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REVIEW

Application prospects of urine-derived stem cells in neurological and musculoskeletal diseases

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Abstract

Urine-derived stem cells (USCs) are derived from urine and harbor the potential of proliferation and multidirectional differentiation. Moreover, USCs could be reprogrammed into pluripotent stem cells [namely urine-derived induced pluripotent stem cells (UiPSCs)] through transcription factors, such as octamer binding transcription factor 4, sex determining region Y-box 2, kruppel-like factor 4, myelocytomatosis oncogene, and Nanog homeobox and protein lin-28, in which the first four are known as Yamanaka factors. Mounting evidence supports that USCs and UiPSCs possess high potential of neurogenic, myogenic, and osteogenic differentiation, indicating that they may play a crucial role in the treatment of neurological and musculoskeletal diseases. Therefore, we summarized the origin and physiological characteristics of USCs and UiPSCs and their therapeutic application in neurological and musculoskeletal disorders in this review, which not only contributes to deepen our understanding of hallmarks of USCs and UiPSCs but also provides the theoretical basis for the treatment of neurological and musculoskeletal disorders with USCs and UiPSCs.

Key Words: Urine-derived stem cells; Urine-derived induced pluripotent stem cells;

Neurological diseases; Musculoskeletal diseases; Treatment prospect

Core Tip: Urine-derived stem cells and urine-derived induced pluripotent stem cells possess high potential of neurogenic, myogenic, and osteogenic differentiation, which are able to be used for the treatment of neurological and musculoskeletal disorders.

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INTRODUCTION

Neurological and musculoskeletal diseases are a large class of complex and heterogeneous disorders. Neurological diseases, including traumatic injuries, cerebrovascular diseases, and neurodegenerative diseases, typically lead to loss of motor function, sensory dysfunction, and memory and cognitive impairment, which seriously threaten the life and health of the patients[1]. Additionally, the muscle and skeletal systems accomplish the daily activities under the control of the nervous system. The disorders in these systems (abbreviated as musculoskeletal diseases) result in local pain, myoatrophy, osteoporosis, fracture, and dyskinesia, which also impair the life quality of the sufferers[2]. Although significant breakthroughs have been made in the treatment of neurological and musculoskeletal diseases, the clinical efficacy of these strategies remains poorly satisfactory.

Stem cells are a class of cells with unlimited proliferation and differentiation potential. According to the developmental stage, stem cells could be divided into embryonic stem cells and adult stem cells. In the light of the differentiation potential, they are divided into totipotent stem cells, pluripotent stem cells, oligopotent stem cells, and unipotent stem cells[3]. Urine-derived stem cells (USCs), obtained from urine, are a kind of pluripotent stem cells with high proliferative ability and multidirectional differentiation potential. Studies have shown that under the stimulation of different inducing factors, USCs could differentiate into neurocytes, osteoblasts, chondrocytes, muscle cells, adipocytes, vascular endothelial cells, rod cells, cone cells, alveolar type II epithelial cells, hepatocytes, *etc*[4-8]. This evidence suggests that USCs might play an important role in the treatment of the diseases induced by damage or loss of these cells. Moreover, USCs could also be reprogrammed into urine-derived induced pluripotent stem cells (UiPSCs) to further expand its application. In fact, USCs and UiPSCs have been reported to hold considerable therapeutic value in urologic diseases[9], cardiac diseases [10], stroke[11], spinal cord injury[12], muscular dystrophy[13], osteoarthrosis, and osteoporosis[14].

Thanks to the great potential of neurogenic, myogenic, and osteogenic differentiation[15-17], the role of USCs and UiPSCs in the treatment of neurological and musculoskeletal diseases should not be ignored. In this review, we summarized the origin and physiological characteristics of USCs and UiPSC, and further elaborated their therapeutic potential in neurological and musculoskeletal diseases.

ORIGIN AND PHYSIOLOGICAL CHARACTERISTICS OF USCS

Origin of USCs

USCs are isolated from urine. The specific steps to obtain USCs are as follows: (1) Collect urine samples (USCs could survive in the urine for 24 h)[18]; (2) Centrifuge the urine samples at a low speed for 10 min to obtain cell precipitation; (3) Resuspend the cell precipitation by a specific medium (keratinocyte serum-free medium: Dulbecco *vs* modified eagle medium = 1:1, with 5% fetal bovine serum), and then inoculate the cell suspension in culture plates to obtain cell clone spheres; and (4) Select appropriate cell clone spheres for subculture and identification[5,19-22] (Figure 1). Due to the high proliferative activity, a considerable number of USCs can be obtained from a single urine sample[4,23]. Evidence showed that USCs from the upper urinary tract urine had a greater proliferative activity than that from the voided urine[24]. Additionally, matrigel and Y-27632, an inhibitor of rho-associated protein kinase, facilitate the isolation, proliferation, and osteogenic or chondrogenic differentiation of USCs[15].

Additionally, USCs may originate from multiple tissues of the urinary system. Firstly, USCs express the specific markers of podocytes and glomerular parietal cells (paired box 2 and paired box 8)[23,25,26], suggesting that USCs originate from kidney tissues. Secondly, USCs express the marker of uroepithelial basal cells and pericytes [cluster of differentiation (CD) 146][4]. Furthermore, evidence demonstrated that spindle-shaped USCs (SS-USCs) might be of renal interstitial origin, and rice-shaped USCs (RS-USCs) might be of renal tubular origin[27]. However, USCs poorly express the markers of hematopoietic stem cells, such as CD34 and CD45, suggesting that they are not derived from hematopoietic cells[28].

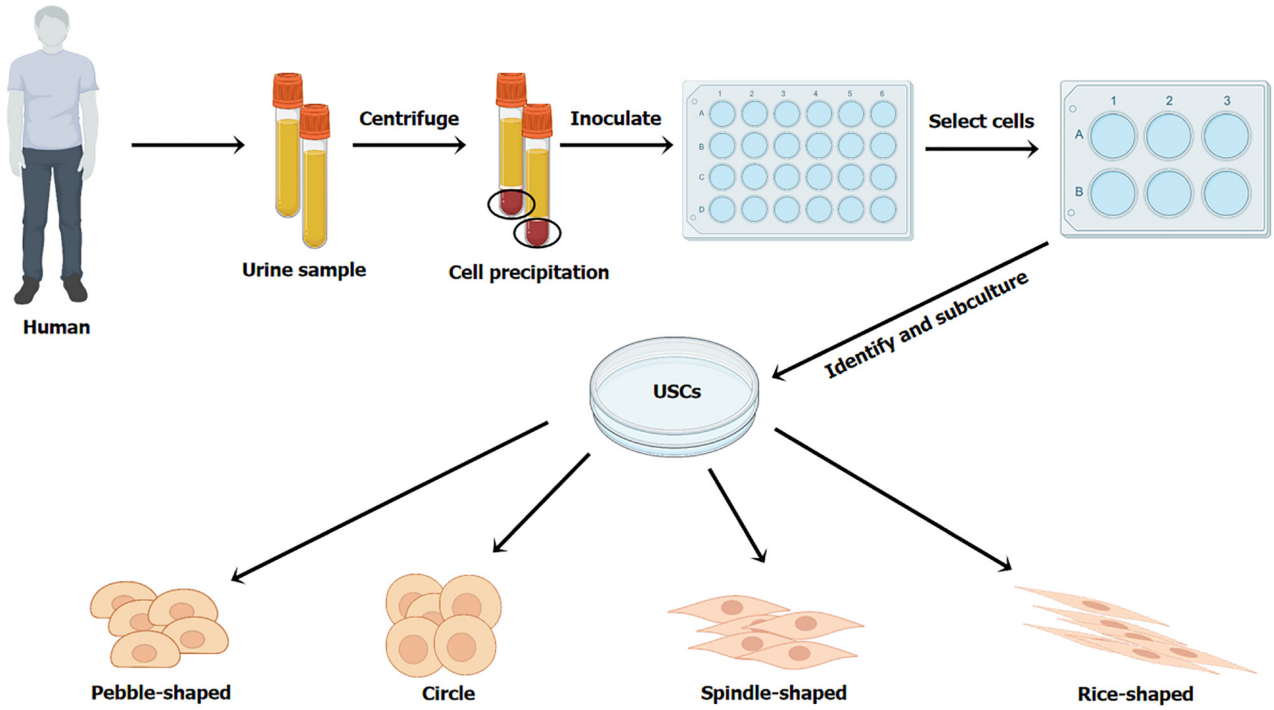

Figure 1 Schematic diagram of obtaining urine-derived stem cells and their morphology. After collecting urine samples, cell precipitation is obtained by low-speed centrifugation. Then cells are resuspended with specific culture medium and inoculated in a 24-well plate. Next, appropriate cell clone spheres are selected and inoculated in a 6-well plate. Finally, spheres are identified and sub-cultivated. Urine-derived stem cells (USCs) can present as the shapes of rice, spindle, circle, and pebble.

Physiological characteristics of USCs

Primary cultured USCs grow adherent to the wall in the shape of rice, spindle, pebble, or circle[13,22,24,29] (Figure 1). Chen *et al*[27] believed that RS-USCs were similar to SS-USCs in terms of colony formation efficiency. The cultured USCs have typical stem cell ultramorphology and can release extracellular vesicles[4]. After passage, USCs are elongated[30] and show fibroblast-like morphology[19,31].

Isolated USCs hold high proliferative activity *in vitro*. The macroscopic colonies of USCs form on the third to fifth day of culture[5,20,24,30]. During the first ten passages, USCs still show accelerated growth and stem cell characteristics *in vitro*[4,20]. After the tenth passage, cell proliferation is significantly weakened[5]. Evidence suggested that the proliferation ability of stem cells is positively correlated with the activity and length of telomere[23]. Of course, this evidence is also extended to USCs. Firstly, as for the USCs from the same donor, the telomerase-positive ones show higher proliferation ability and more stable cell morphology than telomerase-negative ones[32]. Secondly, for the telomerase-positive USCs, their proliferation ability is closely related to the activity and length of telomerase.

It is well known that the telomerase activity is age-related, which decreases with age. Without doubt, USCs derived from the younger population hold higher proliferative potential. Compared with USCs derived from people over 50 years old, USCs isolated from middle-aged people (< 50 years old) harbor longer lengths of telomeres and stronger proliferation ability[33]. Moreover, the USCs in children (5 to 14 years old) show higher proliferative ability than that in adults [30]. Conversely, the USCs from the elderly population (70 to 94 years old) hold much lower proliferative activity[34]. Taken together, the proliferative ability (quality) of the isolated USCs is negatively correlated with age. Unfortunately, there is no evidence to support the correlation between the yield and proliferation activity of USCs and gender. In addition, compared with other pluripotent stem cells [such as basal-derived mesenchymal stem cells (BMSCs) and placenta decidual BMSCs], USCs possess superior proliferation activity[22].

Fortunately, the tumorigenicity of USCs has not been identified[23,24]. For example, researchers found that the USCs that were injected into subcutaneous tissues and the subcapsular space of mice kidneys did not form tumors[23,24,35]. Even the USCs from clear cell renal cell carcinoma patients did not show tumorigenicity[36]. In order to further investigate the tumorigenicity of USCs, scientists conducted a 26-week observation and found no tumors formed by USCs in mice after the subcutaneous and intravenous injection of these stem cells[37].

Like other stem cells, USCs also hold the potential of multidirectional differentiation. Numerous studies proved that USCs could differentiate into neurocytes, osteoblasts, chondrocytes, muscle cells, adipocytes, endothelial cells, and hepatocytes[4,23,38]. Firstly, USCs highly express mesenchymal stem cell (MSC)-like surface markers, including CD29, CD44, CD54, CD73, CD90, CD105, CD166, stromal cell antigen-1, CD24, and CD146[4,23,39] (Table 1), indicating that USCs might hold MSC-like functions (like self-renewal and differentiation into a variety of cell types)[40]. Moreover, USCs harbored better potential to differentiate into adipose, endothelial, and vascular cells than BMSCs and placenta decidual MSCs[22].

Table 1 Surface markers of urine-derived stem cells

Surface markers in USCs		Ref.
MSC-like markers	CD73, CD90, CD29, CD44, CD146	
	CD73, CD29, CD44	
	CD73, CD90, CD44, CD146	
	CD73, CD90, CD105 (high), CD44, CD146	
	CD73, CD90, CD146	
	CD73, CD90, CD105, CD29, CD24, CD146	
	CD73, CD90, CD29	
	CD73, CD90, CD29, CD44, CD54, CD166, CD146	
	CD73, CD90, CD105, CD29, CD44	
	CD90, CD29, CD44	
	CD73, CD90, CD105, CD29, CD44, CD166, STRO-1, CD54, CD146	
	CD73, CD90, CD105, CD44	
	CD73, CD90, CD105, STRO-1 (low), CD146	
	CD73, CD90, CD105, CD24, CD29, CD44, CD117, STRO-1, CD146	
	CD29, CD44, CD73, CD90, CD105 (low)	
	CD24, CD29, CD34, CD44, CD73, CD90	
Other pluripotency markers	TRA-1-60, TRA-1-81, SSEA-4, *SOX2*, *OCT4*, *MYC*, *KLF4*	
	SSEA-4	
	OCT4, *MYC*	
	OCT4, *NANOG*	[20]
	CD133	
Urinary system markers	Nephrin, *WT1*	[20]
	PAX2, *PAX8*	
	Uroplakin Ia, cytokeratin 7, cytokeratin 19	
MP markers	*PAX7*, *MYF5*, *MOYD*, desmin, dystrophin, myogenin, α-smooth muscle actin	[24]

CD: Cluster of differentiation; KLF: Kruppel-like factor 4; MP: Myogenic pedigree; MSC: Mesenchymal stem cells; MYC: Myelocytomatosis oncogene; MYF: Myogenic factor 5; NANOG: Nanog homeobox; OCT4: Octamer binding transcription factor 4; PAX: Paired-box; SOX2: Sex determining region Y-box 2; SSEA-4: Stage-specific embryonic antigen-4; STRO-1: Stromal cell antigen-1; TRA: Tumor resistance antigen; USCs: Urine-derived stem cells; WT: Wilms' tumor.

Secondly, USCs express other pluripotency markers, such as tumor resistance antigen-1-60, tumor resistance antigen-1-81, stage-specific embryonic antigen-4, octamer binding transcription factor 4 (*OCT4*), sex determining region Y-box 2 *(SOX2)*, kruppel-like factor 4 *(KLF4)*, myelocytomatosis oncogene (*MYC)*, Nanog homeobox (*NANOG)*, and CD133[23,24,27,38] (Table 1). Thirdly, USCs express urinary system markers. Specifically, USCs express specific renal markers including nephrin and Wilms' tumor-1[20], and urothelium and smooth muscle markers including uroplakin Ia, cytokeratin 7, and cytokeratin 19 of urothelial lineage[24] (Table 1).

At the same time, USCs express markers of myogenic lineage in various stages, including the early paired-box 7, myogenic factor 5, and myogenic differentiation 1, the intermediate (desmin and dystrophin), and the late (myogenin and α-smooth muscle actin) (Table 1), demonstrating that USCs hold myocyte differentiation potential[30]. Fourthly, USCs could be induced into neural stem cells (NSCs) or other cells of the neural lineage[28]. Expect for that, when co-cultured with hepatic progenitor cells, approximately 10% of USCs undergo hepatocyte differentiation[5].

In addition, USCs with different morphologies hold slightly different differentiation potential. SS-USCs originating from renal interstitium possess higher osteogenic and adipogenic differentiation potential, while RS-USCs originating from renal tubules show greater chondrogenic differentiation potential[27]. Taken together, USCs possess great potential for osteogenic, myogenic, and neurogenic and endothelial differentiation[33]. However, overexpansion and predifferentiation of USCs *in vitro* damage its survival and the capability of tissue repairing[41].

THERAPEUTIC PROSPECTS OF USCS AND UiPSCS

Acquisition of UiPSCs

The emergence of iPSCs makes it possible to obtain the desired cells by using cells from various sources. Urine-derived cells (UCs) or USCs could be easily collected from excreted urine, so they might serve as an ideal cell source for obtaining iPSCs[42]. It is attractive to establish a non-invasive method to generate iPSCs. Mounting evidence suggested that iPSCs could be acquired by delivering reprogramming factors to UCs or USCs through retroviruses, lentiviruses, Sendai virus (SeV), exogenous plasmids, mRNA, self-replicating RNA (srRNA), small molecules, *etc* (Table 2). Among these, SeV and exogenous plasmids are most commonly used to generate iPSCs.

Currently, the reprogramming factors delivered by SeV mainly consists of four transcription factors including *OCT4*, *SOX2*, *KLF4* and *MYC* (the four factors are abbreviated as OSKM)[43,44]. Except the classic OSKM factors, studies also provided other alternative combinations of transcription factors (Table 2). For example, Yu *et al*[45] found that *OCT4*, *SOX2*, *NANOG*, and protein lin-28 induced UCs to generate human UiPSCs. Wang *et al*[46] demonstrated that the combination of jun dimerization protein 2, jumonji C domain-containing histone demethylase 1B, mitogen-activated pro-tein kinase kinase 6, GLIS family zinc finger 1, *NANOG*, estrogen related receptor beta, and spalt like transcription factor 4 could be used for mouse iPSCs reprogramming. In addition, in the presence of OSKM factors, *TEAD2*, *TEAD4*, and *ZIC3* improved the reprogramming efficiency of USCs into UiPSCs[44].

Of note, cell death and timely elimination of SeVs are two issues that cannot be ignored in the reprogramming process. Some researchers have applied the autologous USC feeder culture method to overcome the massive cell death[47]. Also, evidence showed that SeVs usually disappeared on their own after more than five passages, but a method to quickly eliminate them has not been found[43,48,49]. It was advocated that UiPSCs obtained by this reprogramming method should be used as early as possible, although their proliferation potential could last up to five passages after being frozen in liquid nitrogen[50].

As another major reprogramming method, exogenous plasmid vectors carrying reprogramming factors also could induce USCs into UiPSCs. These reprogramming factors included *OCT4*, *SOX2*, *KLF4*, *MYC*, *NANOG*, *LIN28*, Kelch domain-containing protein 4, simian virus 40 large T antigen, *etc* (Table 2). For example, Ncube *et al*[51] successfully induced urine-derived renal progenitor cells into UiPSCs by electro transfecting exogenous plasmids expressing *OCT4*, *SOX2*, *NANOG*, *MYC*, *KLF4*, and *LIN28*. Kibschull *et al*[52] selected Kelch domain-containing protein 4, *LIN28*, *MYC*, *OCT4*, *SOX2*, and P53 short-hairpin RNA as reprogramming factors to reprogram UCs into UiPSCs. Among the exogenous plasmids, episomal plasmid (Epi) was frequently used. Particularly, owing to the replication of Epstein-Barr virus during the process of cell proliferation, the Epstein-Barr virus-carrying Epi had an extended ability to express reprogramming factors[53]. Moreover, the methods that combined the above reprogramming factors with exogenous plasmids (especially Epi) for cell reprogramming have been commercialized[54].

Apart from the two main programming methods mentioned above, researchers have also discovered other reprogramming methods. Firstly, for USCs with low proliferation ability, Li *et al*[47] proposed a complex cocktail of cyclic pifithrin-a (a P53 inhibitor), A-83-01, CHIR99021, thiazovivin, sodium butyrate, and PD0325901 for reprogramming (Table 2). Secondly, Gaignerie *et al*[53] effectively generated iPSCs from UCs through mRNA reprogramming. Due to no genomic abnormalities, the obtained UiPSCs could be applied to clinical therapy. Thirdly, urine-derived renal epithelial cells could be induced into iPSCs through a single application of srRNA (Table 2). Importantly, the resulting UiPSCs did not contain residual srRNA, and karyotype analysis showed no detectable abnormalities (Table 2)[55]. In addition, lentiviral vectors carrying OSKM factors also successfully generated iPSCs from human urine-derived epithelial cells (Table 2)[56].

Therapeutic prospects of USCs and UiPSCs

Using the patient's autologous cells as the cell sources, the obtained UiPSCs do not pose a risk of immune rejection and can differentiate into various required cell types[55]. Moreover, UiPSCs induced by autologous cells have the same genetic background as patients, so these UiPSCs could be applied to explore the pathogenesis of diseases and screen the effective drugs[57-61]. For example, CSUASOi006-A iPSCs[62], CSUASOi001-A iPSCs[63], and SMBCi009-A iPSCs[64] induced by USCs are used to study the mechanism of male pigmented retinitis, X-linked juvenile retinoschisis, and familial hypercholesterolemia, respectively.

It is reported that USCs and UiPSCs exert the therapeutic effects mainly through the targeted differentiation of desired cells and their exosomes (Figure 2). Firstly, USCs and UiPSCs possess the potential of multidirectional differentiation and can be developed into therapeutic stem cells. As stated above, USCs show high neurogenic, myogenic, and osteogenic differentiation potential[33]. Similar to USCs, UiPSCs could also differentiate into nephrocytes, neurocytes, osteoblasts, chondrocytes, and muscle cells[65-68]. Based on this, USCs/UiPSCs were used for neurological, musculoskeletal, and circulatory diseases (shown in Figure 2). For example, UiPSCs in patients with acute kidney injury could be induced to differentiate into kidney progenitor cells, which could be a new therapeutic strategy for acute kidney injury (Table 3)[69].

Additionally, UiPSCs were induced into functional cardiomyocytes by temporal modulation of canonical wingless/integrated (WNT) signaling with small molecules for the treatment of myocardial infarction[56,70]. Evidence indicated that the combination of WNT activators (CHIR99021 and 6-bromoindole-3-oxime) and WNT inhibitors (KY02111 and inhibitor WNT protein 2) were feasible to induce UiPSCs into cardiomyocytes[71]. Moreover, albumin-free GIWI also induced UiPSCs to differentiate into functional cardiomyocytes (Table 3)[44]. Functionally, transplanting these induced cardiomyocytes improved cardiac function by enhancing glucose metabolism of cardiomyocytes and promoting angiogenesis in the infarction sites[10].

Table 2 Reprogramming methods of urine-derived stem cells

Reprogramming method	Vectors	Factors	Ref.
SeV	SeV	OSKM	[15,43,44,48,49,58,60,63,71]
		OCT4, *SOX2*, *NANOG*, *LIN28*	
		JDP2, JHDM1B, MKK6, *GLIS1*, *NANOG*, ESSRB, *SALL4*	
Exogenous plasmids	Epi	*KLD4*, *MYC*, *OCT4*, *SOX2*, *LIN28*, shP53	
		OCT4, *SOX2*, *KLF4*, miR-302-367	
		OCT4, *SOX2*, *NANOG*, *LIN28*, *KLF4* and *MYC*	[85,86]
		OCT4, *SOX2*, SV40 LT, *KLF4* and miR302-367	
		OCT4, *SOX2*, *NANOG*, *MYC*, *KLF4*, *LIN28*	
		OCT4, *SOX2*, *KLF4*, and miR-302-367	
	pCXLE-hOCT4-shP53-F, pCXLE-hSK, pCXLE-h UL	OSKM, shP53, *LIN28*	
	TET-ON-induced expression vector	OSKM	
	pEP4EO2SET2K	*OCT4*, *SOX2*, SV40 LT and *KLF4*, miR-302b, c, a, d and miR-367	
SM		Cyclic pifithrin-a, A-83-01, CHIR99021, thiazovivin, NaB, PD0325901	
mRNA		OSKM LNg	
srRNA		OSKM, NSP 1-4	
Lentivirus	Lentiviral vectors	OSKM	

ESSRB: Estrogen related receptor beta; Epi: Episomal vector; JHDM1B: Jumonji C domain-containing histone demethylase 1B; KLD4: Kelch domain-containing protein 4miR: MicroRNA; MKK6: Mitogen-activated protein kinase kinase 6; NaB: Sodium butyrate; NSP: Non-structural proteins; OSKM: Octamer-binding transcription factor 4, sex determining region Y-box transcription factor 2, kruppel-like factor 4, and myelocytomatosis oncogene; SeV: Sendai virus; shP53: P53 short-hairpin RNA; SM: Small molecules; srRNA: Self-replicating mRNA; SV40 LT: Simian virus 40 large T antigen.

Secondly, USCs/UiPSCs can secrete functional exosomes to achieve therapeutic effects. Exosomes are a class of extracellular vesicles with diameters ranging from 40 nm to 160 nm (average of about 100 nm) and contain a variety of small molecules such as nucleic acids, proteins, lipids, cytokines, and others. Evidence suggested that exosomes play an important role in cell-to-cell communication[72,73]. Moreover, it has been demonstrated that USCs/UiPSCs-derived exosomes (USC-Exos) also promote tissue repair and regeneration in various diseases, including neurological and musculoskeletal diseases. The application of USCs and UiPSCs and the underlying mechanisms in neurological and musculoskeletal diseases are discussed in detail below.

USCS/UiPSCS AND NEUROLOGICAL DISEASES

Generation of neural lineages from USCs/UiPSCs

Human NSCs have great prospects for the treatment of neurological diseases. They could differentiate into neurons to repair neurologic impairment[74]. A growing body of evidence indicates that both USCs and UiPSCs could be induced into NSCs and other neural lineages. Firstly, Guan *et al*[28] induced USCs into neural progenitor cells with human epidermal growth factor, basic fibroblast growth factor, and B27 *in vitro*. Secondly, laminin and platelet-derived growth factor BB (PDGF-BB) could promote neuronal differentiation of USCs *in vitro*[75].

Thirdly, the mixture of valproic acid, CHIR99021, repsox, forskolin, SP600625, GO6983, and Y27632 can induce USCs into neuron-like cells[76]. Fourthly, USCs can be transformed into NSCs by combining a cocktail of small molecules (including puromorphamine, folliculin, vitamin C, and sodium butyrate) with self-replicable mRNA delivery encoding the reprogramming factors including *OCT4*, *SOX2*, *KLF4*, and *GLIS1* (the four factors are abbreviated as OSKG) (Table 3). The advantage of this method was that the obtained NSCs did not contain impurity genes and held no tumorigenicity [74]. Furthermore, USCs also harbor great potential for neural differentiation *in vivo*[28]. In summary, USCs and UiPSCs hold considerable therapeutic prospects in neurological diseases.

Table 3 Differentiation and application of urine-derived stem cells and urine-derived pluripotent stem cells

Cells	Differentiation	Factors	Diseases/animal model	Ref.
USCs	NPCs	hEGF, bFGF		[28]
	Neural lineage cells (astrocytes)	Transplantation	CCI model (rat)	[28]
	Neurons	Laminin, PDGF-BB		
		VPA, CHIR99021, repsox, forskolin, SP600625, GO6983, Y27632		
	NSCs	Cocktail (P, F, V, N) and srRNA (with OSKG)		
	Osteoblasts	Silver nanoparticles	Bone defect model	
		Y-27632		
		Calcium silicate ionic, BMP2		
		BMP2, FAK		
		BCP-CS		
		Surface mineralized BCP		[19]
		BMP2-CSM/Col I hydrogel		
	Chondrocytes	Hyaluronic acid with USCs		
		Y-27632		
		ACM scaffolds		
	Muscle cells	VEGF, IGF-1, FGF-1, PDGF-BB, HGF, NGF		
		HD myogenic differentiation medium		[103]
		Lentiviral with MYOD		
		hp-HA (IGF-1, HGF, PDGF-BB)		
	Hepatocytes	Co-culture with HPCs		[5]
UiPSCs	Cardiac myocytes	Activin A, bFGF, BMP4, DKK1, VEGF		[56]
		Cardiomyocyte differentiation kit (Gibco, catA2921201)		
		CHIR99021, BIO, KY02111, IWP2		
		GIWI2		
		HIR99021, IWP2	MI (rat)	
	KPCs		AKI	[69]
	Kidney organoids	Y-27632, APEL-2, CHIR99021, hFGF9, heparin		
	Neurons, astrocytes	Transplantation	SCI model (rat)	
	NPCs	N2B27, dorsomorphin, SB4315242		
	HPCs	Flavonoid		
	Muscle cells	CHIR99021		[52]
	Neurons, astrocytes, VECs		Simulate the brain microenvironment of diabetes mellitus	
	RCs, CCs	RDM		
	LB	BMP, BMP4, BMP7, bFGF, WNT3A		
	AECs II			
	Hepatocytes			

ACM: Acellular cartilage extracellular matrix; AECs II: Alveolar type II epithelial cells; AKI: Acute kidney injury; BCP-CS: Biphasic calcium phosphate bioceramic ornamented with chitosan sponge; bFGF: Basic fibroblast growth factor; BIO: 6-bromoindole-3-oxime; BMP: Bone morphogenetic protein; BMP2-CSM/Col I hydrogel: BMP2-releasing chitosan microspheres/type I collagen hydrogel; CCs: Cone cells; CCI: Cerebral cortex injury; Cocktail (P): Puromorphamine; DKK1: Dickkopf WNT signaling pathway inhibitor 1; F: Folliculin; FAK: Focal adhesion kinase; FGF-1: Fibroblast growth factor; GIWI2: Albumin-free GIWI; hEGF: Human epidermal growth factor; HFGF9: Human fibroblast growth factor; HGF: Hepatocyte growth factor; hp-HA: Heparin hyaluronic-acid hydrogel; HPCs: Hematopoietic progenitor cells; IGF-1: Insulin-like growth factor-1; IWP2: Inhibitor WNT protein 2; KPCs: Kidney progenitor cells; LB: Lentoid body; MI: Myocardial infarction model; MYOD: Myogenic differentiation 1; N: Sodium butyrate; NGF: Nerve growth factor; NPCs: Neural progenitor cells; NSCs: Neural stem cells; OSKG: Octamer-binding transcription factor 4, sex determining region Y-box transcription factor 2, kruppel-like factor 4, and *GLIS1*; PDGF-BB: Platelet-derived growth factor BB; RCs: Rod cells; RDM: Retinal differentiation medium; SCI: Spinal cord injury model; srRNA: Self-replicating mRNA; UiPSCs: Urine-derived pluripotent stem cells; USCs: Urine-derived stem cells; V: Vitamin C; VECs: Vascular endothelial cells; VEE: Venezuelan equine encephalitis; VEGF: Vascular endothelial growth factor; VPA: Valproic acid; WNT3A: Wingless/integrated family member 3A.

USCs/UiPSCs and neurological diseases

In neurological diseases, USC therapy facilitates neurological recovery. After sudden cardiac arrest and cardiopulmonary resuscitation, transplanted USCs secreted brain-derived neurotrophic factor and vascular endothelial growth factor to suppress cerebral edema and reduce the expression level of serum S100 calcium-binding protein B in the hippocampus and temporal lobe cortex of rats[77]. In addition, USC-Exos also improved ischemia-induced neurological dysfunction. Intravenous injection of USC-Exos resulted in enhanced neurogenesis and alleviated neurological impairment in stroke rats[11]. Moreover, USC-Exos promoted the proliferation and neuronal differentiation of NSCs after oxygen-glucose deprivation/reoxygenation *in vitro*. Mechanistically, the pro-neurogenesis effect of USC-Exos might be attributed to the inhibition of histone deacetylase 6 function by exosomal microRNA-26a[11]. Inhibiting histone deacetylase 6 restored microtubule-dependent transport and facilitated neural recovery in neurons[78]. Additionally, USC-Exos-derived miR-21-5p also promoted early neurogenesis *via* the ephrin receptor A4/TEK receptor tyrosine kinase axis[79].

Beyond that, USC transplantation plays a neuroprotective role in spinal cord injury. Evidence suggested that a considerable proportion of transplanted UiPSCs survived and migrated toward the lesion center of spinal cord injury. They differentiated into neurons and astrocytes to reduce the inflammation and the size of the lesion cavity[80]. In addition, USC transplantation inhibited neuronal apoptosis by promoting the expression of neurotrophic factors (including nerve growth factor and brain-derived neurotrophic factor)[12].

As a frequently occurring disease, lumbar disc herniation is the most common cause of lumbocrural pain[81]. Research showed that USC-Exos inhibited the apoptosis of nucleus pulposus cells and the degeneration of intervertebral disc by controlling protein kinase B and extracellular signal-regulated kinases[82]. Moreover, matrilin-3 carried by USC-Exos also alleviated the degeneration of intervertebral disc and promoted proliferation of nucleus pulposus cells and synthesis of extracellular matrix[83]. In short, USCs-Exos can suppress degenerative changes of the intervertebral disc and promote its structural remodeling.

In addition, since USCs and UiPSCs retain the genetic background of the donor, they are also induced as cell models for neurological diseases and used for pathogenesis study and drug screening. The cell models of paroxysmal kinesigenic dyskinesia[84], diabetic encephalopathy[80], Down's syndrome[85,86], and neurofibromatosis type 1[87] have been developed.

USCS/UiPSCS AND MUSCULOSKELETAL DISEASES

Generation of osteogenic and chondrogenic lineages from USCs/UiPSCs

Mounting evidence demonstrated that USCs could be induced to differentiate into osteoblasts and chondrocytes. Firstly, silver nanoparticles promoted osteogenic differentiation of USCs by activating RhoA protein, inducing actin polymerization and increasing cytoskeletal tension[17]. Secondly, the Rho-associated protein kinase inhibitor Y-27632 promoted USC differentiation into osteoblasts and chondrocytes[15]. Thirdly, calcium silicate ionic extract enhanced osteogenic differentiation of USCs through activating WNT/β-catenin signaling. However, the WNT/β-catenin signaling inhibitor myristin held the opposite effect[88]. Finally, hyaluronic acid was confirmed to facilitate the differentiation of USCs into chondrocytes[89]. Of note, the CD133-positive USC subsets possessed a stronger ability to differentiate into the chondrogenic lineage[90].

Bone morphogenetic protein-2 (BMP2), a member of transforming growth factors B superfamily, plays an essential role in skeletal development and osteoblast differentiation[91]. Actually, whether increasing BMP2 expression through lentivirus or co-culturing with BMP2, USCs can be induced to differentiate into the osteogenic lineage[88,92]. Moreover, focal adhesion kinase could enhance BMP2-induced osteogenic differentiation of USCs by activating adenosine 5'-monophosphate-activated protein kinase and WNT signaling[92].

Clinical trials corroborated the osteogenic differentiation potential of USCs. Furthermore, the differentiation ability of USCs was related to the age of the donors. Compared with the elderly group, the USCs from children held a stronger proliferative activity and osteogenic differentiation capacity[30].

USCs/UiPSCs and skeletal diseases

Owing to the high osteogenic and chondrogenic differentiation, USCs and UiPSCs are also utilized for the treatment of

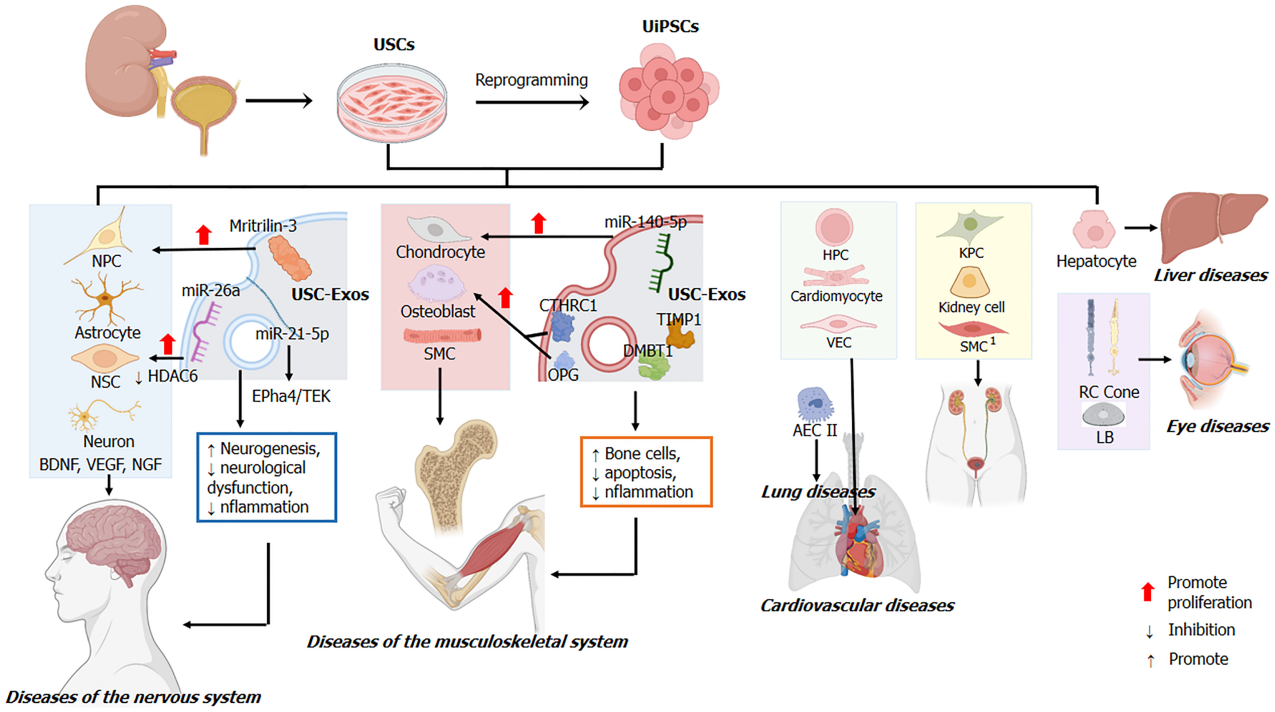

Figure 2 Therapeutic application of urine-derived stem cells and urine-derived induced pluripotent stem cells and the underlying mechanisms. Urine-derived stem cells (USCs) and urine-derived induced pluripotent stem cells (UiPSCs) exert the therapeutic effects mainly through the targeted differentiation of desired cells (including neurocytes, osteoblasts, chondrocytes, muscle cells, adipocytes, vascular endothelial cells, lentoid body, alveolar type II epithelial cells, and hepatocytes) and their exosomes (carrying small molecules such as nucleic acids, proteins, lipids, cytokines, and others). AEC II: Alveolar type II epithelial cell; BDNF: Brain-derived neurotrophic factor; DMBT1: Deleted in malignant brain tumors 1; EPha4/TEK: Ephrin receptor a4/TEK receptor tyrosine kinase axis; HDAC6: The inhibition of histone deacetylase 6; HPC: Hematopoietic progenitor cells; KPC: Kidney progenitor cell; LB: Lentoid body; miR: MicroRNA; NGF: Nerve growth factor; NPC: Neural progenitor cell; NSC: Neural stem cell; RC: Rod cell; SMC: Skeletal muscle cell; SMC[1]: Smooth muscle cell; TIMP1: Tissue inhibitor of metalloproteinases 1; VEC: Vascular endothelial cell; VEGF: Vascular endothelial growth factor.

skeletal diseases. To improve the survival and differentiation ability of USCs *in vivo*, USCs are generally combined with a biological scaffold or biomaterial and implanted into skeletal lesions[19]. At the defective femur sites, the transplantation of USCs wrapped with β-tricalcium phosphate scaffold induced new bone formation[88]. Moreover, USCs loaded with biphasic calcium phosphate bioceramic ornamented with chitosan sponge could differentiate into osteoblasts and promote bone regeneration[93]. Additionally, USCs loaded with acellular cartilage extracellular matrix scaffolds repaired the defects of the knee articular cartilage, and the nascent tissues were mainly hyaline cartilage[94]. Furthermore, BMP2 enhanced the osteogenic differentiation of USCs *in vivo*. Note that the high concentration of BMP2 led to ectopic bone formation or inflammation[95], so it was particularly important to control the amount of BMP2. For instance, the injectable BMP2-releasing chitosan microspheres/type I collagen hydrogel could continuously and slowly release BMP2 to promote bone regeneration[96].

As a key messenger of cell-cell interactions, exosomes derived from USCs could promote tissue repair and regeneration [72,73]. In the mouse model of osteoporosis and cranial osteolysis, USC-Exos enhanced osteogenesis and inhibited osteoclastogenesis to attenuate bone loss and maintain bone strength by transferring collagen triple-helix repeat containing 1 and osteoprotegerin protein[14,97]. In addition, USC-Exos attenuated aseptic osteolysis by promoting the exosome uptake of BMSCs[98]. In glucocorticoid (GC)-induced osteonecrosis of the femoral head model, the intravenous administration of USC-Exos at the early stage of GC exposure rescued angiogenesis impairment, reduced apoptosis of trabecular bone and marrow cells, prevented trabecular bone destruction, and improved bone microarchitecture in the femoral heads of rats[99]. Mechanistically, the pro-angiogenic deleted in malignant brain tumors 1 and anti-apoptotic tissue inhibitor of metalloproteinases 1 proteins contributed to the USC-Exos-induced protective effects against osteonecrosis of the femoral head caused by GC exposure[99]. Moreover, intra-articular injection of USC-Exos overexpressing miR-140-5p enhanced cartilage regeneration and subchondral bone remodeling in rats with knee osteoarthritis[100].

USCs/UiPSCs and muscular diseases

USCs can differentiate myogenic lineage cells *in vitro* and *in vivo* under the stimulation of growth factors (including vascular endothelial growth factor, insulin-like growth factor-1, fibroblast growth factor, PDGF, hepatocyte growth factor, nerve growth factor, PDGF-BB, and myogenic differentiation 1)[16,41,101,102], HD myogenic medium[103], and the small molecule CHIR99021[52] (Table 3). One study has demonstrated that subcutaneous injection of the mixture of USCs, alginate microbeads (containing growth factors), and the collagen gel type 1 enhanced revascularization and innervation and stimulated resident cell growth *in vivo*[16]. Moreover, USCs could be efficiently reprogrammed into skeletal muscle cells by transducing lentiviral vectors that expressed myogenic P.

CONCLUSION

USCs are a class of stem cells with high proliferation and multidirectional differentiation potential. More importantly, they are easy to obtain and cost-effective. Current evidence suggests that USCs are derived from the kidneys, mainly from glomerular wall epithelial cells, and isolated from urine. The cultured USCs are usually rice-like with the typical morphology of stem cells. Of course, they are also spindle, circle, and pebble-like in shape. Moreover, USCs could be reprogrammed into UiPSCs (shown in Table 2), further expanding the application. Evidence indicates that USCs and UiPSCs express MSC-like markers, including CD29, CD44, CD54, CD73, CD90, CD105, CD166, stromal cell antigen-1, CD24, and CD146 (Table 1). Moreover, the surface markers of USCs and UiPSCs are not limited to MSC-like markers (see Table 1).

Under the stimulation of inducing factors, USCs and UiPSCs can differentiate into neurocytes, osteoblasts, chondrocytes, muscle cells, adipocytes, vascular endothelial cells, rod cells, cone cells, alveolar type II epithelial cells, and hepatocytes (shown in Table 3 and Figure 2). Of note, they show higher potential to differentiate into neurogenic, myogenic and osteogenic lineages. Therefore, we focused on the therapeutic prospects of USCs and UiPSCs in neurological and musculoskeletal diseases. A growing body of evidence indicates that USCs and UiPSCs promote nerve regeneration and recovery, enhance osteoangiogenesis and bone-remodeling, improve revascularization and innervation, and reduce inflammation in neurological and musculoskeletal diseases. Therefore, USCs and UiPSCs could serve as a novel perspective therapeutic strategy for these disorders.

However, the current investigations on the physiological effect of USCs and UiPSCs are insufficient. Firstly, the source of USCs needs to be further determined. There is no direct and strong evidence to prove that it comes from glomerular wall epithelial cells. Identifying the exact source of USCs would facilitate its isolation and application selection. Secondly, the therapeutic value of USCs is evaluated by its proliferative ability. Except for age-related telomerase activity and length, could the proliferation ability of USCs be evaluated by other methods? Moreover, further exploration is needed to determine whether the quantity and quality of USCs obtained are related to gender. Thirdly, it is necessary to explore the potential of USCs and UiPSCs to differentiate into other cells. Fourthly, the effectiveness and safety of the existing reprogramming methods to induce USCs or UCs into UiPSCs need to be further assessed. For instance, the risk of infecting host genes and tumorigenicity needs to be eliminated. Of course, more efficient and secure methods need to be explored. Finally, the current investigation on the treatment of USCs and UiPSCs in neurological and musculoskeletal diseases is still in its infancy. Before USCs or UiPSCs enter clinical application, the effectiveness and safety of them must be determined *in vivo*, especially in the human body.

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