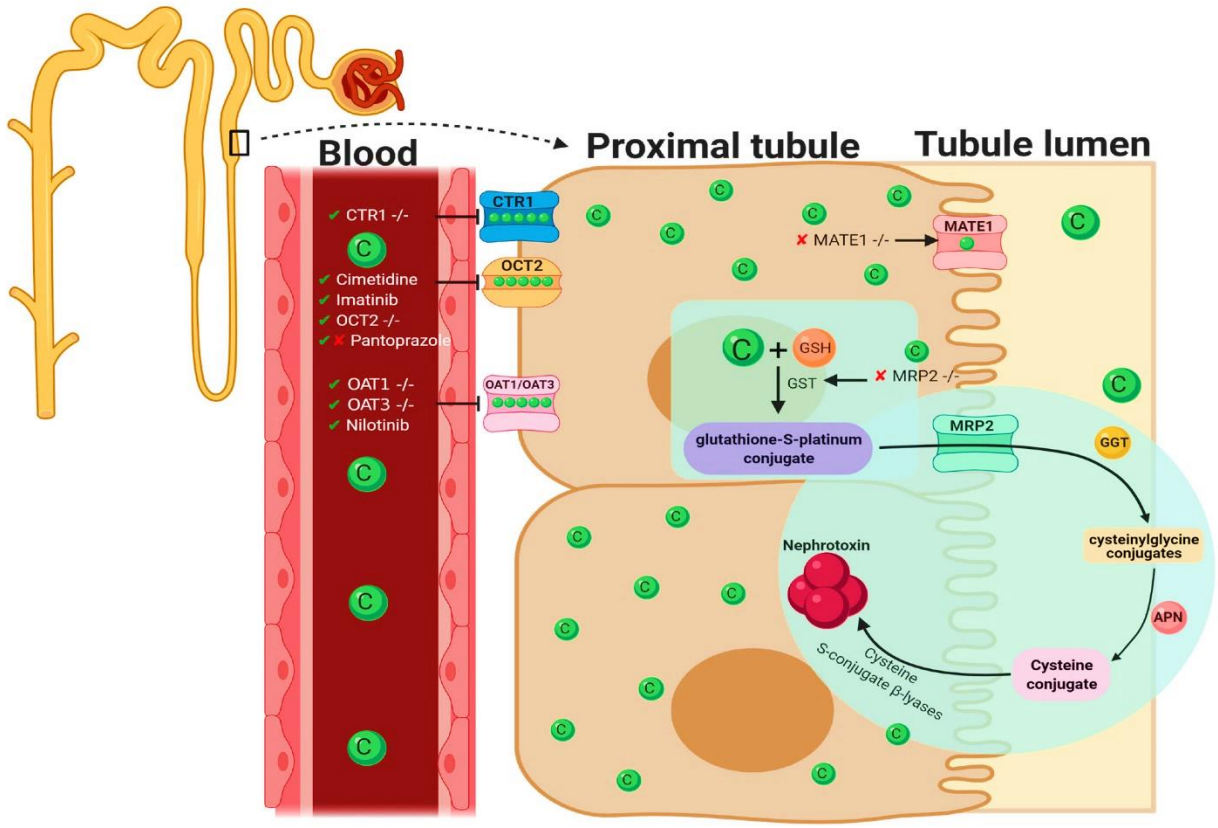

Fig.1 Mechanism of the cisplatin induced acute kidney injury.

the levels of antioxidant enzymes. (Ridzuan, Rashid et al. 2019). Clinically, cisplatin may cause varying degrees of nephrotoxicity at various doses. Patients who get a single dosage of cisplatin may experience reversible kidney damage, whereas high doses or repeated rounds of treatment may result in irreversible renal failure. (Cornelison and Reed 1993). Furthermore, pharmacokinetic studies demonstrate that the long-term accumulation of cisplatin in the kidney and the high volume of cisplatin distribution are the primary causes of nephrotoxicity. (Ibrahim, Chang et al. 2019). Reduced renal blood flow and glomerular filtration rate are the basic pathogenic causes of cisplatin-induced nephrotoxicity. (Li, Bowmer et al. 1994).

3. Histopathological alteration in cisplatin induced nephrotoxicity.

Positive correlation exists between the dose of cisplatin and the histopathological alterations in cisplatin-induced nephrotoxicity. Organic cation transporter 2 (OCT2) allows cisplatin to be passively absorbed into renal tubular cells, where it first hydrates with water molecules, resulting in ongoing buildup in renal cells(Eljack, Ma et al. 2014). The process of cisplatin hydrate production is reversible, and the substance can be released from cells by splitting into cisplatin and water molecules. (Eljack, Ma et al. 2014). Renal tubular epithelial cells with a brush form initially shed due to cisplatin. Epithelial cells experience necrosis and eventually shed with increasing cisplatin accumulation, along with the development of proteinaceous casts. (Ozkok and Edelstein 2014). Additionally, tubules enlarge and the proximal tubule basement membrane thickens. (Yang, Yu et al. 2018). Electron microscope analysis of the ultrastructure of epithelial cells reveals enlarged and vacuolated mitochondria, expanded endoplasmic reticulum, and more lysosomes. (Prasad, Rosangkima et al. 2010).Numerous immune cells, including macrophages, dendritic cells, and T cells, are attracted to damaged renal tubular epithelial cells and produce a variety of inflammatory factors as a result. (Salei, Rambichler et al. 2020). Furthermore, cisplatin might worsen tubular cell damage and limit medullary blood flow, resulting in acute ischemia injury to the kidneys. (Winston and Safirstein 1985). Evident vasoconstriction occurs in cisplatin-induced AKI in place of the typical self-regulatory renal vasodilation in

ischemic kidneys, which in extreme cases might result in hypoxic injury and vascular injury. (Bonventre and Zuk 2004). Recent investigations have demonstrated that OCT2, copper ion transporter 1 (CTR1), and solute carrier family 22 member 2 are involved in the uptake of cisplatin by renal tubular cells. (Yonezawa, Masuda et al. 2005). Additionally, multidrug and toxin extrusion 1 and solute carrier family 47 member 1 secrete cisplatin into the lumen. (Iwata, Aizawa et al. 2012). The Oct2 gene can be knocked down to considerably lessen the nephrotoxicity brought on by cisplatin. (Filipski, Mathijssen et al. 2009). Patients with Oct2 mutations consistently exhibit low OCT2 expression and reduced cisplatin transport into renal tubular cells, which reduces nephrotoxicity. (Ciarimboli 2014).

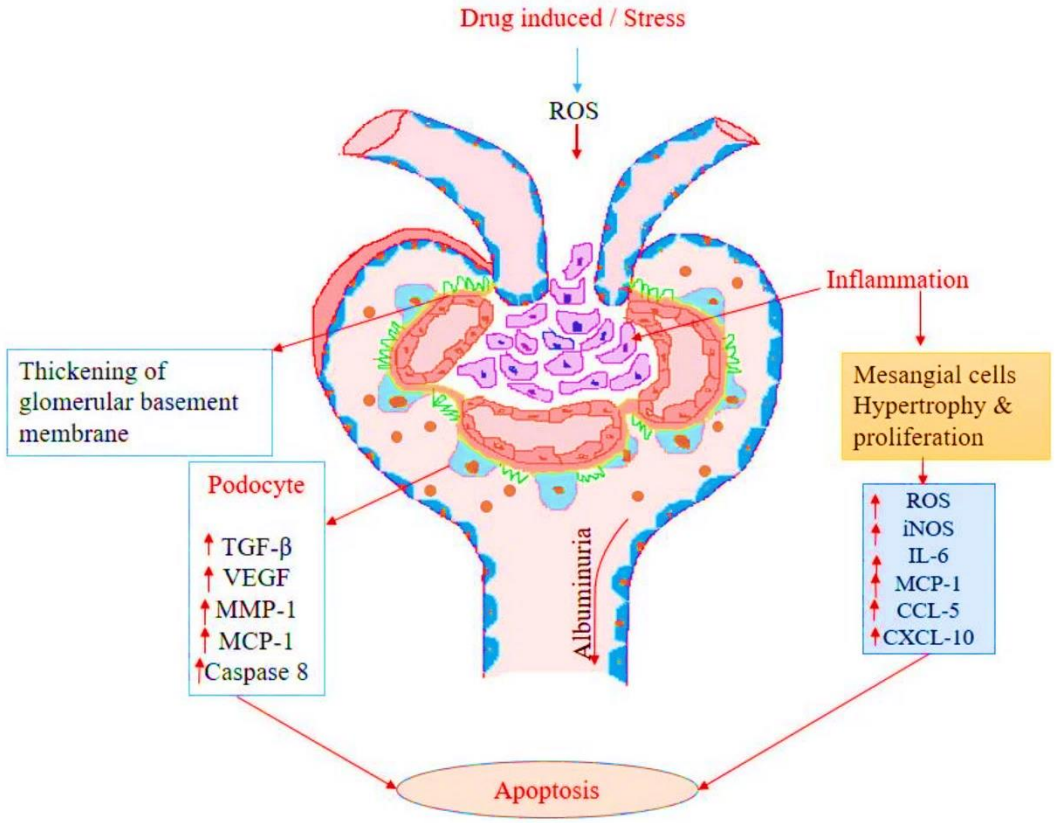

Fig.2 Histological alteration associated with cisplatin induced AKI

Additionally, cisplatin absorption and the associated cytotoxicity are considerably reduced when CTR1 expression is downregulated. (Pabla, Murphy et al. 2009). Additionally, cisplatin is excreted from the body at a higher rate in Prx I-deficient animals than in wild-type mice because these mice have higher expression levels of the renal efflux transporters multidrug resistance-related protein 2 (MRP2) and MRP4 than wild-type mice. (Okada, Ma et al. 2013). In order to produce DNA damage, cisplatin binds to DNA to form adducts, which is how it exerts its cytotoxic effects. (Wang and Lippard 2005). Caspase-dependent and -independent pathways make up the majority of the mitochondria-mediated apoptotic pathways that are triggered by cisplatin. The release of cytochrome c, the second mitochondria-derived activator of caspase/direct inhibitor of apoptosis proteins binding protein with low Pi (isoelectric point), the high temperature requirement A2 (HtrA2/Omi), and the apoptosis-inducing factor (AIF) from mitochondria occurs when the drug cisplatin enters renal tubular epithelial cells. Green and Reed 1998). Then, caspase-9 is activated upon, which ultimately results in apoptosis. (Guerrero-Beltrán, Calderón-Oliver et al. 2010).

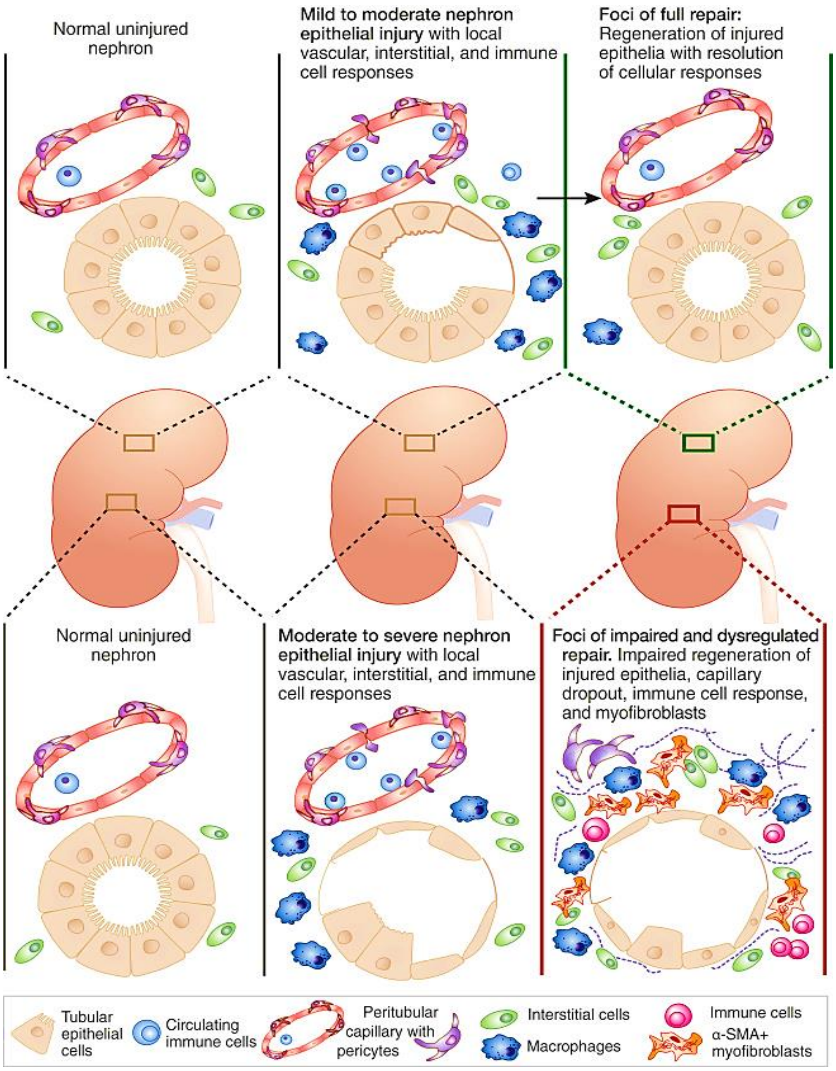

Fig.4 Different stages of developing AKI

After cisplatin-induced apoptotic activation, cytoplasmic Omi/HtrA2 promotes caspase-independent apoptosis as well as the caspase-dependent route by binding and cleaving inhibitors of apoptotic proteins. (Lau 1999)

Recent research has demonstrated that oxidative stress and nitrosative stress are crucial factors in cisplatin-induced nephrotoxicity, which is characterized by elevated levels of malondialdehyde (MDA), 4-hydroxy, 8-hydroxydeoxyguanosine, and 3-nitrotyrosine and decreased levels of superoxide dismutase (SOD) and catalase (CAT). treatment. Therefore, antioxidants and ROS scavengers exhibit powerful protective effects against nephrotoxicity. (Jiang, Wang et al. 2009)

The inflammatory response is connected to cisplatin-induced nephrotoxicity. TNF- inhibition or knockout can significantly reduce cisplatin-induced renal insufficiency and injury, suggesting that increased TNF- expression plays a significant role in cisplatin-induced nephrotoxicity. Renal TNF- expression is increased in a cisplatin-induced nephrotoxic mouse. (Ramesh and Reeves 2004)

It's interesting to note that TNF- in the blood and urine following cisplatin therapy may originate from renal epithelial cells rather than immune cells. nuclear factor kappa-light-chain-enhancer of activated B cells (NF-kB) is activated, which causes the production of proinflammatory cytokines like TNF—α. (Zhang, Ramesh et al. 2007). JSH-23, a kind of NF-kB inhibitor, enhances kidney function in mice by inhibiting NF-kB transcriptional activity. (Ozkok, Ravichandran et al. 2016). The proinflammatory cytokines and chemokines that TNF- α activates cause oxidative stress, which worsens kidney injury. Cisplatin generates hydroxyl free radicals that

are necessary for the activation of p38 mitogen-activated protein kinase (p38 MAPK) and the control of TNF-α synthesis, resulting in the final activation of NF-kB. Therefore, p38 MAPK activation and TNF- α mRNA expression in murine kidneys are inhibited by the hydroxyl radical scavenger dimethyl thiourea. Inhibiting p38 MAPK prevents the generation of TNF- α, thereby preventing kidney injury brought on by cisplatin. (Ramesh and Reeves 2005)

cisplatin-induced nephrotoxicity is also linked to other cytokines, including transforming growth factor-, monocyte chemoattractant protein-1 (MCP-1), intercellular adhesion molecule, and heme oxygenase-1 (HO-1). (dos Santos, Carvalho Rodrigues et al. 2012)

Even though a variety of medications are being utilized in clinical settings to treat kidney damage brought on by cisplatin, these medications all display varying degrees of insufficiency. For instance, in the clinic, hydration and diuresis improve cisplatin efficacy. renal exposure and decrease in excretion(Duffy, Fitzgerald et al. 2018). Thus, searching a novel effective therapeutic strategy to burden the onset of the cisplatin induced AKI is emerging.

4. MSCs as a regenerative tool

For SCs, the word "multipotent" refers to cells that can differentiate into more than one type being a member of the similar embryonic germ layer (Bardanzellu, Faa et al. 2017). Self-renewal and adaptability are characteristics of stem cells (SCs).(Wagers and Weissman 2004). They can be divided into adult stem cells (ASCs) and embryonic stem cells (ESCs).(Bissels, Diener et al. 2016). Hematopoietic stem cells (HSCs), neuronal, endothelial, olfactory, and mesenchymal stem cells (MSCs) are different types of ASCs. (Bongso and Lee 2005). ASCs have recently been successfully used in several therapeutic modalities, including spinal cord damage(Hakim, Covacu et al. 2019). Hepatic cirrhosis(Mu, Zhang et al. 2018), disease of the peripheral vessels(Yan, Tie et al. 2013). Conversely, the homing and differentiability of ASCs may restrict the therapeutic and clinical uses of these cells. (Stonesifer, Corey et al. 2017).

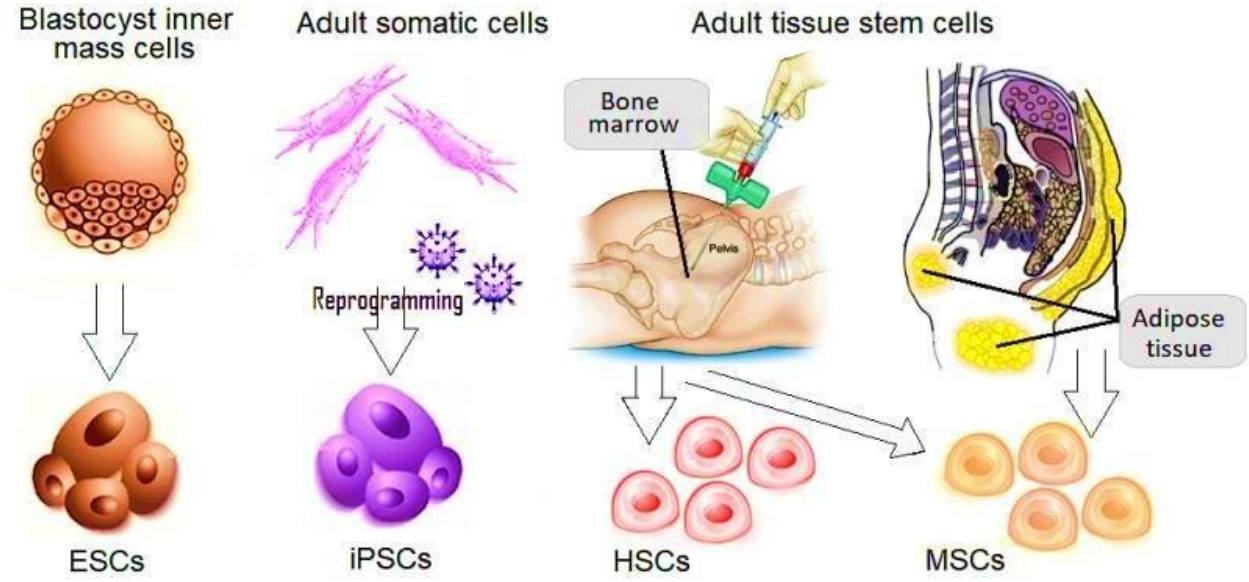

Fig. 3 different types of stem cells.

MSCs are an excellent possibility for therapeutic uses due to they have immunomodulatory(Kassis, Grigoriadis et al. 2008) also anti-inflammatory (Kim, Jo et al. 2015) as well as antiapoptotic(Wang, Yan et al. 2017) capabilities. Additionally, they could minimize oxidative stress. (Francois, Mouiseddine et al. 2013, Sherif, Sabry et al. 2018) and secrete some trophic factors, such as vascular endothelial growth factors (VEGF) and hepatocyte growth factor (HGF). (Kaingade, Somasundaram et al. 2016).They can differentiate into numerous cell types both in vivo(Aydın, Yiğit et al. 2018) and ex vivo(Hassiotou, Beltran et al. 2012).

5. Breast milk mesenchymal stem cells a mystery tool in regenerative medicine.

Breast milk (BM) is an odd fluid with special qualities that makes it the perfect meal during the early newborn period. It can affect both the newborn and the nursing mother for the rest of their lives, as is well known. BM is distinguished by several advantageous elements; a significant part of these is played by BM's unique and specialized microbiome, which has been extensively studied in various research. Furthermore, the use of metabolomics in BM study enabled a more accurate identification of its metabolic pathways, which differ depending on lactation stage and neonatal gestational age. (Bardanzellu, Peroni et al. 2020). The distinctive qualities of breast milk (BM) have been recognized since ancient times, and they have been gradually described over the past decades, however many elements have not yet been fully clarified. (Hassiotou, Heath et al. 2014, Reali, Puddu et al. 2016). This biofluid can enhance host defenses (protecting against several infectious diseases) and promote the development and maturity of the gastrointestinal and nervous systems. It may also enhance breastfeeding mothers' mental and physical health by lowering the prevalence of chronic lung disease (CLD), retinopathy of prematurity (ROP), and necrotizing enterocolitis (NEC). Recent studies also show that breastfed subjects had lower rates of allergy symptoms in addition to decreased rates of infectious diseases. (Sakaguchi, Koyanagi et al. 2018), a lower prevalence of insulin-dependent diabetes mellitus, Crohn's disease, or ulcerative colitis(Garofalo 2010, Brenmoehl, Ohde et al. 2018), also malignant diseases (Fanos, Pintus et al. 2017). There are currently conflicting findings about the function of BM in various areas of health; some research indicates that BM would lower the risk of obesity and cardiovascular disease and might have a good impact on cognitive abilities. (Demmelmair, Prell et al. 2017, Marincola, Dessì et al. 2015, Fanos, Pintus et al. 2017, Kaingade, Somasundaram et al. 2017, Garwolińska, Namieśnik et al. 2018). The presence of bioactive components in BM is of great interest, particularly immunoglobulins, lactoferrin, lysozymes, cytokines, and other immunological substances that play a significant role in the development of the neonatal immune system (both versions, active and passive immunity), organogenesis, and precocious microbial colonization. (Witkowska-Zimny and Kaminska-El-Hassan 2017, Brenmoehl, Ohde et al. 2018).

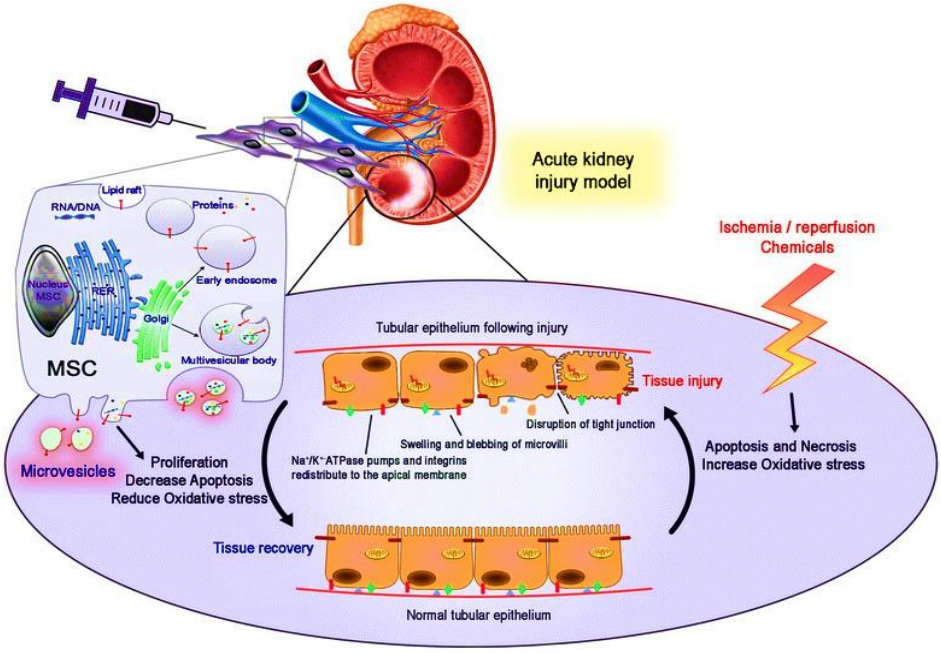

Fig.5 Mechanism of MSCs in repairing the degenerative changes in AKI.

6. Definition of the autophagy process.

Long-lived proteins and cytoplasmic organelles are degraded and recycled by a key intracellular mechanism called autophagy. Autophagy is a crucial component of multicellular organisms' ability to control growth and maintain homeostasis, much like apoptotic programmed cell death. As an adaptive reaction to several extracellular and intracellular stimuli, such as food deprivation, hormonal or pharmacological therapy,

bacterial infection, aggregated and misfolded proteins, and damaged organelles, autophagic vacuole formation is also triggered. Trimeric G proteins, which mediate the class I and class III PI3 kinase signaling pathways, and autophagosome production during the stress response are key players in this process. Several clinical ailments, including vacuolar myopathies, neurodegenerative illnesses, liver disease, and several types of cancer, have defective autophagy as their underlying cause. In addition to describing the harmful effects of autophagy's dysregulation. Moreover, morphological and molecular underpinnings of autophagosome production and provides a look into the function of autophagy in healthy growth and development. (Kelekar 2006). The lysosomal autophagic pathway has become better understood in recent years. Unraveling new protein-conjugation systems and shedding light on the significance of autophagy in physiology and disease, the identification of a family of genes involved in the creation of autophagosomes and conserved from yeast to humans has revolutionized our understanding of these processes.

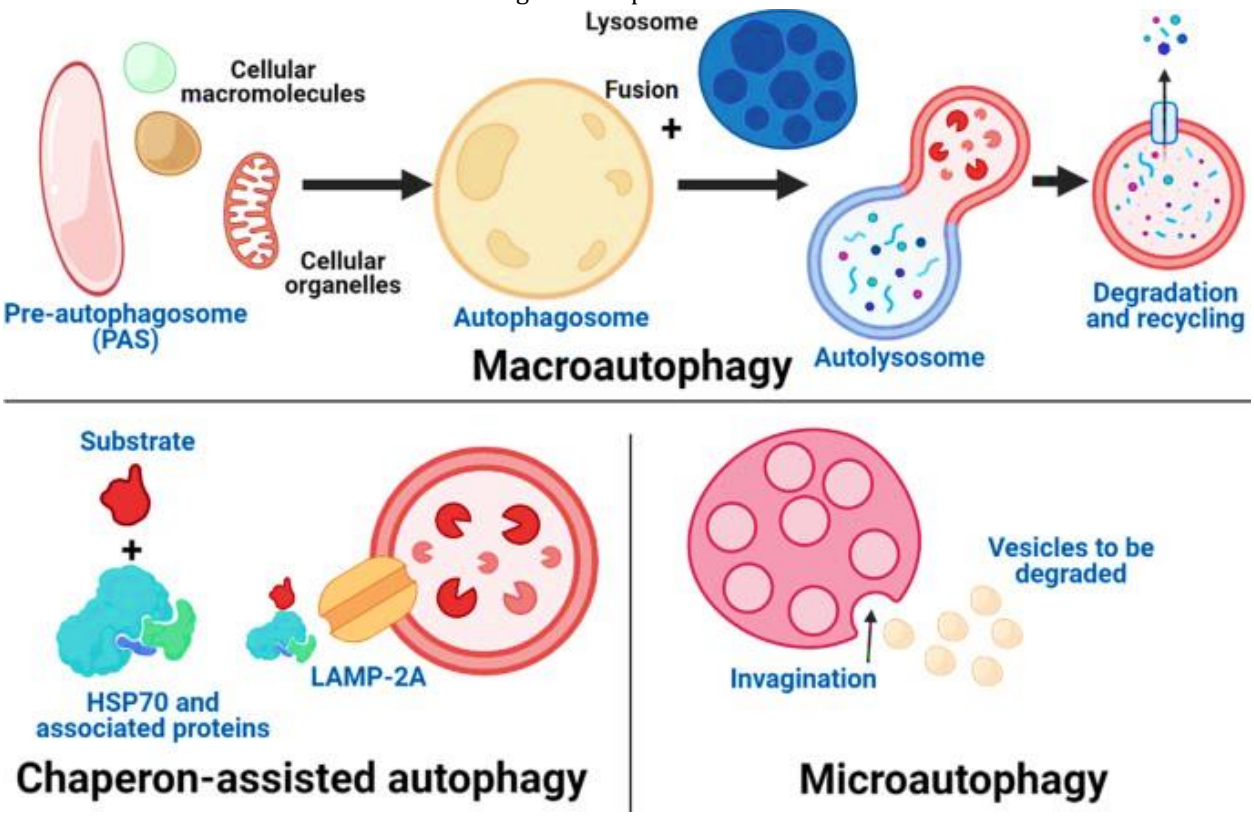

Fig. 6 different types of the autophagy process.

7. Mechanism of the autophagy process.

A deeper comprehension of autophagy's function during cell death will result from the clarification of its molecular regulation. It is not surprising that several signaling pathways are involved in the regulation of autophagy given that a variety of extracellular stimuli, such as starvation, hormonal changes, or therapeutic treatments, as well as intracellular stimuli, such as the buildup of misfolded proteins or microbial invasion, can alter the autophagic response. Because it can detect nutritional, metabolic, and hormonal cues, the mammalian Target of Rapamycin (mTOR) signaling pathway is crucial in the transmission of autophagic stimuli. Additionally, just like the vesicular transport along the exocytic/endocytic route, GTPases control autophagy, which is characterized by a flux of membrane from the creation of the autophagosome to the fusion with the lysosome. The purpose of this article is to provide an overview of autophagy and to examine how mTOR activators and effectors as well as GTPases control it. (Meijer and Codogno 2004).The primary intracellular proteolytic system, the lysosomal network, is responsible for more than 98% of the long-lived bulk protein degradation and recycling, notably in tissues like the liver and muscles.

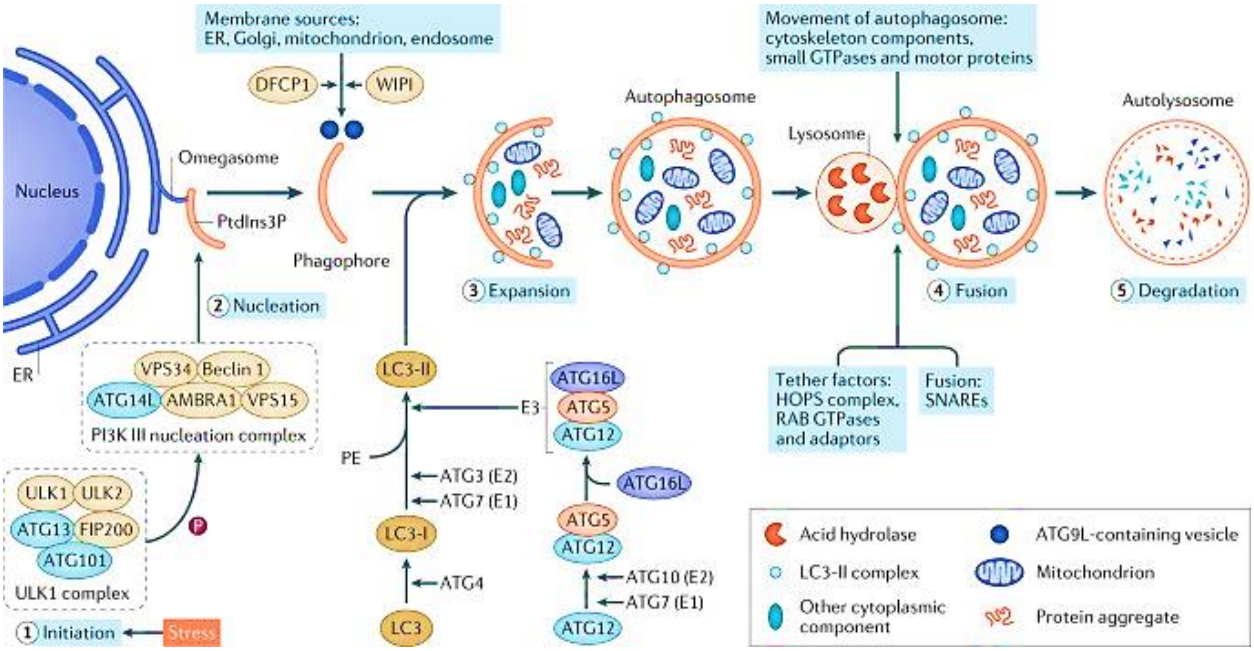

Fig.7 Cellular and molecular mechanism of the autophagy process

8. Types of the autophagy process.

The processes of macroautophagy and chaperone-mediated autophagy (CMA) are used to identify and sequester intracellularly damaged structures, and the end destination is the lysosome. Long-lived proteins, other macromolecular aggregates, and damaged intracellular organelles are first ingested by autophagosomes before being consumed by macroautophagy. Because of their limited ability to degrade, autophagosomes must fuse with lysosomes. Contrary to macroautophagy, CMA does not necessitate the creation of intermediary vesicles, and the cytosolic proteins it recognizes are sent directly to the lysosomal membrane. The ubiquitous phenomenon of aging is characterized by the steady decline of cells and organs brought on by the buildup of macromolecular and organelle damage. Cellular homeostasis is guaranteed, and the aging process is slowed down by the regular replacement of worn-out parts with freshly produced ones. A growing body of research suggests that as people get older, autophagosome creation, maturation, and lysosome fusion rates also slow down. Further reducing the effectiveness of lysosomal protein breakdown is a steady rise in the concentration of free radicals and the aging pigment lipofuscin within the lysosome. As a result, it appears that aging progresses in a way that depends on the autophagosomal-lysosomal network's integrity. Understanding the many biochemical pathways that may be implicated in aging and senescence has been made possible by the discovery of the genes involved in the process of autophagy. This review covers the cellular and molecular mechanisms of autophagy as well as the function of the autophagosome/lysosome network in aging. (Rajawat, Hilioti et al. 2009). A part of the cytoplasm is wrapped in cytosolic double-membrane vesicles and transported to the lysosome/vacuole during the cellular self-degradation process known as autophagy. All eukaryotic cells go through this process, which is partially a stress response; hypoxia and starvation trigger the induction of autophagy. Autophagy, however, also contributes to development and is linked to a number of diseases. Increasing evidence also points to autophagy's role in aging. Autophagy may be involved, for instance, in the expansion of life span through numerous hormones and nutrient sensing mechanisms. Like mitochondria, which may have a direct effect on aging, autophagy is the main method for eliminating damaged organelles. Here, we discuss the function of autophagy with a focus on the regulatory signaling pathways involved and the effects of autophagy activation on aging. (Yen and Klionsky 2008). All eukaryotic cells have baseline macroautophagy/autophagy, which is essential in regulating molecular breakdown and organelle turnover and for preserving bio-energetic balance. It can be stimulated by environmental factors like famine, and it is dysregulated in a variety of illnesses include cancer, autoimmune diseases, and neurodegenerative disorders.

9. Interplay between mesenchymal stem cells and autophagy process.

It's interesting to note that mesenchymal stem cells' (MSCs') control of autophagy is a potential method that, by altering MSC characteristics, may influence their capacity for regeneration and treatment. Additionally, it has recently been suggested that MSCs may play a role in the regeneration of damaged tissues and organs due to their capacity to influence the autophagy of cells in injured tissues and organs. MSCs could influence autophagy in immune cells responsible for injury-induced inflammation, lowering their survival, proliferation, and functionality and promoting the resolution of inflammation. Additionally, MSCs can influence endogenous adult or progenitor cells' autophagy, increasing their survival, proliferation, and differentiation in support of the repair of functional tissue. For the first time, this review summarizes the studies that suggest a connection between the therapeutic benefits of MSCs and their capacity to modulate autophagy. It also lists examples of disorders for which these benefits have been linked to such modulation. A clearer understanding of the mechanism(s) by which MSCs can influence target cells' autophagy and how autophagy can alter MSCs' therapeutic characteristics can offer a broader perspective on the clinical use of MSCs in the treatment of numerous disorders. .(Ceccariglia, Cargnoni et al. 2020)

10. Role of autophagy in preserving kidney against nephrotoxicity.

AKI is described as a potentially fatal condition that develops over a few hours or days as a result of bacterial, ischemia, or toxic assaults. (Schrier, Wang et al. 2004). In order to preserve cellular homeostasis and survive the nephrotoxicity caused by cisplatin, autophagy is crucial. Increases in autophagy and apoptosis were both decreased in NRK-52E cells treated with cisplatin following beclin-1 knockdown, demonstrating that autophagy mediates cell damage. (Inoue, Kuwana et al. 2010). Another study, however, demonstrated the protective role of autophagy in cisplatin-induced kidney injury by showing that autophagy suppression accelerated apoptosis. (Jiang, Wei et al. 2012). Additionally, autophagy can stop cisplatin-induced proximal tubule apoptosis and AKI. (Kaushal 2012). According to studies, the inhibition of mTOR activity reduces the inhibitory phosphorylation of Unc-51-like autophagy activating kinase 1, which results in the activation of autophagy. (Gong, Pan et al. 2020). In rats with ischemia/reperfusion, rapamycin, a mTOR inhibitor, induces autophagy as a pretreatment to enhance kidney function. (Su, Lu et al. 2018).

11. Interplay between oxidative stress and autophagy.

It's interesting to note that the oxidative stress barrier NAD(P)H quinone dehydrogenase 1 deletion increases the effects of rapamycin and increases tuberous sclerosis complex 2 phosphorylation, suggesting that autophagy may be activated to combat the increased stress and prevent AKI. (Kim, Kim et al. 2016). Damaged macromolecules and organelles are eliminated through the primary cellular digestive process known as autophagy. Additionally, the process of autophagy is essential for supplying energy and molecular building blocks by recycling macromolecules in response to nutritional and environmental stress (Mizushima and Komatsu 2011)

12. Autophagy as a tool for cellular energy preservation

A self-degradative mechanism called autophagy is crucial for balancing energy sources during crucial stages of development and in response to nutritional stress. Additionally, autophagy cleans up damaged organelles including the mitochondria, endoplasmic reticulum, and peroxisomes, gets rid of intracellular infections, and removes misfolded or aggregated proteins. So, although its dysregulation has been connected to non-apoptotic cell death, autophagy is typically considered regarded as a survival strategy. Although the mechanisms governing some elements of selective autophagy are still being worked out, autophagy can be either non-selective or selective in the removal of organelles, ribosomes, and protein aggregates. Along with removing intracellular aggregates and damaged organelles(Glick, Barth et al. 2010).

13. Conclusion

Cisplatin is a widely used effective anticancer which trigger the nephrotoxicity that has a limited therapeutic intervention. Autophagy process is a crucial cellular preserving mechanism that so-called cellular quality control system. MSCs represent a mystery regenerative tool which, could abate the cisplatin induced nephrotoxicity via a several mechanisms, modulating renal autophagy process is one the most supposed regenerative mechanism of MSCs to maintain renal vitality. Several experimental, preclinical, and clinical studies are required to further address this regenerative modality.

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