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Pretreatment can alleviate programmed cell death in mesenchymal stem cells

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Abstract

In this editorial, we delved into the article titled "Cellular preconditioning and mesenchymal stem cell ferroptosis." This groundbreaking study underscores a pivotal discovery: Ferroptosis, a type of programmed cell death, drastically reduces the viability of donor mesenchymal stem cells (MSCs) after engraftment, thereby undermining the therapeutic value of cell-based therapies. Furthermore, the article proposes that by manipulating ferroptosis mechanisms through preconditioning, we can potentially enhance the survival rate and functionality of MSCs, ultimately amplifying their therapeutic potential. Given the crucial role ferroptosis plays in shaping the therapeutic outcomes of MSCs, we deem it imperative to further investigate the intricate interplay between programmed cell death and the therapeutic effectiveness of MSCs.

Key Words: Mesenchymal stem cells; Programmed cell death; Apoptosis; Autophagy; Ferroptosis

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Core Tip: As ferroptosis, a distinct form of programmed cell death, significantly impairs the post-engraftment viability of donor mesenchymal stem cells (MSCs), it assumes paramount importance in dictating the therapeutic efficacy of these cells. Recognizing the pivotal role ferroptosis exerts in shaping the outcome of MSC-based therapies, we underscore the urgency to delve deeper into the intricate relationship between this mode of cell death and the therapeutic potency of MSCs. In this context, we presented our viewpoint on the recently published editorial entitled “Cellular preconditioning and mesenchymal stem cell ferroptosis,” offering insights into this intricate interplay.

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INTRODUCTION

Mesenchymal stem cells (MSCs), derived from a diverse array of sources, exhibit remarkable ease in *in vitro* culturing, along with pluripotent differentiation capabilities and robust self-renewal potential[1]. Their therapeutic applications have been demonstrated to effectively alleviate various conditions, including diabetes and recalcitrant wounds, while offering promising immunosuppressive treatment strategies for a spectrum of inflammatory diseases[2,3]. Despite the ability of MSCs to modulate the organ microenvironment and enhance cellular differentiation and regeneration, their clinical success is still constrained by limited understanding of the underlying mechanisms *in vivo* and the absence of standardized criteria for patient selection[4,5]. Further research is urgently needed to address these challenges.

One of the significant challenges in MSC therapy is the decreased survival and increased cell death of MSCs following transplantation into recipients. To enhance the survival rate of grafted MSCs, it is crucial to minimize MSC death. As a potential solution, preconditioning strategies, such as cytokine preconditioning, can be employed to bolster the vitality of MSCs[6]. For instance, our laboratory has explored the transfection of c-Jun plasmid into human umbilical cord MSCs (HUCMSCs) to boost their wound healing capabilities by enhancing their survival rates[7]. Furthermore, we have utilized hydrocolloid dressings to cover MSCs, which facilitates vascular reconstruction by increasing the vitality of these cells[8]. These studies underscore the critical role of reducing MSC death in clinical MSC treatments.

DIFFERENT TYPES OF CELL DEATH

In general, MSC death occurs in two distinct manners. Firstly, there is a passive and unregulated process triggered by tissue damage, known as accidental cell death or necrosis. This occurs when MSCs are exposed to severe stress conditions, such as exposure to highly toxic compounds, starvation, DNA damage, and other factors. Under such conditions, MSCs are unable to maintain intracellular homeostasis, leading to rapid cellular swelling and rupture of the plasma membrane. This, in turn, results in the passive release of intracellular material into the microenvironment[9,10].

The second manner of MSC death involves highly regulated mechanisms that involve various signaling cascades to elicit different effector functions. This type of death is referred to as programmed cell death (PCD)[11,12]. PCD is a genetically determined and actively orderly process and is ubiquitous in the development of living organisms. It represents the suicide protection measures triggered by gene regulation in response to stimuli from both internal and external environmental factors[13]. This process involves the activation of specific molecular mechanisms and genetic programming, leading to the elimination of non-essential cells or cells destined for specialization from the body.

The various pathways of PCD, including apoptosis, necroptosis, autophagy, ferroptosis, pyroptosis, PANoptosis, *etc.* exhibit distinct morphological and biochemical characteristics[14-18]. By understanding these mechanisms, we can gain insights into the complex cellular processes that underlie organismal development and homeostasis. Unlike accidental cell death, PCD is a controlled process that is essential for maintaining tissue homeostasis and regulating cellular responses to various stimuli.

Both forms of MSC death have important implications for MSC therapy. Understanding the mechanisms underlying these processes is crucial for developing effective strategies to enhance the survival and functionality of MSCs and improve the outcomes of cell-based therapies.

Apoptosis, a fundamental biological process of the cell, serves as a crucial mechanism for eliminating unwanted or abnormal cells in multicellular organisms. It plays a pivotal role in the evolution of organisms, the maintenance of internal environmental stability, and the development of various systems. Beyond being a specific form of cell death, apoptosis holds significant biological importance and is governed by intricate molecular biological mechanisms. This process is tightly regulated by multiple genes that exhibit remarkable conservation across species, including the Bcl-2 family, the caspase family, oncogenes like *c-myc*, and the tumor suppressor gene *P53*[19,20]. These genes work in concert to orchestrate the orderly and controlled dismantling of cells, ensuring the precise removal of nonfunctional or potentially harmful cells from the body[21].

Necroptosis, also known as necrotic apoptosis, is a cellular self-destruction process triggered by either extracellular signals or intracellular signals[22,23]. During necroptosis, distinct morphological changes occur, including organelle swelling, cell membrane rupture, and the breakdown of the cytoplasm and nucleus[24,25]. Notably, necroptosis differs from apoptosis and other forms of PCD in its independence from caspase activity. Instead, it relies on receptor-interacting protein kinase 3-regulated phosphorylation of mixed lineage kinase domain-like protein. This phosphorylation triggers mixed lineage kinase domain-like protein to form a pore complex at the plasma membrane, resulting in the secretion of damage-associated molecular patterns, cell swelling, and ultimately, membrane rupture[26].

Whether autophagy is a PCD type is currently controversial. Although autophagy is sometimes called autophagic cell death, there are also many researchers who report autophagy as a type of PCD[27,28]. Cell death mediated by autophagy is characterized by cytoplasmic vacuolization, the formation of autophagic vesicles, and the lysosomal degradation of cellular material[29]. Autophagy can be classified into three types: Macroautophagy; microautophagy; and selective autophagy[30]. In macroautophagy, autophagosomes, which are double-membraned vesicles, envelope a portion of the cell. These autophagosomes then fuse with lysosomes to create autolysosome, where the contents are degraded by proteases. Microautophagy involves the direct interaction and fusion of vesicles containing organelles or inclusions with lysosomes. This process is more specific than macroautophagy and can be triggered by signaling molecules on the surface of damaged organelles. Selective autophagy, also known as chaperone-mediated autophagy, involves the fusion of cytoplasmic proteins with lysosomes *via* cytoplasmic chaperones[31]. These chaperones interact with pentapeptides within the amino acid sequence of the substrate proteins.

Pyroptosis is triggered by intracellular infections of bacteria, viruses, fungi, and protozoa in the presence of either pathogen-associated molecular patterns or cell-derived damage-associated molecular patterns[32]. It typically serves as the primary mode of cell death in response to pathogen infection and is commonly observed in cells of the innate immune system, such as monocytes, macrophages, and dendritic cells[33]. The classical pathway of pyroptosis unfolds through a two-step process. Initially, nuclear factor- κ B is activated, initiating the expression of multiple proteins. Then, caspase-1 is activated to cleave gasdermin D and cytokines, pro-interleukin (IL)-1 β and pro-IL-18. These cytokines are then proteolytically hydrolyzed into their proinflammatory forms, IL-1 β and IL-18[34,35]. Additionally, caspase-1 cleaves the amino-terminal fragment of the key protein, gasdermin D, leading to its oligomerization and the formation of a pore in the cell membrane[36]. This pore formation results in cytokine secretion, water influx, and ultimately, cell rupture.

Ferroptosis exhibits no chromatin condensation or loss of plasma membrane integrity, yet it is characterized by mitochondrial condensation, reduction of mitochondrial cristae, and an increase in membrane density[37-39]. The process of iron death is primarily governed by iron homeostasis and oxidative stress pathways. Iron homeostasis is partially controlled by ferritin, and the levels of ferritin are modulated through “ferritin autophagy,” a process facilitated by nuclear receptor coactivator 4 (NCOA4), which serves as a selective cargo receptor for ferritin[40]. Ferritin autophagy is a meticulously orchestrated process, which is distinctly marked by the liberation of iron. In this intricate pathway, the pivotal NCOA4 plays a crucial role by directly recognizing and engaging with ferritin heavy chain 1, the ferritin subtype harboring iron. Subsequently, NCOA4 facilitates the targeted delivery of iron-laden ferritin to autophagosomes, which then undergo lysosomal degradation, ultimately releasing the sequestered iron. Experimental findings indicate that iron death can be suppressed through the use of common iron chelators, such as desferrioxamine.

Multiple forms of PCD such as pyroptosis, apoptosis, and necroptosis occur extensively in complex crosstalk and coordination, which cause a newly emerging concept known as PANoptosis[41,42]. PANoptosis is usually triggered by infectious and inflammatory factors[43,44]. Like other PCD types, PANoptosis has a multimeric protein complex (*e.g.*, ZBP1-NLRP3), which was named the PANoptosome. However, the exact role of PANoptosis remains unclear.

PRETREATMENT CAN REDUCE PCD OF MSCS

The programmed death of MSCs results in a significant reduction in their transplantation efficiency, and a variety of factors can lead to PCD of MSCs. Most reported cell death in PCD is apoptosis, while necroptosis, PANoptosis and pyroptosis are rarely reported. To address this problem, various pretreatment has been used to enhance the survival of MSCs.

APOPTOSIS

Cytotoxicity, stimuli, virus infection, and radiation can all trigger apoptosis in MSCs. It has been demonstrated that pretreatment with drugs reduces the apoptosis of MSCs and improves the efficacy of MSCs. Recently, preconditioning with prostaglandin E1 (PGE1) has been shown to enhance the protein expression of hypoxia-inducible factor-1 α (HIF-1 α) in MSCs[45]. This upregulation of HIF-1 α not only mitigates MSCs apoptosis but also boosts the protein levels of C-X-C chemokine receptor type 4, thus enhancing MSCs migration and promoting the secretion of vascular endothelial growth factor. These findings suggest that PGE1 modulates the properties of MSCs through the regulation of the HIF pathway. This understanding provides valuable insights into how PGE1 preconditioning can potentially enhance the therapeutic benefits of MSCs in the treatment of pulmonary arterial hypertension.

Myricetin could alleviate hydrogen peroxide-induced senescence and apoptosis in rat nucleus pulposus-derived MSCs through the silent information regulator 1/proliferator-activated receptor gamma coactivator-1 α pathway[46]. Preconditioning MSCs with 1.5% oxygen significantly enhances their activities, effectively boosting proliferation, migration, angiogenesis, antioxidant, antiapoptotic, and antifibrotic properties[47]. Preconditioning MSCs with 2%

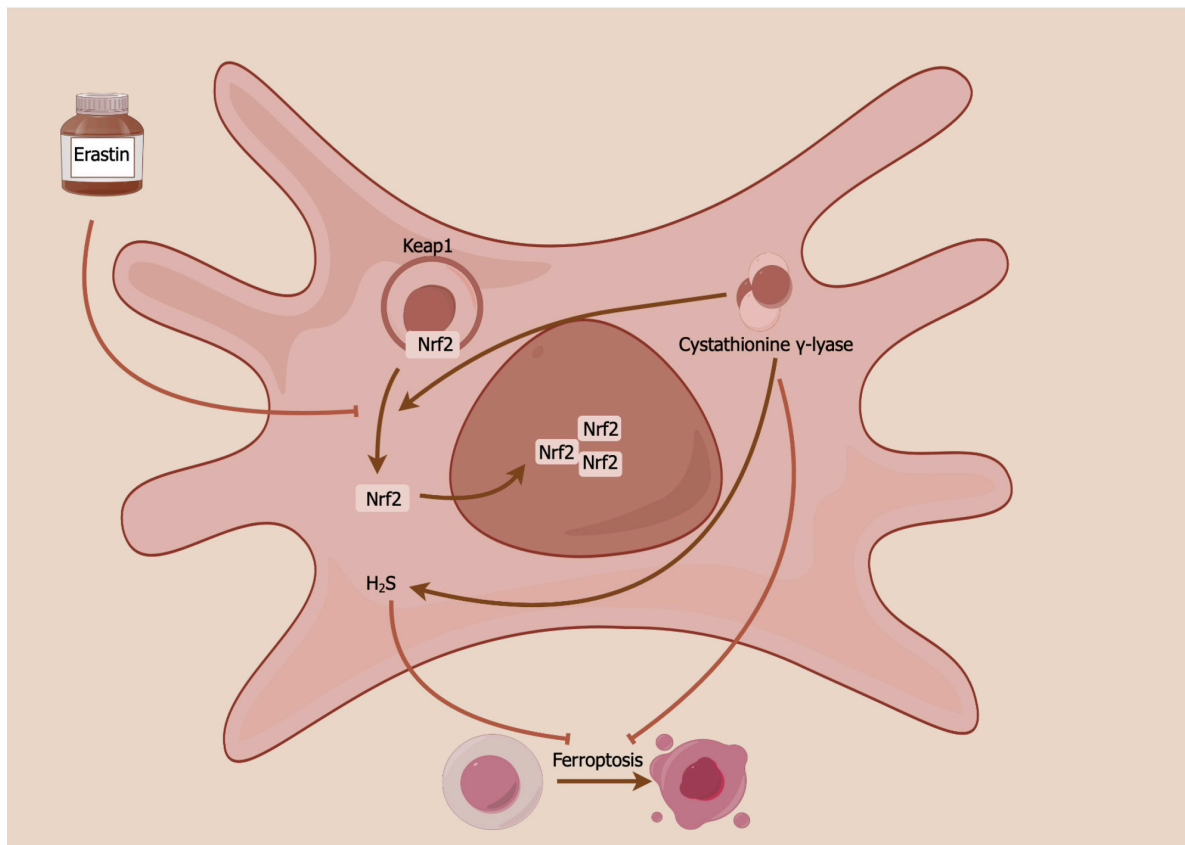


Figure 1 A novel ferroptosis mechanism of human umbilical cord mesenchymal stem cells through the cystathionine γ -lyase/hydrogen sulfide pathway. Cystathionine γ -lyase facilitates the liberation of nuclear factor erythroid 2 from the Keap1 complex within the cytoplasm, whereupon liberated nuclear factor erythroid 2 (Nrf2) is shuttled to the nucleus for subsequent activation. This process plays a pivotal role in inhibiting iron death in mesenchymal stem cells. Additionally, cystathionine γ -lyase enhances the direct suppression of iron death through the production of hydrogen sulfide (H_2S).

oxygen optimizes the expression of prion protein, activating prion protein-dependent Janus kinase 2 and signal transducer and activator of transcription 3 signaling pathways. This, in turn, upregulates the activity of superoxide dismutase and catalase, effectively inhibiting oxidative stress-induced apoptosis of MSCs and promoting the recovery of ischemic tissue[48].

AUTOPHAGY

The coordination of autophagy and apoptosis is the key to maintaining homeostasis in bone marrow MSCs (BM-MSCs). Hypoxic stress increases autophagy and apoptosis in BM-MSCs time dependently, and the increased autophagy and apoptosis in BM-MSCs induced by hypoxia are abolished by AMP-activated protein kinase (AMPK) inhibitor compound C[49]. Hypoxia pretreatment could promote BM-MSC survival by inducing autophagy through HIF-1 α [50]. Besides, iron overload (IO) could significantly induce cell apoptosis and reduce cell viability in MSCs. This process is accompanied by extensive mitochondrial fragmentation and an enhancement of autophagy, both of which were dependent on reactive oxygen species (ROS). Notably, MSCs exposed to IO exhibited a marked decrease in ATP concentration, attributed to elevated ROS levels and a reduction in electron respiratory chain complex II/III activity. This depletion of ATP led to the phosphorylation of AMPK, which in turn triggered mitochondrial fission. Furthermore, genetic ablation of AMPK using CRISPR/Cas9 technology effectively mitigated cell apoptosis, enhanced cell viability and attenuated the mitochondrial fragmentation and autophagy triggered by IO in MSCs. These findings provide a deeper understanding of the cellular mechanisms underlying the deleterious effects of IO on MSCs and suggest potential therapeutic targets for mitigating these effects[51].

FERROPTOSIS

There is little research focused on ferroptosis in pretreated MSCs. A recently published article in the *World Journal of Stem Cells* showed a novel ferroptosis mechanism of MSCs through the cystathionine γ -lyase (CSE)/hydrogen sulfide (H_2S) pathway (Figure 1)[52]. MSC overexpression of CSE has been shown to enhance H_2S production and various ferroptosis-related indices, encompassing cell viability, iron concentration, ROS generation, cystine absorption, lipid peroxidation,

mitochondrial membrane density, and ferroptosis-related protein expression, in erastin-treated HUCMSCs. By modulating the CSE/H₂S pathway, ferroptosis in HUCMSCs was mitigated, subsequently leading to improved vascular remodeling in mice with hypoxia-induced pulmonary arterial hypertension. This occurs by maintaining a delicate balance between stem cell maintenance and differentiation. The CSE/H₂S pathway exerts its protective effects against ferroptosis in HUCMSCs through the mediation of S-sulfhydrated Keap1/nuclear factor erythroid 2-related factor 2 signaling[52,53].

CONCLUSION

Enhancing the transplantation efficacy of MSCs by decreasing programmed death of MSCs can significantly increase their survival rate, boost their differentiation potential, and modulate the immune microenvironment of the body. Although research on PCD types such as necroptosis, PANoptosis, and pyroptosis is still limited, MSC transplants can prevent various kinds of cells from necroptosis, PANoptosis and pyroptosis. As investigations progress, more types of PCD will be reported in MSCs. To improve the efficacy of MSCs, it is very important to inhibit PCD of MSCs, which can increase the survival of MSCs after transplants. Currently, the majority of preconditioning drugs aim to modulate apoptosis. However, with an enhanced comprehension of PCD, we can now target the prevention of various forms of cell death in MSCs. For example, the recently reported ferroptosis of MSCs suggests that we can target CSE to enhance the survival of MSCs. This represents a pivotal guideline in our efforts to enhance the therapeutic effectiveness of MSCs.

FOOTNOTES

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