

# World Journal of *Stem Cells*

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## Programmed cell death in stem cell-based therapy: Mechanisms and clinical applications

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### Abstract

Stem cell-based therapy raises hopes for a better approach to promoting tissue repair and functional recovery. However, transplanted stem cells show a high death percentage, creating challenges to successful transplantation and prognosis. Thus, it is necessary to investigate the mechanisms underlying stem cell death, such as apoptotic cascade activation, excessive autophagy, inflammatory response, reactive oxygen species, excitotoxicity, and ischemia/hypoxia. Targeting the molecular pathways involved may be an efficient strategy to enhance stem cell viability and maximize transplantation success. Notably, a more complex network of cell death receives more attention than one crucial pathway in determining stem cell fate, highlighting the challenges in exploring mechanisms and therapeutic targets. In this review, we focus on programmed cell death in transplanted stem cells. We also discuss some promising strategies and challenges in promoting survival for further study.

**Key Words:** Programmed cell death; Apoptosis; Autophagy; Stem cell; Therapeutic strategies

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**Core Tip:** The point of interest of this work is the complex mechanisms of the programmed cell death in stem cells (SCs), which suggests a series of targets as an efficient, reliable, and potential strategy to promote the SC-based therapy.

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## INTRODUCTION

Cell-based therapies have raised tremendous expectations and presented favorable curative effects in repairing damaged tissue and enhancing functional repair[1-3]. Stem cells (SCs) could serve as a cellular reservoir to maintain, produce, repair, and even regenerate multiple tissues with the characteristic properties of self-renewal and differentiation. Thus, SCs are developed as the preferred sources for cell-based therapies due to their ability to differentiate into a wide range of cell types and their capacity of secretion regulated by the microenvironment, also termed the “niche”[4]. Based on the stage of development, SCs can be divided into three types: Embryonic SCs (ESCs), induced pluripotent SCs (iPSCs), and adult SCs (ASCs)[5]. ESCs are derived from the inner cell mass of a blastocyst[6]. There are ethical limitations to the use of ESCs in therapy[7]. Compared with ESCs, iPSCs derived from mature body cells could be regulated to dedifferentiate into pluripotent SCs as a renewable source of alternative cells and tissues[8]. ASCs or somatic SCs (SSCs) can be found in various adult tissues, including neural SCs (NSCs), hematopoietic SCs (HSCs), mesenchymal SCs (MSCs), and epidermal SCs. Many trials have shown that ASCs can be used to treat diseases[9,10]. For example, bone marrow mononuclear cells[11], NSCs[12], and MSCs[13] are usually used to treat stroke.

SCs-based therapies are widely used in the treatment of various diseases[14-18]. Limbal stem cell therapy is used for treating burn-related corneal destruction[19], NSCs in gastrointestinal tract disorders[20], bone marrow-derived mesenchymal SCs (BM-MSCs) in diabetic cardiomyopathy[21], and MSCs in multiple sclerosis[22] and several clinical conditions. However, SC-based therapies also have limitations. Impaired cell homing regulated *via* various factors (such as chemokines) causes *in situ* tissue regeneration failure[23]. Also, a high death rate of transplanted SCs limits the therapies[24,25]. After MSC injection, over 99% of injected cells die in the left ventricular myocardium within 4 d[26].

Accumulated evidence shows a close tie between multiple types of programmed cell death (PCD) and SCs, including apoptosis, autophagy, ferroptosis, pyroptosis, and necroptosis. Studies demonstrate that p53 induces apoptosis of human ESCs (hESCs) through a mitochondrial pathway shown to be extremely sensitive to FasL-induced cell death in MSCs[27,28]. Ohgushi *et al*[29] observed that Rho-associated coiled-coil-containing protein kinase (ROCK)-dependent hyperactivation of myosin directly caused dissociation-induced apoptosis in hESCs and immediate activation of the Rho/ROCK/MLC2 signaling cascade. In 2010, the María group found that inhibitors of apoptosis proteins (IAPs) could promote the numbers of hematopoietic stem and progenitor cells and improve resistance to cell death[30]. Moreover, reports suggest that high levels of pro-apoptotic B-cell lymphoma 2 (Bcl-2) family members were overexpressed in hESCs[31]. Autophagy in SCs traces its history to 1980 where marrow cells revealed several abnormalities within an intrinsic myeloid precursor cell defect[32]. Lately, the role of autophagy in SC fate and aging is drawing attention due to the ability of the autophagy activator rapamycin to restore the biological properties of aged SCs by increasing their differentiation and proliferation capacity and decreasing adipogenic differentiation capacity, including the molecular mechanisms targeting 5' AMP-activated protein kinase (AMPK) and rapamycin (mTOR)[33,34]. Research on necroptosis in SCs started relatively late but progressed rapidly to show that tumor necrosis factor  $\alpha$  (TNF- $\alpha$ ) could act on HSCs and progenitors for facilitating hematopoietic clearance and promoting regeneration. Furthermore, pharmaceutical inhibition of receptor-interacting protein kinase-3 (RIP3) showed a curative effect in



promoting SCs, such as targeting necroptosis of intestinal SCs[35]. Some other cell death-related molecules have been increasingly recognized in SCs, such as the PI3K/AKT signaling pathway[36], MAP kinases ERK[37], JNK, and p38[38].

Some methods have been used to control programmed cell death in SCs. The concept of preconditioning was proposed by Charles E. Murry in 1986[39]. Presently, several strategies, such as using heat shock, free radical scavengers, over-expressing anti-apoptotic proteins, anti-inflammatory therapy, and co-delivery of extracellular matrix molecules, have been introduced[40-45]. Besides genetic strategies, three-dimensional culture technology and co-transplantation are novel ideas to enhance SC-based therapies.

Exploring cell death mechanisms in SCs and targeting these potential therapeutic molecules are vital to successful SC-based therapies (shown in Table 1[19-21,46-92]). In this review, we highlight the conditions or reasons leading to cell death in SC-based therapeutic approaches. Also, we demonstrate the cell death mechanism in SCs, which may provide a novel, efficient, reliable, and potential strategy in promoting SC-based therapy.

## A QUICK LOOK AT PCD

According to the death inducers, cell morphologic changes, and molecular mechanisms, cell death can be divided into two types: Non-programmed cell death caused by an external injury leading to instantaneous and irreversible cell damage[93,94], and PCD (*e.g.*, apoptosis, autophagy, necroptosis, and pyroptosis), a common occurrence in the development of organisms without strong immune responses[95].

PCD occurs extensively during the development of pathology in various tissues. It is closely related to the therapeutic efficacy and prognosis of SC-based treatment. Robey *et al*[25] indicated that most cell death occurs in the first week post-transplantation. In NSC transplantation for neurological disorders in the brain, less than 4%-10% of primary NSCs survived within the first few days[96]. Similarly, Yasuda and Hayashi's groups showed that 15% of transplanted cells survived at 1 wk and 9% at 4 wk in a rat infarction model[97]. A significantly high death rate occurred, and over 99% of MSCs died within 4 d after transplantation into the left ventricular myocardium of mice[26]. Thus, cell death may be a significant concern that needs attention.

### Apoptosis

Apoptosis is the classic form of PCD without spillage of contents into the surrounding environment[98]. Apoptosis plays an important role in the orderly and efficient removal of damaged SCs to prevent cancer through two classical apoptotic pathways: The intrinsic pathway and the extrinsic pathway[99]. The intrinsic pathway, also called the mitochondrial pathway, shows a close relation with SCs[100,101]. It is closely regulated by a group of cytokines, especially the Bcl-2 family[102,103]. The extrinsic pathway is triggered by ligand-receptor binding. TNF-family receptors and cysteine-aspartic proteases, known as caspases, play a vital role in the extrinsic pathway[104].

### Autophagy

Autophagy is a eukaryotic cell recycling process involving the degradation of cytoplasmic organelles, proteins, and macromolecules with the recycling of decomposition products *via* the mTOR/Ras-cAMP-PKA axis to maintain cellular homeostasis and enhance stem cell survival[105]. Autophagy is divided into three major types: Microautophagy, macroautophagy, and chaperone-mediated autophagy (CMA)[106]. During microautophagy, cargos are captured by lysosomal membrane invaginations or protrusions[107]. In macroautophagy, autophagosomes are regarded as typical signatures[108]. CMA focuses on molecular chaperones to identify cargo proteins containing specific pentapeptide sequences without using membrane structures to isolate cargo[109].

### Necroptosis

Necroptosis is a pro-inflammatory lytic form of PCD. Necroptosis could be induced through several innate immune signaling pathways triggered by stimulating RIG-I-like receptors, TLRs, and death receptors[110,111]. Receptor-interacting serine-threonine kinases 1 and 3 (RIPK1 and 3) are phosphorylated and activated through these signaling pathways[112]. Subsequently, mixed lineage kinase domain-like

**Table 1 Summary of programmed cell deaths in stem cell-based therapy**

Disease	SCs	Therapy models	Therapeutic effects	PCDs in SCs	Ref.
Myocardial infarction	MSCs	Canine; porcine; mice; human	Inducing cardiac regeneration; increasing angiogenesis; repair by differentiating into cardiomyocytes	Apoptosis, autophagy, pyroptosis	[46-48]
	iPSCs	Porcine; murine; rats; mice; non-human primates	Showing heart regeneration potential; regenerating the injured tissues; promoting a cardiomyogenic and angiogenic response	Apoptosis, autophagy, ferroptosis	[48,49]
	ESCs	Non-human primates	Showing heart regeneration potential; increasing angiogenic differentiation	Apoptosis, autophagy, pyroptosis	[48,50]
Intracerebral hemorrhage	MSCs	Rats; primates; human	Repairing <i>via</i> differentiating into neurons or neuron-like cells; promoting axonal regeneration, neurogenesis, and angiogenesis	Apoptosis, autophagy, pyroptosis	[51-54]
	NSCs	Mice, rats	Differentiating into neurons or glial cells; promoting neurogenesis and angiogenesis; promoting regeneration	Apoptosis, autophagy	[51,55-57]
	ESCs	Rats	Differentiating into neurons or glial cells; promoting neurogenesis and angiogenesis	Apoptosis, autophagy, pyroptosis	[51,58,59]
	iPSCs	Rats	Differentiating into neuroepithelium-like/neuroepithelioid SCs and neural cells; promoting neurogenesis and angiogenesis	Apoptosis, autophagy, ferroptosis	[51,60-62]
Corneal reconstruction	LSCs	Human	Regenerating the corneal epithelium; differentiating into cells of the corneal epithelium	Apoptosis.	[19]
	MSCs	Mice; rats; rabbits; human	Regenerating the corneal epithelium and corneal stroma; angiogenesis	Apoptosis, autophagy, pyroptosis	[63]
Neurodegenerative disorders of the gastrointestinal tract	ESCs	Mice	Differentiating into enteric neuronal and glial cells	Apoptosis, autophagy, pyroptosis	[20,64]
	iPSCs	Rats, mice	Differentiating into neural and glial cells	Apoptosis, autophagy, ferroptosis	[20,65]
	CNS-NSCs	Mice	Differentiating into neurons; regenerating and repairing ENS	Apoptosis, autophagy	[20,66,67]
	ENSCs	Mice; rats	Stimulating a local regenerative response; regenerating and repairing ENS; differentiating into new neurons	Apoptosis, autophagy	[20,68,69]
Diabetic cardiomyopathy	MSCs	Mice; rats	Promoting angiogenesis; regenerating tissues; differentiating into cardiomyocytes and vasculature cells	Apoptosis, autophagy, pyroptosis	[21,70]
	EPCs	Rats	Differentiating into endothelial cells to form new blood vessels and promoting neovascularization	Apoptosis	[70,71]
	CSCs/CPCs	Rats	Differentiating into newborn cardiomyocyte; promoting heart regeneration	Apoptosis	[70,72]
	iPSCs	Rats; mice	Attenuating oxidative stress and fibrosis; diminishing pro-oxidant expression and enhancing antioxidant (catalase and MnSOD) concentration; promoting heart regeneration	Apoptosis, autophagy, ferroptosis	[70,73]
Diabetic retinopathy	ASCs	Rats; mice	Promoting angiogenesis; improving ischemia; offering protection against nerve damage; differentiating into photoreceptor and glial-like cells in the retina	Apoptosis	[74-77]
	HSCs	Murine; rats	Promoting angiogenesis	Apoptosis, autophagy	[74,78]
	BM-MSCs	Murine; rats; mice	Differentiating into retinal glial cells; stimulating angiogenesis; promoting resident neural progenitors to regenerate neuro-retinal tissue	Apoptosis, autophagy, pyroptosis	[74,79,80]
	iPSCs	Rats; mice	Differentiating into cells expressing features of retinal pigment epithelial cells, retinal progenitor	Anti-apoptosis, autophagy,	[75,81]

			cells, and retinal ganglion cells, and slowing down retinal degeneration	ferroptosis	
Neurological disorders	NSCs	Mice, rats, monkeys, pigs, human	Differentiating into neurons and supporting glial cells; releasing angiogenic factors to promote local tissue regeneration	Apoptosis, autophagy	[82-85]
	HSCs	Human	Promoting cell survival; stimulating proliferation and migration of NSCs; inducing regeneration of damaged brain cells; promoting angiogenesis	Apoptosis, autophagy	[82,86]
	MSCs	Human	Promoting neuronal regeneration; promoting angiogenesis	Apoptosis, autophagy, pyroptosis	[82,86]
Diabetes	ESCs	Mice, rats	Differentiating into cluster of insulin producing beta cells	Apoptosis, autophagy, pyroptosis	[87-89]
	Hepatic and intestinal stem cells	Mice	Differentiating into beta cells in response to high glucose concentration	Apoptosis	[87,90]
	Spleen stem cells	Mice	Differentiating into insulin secreting beta cells; regenerating islet	Apoptosis	[87,91]
	HSCs	Mice	Differentiating into beta cells and vascular endothelial cells of the pancreas; inducing beta cell regeneration from the host cells residing in pancreas	Apoptosis, autophagy	[87,92]

SC: Stem cell; MSCs: Mesenchymal stem cells; NSCs: Neural stem cells; ESCs: Embryonic stem cells; iPSCs: Induced pluripotent stem cells; LSCs: Limbal stem cells; CNS-NSCs: CNS-derived NSCs; ENSCs: Enteric neural stem cells; CSCs/CPC: Cardiac stem/progenitor cells; ASCs: Adipose stem cells; HSCs: Hematopoietic stem cells; BM-MSCs: Bone marrow derived mesenchymal stem cells; ENS: Enteric nervous system; EPCs: Endothelial progenitor cells; PCD: Programmed cell death.

(MLKL) could be activated[113].

Others

Pyroptosis, dependent on multiple molecules, such as caspase-1 and caspase-11, is widely believed to play an important role in resisting the invasion of pathogens[114]. Ferroptosis, an iron-dependent form of regulated cell death (RCD), is induced through an excessive accumulation (*e.g.*, ROS and lipid peroxidation products) characterized by mitochondria shrinkage or dysmorphic small mitochondria[115,116]. Moreover, other types of cell death are also crucial during a series of events, such as failures in SC-based therapies. The biological correlations between the different PCD pathways are complex, where it is especially significant as a network among these pathways regarding PCD of transplanted SCs[117,118].

PCD AND ITS KEY MOLECULES IN STEM CELLS FOR TRANS-PLANTATION THERAPY

PCD of SCs is usually caused by a hostile pathological environment created due to multiple conditions, including apoptotic cascade activation, excessive autophagy, inflammatory response, ROS, excitotoxicity, and ischemia/hypoxia[39]. This section systematically reviews the molecular mechanisms involved in cell death pathways and we also summarize these key molecules in Table 2[35,38,119-134].

Apoptosis

Recently, an emerging body of evidence has highlighted a vital role of the apoptosis effect on several cell types, including SCs[135]. Hence, it is crucial to investigate and understand the mechanisms underlying apoptosis for analysis of SC transplantation and the development of drugs targeting specific apoptotic molecules. According to the inducing signaling, apoptosis could be divided into two types: Intrinsic pathway initiated by intracellular stresses (shown in Figure 1), and extrinsic pathway responding to extracellular cues (shown in Figure 2).

**The intrinsic pathway of apoptosis:** In the intrinsic pathway, the initiators (*e.g.*, ROS and radiation induced DNA damage) cause various cascade reactions resulting in the

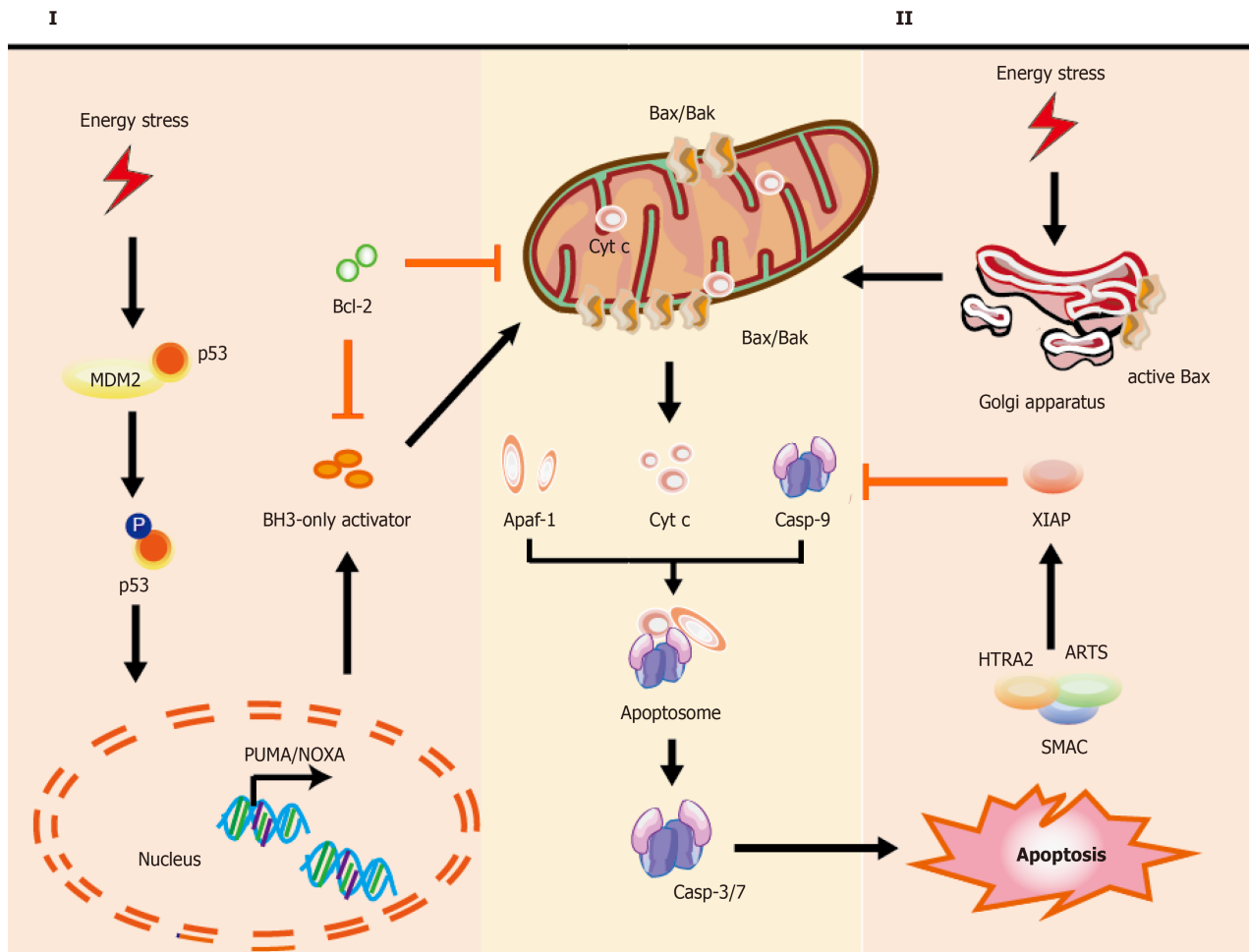


**Table 2 Molecular mechanisms and therapeutic targets of programmed cell deaths in stem cells**

PCDs	SCs	Molecular pathways of PCDs	Therapeutic target(s)	Therapeutic effects	Ref.
Apoptosis	hESCs	Mitochondrial priming and p53 signaling pathway	Bcl-2	Preventing damaged cells from compromising the genomic integrity of the population	[119]
	HSCs	ASPP1 stimulated p53 signaling pathway	ASPP1, RUNX1	Preventing hematological malignancies	[120]
	ISCs	ARTS/XIAP/caspase 9 axis	XIAP	Controlling ISC numbers and preventing the propagation of abnormal progeny	[121]
	MSCs	p38 MAPK regulated early apoptosis while JNK regulated late apoptosis	p38	Protecting MSCs from oxidative stress damage	[38]
	NSCs	p38 MAPK signaling	TNF- $\alpha$ , p38	Impairing cell viability, decreasing therapeutic effects	[122]
Autophagy	iPSCs	AMPK/mTOR/ULK1 complex/PI3K complex/conjugation cascade complexes with LC3 and Atg9 during macroautophagy;KFERQ domain/Hsc 70/LAMP2A during CMA	LC3	Removing unnecessary or dysfunctional components	[123]
	HSCs	type III PI3K mammalian Atg6/PI3P/(Atg12-Atg5-Atg16) or (Atg4/LC3-I/Atg7/Atg3/LC3-II/PE) axis	LC3-II	Recycling cytoplasmic constituents and restoring metabolic homeostasis, and maintaining cells survival under harsh conditions	[124]
	NSCs	PI3K-AKT-mTOR/ULK1/the class III PI3-kinase-Beclin1 complex/PI3/PI3P/ the complex of Atg12-Atg5-Atg16L1/LC3-I/LC3-II axis	mTOR	Being involved in modulation of the embryonic neurogenesis as well as the injury repair of adult brain	[125]
	MSCs	PI3K/AKT/mTOR/ULK1/the class III PI3-kinase-Beclin1 complex/PI3/PI3P/the complex of Atg12-Atg5-Atg16L1/LC3-I/LC3-II axis	AKT, mTOR	Eliminating damaged organelles and biomacromolecules to maintain cellular homeostasis	[126,127]
	ESCs	AMPK/ mTORC1/ULK1 axis	Atg5, Atg12	Maintaining the undifferentiated state of ESCs <i>in vitro</i>	[128]
Necroptosis	ISCs	ZBP1/RIP3/MLKL axis	ZBP1	Disrupting homeostasis of the epithelial barrier and promoting bowel inflammation	[35,129]
	SSCs	RIP1 signaling pathway	RIP1	Using Nec-1 to target RIP1 for reducing both necroptosis and apoptosis, which benefits for recovery rate and proliferation potential	[130]
	NPSCs	RIPK1/RIPK3/MLKL axis	HSP90	Protecting SCs from PCD <i>via</i> alleviating mitochondrial dysfunction (mitochondrial membrane potential loss and ATP depletion) and oxidative stress (production of mitochondrial ROS), cellular total ROS and MDA, and downregulation of superoxide dismutase	[131]
Pyroptosis	MSCs	Exosome/circHIPK3/ FOXO3a axis	circHIPK3	Preventing pyroptosis and repairing ischemic muscle injury through a novel exosome	[132]
	ESCs	Caspase-1 signaling pathway	N/A	Embryonic stem cell-derived exosomes inhibit doxorubicin-induced pyroptosis	[133]
Ferroptosis	NPCs and iPSCs	Ferritin/ROS/lipid peroxidation axis	NCOA4, p53	Decreasing stem cells and triggering neuronal death	[134]

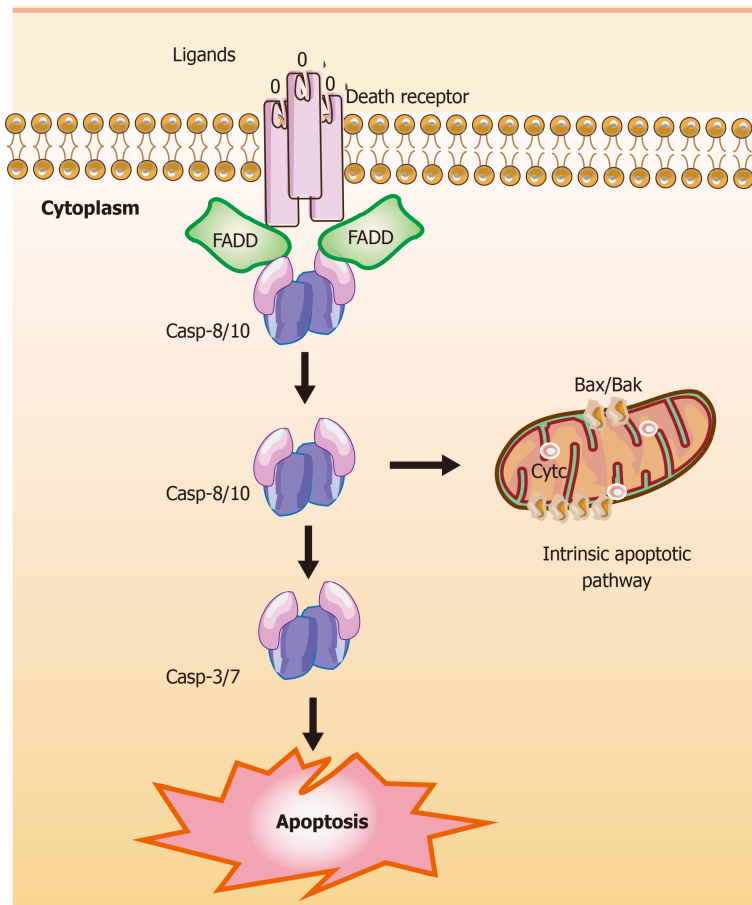
ISCs: Intestinal stem cells; iPCs: Induced pluripotent stem cells; HSCs: Hematopoietic stem cells; ESCs: Embryonic stem cells; NSCs: Neural stem cells; MSCs: Mesenchymal stem cells; EPCs: Endothelial progenitor cells; CPCs: Cardiac progenitor cells; IPSC: Pluripotent stem cells; ZBP1: Z-DNA-binding

protein 1; RIP3: Receptor-interacting serine/threonine kinase 3; MLKL: Mixed lineage kinase domain like protein; PUMA: p53 upregulated modulator of apoptosis; NOXA: Known as PMAIP1, phorbol-12-myristate-13-acetate-induced protein 1; Bax: Bcl-2 associated X protein; Bak: Bcl-2 antagonist/killer 1 protein; cyt c: Cytochrome C; Apaf-1: Apoptosis protease activating factor-1; casp: Caspase; FADD: Fas-associated death domain; Bcl-2: B-cell lymphoma 2; AMPK: AMP-activated protein kinase; mTOR: Mammalian target of rapamycin; ULK1: Unc-51-like kinase complex; ROS: Reactive oxygen species; MDA: Malondialdehyde; GPX4: Glutathione peroxidase 4; circHIPK3: One of the most abundant circRNA in muscle; FOXO3a: A transcription factor of the O subclass of the forkhead family; lncRNA: Long non-coding RNAs; KLF3-AS1: Localize at chromosome 4p14 according to the exocarta database; mTOR: Mammalian target of rapamycin; ULK1: Atg1/unc-51-like kinase; LC3: Light chain 3; PI3K: Beclin-1/class III phosphatidylinositol 3-kinase; CMA: Chaperone-mediated autophagy; Hsc 70: Heat shock cognate 71 kDa protein; LAMP2A: Lysosomal-associated membrane protein type 2; Atg: Autophagy-associated gene; Atg6: Vps34/Beclin-1; PIP3: Phosphatidylinositol (3,4,5) P3; PE: Phosphatidyl ethanolamine; SSCs: Spermatogonial stem cells; Nec-1: Necrostatin-1, a necroptosis inhibitor; NPSCs: Nucleus pulposus-derived stem/progenitor cells; HSP90: Heat shock protein 90; ROS: Reactive oxygen species; PCD: Programmed cell death.



**Figure 1 Mechanisms of intrinsic apoptotic pathways in stem cells.** Cell stress from various damage causes a rapid response leading to apoptosis via BH3-only activator (Way I) or active Bax directly from the Golgi (Way II) to the mitochondria, which subsequently induces a co-pathway [MOMP, cytochrome C (cyt C) releasing, etc.]. I: Stress inducers, such as DNA damage could stabilize and activate p53, which leads to p53 nuclear translocation. Subsequently, p53 exerts an impact on transcription of apoptotic genes via DNA-binding activity and its transcriptional activity (e.g., PUMA, NOXA, and Bax); II: Bax, which is monomeric in the cytoplasm, could be activated via stabilized p53 and active-Bax translocates from the Golgi to the mitochondrion. Once instigated with the apoptotic signals, active-Bax could lead to the alteration of MOMP, which undergoes dimerization and transfers to the OMM, so that relevant proteins (such as cyt C) are released into the cytosol usually confined in the intermembrane space. The released cyt C is involved in apoptosome formation via binding to the cytosolic Apaf-1. This complex recruits and activates initiator pro-casp-9, and then act-casp-9 activates downstream executor casp-3/-6/-7, leading to apoptotic cell death. In the cytoplasm, IAP antagonists (e.g., SMAC, ARTS, and HTRA2) could bind and suppress XIAP, causing the activation of casp-9 for the apoptotic pathway. The T-shaped lines indicate inhibitory interactions involved in this pathway, while the solid arrows indicate activating interactions. Bax: Apoptosis regulator Bcl-2 associated X protein; OMM: Outer membrane permeabilization; MOMP: Mitochondrial outer membrane permeabilization, cyt C: Cytochrome C; PUMA: p53 upregulated modulator of apoptosis, NOXA: Pro-apoptotic BH3-only protein, also known as PMAIP1, phorbol-12-myristate-13-acetate-induced protein 1; Apaf-1: Apoptosis protease activating factor-1; IAP: Inhibitor of apoptosis; SMAC: Second mitochondria-derived activator of caspase; ARTS: Apoptosis-related protein in the transforming growth factor- $\beta$  signaling pathway; HTRA2: High-temperature-required protein A2.

release of cytochrome C (cyt C), p53, and mitochondrial outer membrane permeabilization (MOMP). For example, hematopoietic stem and progenitor cells (HSPCs) are



**Figure 2 Mechanisms of extrinsic apoptotic pathways in stem cells.** The extrinsic apoptotic pathway (also known as the death receptor-dependent pathway) is induced by the connection between death receptors exposed on the cell surface [tumor necrosis factor (TNF) receptor] and the specific TNF family ligands. Subsequently, this signaling causes a conformational change leading to the recruitment of Fas-associated death domain (FADD) and allows interactions between FADD and casp-8 and/or the casp-10, resulting in the cleavage and activation of casp-3 and casp-7 through their death domain. Finally, the active and cleaved casp-3 induces changes in phosphatidylserine exposure, DNA fragmentation, and the formation of apoptotic bodies. Also, casp-8 can target the BH3-only protein Bid and cleave Bid to a truncated fragment t-Bid, which could connect to the extrinsic apoptotic pathways. The T-shaped lines indicate inhibitory interactions involved in this pathway, while the solid arrows indicate activating interactions. FADD: Fas-associated death domain.

used for treating acquired and primary immunodeficiencies, thalassemia, and sickle cell disease. However, the presence of intrinsic apoptosis is shown in HSPC-based therapy in which excess DNA damage can trigger cumulative p53 pathway, constraining proliferation, yield, and engraftment of HSPCs, while moderate damage can lead to reversible function impairment by transient p53 inhibition[136]. According to the downstream activators of p53, two main pathways could be described: BH3-only activator (Way I shown in the left part of Figure 1) and active BAX from the Golgi (Way II shown in the right part of Figure 1) to the mitochondria.

**Part I during the intrinsic pathway:** During the intrinsic pathways, DNA damage, as a significant inducer, can stabilize and activate p53 by phosphorylation (for example, the phosphorylation of p53 at Ser46 can induce the p53-dependent apoptotic pathway caused by DNA damage[137]), leading to p53 nuclear translocation[119]. Subsequently, p53 exerts an impact on transcription of apoptotic proteins (namely, the related proteins) *via* DNA-binding activity and its transcriptional activity, such as the pro-apoptotic proteins p53 upregulated modulator of apoptosis (PUMA), NOXA (the pro-apoptotic BH3-only proteins, also known as PMAIP1 [phorbol-12-myristate-13-acetate-induced protein 1]), and apoptosis regulator Bcl-2 associated X protein (Bax)[138,139].

PUMA and NOXA can bind and activate Bax and Bcl-2 antagonist/killer-1 protein (Bak) in the cytoplasm, resulting in MOMP and release of cyt C[140]. Further, p53 can directly interact with Bax and Bak to modulate MOMP[141,142]. Of note, in the absence of cellular stress, p53 could rapidly produce and degrade in human pluripotent SCs (hPSCs), and the stabilization of p53 occurred upon DNA damage or *via* inhibition of MDM2 (the E3 ubiquitin ligase mouse double minute 2 homolog,

which maintains low p53 levels through triggering p53 degradation)[143,144]. Interestingly, the activation of p53 is also involved in other types of cell death, such as ferroptosis[134].

**Part II during the intrinsic pathway:** Typically, Bax is monomeric in the cytoplasm. Studies show that active Bax localized to the Golgi held away from the mitochondrion in some hPSC lines, whereas active BAX could transform the mitochondria after cell stress as DNA damage *via* a rapid p53-dependent pathway during apoptosis[145]. Once instigated with the apoptotic signals, Bax could undergo dimerization and transfer to the outer membrane of mitochondria, leading to the alteration of MOMP[146], so that relevant proteins (such as cyt C) were released into the cytosol usually confined in the intermembrane space[147]. The released cyt C is involved in apoptosome formation *via* binding to the cytosolic apoptosis protease activating factor-1 (Apaf-1)[148]. This complex recruits and activates initiator pro-caspase-9, and then act-caspase-9 activates downstream executor caspases-3/-6/-7, leading to apoptotic cell death[148,149]. In the cytoplasm, the inhibitor of apoptosis (IAP) antagonists could bind and suppress XIAP (X-linked inhibitor of apoptosis, E3 ubiquitin-protein ligase), causing the activation of caspase-9 for the apoptotic pathway[121]. These IAP antagonists include second mitochondria-derived activator of caspase (SMAC), apoptosis-related protein in the transforming growth factor- $\beta$  signaling pathway (ARTS), and mitochondrial serine protease high-temperature-required protein A2 (HTRA2)[121,148]. Koren *et al*[121] found highly expressed ARTS in cells comprising the intestinal SC niche, which protects Paneth cells from undergoing apoptosis.

**The extrinsic pathway of apoptosis:** The extrinsic apoptotic pathway is also known as the death receptor-dependent pathway induced *via* the connection between death receptors exposed on the cell surface (one of the numbers in the tumor necrosis factor receptor (TNFR) family) and the specific TNF family ligands mentioned above[150]. Previous research reported the effect of TNF $\alpha$  on the development of human hematopoietic progenitors *in vitro* within the role of inhibition[151] or promotion[152]. These TNF $\alpha$ -driven mechanisms play a vital role in HSC response to inflammatory stress for removing damaged cells and activating SCs[153]. Recently, HSC transplantation for malignancy has shown anti-tumor activity *via* TNF $\alpha$ -driven pathways[153,154]. Death receptors and their ligands cause a conformational change, which leads to the recruitment of Fas-associated death domain (FADD)[155] and allows interactions between FADD and caspase-8 and/or the caspase-10, resulting in the cleavage and activation of caspase-3 and caspase-7 through interactions between their death domain (DD)[156]. Finally, the active and cleaved caspase-3 induces changes in phosphatidylserine exposure, DNA fragmentation, and the formation of apoptotic bodies. However, reports suggest that caspase-3 activity could be elevated in nonapoptotic pathways in neural SCs[157].

Remarkably, caspase-8 can target the BH3-only protein Bid (BH3-interacting domain death agonist) and cleave Bid to a truncated fragment t-Bid[158]. Capper *et al*[159] and Jia *et al*[160] showed that decreased Bid could inhibit apoptosis, promote proliferation, and delay senescence in human periodontal ligament SCs (h-PDLSCs) *via* activated Yes-associated protein, and low levels of caspase-8 were detected in stem cell features through hypermethylation. Subsequently, t-Bid could directly translocate to the outer mitochondrial membrane after activating apoptotic regulator Bax and inhibiting Bcl-2, leading to co-engages between the intrinsic apoptotic pathway and the extrinsic apoptotic pathway[158]. Some evidence shows that activation of the extrinsic pathway and inhibition of caspase-8 can induce necroptosis[161,162].

Emerging findings indicate that Bcl-2 family proteins play a vital role in SCs (*e.g.*, overexpression of Bcl-2 in MSCs[163], ESCs[164], and neuroepithelial SCs (NECs)[165] improved their survival). The three functional groups Bak and Bax, BH3-only proteins, and Bcl-2 maintain a balance between SC survival and death. For example, high levels of Bcl-2 were measured in HFSCs for antiapoptosis in contrast to differentiated cells[166,167]. In the SCs, Bax performs as an activated conformation sequestered in the Golgi apparatus held away from the mitochondrion. Following stresses such as DNA damage, active Bax translocates to the mitochondrial outer membrane to initiate MOMP and the apoptotic cascade, which bypasses the conventional intrinsic and extrinsic apoptotic pathways[168,169]. However, the mechanism underlying the localization of active Bax at the Golgi and active Bax-induced pore formation in the Golgi stacks is unclear.

## Autophagy

As a self-protective catabolic mechanism within the cells, autophagy exerts a key

influence in sustaining SC homeostasis by maintaining stemness, upregulating quiescence, managing differentiation *via* remodeling, and self-renewal *via* metabolic reprogramming[170-173]. Autophagy contributes to metabolic regulation through increased glycolysis to generate ATP in the hypoxic milieu for balancing SC fate[174,175]. For example, autophagy plays a vital role in maintaining the quiescence of SCs (*e.g.*, HSCs and muscle SCs (MuSCs)) *via* rejuvenating aged quiescent SCs controlled by various autophagy pathways such as the p38/mitogen-activated protein kinase (MAPK) signaling pathway[176,177]. Uncovering the autophagy mechanisms underlying SC quiescence presents novel therapeutic strategies to release the cells out of the quiescent state, promoting their proliferation and differentiation (such as induced activation of quiescent NSCs for neuron injury), or re-establishing quiescence to prevent aberrant proliferation and differentiation or premature senescence (such as anti-cancer therapeutics), which carry the risk of cancer SCs (CSCs)[178,179]. These stressors (*e.g.*, starvation, oxidative stress, infection, and hypoxia) stimulate the cascade of autophagy as follows (shown in Figure 3)[180].

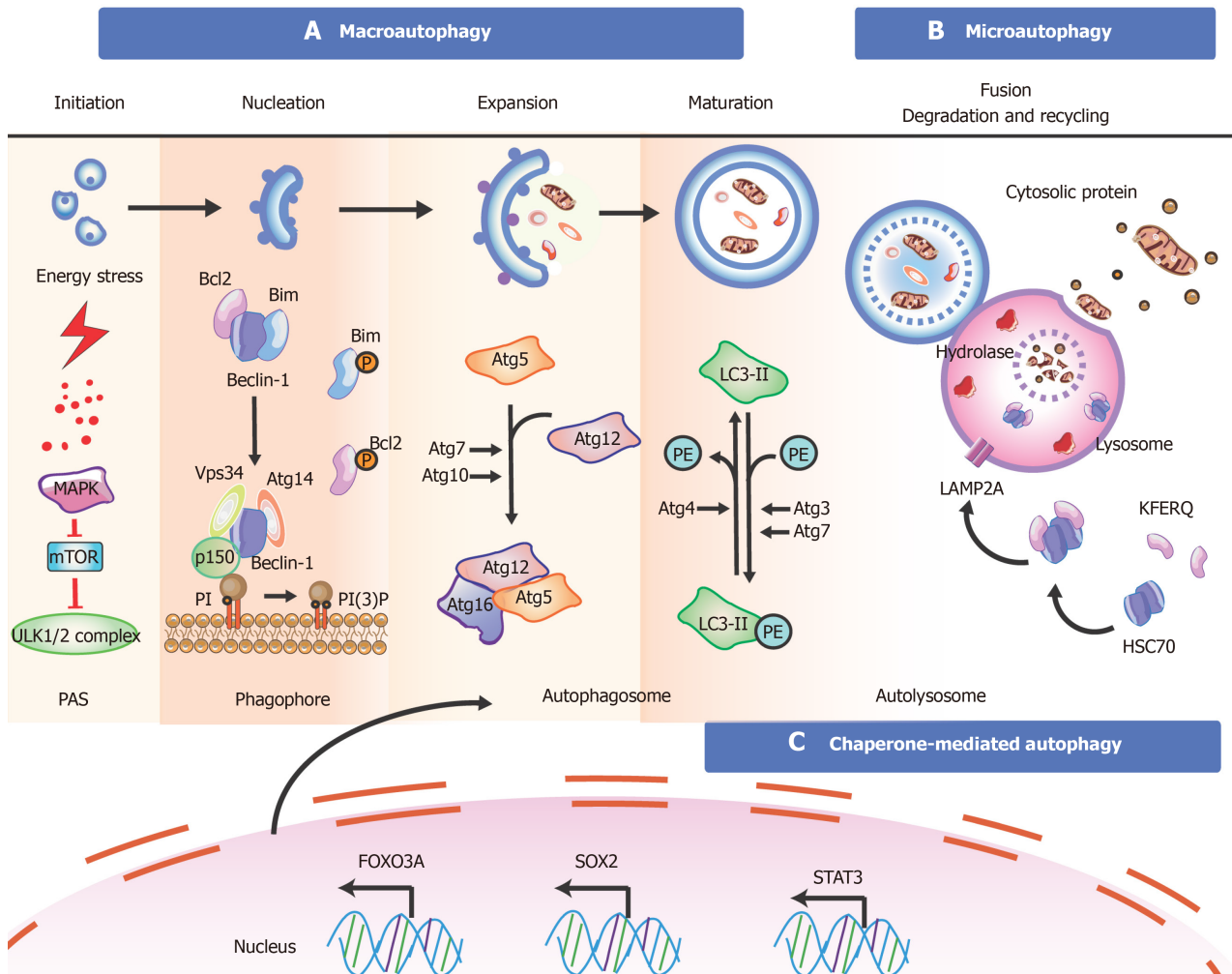
During autophagy, the formation of multi-protein complexes is associated with morphologic changes (shown in Figure 3). Initiation of autophagy is controlled by nutrient sensors, namely, mTOR and AMPK[173,181]. Typically, the mTORC1 complex functions as an inhibitor for autophagy. Under environmental stresses and physiological stressors, AMPK is activated to inhibit the activity of mTORC1, leading to a release of the ULK1 (Unc-51-like kinase complex, also known as ATG1) complex to induce autophagy, which is usually inhibited by mTORC1[182]. This initiation process is known as the phagophore assembly site (PAS) formation, which is regarded as indispensable for nucleation in the next stage. Compared with somatic mouse embryonic fibroblasts, whole-cell extracts of iPSCs and ESCs express high levels of AMPK and phosphorylated AMPK[183]. Interestingly, AMPK inhibition in mouse bone marrow-derived MSCs can upregulate both autophagy and apoptosis in hypoxia and serum deprivation conditions, suggesting crosstalk between autophagy and apoptosis through AMPK-ULK1 pathways[184,185]. Mutations in mTOR lead to smaller brains in mouse cortical development, and fewer proliferating neural progenitors result from disruption of NSC self-renewal[181].

Next, PI3 is phosphorylated to PI3P *via* the class III PI3-kinase-Beclin1 complex formed by core subunits of Beclin1 (Atg6), Atg14 L, and Vps34-Vps15, resulting in autophagosome formation[186,187]. The Atg12-Atg5-Atg16L1 complex acts as a regulator for enveloping and translocating the cytoplasmic cargo to the lysosome within misfolded-protein degradation[188]. Atg4 can cleave LC3 (Atg8) to generate cytosolic LC3-I. Atg3 (E2 enzymes) and Atg7 (E1-like enzymes) can lead the conjugation of PE to LC3-I to form lipidated LC3-II, which is combined with the autophagosome membrane to complete and elongate autophagosome formation[189]. Finally, the autophagosome contents undergo degradation due to low lysosomal pH. Some evidence demonstrates that autophagy plays an important role in reprogramming to form iPSCs, while iPSCs colony formation shows reprogramming failure due to the lack of Atg3, Atg5, or Atg7[190,191]. Autophagy is necessary for SC survival and sustenance. It is critical for SC differentiation in which co-localized dots of Tuj1-positive and GFP-LC3-positive cells are monitored and progress increasingly during NSC differentiation[192].

In microautophagy, misfolded or/and toxic proteins can be directly engulfed by the lysosomal membrane and degraded in the lysosome[193]. During chaperone-mediated autophagy, the heat shock cognate 70 kDa protein (HSC70) chaperones attach to the pentapeptide motif KFERQ (namely Lys-Phe-Glu-Arg-Gln) for delivery to lysosomes *via* a specific receptor LAMP2A. Reports suggest that targeting peptide HSC70 during autophagy can dramatically decrease amyloid- $\beta$  (A $\beta$ ) oligomers in iPSCs with superior neuroprotective activity[194]. However, the molecular mechanism between autophagy and SCs is still unclear and remains to be further explored.

Apart from these vital targets, key transcription factors are closely linked to the stem cell state and the occurrence of autophagy (shown in Figure 3). For example, FOXO3A can enhance autophagosome formation *via* autophagy gene expression in hematopoietic SCs and breast cancer stem-like cells, which is needed to mitigate an energy crisis and allow cell survival[182,195]. Moreover, an elevated level of SOX2 is detected in NSCs, which is important for self-renewal; downregulation of SOX2 is observed in differentiated neurons and glia[196]. Besides SOX2, other transcription factors such as STAT3, OCT4, KLF4, and c-Myc are also vital for reprogramming in the initial creation of iPSCs at the genetic level[197].





**Figure 3 Overview of the mechanisms during autophagy in stem cells.** There are three types of autophagy [macroautophagy (section a), microautophagy (section b), and chaperone-mediated autophagy (section c)] based on different pathways; however, they produce the same results. Besides these proteins, key transcription factors closely related to autophagy are shown. The T-shaped lines indicate inhibitory interactions involved in this pathway, while the solid arrows indicate activating interactions. A: Typically, the mTORC1 complex functions as an inhibitor to control the initiation of autophagy. Under environmental stresses and physiological stressors, AMPK is activated to inhibit the activity of mTORC1, leading to a release of the ULK1 (Unc-51-like kinase complex, also known as ATG1) complex to induce autophagy. This initiation process is known as the phagophore assembly site (PAS) formation. Next, PI3 is phosphorylated to PI3P via the class III PI3-kinase-Beclin1 complex formed by core subunits of Beclin1 (Atg6), Atg14 L, and Vps34-Vps15, resulting in autophagosome formation. The Atg12-Atg5-Atg16L1 complex acts as a regulator for enveloping and translocating the cytoplasmic cargo to the lysosome in misfolded-protein degradation. Atg4 can cleave LC3 (Atg8) to generate cytosolic LC3-I. Atg3 (E2 enzymes) and Atg7 (E1-like enzymes) can lead the conjugation of PE to LC3-I to form lipidated LC3-II, which is combined with the autophagosome membrane to complete and elongate autophagosome formation. Finally, the autophagosome contents undergo degradation due to low lysosomal pH; B: In microautophagy, misfolded or/and toxic proteins can be directly engulfed by the lysosomal membrane and degraded in the lysosome; C: During chaperone-mediated autophagy, the heat shock cognate 70 kDa protein (HSC70) chaperones attach to the pentapeptide motif KFERQ (namely Lys-Phe-Glu-Arg-Gln) for delivery to lysosomes via a specific receptor LAMP2A. Also, some of the key transcription factors are closely linked to the stem cell state and the occurrence of autophagy (bottom). FOXO3A can enhance autophagosome formation via autophagy gene expression in hematopoietic stem cells and breast cancer stem-like cells, which is needed to mitigate an energy crisis and allow cell survival. Besides FOXO3A, other transcription factors such as SOX2, STAT3, OCT4, KLF4, and c-Myc are also vital for reprogramming in the initial creation of stem cells at the genetic level during autophagy.

### Necroptosis

The occurrence of necroptosis in SCs has recently been reported. Wang *et al*[35] found that gut stem cell necroptosis resulting from genome instability triggered bowel inflammation. Moreover, TNF- $\alpha$  could promote the survival and myeloid differentiation of HSC *via* activating a strong and specific p65-nuclear factor  $\kappa$ B (NF- $\kappa$ B)-dependent gene program that prevents necroptosis rather than apoptosis to poise HSCs for myeloid cell production[153].

### Others

In addition to apoptosis and autophagy (mentioned above), reports on other cell death types have led to studies exploring cell death mechanisms, such as ferroptosis and pyroptosis[35,132,198-203]. Notably, different cell death mechanisms can simultan-

ously occur in disease (termed as 'PANoptosis'), suggesting a complex but practical integrated network between various cell death mechanisms in SCs[204,205].

Ferroptosis had been observed in SCs with an imbalance of iron homeostasis, a significant upregulation of cytosolic free iron content, and DNA/protein/lipid oxidative damage, leading to an obvious senescence phenotype and spontaneous death in iPSC-derived neuronal precursor cells (NPCs)[134,206]. iPSCs and gene-correction are used for treating Pelizaeus-Merzbacher disease (PMD) but subsequently undergo cell death after the pre-myelinating stage with evidence for caspase-3-dependent apoptosis in approximately 40% of cells and ferroptosis[205]. Thus, iron chelators and lipophilic antioxidants can lead to downregulation of apoptosis and ferroptosis[205]. Further, transfusional iron overload (IOL) may have clinical importance as a character close to transplant-related mortality in hematopoietic stem cell transplantation (SCT) for hematologic malignancies (HM)[198].

For pyroptosis (TLR4-NLRP3-mediated cell death pathway), a large body of evidence shows that stem cell transplantation can function as an inhibitor for pyroptosis, suggesting a novel approach called stem cell-derived exosome treatment[207,208], and numerous molecular pathways, such as exosome/LncRNA KLF3-AS1/miR-138-5p/Sirt1 axis and exosome/circHIPK3/FOXO3a axis, are presented[132,133,209].

All kinds of RCDs contribute to making a constant effort to maintain a homeostatic balance, in which it is especially significant for the therapeutic effects of SC-based therapy. As for apoptosis in SCs, the intrinsic and extrinsic pathways play a synergistic role in ensuring the multi-cellular organisms to keep normal cells, and remove abnormally proliferating cells or other defective cells. Failure to regulate apoptosis would lead to the uncontrolled growth and division of cells during pathological process. In this regard, whether the SCs that we utilized in transplantation would be uncontrolled someday is also a potential challenge. Compared with apoptosis, autophagy could be regarded as a source of energy through digestion of cellular structures and/or organelles against multiple stresses such as nutrient deprivation (caloric restriction). These two main RCD pathways are widely studied and also some novel ways such as active-Bax in Golgi to inducing apoptosis will be further dug out. Remarkably, Bcl-2 as a co-regulator during these two pathways might be a potential target not only for apoptosis but also for autophagy. Others RCDs such as necroptosis, pyroptosis, and ferroptosis are also found in transplanted SCs, but their detail signaling and application need to keep digging. All in all, various cell death mechanisms are under investigation (apart from the cell death types described). Notably, it is necessary to focus on the overall network between different molecular cell death pathways.

## STRATEGIES TO PROMOTE STEM CELL SURVIVAL FOR TRANSPLANTATION THERAPY

As mentioned above, the microenvironment exerts a vital role in the survival of SCs. Many studies have contributed to providing a wide range of strategies to enhance stem cell transplantation therapy *via* improving the microenvironment, including preconditioning strategy (*e.g.*, exposure to oxidative stress, heat shock, and ischemic/hypoxic injury), pretreatment (*e.g.*, drug treatment, cytokines, antioxidants, nitric oxide, glucose deprivation, growth factors, miRNAs, and exosomes), genetic modification, and co-transplantation of different cell types (shown in Figure 4 and Table 3[210-228]).

### Preconditioning strategy

Preconditioning strategies mainly help to promote tolerance of SCs and progenitor cells derived from SCs. These triggers aim to alter cell signaling and metabolism for adaptation to appropriate and mild stress conditions and sublethal insults [*e.g.*, ischemic preconditioning (IPC), hypoxia, anoxia, hydrogen sulfide (H<sub>2</sub>S), hydrogen dioxide (H<sub>2</sub>O<sub>2</sub>), and carbon monoxide (CO)].

In detail, IPC of SCs is considered an efficient method to promote cell survival. After a repeated short cycle of ischemic/reperfusion (I/R), some of the chemical signals (*e.g.*, ROS, NO, and adenosine) can release and trigger cell protection *via* a cascade of survival factors such as the activation of protein kinase C (PKC), protective protein kinase B (PKB or Akt), nuclear factor  $\kappa$ B (NF- $\kappa$ B), and Src protein tyrosine kinases, and subsequent upregulation of cyclooxygenase-2 (COX-2), inducible NO synthase (iNOS), heme oxygenase-1 [HO-1], Mn superoxide dismutase, aldose reductase, and anti-

Table 3 Strategies to enhance stem cell transplantation therapy

Strategy	Method	Target	Effects	Molecular mechanisms	Ref.
Preconditioning	Short repeated ischemia/reperfusion	ESCs	Enhancing the tolerance of subsequent prolonged lethal ischemia	Promoting the expression of trophic factors, inducing the release and activation of PKC, PKB, or Akt, NF- $\kappa$ B and Src protein tyrosine kinases, and subsequently upregulating COX-2, iNOS, HO-1, Mn superoxide dismutase, aldose reductase, and antiapoptotic genes	[210-212]
	Hypoxia	MSCs	Promoting mesenchymal stem cell migration and survival	Increasing the expression of lncRNA-p21, HIF-1 $\alpha$ , and CXCR4/7(both were chemokine SDF-1 receptors)	[213]
		CSCs	Promoting survival and cardiogenic differentiation	Inducing the activation of the HIF-1 $\alpha$ /apelin/APJ axis	[214]
		NSCs	Promoting survival and neuroprotective properties, and facilitating functional recovery <i>in vivo</i>	Upregulating HIF1- $\alpha$ and HIF target genes such as <i>EPO</i> and <i>VEGF</i> and neurotrophic, and growth factors	[215]
	Hydrogen peroxide preconditioning	BMSCs	Improving the therapeutic potential for wound healing	Upregulating cyclin D1, SDF-1, and its receptors CXCR4/7 expression, and activating the PI3K/Akt/mTOR pathway, but inhibiting the expression of p16 and GSK-3 $\beta$	[216]
	Nitric oxide donor preconditioning	hCSCs	Enhancing survival	Upregulating phosphorylation of NRF2, NF $\kappa$ B, STAT3, ERK, and AKT, as well as increasing the protein expression of HO-1 and COX2	[217]
	Heat shocking	MSCs	Promoting migration	Triggering the activation of ERK and PI3K/Akt signaling pathways <i>via</i> HSP90	[218]
Pretreatment	Oxytocin	MSCs	Antiapoptosis and cell protection	Increasing the expression of Akt and phospho-ERK1/2 proteins, rapid calcium mobilization, and upregulation of antiapoptotic and angiogenic genes including <i>HSP27/32/70</i> , <i>TIMP-1/2/3</i> , <i>VEGF</i> , thrombospondin, and matrix metalloproteinase-2	[219]
	Minocycline	NSCs	Increasing the capacity of migration, proliferation, and differentiation to improve neurological recovery	Increasing the expression of Nrf2	[220,221]
	Melatonin	MSCs	Inducing fewer fibrotic damage	Downregulating the levels of TNF- $\alpha$ , TGF- $\beta$ , and $\alpha$ -SMA, and upregulating the expression of E-cadherin	[222]
	Extremely low-level lasers	MSCs	Enhancing the migration of MSCs; promoting the proliferation rate of SCs	Allowing the FAK and ERK1/2 pathways and increasing PDGF and HGF; inducing the up-regulation of mitochondrial ROS and NO	[223,224]
Genetic strategies	Overexpressing pro-survival factors	hNSCs	Improving short- and long-term survival	Overexpression of Bcl-2, Bcl-xl, Hif1a, or/and Akt1	[225]
	Genetic modification	MSCs	Potentiating MSC survival	Overexpression of ERBB4 and ILK	[226]
3D technology	Hydrogels mimicking	MSCs, ESCs, EPCs	Role in stem cell differentiation, changing matrix stiffness, mechanical stress and strain, nonlinear elastic, microenvironments and viscoelastic microenvironments	N/A	[227]
Co-transplantation	Co-transplantation of MSCs and HSCs	MSCs HSCs	Enhancing therapeutic effects	N/A	[228]

ESCs: Embryonic stem cells; NSCs: Neural stem cells; MSCs: Mesenchymal stem cells; HSCs: Hematopoietic stem cells; EPCs: Endothelial progenitor cells; hNSCs: Human neural stem cells; SCs: Stem cells; Hsp70/90: Heat shock protein

70/90; ERK: Extracellular regulated protein kinases; Nrf2: Nuclear factor erythroid 2; TNF: Tumor necrosis factor; TGF: Tumor growth factor; SMA: Smooth muscle actin; HGF: Hepatocyte growth factor; ROS: Reactive oxygen species; Bcl-2: B-cell lymphoma 2; ERBB4: Erb-b2 receptor tyrosine kinase 4; ILK: Integrin-linked kinase; SDF-1: Stromal-derived factor-1; EPO: Erythropoietin; VEGF: Vascular endothelial growth factor; TIMP: Tissue inhibitor of metalloproteinase; PDGF: Platelet-derived growth factor.

apoptotic genes (*Bcl-xL*, *Mcl-1*, *c-FLIPS*, and *c-FLIPL*)[210]. During ischemia/hypoxia or heat shock preconditioning, the level of Hsp70 and Hsp90 is upregulated. Reports suggest that Hsp70/90 can inhibit SMAC in the myocardium to prevent activation of caspase-3/9 (pathway described above)[211,212].

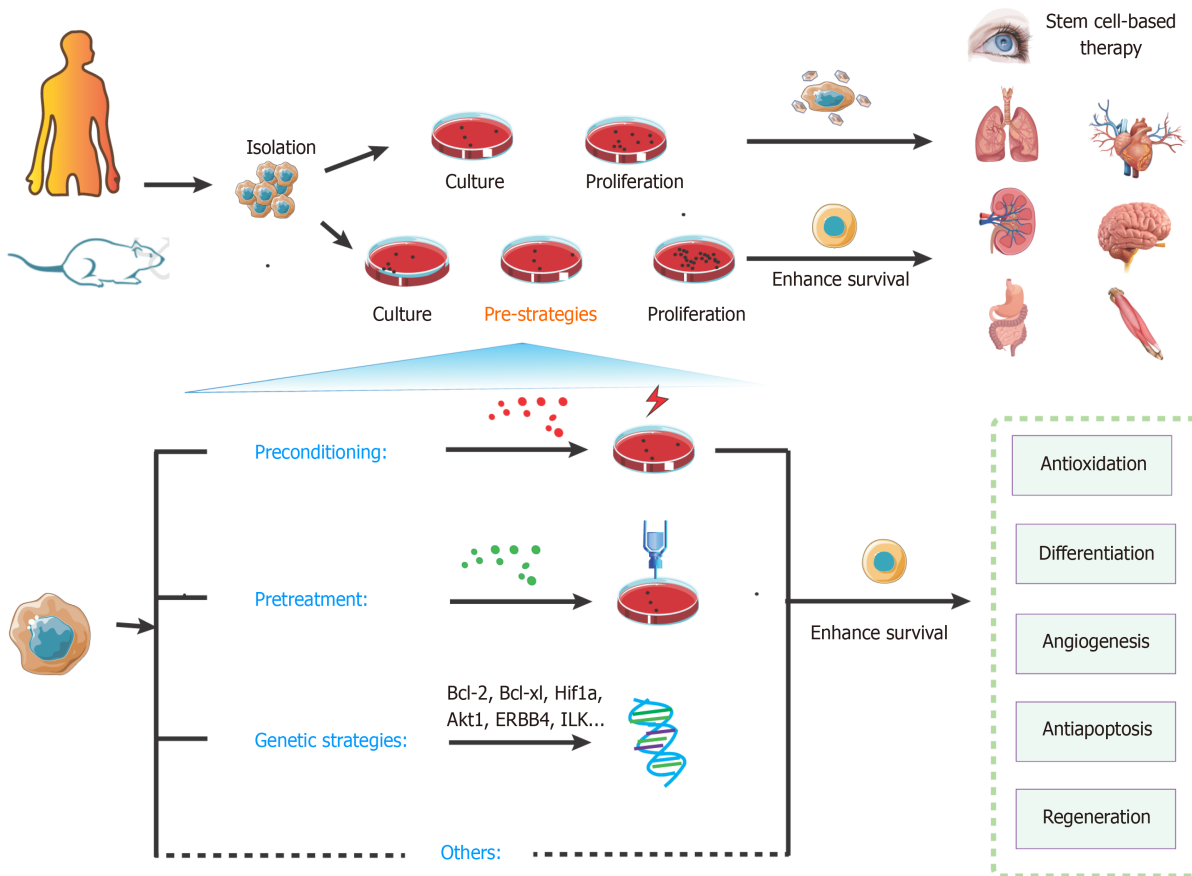
Similarly, hypoxia-inducible factor (HIF-1) is upregulated during hypoxia preconditioning to inhibit tumor suppressor p53, reduce oxidative phosphorylation, upregulate VEGF receptor levels, and promote the activation of Akt to target caspases and Bcl-2 for anti-apoptosis[229,230]. Recent findings reveal that OM-MSC (olfactory mucosa mesenchymal SC) with hypoxic preconditioning functions as an inhibitor for apoptosis and pyroptosis in microglial cells through activation of HIF-1 $\alpha$  *in vitro*[231]. Hypoxia-preconditioned SCs can also upregulate paracrine activity, and their exosomes are also considered a novel transplantation therapy. For example, MSC-derived exosomes with hypoxia preconditioning show promising potential as an effective means for optimized bone fracture healing *via* exosomal miR-126 and the SPRED1/Ras/Erk signaling pathway[232].

Besides preconditioning with ischemia and hypoxia, oxidative stress and heat shocking are also the most common preconditions for SCs within a similar rationale. Chronic exposure to oxidative stress (*e.g.*, H<sub>2</sub>O<sub>2</sub>, H<sub>2</sub>S, and CO) produces protective effects by activating mitochondrial ROS production, resulting in ERK activation and anti-apoptotic protein expression for cell proliferation, migration, anoikis, autophagy, and survival[216,233,234]. Moreover, heat shocking precondition of mesenchymal SCs can induce HSPs to activate ERK and PI3K/Akt signaling pathways, resulting in increased expression of trophic factors, proteins, and genes for cell protection[218].

### Pretreatment strategy

Pretreatment is a strategy for successfully protecting transplantable SCs, using various factors before implantation, whereas preconditioning refers to providing a specific environment within sublethal insults. These factors include antioxidants, cytokines, growth factors, and drug therapy (phosphodiesterase inhibitors, glucose deprivation, pro-survival protein expression, and anti-apoptotic proteins).

To date, various drugs have been developed for the pretreatment of SCs. Pretreatment with pharmacological inhibitors can result in increased expression of survival signaling and a high Bcl-2/Bax ratio in the early phase (2 h), and activation of the JAK/STAT signaling pathway in the late phase (24 h) for cardioprotection[210]. Also, Ji group has reported the protective effect of histochrome pretreatment against oxidative stress in cardiac progenitor cells (CPCs) *via* upregulating Bcl-2 and Bcl-xL and downregulating Bax and H<sub>2</sub>O<sub>2</sub>-induced cleaved caspase-3[235]. Moreover, short-term incubation either with an antioxidant N-acetyl-L-cysteine (NAC) or a specific



**Figure 4 Overview of key strategies to enhance stem cell transplantation therapy.** The steps of stem cell-based transplantation therapy include drawing the materials, isolation, culture, proliferation, and transplantation. Compared with the classic approaches, pre-strategies could enhance survival of stem cells. These pre-strategies mainly include preconditioning, pretreatment, genetic strategies, and other methods. They can effectively activate various signaling pathways for protecting cells from injury and promoting survival.

inhibitor of TNFR 1 signaling can prevent TNF- $\alpha$ -mediated ROS accumulation in HSCs[154]. MSC pretreatment with oxytocin (OT) [10(-10) to 10(-6) M] in response to signaling events can induce Akt and phospho-Ras-dependent extracellular signal-regulated kinase (ERK)1/2, rapid calcium mobilization, and upregulation of anti-apoptotic and angiogenic genes, including *HSP27/32/70*, tissue inhibitor of metalloproteinase (TIMP)-1/2/3, vascular endothelial growth factor, thrombospondin, and matrix metalloproteinase-2[219]. Minocycline preconditioning increases Nrf2 expression and neuroprotective paracrine secretion. It promotes migration, proliferation, and differentiation of NSCs to improve neurological recovery after NSC transplantation[220,221]. The molecular mechanism involves upregulation of antioxidant genes and reduced oxidative stress grafted cell death following transplantation, resulting in low-rate cell death[221]. Some studies have shown the benefits of melatonin pretreatment on MSC-based therapy with a reduction in the levels of TNF- $\alpha$ , TGF- $\beta$ , and  $\alpha$ -SMA, and upregulation of E-cadherin expression that induces less fibrotic damage[222].

Trophic factors and cytokines are also considered effective pretreatment approaches for regulating MSC fate. For example, SC pretreatment with IL-1 $\beta$  can promote migration and survival of MSCs and improve function in type 2 diabetes, acute myocardial infarction, and neural disorders *via* upregulating the expression of various cytokines, chemokines, and adhesion molecules [e.g., IL-6/8/23A, TNF- $\alpha$ , CCL5/20, CXCL1/3/5/6/10/11, VCA-1 (vascular cell adhesion molecule 1), and ICAM-1/4 (intercellular adhesion molecule 1 and 4)]. IL-1 $\beta$  can induce phosphorylation of NF- $\kappa$ B, but not PI3K/AKT and ERK1/2 pathways[236]. In the NSC pretreatment strategy, a series of experiments using IL-6 show that it can reprogram NSCs to tolerate hostile environments *via* activating STAT3 to increase the levels of superoxide dismutase 2 (SOD2) for anti-apoptosis against inflammatory cytokines and oxidative stress *via* mitochondrial-dependent apoptotic pathways[237,238]. Some other molecular targets, including Rho-associated kinase inhibition, TGF- $\beta$ 2 treatment, SDF-1 signaling of



PI3K/Akt, and p38 MAPK inhibition *via* anti-apoptotic pathways, also enhanced SC survival during treatment[239].

Compared with chemical pretreatment methods discussed above, physical factors such as extremely low-level lasers, pulsed electromagnetic fields (PEMF), mechanical stretch, and nanochelating-based nanocomplexes (*e.g.*, GFC7) are also used as pretreatment methods to enhance SC-based therapy[240-243]. For example, pretreatment with extremely low-level lasers improves the migration ability of MSCs *via* activation of FAK and ERK1/2 pathways and increased expression of platelet-derived growth factor (PDGF) and HGF. Furthermore, it also promotes the proliferation rate of SCs by inducing the upregulation of mitochondrial ROS and NO and enhancing the expression of the S-phase proportion in MSCs[223,224].

### Genetic strategy

Genetic strategies have raised hopes for better SCs-based therapy since they were introduced more than a decade ago[244,245]. The core idea of this technology is to target key genes and the expression of factors related to the fate of SCs. Under different death stimuli, overexpression of various factors such as TNFR, Akt1, stromal cell-derived factor-1 (SDF-1), and hepatocyte growth factor (HGF) is beneficial for the repopulation of SCs[246]. Studies on modified transplanted hNSCs show improved short- and long-term survival of transplanted hNSCs *via* overexpression of these pro-survival factors, including Bcl-2, Bcl-xL, Hif1a, or/and Akt1[225]. Genetic modification for ERBB4 (erb-b2 receptor tyrosine kinase 4) and ILK overexpression could potentiate MSC survival[226]. In recent years, the CRISPR/Cas9 system has been widely used for genome editing applied in genetic modification of SCs for *in vivo* applications such as neural regeneration, bone regeneration, treatment of blood disorders, and cartilage tissue engineering[247]. Although gene modification promises to enhance tolerance to damage "at the root," there are still formidable predictability challenges and potential long-term side effects.

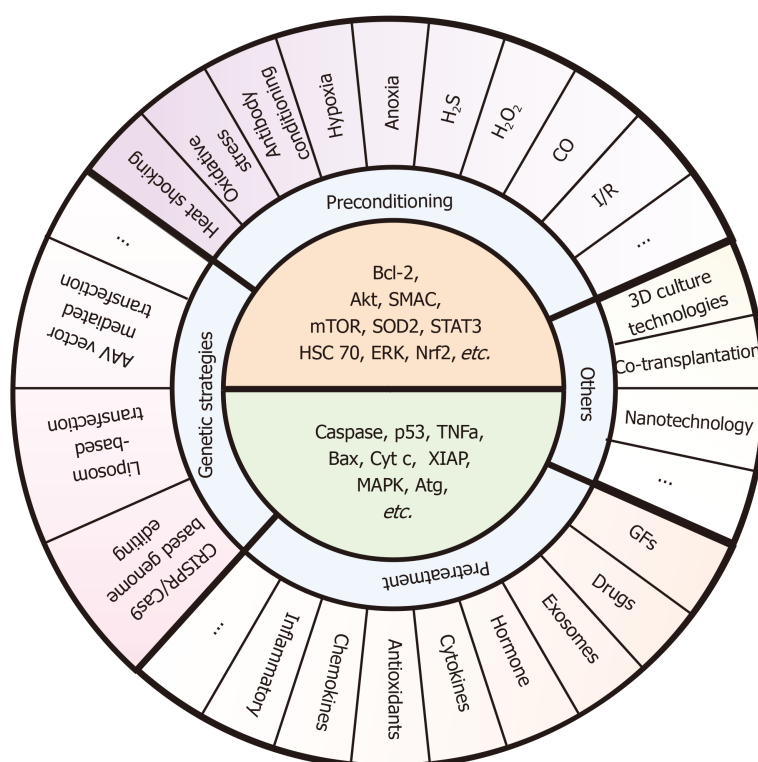
### Others

Recently, three-dimensional culture technologies (*e.g.*, MSC encapsulation technique) mimicking the physical environment to sustain the viability of SCs to induce multi-lineage differentiation are used to protect SCs from PCD as an innate immune system and provide favorable mediators such as cytokines and growth factors[227,248]. However, the time, cost, and labor efficiency of three-dimensional technologies for SCs may be non-negligible challenges, and a combination of biocompatible materials based on simple and easy methods is needed for SC-based therapy. Moreover, co-transplantation of different cell types offers an alternative strategy to improve outcomes of SC-based treatment. Studies show promising results with co-transplantation of human fetal mesenchymal and hematopoietic SCs in type 1 diabetes, epidermal neural crest SCs (EPI-NCSC), and olfactory ensheathing cells (OEC)[228,249]. However, the significance of co-transplantation for SC-based therapy is still unclear[250,251].

As described above, these pre-strategies could provide transplanted stem cell with a certain microenvironment to improve the survival. The core ideas of these methods are to upregulate the survival factors (*e.g.*, Bcl-2, Akt, SMAC, mTOR, SOD2, STAT3, HSC 70, ERK, and Nrf2) and downregulate the death catalyzers (*e.g.*, caspase, p53, TNF $\alpha$ , Bax, cyt C, XIAP, MAPK, and Atg) (shown in Figure 5). Bcl-2 might be regarded as a key molecule that raised tremendous expectations, which plays a vital role in both apoptotic and autophagy pathways. Given the fact that gene strategies seem to be hardly accepted in clinical trials to improve effectiveness of SC-based transplantation, preconditioning and pretreatment may provide a cost-effective and handy option. Remarkably, distinct types of transplanted cells or distinct aiming organs show noticeable differences not only in their signaling but also their response to the local area, so studies need to find a right composition as well as an effective target of any applied transplanted SC system.

## CONCLUSION

The SC pool plays a driving role in tissue homeostasis and harm repair. Lately, SC-based therapies may be regarded as a potential strategy that raised tremendous expectations and presented favorable curative effects in enhancing functional repair and repairing damaged tissue. Given the fact that a considerable number of studies on SC-based therapy verify that RCDs occur extensively during the development of the

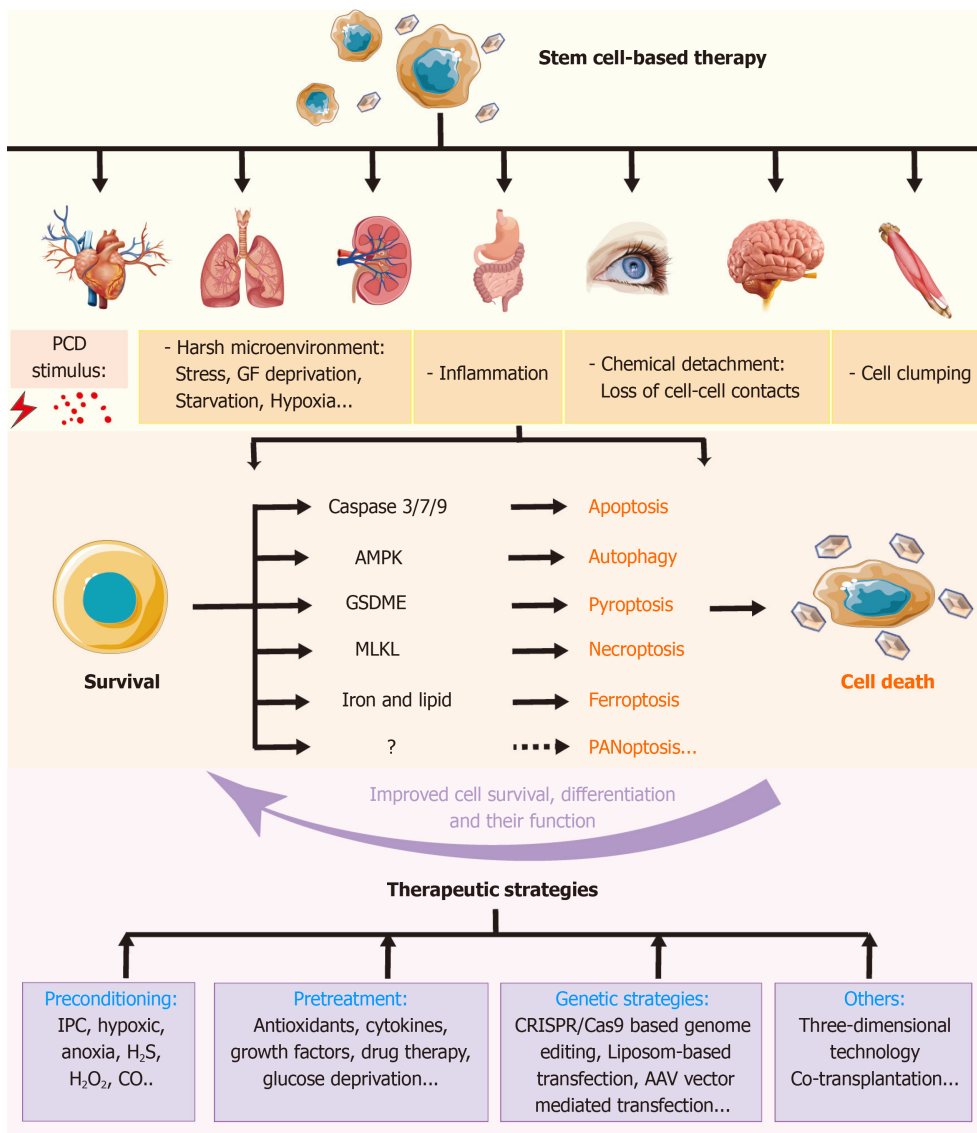


**Figure 5 Specific pre-strategies and their key molecule targets for enhancing stem cell transplantation therapy.** These pre-strategies mainly include preconditioning (e.g., exposure to oxidative stress, heat shock, and ischemic/hypoxic injury), pretreatment (e.g., drug treatment, cytokines, antioxidants, nitric oxide, glucose deprivation, growth factors, miRNAs, and exosomes), genetic strategies (e.g., AAV vector mediated transfection, Liposome-based transfection, and CRISPR/Cas9-based genome editing), and other methods (e.g., 3D culture technologies, co-transplantation, and nanotechnology). The core ideas of these pre-strategies are to upregulate the survival factors (e.g., Bcl-2, Akt, SMAC, mTOR, SOD2, STAT3, HSC 70, ERK, and Nrf2) and downregulate the death catalysts (e.g., caspase, p53, TNFa, Bax, Cyt c, XIAP, MAPK, and Atg). However, there are few methods targeting all of these molecules at the same time during the co-network. Also, studies pay more attention to certain signaling such as Bcl-2 and mTOR, and other signals such as Atg or XIAP still need further mining.

transplanted SCs, RCDs show a crucial role in the therapeutic efficacy and progression of this treatment. Also, RCD interventions may offer opportunities for a better clinical application.

Recently, there have been tremendous strides in understanding the fate of SCs post-transplantation related to self-condition and microenvironment. Along this line, targeting multiple signal transduction pathways in PCDs and survival processes would provide novel approaches for enhancing SC-based therapies. However, the interactions are complex and involve multiple networks rather than one crucial pathway (as the recent term 'PANoptosis'), thus necessitating further research. Moreover, various factors involved in specific pathways may change during stem cell differentiation or show microenvironmental divergence in different cell types, stages of development, and stimuli.

Several approaches can prevent the loss of a vast majority of transplanted SCs, such as preconditioning, pretreatment, and genetic strategies. Important insights into the molecular pathways that control PCD of SCs may unlock novel and potential avenues for regenerative drugs and more efficient therapy. These pre-strategies provide SCs with harsh or nutrient-rich environment to improve the SCs *via* upregulating the survival factors and downregulating the death catalysts. A summary diagram is shown in Figure 6. Recently, some of the novel technologies such as 3D culture technologies, co-transplantation, and nanotechnology also show promising prospects. Furthermore, safer use, better results, and highly feasible and beneficial methods are required for clinical applications.



**Figure 6 Role of regulated cell deaths in stem cell-based transplantation and therapeutic pre-strategies to improve the therapy.** Stem cell-based therapy has been used in various diseases. A number of stimuli may induce regulated cell deaths (RCDs) in transplanted stem cells (SCs), which results in poorer outcomes. Different signals involved in distinct types of RCDs may provide some targets to improve SC-based transplantation. These therapeutic strategies include preconditioning, pretreatment, gene strategies, and so on. IPC: Ischemic preconditioning; PCD: Programmed cell death; MLKL: Mixed lineage kinase domain like protein; GSDME: Gasdermin E.

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