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An Overview on Promising Somatic Cell Sources Utilized for the Efficient Generation of Induced Pluripotent Stem Cells

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Abstract

Human induced Pluripotent Stem Cells (iPSCs) have enormous potential in understanding developmental biology, disease modeling, drug discovery, and regenerative medicine. The initial human iPSC studies used fibroblasts as a starting cell source to reprogram them; however, it has been identified to be a less appealing somatic cell source by numerous studies due to various reasons. One of the important criteria to achieve efficient reprogramming is determining an appropriate starting somatic cell type to induce pluripotency since the cellular source has a major influence on the reprogramming efficiency, kinetics, and quality of iPSCs. Therefore, numerous groups have explored various somatic cell sources to identify the promising sources for reprogramming into iPSCs with different reprogramming factor combinations. This review provides an overview of promising easily accessible somatic cell sources isolated in non-invasive or minimally invasive manner such as keratinocytes, urine cells, and peripheral blood mononuclear cells used for the generation of human iPSCs derived from healthy and diseased subjects. Notably, iPSCs generated from one of these cell types derived from the patient will offer ethical and clinical advantages. In addition, these promising somatic cell sources have the potential to efficiently generate *bona fide* iPSCs with improved reprogramming efficiency and faster kinetics. This knowledge will help in establishing strategies for safe and efficient reprogramming and the generation of patient-specific iPSCs from these cell types.

Keywords Induced pluripotent stem cells · Somatic cells · Keratinocytes · Urine cells · Peripheral blood mononuclear cells

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and their unsuitability for autologous cell therapy. To obviate this, a pioneering study was carried out by Yamanaka's group to utilize fibroblasts as the starting cellular source, and they could succeed in deriving pluripotent cells with a molecular and functional resemblance to ESCs, termed as induced pluripotent stem cells (iPSCs) [4]. The initial studies involved derivation of human iPSCs from fibroblasts by overexpression of a quartet of reprogramming factors, namely OCT4, SOX2, KLF4, and c-MYC (OSKM; also known as Yamanaka factors) or OCT4, SOX2, NANOG, and LIN28 (OSNL; also known as Thomson factors) [5, 6]. Subsequent studies by various investigators worldwide has brought about enormous improvements in the technology in terms of efficiency and time regimen required in generating iPSCs [7–11]. Moreover, human iPSCs have also been differentiated successfully into a wide variety of desired cell types, namely cardiomyocytes, neurons, β-cells, hepatocytes, blood lineages, and so forth for research and biomedical applications [7, 12, 13]. Notably, iPSCs allow derivation of autologous pluripotent stem cells circumventing the embryonic cell source [14]. Thus, the generation of patient-specific and disease-specific iPSCs has revolutionized stem cell research to influence regenerative medicine, drug discovery and improve our fundamental understanding of early embryonic development and specific disease mechanisms.

iPSCs have been generated from a variety of somatic cell sources, namely fibroblasts, myoblasts, keratinocytes, melanocytes, hepatocytes, β-cells, dental pulp cells, blood cells, urine-derived renal epithelial cells, amniotic fluid stem cells, muse cells, adult stem cells, and so forth [12, 13, 15–23] with varied reprogramming efficiencies and kinetics, demonstrating that the origin of starting cell source is a crucial determining factor. Among these, fibroblasts are the most widely used somatic cell source employed for the generation of iPSCs due to commercial availability, easy handling, economical culture media, and well-established cell culture and reprogramming protocols [24]. However, this cell type is not an optimal cell source due to several disadvantages. It requires skin biopsy for its isolation, which is undesirable in children and patients with abnormal wound healing or coagulation or skin disorders. It generally takes at least four weeks for its expansion to have sufficient cells for reprogramming. The patient age and the passage number used for reprogramming also play a deterministic role in successful reprogramming to obtain iPSCs [25–27]. Hence, reprogramming fibroblasts from aged patients is generally highly inefficient. The epigenetic state of fibroblasts also acts as a major barrier to efficient reprogramming and requires remodeling of the epigenome. Furthermore, fibroblasts are generally considered a heterogeneous cell population comprising mesenchymal and non-mesenchymal cell types [28, 29]. In addition, the presence of several reprogramming barriers and the requirement to undergo mesenchymal-to-epithelial (MET) transition also add to the lower reprogramming efficiency in fibroblasts [10, 30, 31]. Also, fibroblasts have a potential risk of accumulating mutations due to constant exposure to stressors, such as UV rays. Due to this, high frequencies of pre-existing coding mutations have been observed in the original somatic cell source and the iPSCs derived from them [32–34].

For future biomedical applications, it is ideal if genetically stable iPSCs could be generated from a somatic cell source with these essential criteria: (i) should be abundantly present in a tissue, (ii) should be accessible with ease, so that it can be isolated using minimally invasive procedure, (iii) should be easy to culture and expand to get a sufficient number of cells for reprogramming in a shortest possible time, (iv) primarily free from critical somatic mutations and chromosomal aberrations, (v) should be easy to reprogram with high efficiency and faster kinetics, (vi) should reprogram cells from subjects of different ages and diseased states. This review provides an overview of the most promising somatic cell sources [keratinocytes, urine cells, and peripheral blood mononuclear cells (PBMCs)] that fulfill these criteria and aid in yielding *bona fide* iPSCs with higher efficiency.

Keratinocytes

Keratinocytes are one of the most promising cell sources utilized for the generation of iPSCs [35]. These cells are keratin protein-enriched epithelial cells that generate the outer protective epidermal layer of the skin and appendages such as nails and hairs. The process of keratinocyte generation continues throughout life due to the presence of self-renewing keratinocyte stem cells [36]. Keratinocytes are one of the most easily accessible cell sources from the human body (from skin epidermis and hair follicles) [35], and hair is the most readily available source for keratinocytes. Keratinocytes can be obtained in a non-invasive manner by merely plucking a hair (Fig. 1). This results in the isolation of transit-amplifying cells having short-term culture potential [37]. They have three growth phases, namely anagen (growth phase), catagen (regression phase), and telogen (resting phase) [38]. Hair root in the anagen phase is active and is preferred for keratinocyte culture, whereas it is inactive in the catagen or telogen phase [39]. Only the outer root sheath needs to be cultured in the medium, whereas the rest of the hair shaft can be removed (Fig. 1). Once the hair is plucked, it can be kept in the media at room temperature for about two days to grow and expand keratinocytes [40]. Several media have been developed for keratinocyte culture, which share a common feature of low calcium concentration to prevent early senescence [40, 41]. Notably, the number of passages for reprogramming experiments should not be high

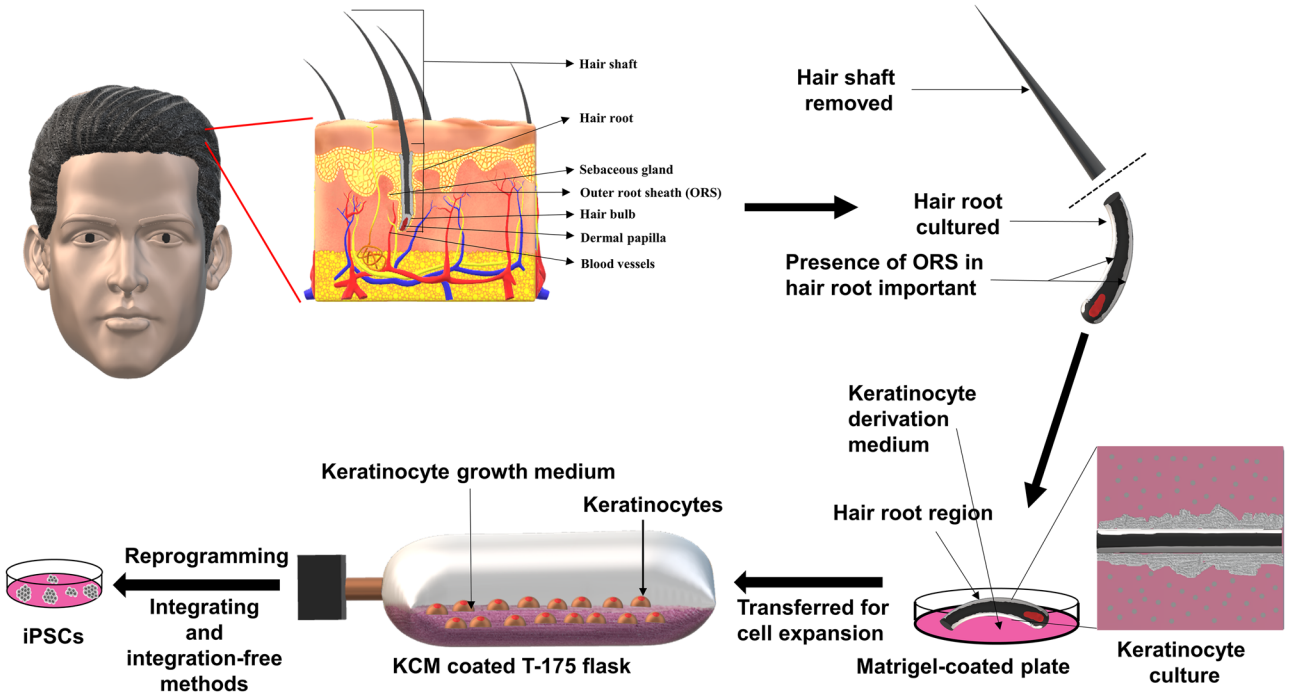

Fig. 1 Isolation and culturing of human keratinocytes derived from human hair and reprogramming them using integration-based or integration-free reprogramming methods to generate iPSCs

(not more than five passages) to prevent complete differentiation and chromosomal aberration(s) [40]. Even though several research groups investigated keratinocytes as a starting cell source for the generation of iPSCs due to their non-invasive derivation from healthy and diseased subjects and easy handling [42–44], it is still not commonly used to date due to their incompatibility with available reprogramming media and certain reprogramming methods like RNA-based approaches [40].

Keratinocytes were first reprogrammed to pluripotency in 2008 using retroviral transduction of Yamanaka factors or three (OSK) factors [42]. Reprogramming keratinocytes with four factors was reported to be 100-fold more efficient and two times faster than reprogramming human fibroblasts [42]. iPSCs derived from keratinocytes had fewer retroviral integrations than fibroblast-derived iPSCs [42]. Similarly, other studies have also reported that keratinocytes are more amenable to efficient reprogramming with faster kinetics when compared to fibroblasts [44–47] and cord blood-derived cells [46]. Notably, keratinocytes are found to have the endogenous expression of pluripotency-associated genes, namely KLF4 and c-MYC and stem cell marker CD24 [42]. Therefore, attempts have been made to reprogram them using fewer factors. Although keratinocytes endogenously express KLF4, reprogramming without it was unsuccessful [42]. However, retroviral transduction of three-factor combination (OSK) generated iPSCs in approximately 20 days [42, 46]. Inclusion of Tranylcypromine (an inhibitor of lysine-specific demethylase 1 and H3K4 demethylation) and CHIR99021 (Glycogen synthase kinase inhibitor) resulted in reprogramming of human keratinocytes with just two factors, OCT4 and KLF4 [48].

In addition, iPSCs have been derived using a single polycistronic excisable lentiviral vector harboring Yamanaka factors with molecular and functional characteristics similar to human ESCs [49]. However, integrating viral-based approaches involve permanent undesirable integrations of transgenes into the target cell genome [11, 50–52]. Therefore, various integration-free reprogramming approaches have been employed to convert keratinocytes into iPSCs efficiently. Non-integrating techniques like Sendai viral vectors [43, 53], adenoviral vectors [54], and episomal vectors [27, 39, 44, 55] have been successfully used to derive iPSCs. But using non-integrative approaches for reprogramming affects the kinetics as it takes around 18 to 34 days [27, 39, 43, 44, 53, 56, 57] when compared to integrative approaches, which takes around 10-14 days [42, 46, 58]. Various studies reporting reprogrammed human keratinocytes are summarized in Table 1.

iPSCs are either cultured on growth-arrested feeder cells [59] or feeder-free conditions, the latter using matrix proteins like collagen or protein mixtures like Matrigel [60]. Therefore, iPSCs either require a matrix or a feeder layer to adhere and grow, maintaining their stem cell identity and

Table 1 Various studies that have reported the generation of iPSCs from human keratinocytes

Somatic cell source(s)	Reprogramming factors	Reprogramming method	Reprogramming efficiency	Reprogramming kinetics[a]	*In vitro* characterization	*In vivo* characterization	Reference(s)
Human keratinocytes	OSKM and OSK	Retroviral transduction	~1% and 0.04-0.06%	14 days 20 days	Yes	Yes	[42]
Human keratinocytes	OSK	Retroviral transduction	1.38 ± 0.51%	12-15 days	Yes	ND	[46]
Human keratinocytes	OK + sm	Lentiviral transduction	0.002%	~49 days	Yes	Yes	[48]
Human keratinocytes	OSKM	Lentiviral transduction	0.03±0.002%	21-25 days	Yes	Yes	[49]
Human keratinocytes	OSKM	Lentiviral transduction	2.8%	14 days	Yes	Yes	[58]
Human keratinocytes	OSKMNL	Episomal vectors	ND	21 days	Yes	No	[55]
Human keratinocytes	OSLN OSKM	Lentiviral transduction	0.01% 0.03%	35-42 days	Yes	Yes	[25]
Human keratinocytes	OSKL^{m}L + shp53	Episomal vectors	0.14%	21-30 days	Yes	Yes	[44]
Human keratinocytes	OSKL^{m}L + shp53	Episomal vectors	ND	21 days	Yes	ND	[39]
Human keratinocytes	OSKL^{m}L + shp53	Adenoviral transduction	ND	18-28 days	Yes	Yes	[54]
Human keratinocytes	OSKM	Retroviral transduction	0.59±0.03%	14-28 days	Yes	No	[45]
Human keratinocytes	OSKM (feeder-free)	Sendai viral transduction	ND	26 days	Yes	No	[75]
Human keratinocytes	OSKM	Sendai viral transduction	0.002-0.01%	14 days	ND	ND	[76]
Human keratinocytes	OSKM (feeder-free)	Sendai viral transduction	ND	28-31 days	Yes	No	[43]
Human keratinocytes	OSKM	Sendai viral transduction	0.01%	28-35 days	Yes	Yes	[53]
Human keratinocytes	OSKM (feeder-free)	Sendai viral transduction	ND	10-12 days	Yes	No	[77]
Human keratinocytes	OSKM (feeder-free)	Sendai viral transduction	ND	18-35 days	Yes	Yes	[78]

O OCT4, *S* SOX2, *K* KLF4, *M* c-MYC, *L* LIN28, *N* NANOG, *L^{m}* L-MYC, *sm* small molecules, *shp53* short hairpin RNA against p53, *ND* Not determined

[a]The time line mentioned in this column is the day when iPSC-like colony was picked for further expansion and characterization

function. The most commonly used cells for the feeder layer are irradiated MEFs [42, 61]. Interestingly, a study showed that the type of cell used as a feeder layer could also influence reprogramming efficiency. Using rat embryonic fibroblasts as a feeder layer, a study has reported enhanced reprogramming efficiency of keratinocytes due to the upregulation of secreted growth factors, namely *Tgfb1*, *Inhba*, and *Grem1*, and downregulation of *Bmp4* [58].

Keratinocytes have multiple advantages over fibroblasts for reprogramming. For instance, fibroblasts have to undergo a mesenchymal-to-epithelial transition to be successfully reprogrammed to iPSCs [30], whereas keratinocytes are of epithelial origin, and therefore this step is not required [62]. The exogenous expression of the pluripotency-associated genes, namely OSKM, plays a major role in the mesenchymal-to-epithelial transition process in fibroblasts [30]. Also, keratinocytes retain their epithelial gene signature, which might help improve reprogramming [62]. Importantly, genomic characterization of cells from different stages of reprogramming suggests that in most somatic cells, pluripotency-associated genes are hypermethylated, thereby inhibiting their expression. Therefore, reactivation of these hypermethylated pluripotency-associated genes is vital for successful reprogramming into iPSCs [63]. Evidently, the hypermethylation pattern at CpGs and tissue-specific genes in keratinocytes are more similar to ESCs than fibroblasts [64]. This might be the reason why keratinocytes are efficiently reprogrammed to iPSCs than fibroblasts. Moreover, iPSCs derived from keratinocytes have a methylation profile very much similar to ESCs than that of iPSCs from fibroblasts [64]. Furthermore, analyzing the cellular metabolism of iPSCs has revealed that they are highly glycolytic compared to somatic cells [65]. Interestingly, comparing cellular metabolism of fibroblasts and keratinocytes has indicated that keratinocytes have a close resemblance to iPSCs bioenergetically than fibroblasts, and this might also be the reason for the higher reprogramming efficiency of keratinocytes [65, 66]. Furthermore, the tumor suppressor genes decrease

cell proliferation rate and compromise reprogramming efficiency [67]. Therefore, inhibition of these tumor suppressor genes and their pathways will pave the way for enhanced reprogramming [67]. A gene named *Ink4a/Arf* activates the p53 pathway by activation of effector genes, which eventually affects the efficiency of reprogramming. Hence, silencing of *Ink4a/Arf* locus in keratinocytes helped to enhance reprogramming efficiency by almost 100-fold [68]. Besides, it was found that the inherent expression of p53 and p21 in keratinocytes is low, which might account for its high reprogramming efficiency [67]. Nevertheless, further suppression of the p53 pathway in keratinocytes lends an additive effect to help improve the reprogramming efficiency [67]. Notably, downregulation of pRb in keratinocytes resulted in a 3-fold increase in reprogramming efficiency [69]. In addition, the potent senescence roadblock in keratinocytes can be overcome by telomerase overexpression for efficient derivation of mouse and human iPSCs [70]. Thus, keratinocytes have multiple intrinsic advantages that enable their efficient reprogramming.

Certain caveats still remain to be addressed pertaining to the generation of iPSCs from keratinocytes. First, keratinocytes have the propensity to undergo senescence after a few passages [37]. Second, they have a longer doubling time, leading to a need to carefully cultivate these cells [37]. Also, non-integrating and safer approaches like the Sendai viral method have yielded a lower reprogramming efficiency of 0.01% [53]. This might be because the protocols for Sendai viral transduction are sub-optimal for keratinocytes. In addition, reprogramming using an RNA-based approach, which has been successfully carried out for other cell types [40, 71, 72], is problematic in keratinocytes as it requires multiple passages and hence may trigger their senescence.

Despite these disadvantages, keratinocytes are an appropriate cell source for reprogramming because of their collection in a non-invasive manner, easy isolation and capability to generate iPSCs. Therefore, keratinocyte-derived iPSCs are already finding applications to develop disease models and form organoids [73]. Specifically, they are preferred to derive cells of neural origin as they have a higher tendency than other iPSCs to differentiate towards neural precursor cells, possibly due to common ectodermal origin [74]. Therefore, they are being explored as a means to generate disease models for conditions like Attention Deficit Hyperactivity Disorder [43] as well as a source of autologous stem cells for Spinal Cord Injuries [24]. Disease-specific iPSCs have also been generated from keratinocytes by various studies for disease modeling and developing novel cell therapy applications (Table 2). Thus, with more research on keratinocytes, it can serve as a non-invasive, easily accessible, and viable cell source for the generation of iPSCs [35]. These keratinocyte-derived iPSCs can be widely employed for 'disease-in-a-dish' modeling and cell-based therapeutics.

Table 2 Various studies that have reported the generation of iPSCs from human keratinocyte cells isolated from patients

Reprogramming method	Disease	Reference(s)
Retroviral transduction	Cystic Fibrosis	[79]
Lentiviral transduction	Crohn's disease	[73]
Sendai viral transduction	Attention deficit hyperactivity disorder	[43]
	Epidermolysis bullosa	[76]
	Atopic dermatitis	[80]
Episomal vectors	Sickle cell disease	[54]

Urine Cells

The search for better cell sources for iPSCs generation perhaps leads to an unlikely source of cells for reprogramming, i.e., human urine (Fig. 2). Human urine satisfies the mentioned criteria for an ideal cell source; i.e., it should be readily available, universal (regardless of age, sex, and disease condition), and involve non-invasive collection [14, 81]. Moreover, they can be collected without any medical assistance [81]. In mammals, the urinary tract consists of the kidney, ureter, urinary bladder, and urethra [82]. Approximately 2000 to 7000 cells of various types detach from the urinary tract and are excreted via urine daily [83]. Urine cells are a heterogeneous population of diverse cells, including renal tubular epithelial cells, fibroblast-like cells, urothelial cells, and urine-derived adult stem cells [82], which endogenously express KLF4 and c-MYC with high telomerase activity [84] and cell surface markers such as TRA-1-60 and TRA-1-81 [85]. These urine-derived stem cells are capable of myogenic and uroepithelial differentiation [86, 87]. The idea of culturing urine cells began as early as 1972. The fact that during the gestation period, fetal urine contributes to amniotic fluid lead to a reasonable possibility that cells in urine also can be cultured [88].

Collection of urine is routinely done for medical diagnosis. Thus, people find it to be an acceptable practice to donate urine samples. Around 50 to 200 ml of urine collected from midstream during micturition was shown to have a 90% success rate in generating epithelial cell cultures [89]. These cells can then be used for reprogramming experiments. Contrastingly, another study reported a lower success rate for human urine cell culture [57]. The study found that osmolality is an important factor for determining successful human urine cell isolation. They deduced that the optimal osmolality range for efficient isolation of human urine cells was between 241 to 598 mmol/l [57]. Moreover, urine epithelial cells can be successfully isolated from urine samples stored for 48 hours at 4 °C [90]. This is advantageous for transporting samples using simple storage conditions [90]. Generally, a minimum of 50 ml of urine is required to successfully isolate urine cells and subsequent reprogramming [91]. Moreover, the collection of urine should be carried out

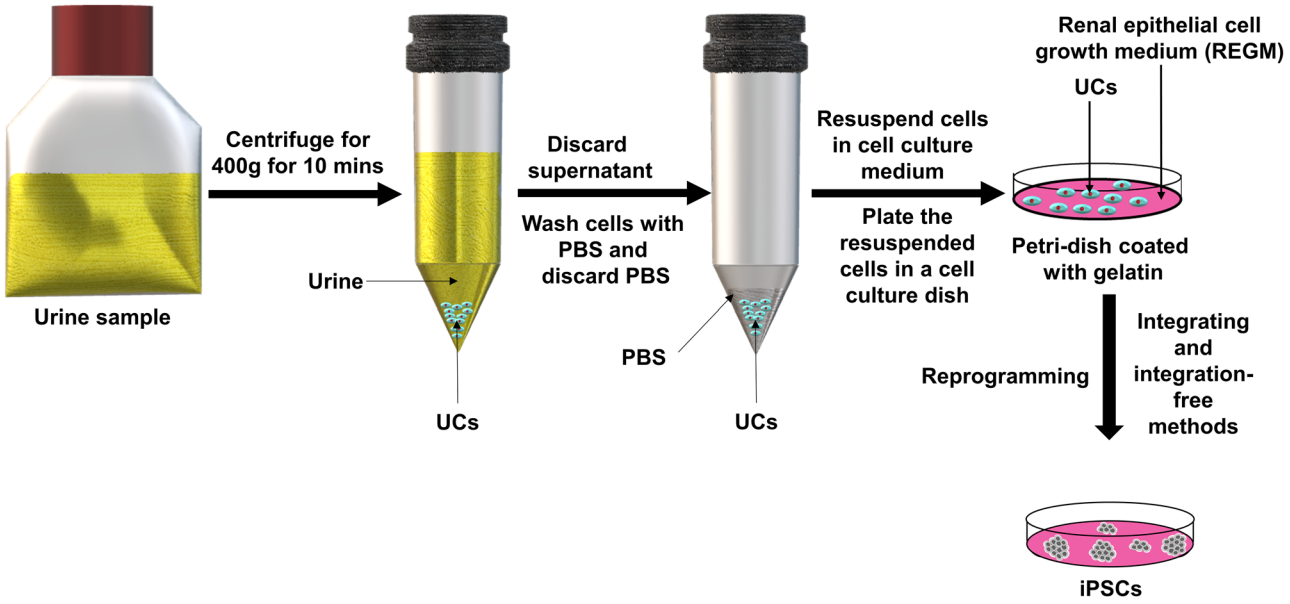

Fig. 2 Isolation and culturing of human urine cells derived from human urine and reprogramming them using integration-based or integration-free reprogramming methods to generate iPSCs

under aseptic conditions. Interestingly, Mulder and his colleagues successfully isolated urine cells obtained from urine as minimum as 10 ml, collected in urine bags [91]. This study showed that the collection of urine samples is one of the easiest and universal methods. All these characteristics make urine one of the ideal cell sources for reprogramming.

In 2011, the researchers reported for the first time that exfoliated renal tubular cells extracted from urine can be infected with retroviral vectors encoding human OCT4, SOX2, KLF4, and c-MYC to generate iPSCs with high efficiency (0.1-4%) [81]. In addition to integrating, several non-integrating approaches have also been applied to reprogram urine cells to develop safe iPSC lines that can be used for therapeutic purposes (Table 3). Sendai virus [92], episomal plasmids [89], RNA-based approaches [93–95], and a combination of episomal plasmids and small molecules [57] have all been able to reprogram human urine cells successfully. The urine-derived cells were reprogrammed successfully using an mRNA approach with faster kinetics than that of fibroblasts and dental pulp cells [93]. One caveat of using mRNA-based reprogramming is that the expression of reprogramming factors is transient, and therefore, multiple transfections are needed to reprogram utilizing this approach [93, 94]. But this can be overcome by using the self-replicative RNA approach, which can generate iPSCs in a single transfection [94, 95]. In addition, several small molecule cocktails have also been reported to promote the reprogramming of human urine cells to iPSCs [57]. Moreover, iPSCs can also be generated under feeder-free conditions from human urine cells, which circumvents the problem of cross-contamination of feeder cells [89, 93, 96]. Various studies that have reprogrammed human urine cells are summarized in Table 3.

Besides being a readily available and non-invasive cell source, human urine cells have other intrinsic advantages over other cell sources. Being epithelial, they do not have to undergo MET, which significantly enhances their reprogramming efficiency and kinetics than fibroblasts [84, 85]. As mentioned earlier, these cells endogenously express stem cell-specific genes such as c-MYC and KLF4 with high telomerase activity [84] and stem cell surface markers such as TRA-1-60 and TRA-1-81 [85]. Apart from introducing pluripotency-associated genes, additional factors like miR302-367 and simian virus 40 large T antigen (SV40LT) have proven to be effective in the generation of iPSCs [85, 89]. In addition, miR302-367 can also be used as a substitute for the oncogene c-MYC in the reprogramming process [89]. This substitution has proven to be effective only in the case of urine cells, not in fibroblasts, which demonstrates that urine cells are easier to reprogram [89].

Stem cells, in general, largely depend on their extracellular environment or otherwise called "niche," for their function and maintenance [97]. The extracellular environment plays a vital role in cell-matrix adhesion and influences cell-cell adhesion. Therefore, modifying the extracellular microenvironment of iPSCs might favor enhanced reprogramming efficiency. Recently, reprogramming human urine cells in a three-dimensional self-assembling peptide hydrogel Puramatrix, rather than a regular two-dimensional Matrigel, has shown efficient generation of iPSC colonies [98]. Although

Table 3 Various studies that have reported the generation of iPSCs from human Urine Cells (UCs) derived from healthy subjects

Somatic cell source	Reprogramming factors	Reprogramming method	Reprogramming efficiency	Reprogramming kinetics[a]	*In vitro* characterization	*In vivo* characterization	Reference(s)
Human UCs	OSKM	Retroviral transduction	0.01-4%	16-25 days	Yes	Yes	[81]
Human UCs	OSK + SV40LT + miR302/367 + sm (feeder-free)	Episomal vectors	0.2%	~25 days	Yes	No	[114]
Human UCs	OSKML + SV40LT	Episomal vectors	0.0001-0.007%	20-30 days	Yes	Yes	[89]
Human UCs	OSKM (feeder-free)	Lentiviral	0.1-0.5% (TA↑) 0.002-0.007% (TA↓)	17 days	Yes	Yes	[84]
Human UCs	OSKL^{m}L + shp53 + SV40LT (xeno-free)	Episomal vectors	~0.3%	18-23 days	Yes	Yes	[96]
Human UCs	OSKL^{m}L + p53mutant + miR302/367 (feeder-free)	Episomal vectors	1.5%	20-30 days	Yes	No	[85]
Human UCs	OSKM	Sendai viral transduction	ND	10 days	Yes	No	[115]
Human UCs	OSKM (feeder-free)	Sendai viral transduction	0.0049%	20-25 days	Yes	Yes	[90]
Human UCs	OSKL^{m}L + shp53 (feeder-free)	Episomal vectors	0.0028%	35 days	Yes	Yes	[90]
Human UCs	OSKM (with and without feeder)	Sendai viral transduction	0.001-0.1%	16 days	Yes	Yes	[112]
Human UCs	OSKL^{m}L + EBNA1 + shp53	Episomal vectors	ND	20 days	No	No	[116]
Human UCs	OSKM	Sendai viral transduction	ND	ND	Yes	No	[117]
Human UCs	OSKL^{m}G + miR-302 cluster	Episomal vectors	0.00021-0.0741%	19 days	Yes	Yes	[118]
Human UCs	OSKM	Sendai viral transduction	ND	21 days	Yes	Yes	[106]
Human UCs	OSKM	srRNA transfection	ND	26-33 days	Yes	Yes	[94]
Human UCs	OSK+SV40LT+ miR302/367 (feeder-free)	Episomal vectors	ND	18-25 days	Yes	No	[119]
Human UCs	OSK + SV40LT+ miR302/367 (feeder-free)	Episomal vectors	~0.05%	20 days	Yes	Yes	[98]
Human UCs	OSKMG (feeder-free)	srRNA transfection	0.008-0.17%	18-21 days	Yes	No	[95]

O OCT4, *S* SOX2, *K* KLF4, *M* c-MYC, *SV40LT* simian virus 40 large T antigen, *miR* microRNA, *sm* small molecules, *L* LIN28, *L^{m}* L-MYC, *G* GLIS1, *shp53* short hairpin RNA against p53, *TA*↑ high telomerase activity, *TA*↓ low telomerase activity, *srRNA* self-replicative RNA, ND: Not determined

[a]The time line mentioned in this column is the day(s) when iPSC-like colony was picked for further expansion and characterization

reprogramming efficiencies were comparable between the two stated approaches, the iPSC colonies in the former case were found to be more homogeneous [98]. Studies have also shown that human iPSCs have remnants of epigenetic memory of their starting cell source [74], which makes them biased towards differentiating into specific lineages only. Interestingly, iPSCs derived from urine cells have shown no such propensity to differentiate into particular lineages only [99]. However, the major issue concerning the derivation of iPSCs from human urine cells is that the efficiency differs significantly from donor to donor [81]. The reprogramming efficiency also decreases with increasing passages of human urine cells [81]. Moreover, urine cannot be collected from people with rare renal defects like renal insufficiency and cystectomy [82].

Notably, the applicability of urine-derived iPSCs in the field of therapeutics has been widely studied and analyzed. Urine-derived iPSCs have been of immense help for developing disease models for diseases like dystrophic cardiomyopathy [84, 92, 100], ventricular septal defects [101], hemophilia A [102], diabetes mellitus [103], hepatocyte polarity [104], systemic lupus erythematosus [105], and neurodevelopment diseases like autism spectrum disorder [106, 107], and multiple sclerosis [108]. Furthermore, the application of urine-derived iPSCs have been investigated by developing patient-specific cells or organoids like microvascular grafts for hemophilia A [109], kidney organoids for congenital anomalies [91], tooth-like structures [110], retinal organoids [111], neural progenitor cells for spinal cord injuries [112], and cerebral organoids [113]. These applications undoubtedly exemplify the enormous potential and utility of urine-derived iPSCs. Patient- and disease-specific iPSCs have also been generated from urine cells by several studies for disease modeling and developing novel cell therapy applications (Table 4). Human urine cells are therefore considered as a viable source for the generation of iPSCs, which

then have broad applications in the field of disease modeling and therapeutics.

Peripheral Blood Mononuclear Cells (PBMCs)

PBMCs can be isolated from various sources, namely cord blood, bone marrow, and peripheral blood. PBMCs isolated from blood serve as one of the most popular somatic cell sources for iPSCs generation (Fig. 3). Culturing and expansion of PBMCs are simpler and easier. While the collection of peripheral blood and cord blood for isolation of mononuclear cells is less invasive, the same for bone marrow is highly invasive. PBMCs are usually extracted from the buffy coat layer by Ficoll-Paque density gradient centrifugation from whole blood (Fig. 3) [126]. Isolated PBMCs consist of monocytes, natural killer cells, lymphocytes, dendritic cells, and hematopoietic stem cells/hematopoietic progenitor cells. Among these, lymphocytes contribute to a large fraction of the PBMCs population.

The initial studies reprogrammed terminally differentiated mature T and B lymphocytes to give rise to iPSCs using viral-based techniques [127–130]. Also, integration-free methods have been successfully employed to efficiently reprogram B and T lymphocytes and Epstein Barr Virus immortalized lymphoblastoid cells [19, 127, 131–136]. Although B and T lymphocytes are ample in PBMCs and easier to culture, they are not preferred for reprogramming as they are subjected to intrinsic DNA rearrangements at the V(D)J as well as T cell receptor loci to give rise to a vast and highly diverse repertoire of antigen-specific surface immunoglobulins from a relatively limited number of genes [137]. These irreversible DNA rearrangements are then perpetuated in iPSCs derived from these cells, and their potential effect on the proper differentiation of iPSCs is not yet investigated. Additionally, reprogrammed T cells have been shown to induce spontaneous T cell lymphomas in mice [138], limiting their broad applications in regenerative medicine. Therefore, a protocol that enriches erythroblast-like cells and eliminates lymphocytes is preferred [139]. Interestingly, B cells isolated from the human fetal liver are reprogrammed much more efficiently than B cells isolated from peripheral blood or cord blood [136]. This result shows that cell ontogeny might influence reprogramming efficiency. On the other hand, the $CD34^+$ cells, present in PBMCs, are highly proliferative and efficiently reprogrammable [129, 137, 140–144]. But this cell population is rare (<0.01%) in PB [137], which is why patients are subcutaneously injected with stem cell mobilizers such as granulocyte colony-stimulating factor to obtain these progenitor cells in large numbers from circulating peripheral blood. This is only possible if the human subject is in good medical condition. Also, stem cell mobilization is associated with major side effects in patients and requires a multi-day dosing regimen [145, 146]. A study

Table 4 Various studies that have reported the generation of iPSCs from human urine cells isolated from patients

Reprogramming method	Disease	Reference(s)
Lentiviral transduction	Systemic lupus erythematosus	[105]
	Duchenne muscular dystrophy	[84]
Sendai viral transduction	Muscular dystrophy	[92]
	Fibrodysplasia ossificans progressive	[120]
	Attention deficit hyperactivity disorder	[121]
	Ventricular septal defect	[101]
	Autism spectrum disorder	[106, 122]
	Hearing loss	[123]
	Type 2 diabetes mellitus	[103]
Episomal vectors	Alports disease	[89]
	Type 2 long QT syndrome	[124]
	Hemophilia A/B	[89, 109]
	Amyotrophic lateral sclerosis	[89]
	β-thalassemia	[89]
	Multiple sclerosis	[108]
	Autism spectrum disorder	[107]
	Congenital anomalies of the kidney and urinary tract	[91]
	Spinocerebellar ataxia type 1	[125]

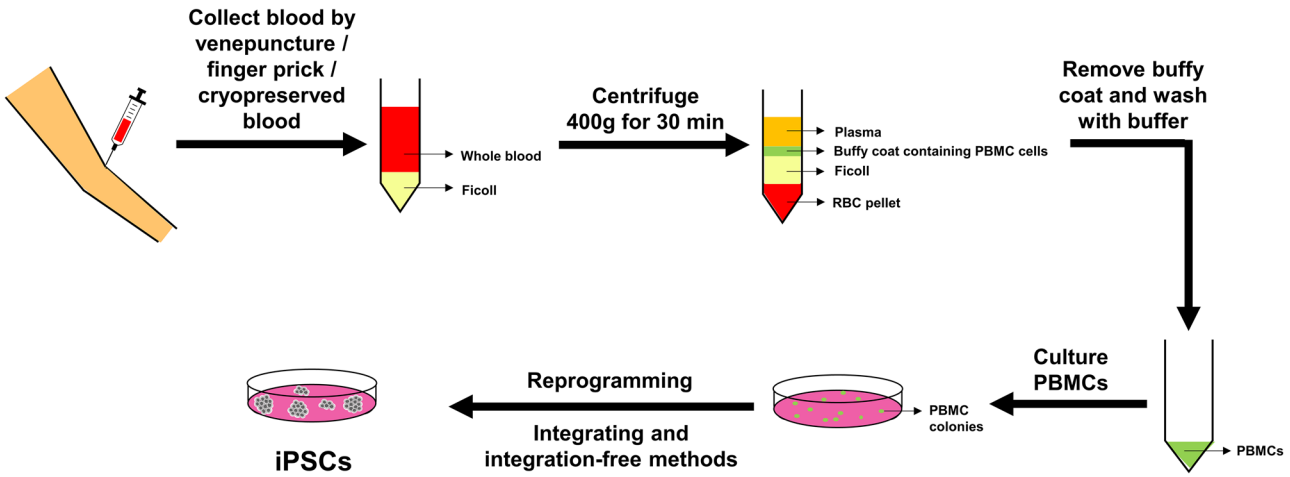

Fig. 3 Schematic representation of isolation of PBMCs from whole blood (collected by venipuncture/finger prick/cryopreserved blood) by density gradient centrifugation using Ficoll-paque and its subsequent reprogramming into iPSCs using integration-based and integration-free methods

has reported functional differences between cells from mobilized and non-mobilized blood samples, indicating that the intrinsic characteristics of the cells have been altered [147]. In addition, it has been reported that chromosomal aneuploidy can occur in cells mobilized with granulocyte colony-stimulating factor [148]. In agreement with this, genetic and epigenetic abnormalities have been observed in cells isolated from patients mobilized with granulocyte colony-stimulating factor [148, 149]. These observations highlight the possibility of introducing similar genomic and epigenomic modifications that would perpetuate into iPSCs derived from mobilized cells and potentially affect their function. Therefore, it is more desirable to acquire blood that does not necessitate donors to receive these mobilizers to circumvent the adverse side effects and chromosomal abnormalities. In addition, the iPSCs derived from non-lymphocytes having intact genomes will be more appropriate for therapeutic applications [139].

The first study to reprogram PBMCs (from mobilized human $CD34^+$ cells from PB) to iPSCs was carried out by Loh and colleagues [140]. In this study, the researchers delivered Yamanaka factors retrovirally to generate iPSCs, which were indistinguishable from human ESCs with respect to morphology, expression of cell surface and pluripotency-associated markers, DNA methylation at key pluripotency genes, and the ability to differentiate *in vitro* and *in vivo* into all three germ layers. Subsequently, the same lab derived iPSCs from both $CD34^+$ cells and mononuclear cells from the PB (non-mobilized) obtained from healthy donors via lentiviral transduction of Yamanaka factors [129]. Another study generated iPSCs from nonmobilized human PBMCs by retroviral transduction of Yamanaka factors [150]. The authors in this study observed that $5x10^5$ PBMCs, which corresponds to less than 1 mL of peripheral blood, were sufficient for the derivation of numerous iPSC colonies. Although the usage of viral vectors gives higher reprogramming efficiencies, their integration into the host genome causes genetic instability in iPSCs due to high frequencies of insertional mutagenesis [151], which, very likely, will affect its biological function. Therefore, non-integrative approaches like the Sendai virus and episomal vectors are preferred for reprogramming for potential clinical applications [8, 9, 11]. Therefore, studies have demonstrated that integration-free approaches such as Sendai virus and episomal vectors can also be efficiently employed for reprogramming PBMCs isolated from healthy subjects [131, 142–144, 152–165] and patients [153]. The iPSCs derived in these studies were free from any genomic integration, expressed pluripotency-associated genes, karyotypically normal, and efficiently differentiated into various cell types *in vitro* and *in vivo*. Notably, studies have also demonstrated that iPSCs can be generated from PBMCs isolated from less than 10 ml of blood [142, 143, 150, 153, 156–161, 163, 165–174]. Importantly, the epigenetic signatures and gene expression patterns of PBMCs are closer to ESCs and iPSCs than those of the age-matched fibroblasts, which results in faster reprogramming (14 days) of PBMCs compared to age-matched fibroblasts (28 days) [141, 175]. Incorporating a histone deacetylase

inhibitor (sodium butyrate or valproic acid) has also been reported to enhance the reprogramming efficiency [175]. Reprogramming kinetics and efficiency can also be further improved by including some additional factors apart from OSKM. Specifically, the inclusion of an anti-apoptotic factor, BCL-XL, increases the reprogramming efficiency by 10-fold [161, 176]. Recently, the episomal vector combination was fine-tuned to demonstrate ~100-fold improvement in the reprogramming of human adult PBMCs [177]. To accomplish this, OCT4 and SOX2 were cloned in a single episomal vector and connected by a 2A peptide linker for their equimolar expression. Additionally, two separate episomal vectors having c-MYC and KLF4 were used to achieve a higher and steadier increase in c-Myc over KLF4 expression during the course of cell reprogramming. These alterations, along with the expression of BCL-XL, contributed to improved efficiency [177]. However, addition of other factors episomally along with OSKM like LIN28 in PBMCs, and LIN28 and shRNA against p53 in lymphoblastoid cells gave comparable efficiencies to that of iPSCs generated from PBMCs by transfection of OSKM factors episomally [134, 178]. It is reported that PBMCs are 50-fold less efficient than cord blood mononuclear cells for iPSCs generation. The efficiency can also be further improved by including additional factors like SV40 Large T antigen and EBNA1 [137, 160, 175]. Numerous studies that have reprogrammed human PBMCs are summarized in Table 5. Patient- and disease-specific iPSCs have also been generated from PBMCs by numerous studies for disease modeling and developing novel cell therapy applications (Table 6).

Most methods require 10 ml of whole blood, requiring minimal invasiveness for PBMC isolation. Interestingly, iPSCs can also be generated successfully by reprogramming cells isolated from whole blood as little as 10 µl collected by the finger-prick method [157]. The finger-prick method of collecting blood is considered one of the least invasive and less complicated procedures [157]. Besides, blood cells can also be cryopreserved and reprogrammed in the future without any compromise in reprogramming kinetics and efficiency [165]. Also, PBMCs are stable at room temperature for up to 24-48 hours and can resist multiple freeze-thaw cycles while maintaining their genomic integrity and reprogramming ability [153, 163]. This ease in access, isolation, and maintenance makes them an attractive candidate as a somatic cell source for reprogramming. However, the major limitation of using PBMCs as a source for iPSC generation is that whole blood samples from patients with clotting disorders may not give quality iPSCs. Further, the epigenetic marks from PBMCs like V(D)J rearrangements in B and T lymphocytes might transfer to iPSCs, hindering its differentiation potential [137]. Therefore, a thorough screening of iPSC clones reprogrammed only from purified hematopoietic progenitors or myeloid-erythroid cells is required before its further use. Also, the reprogramming efficiency relies on the donor, i.e., different reprogramming efficiency is reported for different donors even when the same reprogramming technique and factors were used [175].

In general, PBMCs serves as the most abundant and convenient source of somatic cells because sample collection is less cumbersome, cheap, easily accessible, less exposed to environmental mutagens, and devoid of ethical complications than other somatic cell sources such as hepatocytes, β-cells, and so forth. Also, it allows access to several frozen samples stored at blood banks worldwide, and iPSCs can also be derived from these frozen human peripheral blood samples [160, 179]. iPSCs derived from such samples can provide abundant cells to screen for genetic factors and to elucidate the molecular mechanisms fundamental to lymphoid and myeloid blood disorders. Moreover, the "epigenetic memory" of blood-derived iPSCs will drive their differentiation, particularly towards blood cell type [66, 74], making them suitable for the development of disease models, pre-clinical drug screening, and identifying a cure for various hematopoietic diseases [180]. Despite this, PBMC-derived iPSCs can be coaxed to differentiate towards other cell types such as mesenchymal stem cells, neural stem cells, cardiomyocytes, hepatocytes, and so forth [144, 164, 165, 180, 181]. Importantly, the iPSCs generated using PBMCs are of good quality with better efficiencies and kinetics. Notably, all the colonies picked from reprogrammed PBMCs established stable iPSC clones, which could be expanded and cryopreserved compared to those picked from reprogrammed fibroblasts [166]. In fact, the clinical significance and advantage of using PBMCs as a somatic cell source for iPSCs generation can be seen in Japan's iPSC stock project, which started in 2013 [182]. Their main objective is to generate a human leukocyte antigen homozygous haplobank and support research related to it. The prospect of iPSC banking seems exciting and opens up new opportunities for personalized medicine, although there is still a long way to go, and PBMCs seem to be one of the most practical sources with promising results.

Conclusion and Future Perspectives

Numerous studies have reported the derivation of iPSCs from a variety of cell sources using integration-based and integration-free approaches [7–9, 11, 211, 212]. The potential applications of iPSCs are limited due to several barriers that act as roadblocks to prevent efficient reprogramming [7,

Table 5 Various studies that have reported generation of iPSCs from PBMCs[a] isolated from healthy individuals

Somatic cell source(s)	Reprogramming factors	Reprogramming method	Reprogramming efficiency	Reprogramming kinetics[b]	*In vitro* characterization	*In vivo* characterization	Reference(s)
PBMCs ($CD34^+$)	OSKM	Retroviral transduction	ND	14 days	Yes	Yes	[140]
PBMCs ($CD34^+$)	OSKM	Lentiviral transduction	0.002%	21 days	Yes	Yes	[129]
PBMCs	OSKM	Lentiviral transduction	0.0008-0.001%	35 days	Yes	Yes	[129]
PBMCs	OSKM	Sendai viral transduction	0.1%	25 days	Yes	Yes	[131]
PBMCs	OSKM	Lentiviral transduction	0.001-0.0002%	25-40 days	Yes	Yes	[179]
PBMCs ($CD34^+$)	OSKML	Episomal vectors	0.001%	14 days	Yes	Yes	[175]
PBMCs	OSKM	Retroviral transduction	ND	12-23 days	Yes	Yes	[150]
PBMCs ($CD34^+$)	$OSKL^mL$ + SV40LT	Episomal vectors	~0.005%	ND	Yes	Yes	[143]
PBMCs	OSKM (feeder-free)	Lentiviral transduction	0.002-0.01%	14-21 days	Yes	Yes	[60]
PBMCs	OSKML	Episomal vector	ND	14 days	Yes	Yes	[139]
PBMCs	OSKM	Lentiviral transduction	ND	21-31 days	Yes	No	[166]
PBMCs	OSKM	Sendai viral transduction	ND	18-20 days	No	No	[183]
PBMCs ($CD34^+$)	OSKM	Lentiviral transduction	ND	18-35 days	Yes	Yes	[142]
PBMCs ($CD34^+$)	OSKML + shp53 + SV40LT + EBNA1	Episomal vectors	0.0005%	16-25 days	Yes	Yes	[160]
PBMCs ($CD34^+$)	OSKM + BCL-XL	Episomal vectors	0.2%	21-28 days	Yes	Yes	[161]
PBMCs	OSKM	Sendai viral transduction	0.02-0.27%	21-28 days	Yes	Yes	[156]
PBMCs	OSKM	Lentiviral transduction	ND	ND	Yes	Yes	[180]
PBMCs	OSKM	Sendai viral transduction	0.008-0.024%	~20 days	Yes	Yes	[157]
PBMCs	OSKM	Sendai viral transduction	0.011±0.006%	16 days	Yes	No	[174]
PBMCs	$OSKLL^m$ + shp53 + EBNA1	Episomal vectors	~0.01%	20-30 days	Yes	Yes	[162]
PBMCs	OSKM	Sendai viral transduction	ND	20-40 days	No	No	[168]
PBMCs	OSKM	Sendai viral transduction	0.0015-0.06%	~14 days	Yes	No	[163]
PBMCs	OSKM + BCL-XL (feeder-free; xeno-free)	Episomal vectors	0.04-0.045%	14 days	Yes	Yes	[137]
PBMCs	OSKM and OSKMLN (xeno-free)	Episomal vectors	0.00025% and 0.00085%	12-30 days	Yes	Yes	[27]
PBMCs	$OSKL^mL$	Episomal vectors	0.033%	14 days	Yes	No	[164]
PBMCs	OSKM	Sendai viral transduction	0.15–0.32 %,	7-10 days	Yes	No	[165]
PBMCs	OSKM	Sendai viral transduction	~0.003-0.06%	14-21 days	Yes	No	[169]
PBMCs	OSKM + BCL-XL	Episomal vectors	ND	ND	Yes	Yes	[158]
PBMCs	OSKM + BCL-XL	Episomal vectors	0.01-0.2%	14-19 days	Yes	Yes	[177]
PBMCs	OSKML	Episomal vectors	ND	20-26 days	Yes	No	[184]
PBMCs	OSKM	Sendai viral transduction	ND	ND	Yes	No	[170]
PBMCs	OSKM	Sendai viral transduction	ND	~21 days	Yes	No	[171]
PBMCs	OSKM	Sendai viral transduction	0.1-0.5%	~27 days	Yes	No	[159]
PBMCs	OSKM (feeder-free)	Sendai viral transduction	0.01%	21-28 days	Yes	Yes	[172]
PBMCs	OSKM (feeder free)	Sendai viral transduction	0.17%	8-14 days	Yes	No	[153]
PBMCs ($CD34^+$)	OSKM (feeder free)	Sendai viral transduction	5.58%	8-14 days	Yes	No	[153]

Table 5 (continued)

Somatic cell source(s)	Reprogramming factors	Reprogramming method	Reprogramming efficiency	Reprogramming kinetics[b]	*In vitro* characterization	*In vivo* characterization	Reference(s)
PBMCs	OSKM + BCL-XL	Episomal vectors	ND	18-21 days	Yes	Yes	[144]
PBMCs	OSKM (feeder-free)	Sendai viral transduction	0.008-0.1%	14 days	Yes		
	OSKM (feeder-free)		0.01-0.19%	14 days	Yes		

PBMCs Peripheral blood mononuclear cells, *O* OCT4, *S* SOX2, *K* KLF4, *M* c-MYC, L^m L-MYC, *L* LIN28, *N* Nanog, *SV40LT* Simian vacuolating virus 40 large T antigen, *shp53* short hairpin RNA against p53 *EBNA1* Epstein-Barr nuclear-antigen 1 *BCL-XL* B-cell lymphoma-extra large *ND* Not determined

[a]Only studies that have reprogrammed PBMCs (without purification) are discussed in this table. Studies involving reprogramming of lymphocytes (T or B) have been excluded due to reasons mentioned in the manuscript

[b]The time line mentioned in this column is the day when iPSC-like colony was picked for further expansion and characterization

10, 211, 213]. To realize the full potential of this technology, attempts have been made to reprogram a diverse array of cell types derived from different cell sources, some of which are discussed in this review, namely keratinocytes which are easier to obtain, isolate and reprogram, urine cells which are easier to collect and universally applicable to all irrespective of age and gender, and PBMCs which is the most commonly collected sample for diagnostics (also

Table 6 Various studies that have reported the generation of iPSCs from PBMCs isolated from patients

Reprogramming method	Disease	Reference(s)
Retroviral transduction	Myeloproliferative disorders	[141]
Lentiviral transduction	Mucopolysaccharidosis type II	[185]
Sendai viral transduction	Craniometaphyseal dysplasia	[167]
	Bernard–Soulier syndrome	[186]
	Schizophrenia	[187]
	Early onset Alzheimer's disease	[188]
	Late onset Alzheimer's disease	[189]
	Triple negative breast cancer	[190]
	Parkinson Disease	[191]
	Sickle cell anemia	[192]
	Autism Spectrum Disorder	[193]
	Werner syndrome	[194]
	Amyotrophic lateral sclerosis	[195]
	Familial Platelet Disorder with associated Myeloid Malignancy	[196]
	Autism-related Activity-Dependent Neuroprotective Protein	[197]
	Cri du Chat Syndrome	[198]
	Attention deficit hyperactivity disorder	[199]
	Catecholaminergic polymorphic ventricular tachycardia	[200]
	Noonan syndrome	[155]
	Pulmonary arterial hypertension	[201]
	β-thalassemia	[202]
Episomal vectors	Alzheimer's disease	[203, 204]
	Parkinson Disease	[205]
	Cystic fibrosis	[206]
	α-1 antitrypsin deficiency	[206]
	Sickle cell anemia	[207]
	Duchenne muscular dystrophy	[173]
	Young-onset Parkinson's disease	[208]
	Amyotrophic lateral sclerosis	[178]
	Multiple Sclerosis	[176]
	Immunoglobulin A nephropathy	[209]
	Maple syrup urine disease	[210]

other promising cell sources such as adult stem cells; not discussed in this review due to their isolation in an invasive manner) to generate mouse and human iPSCs efficiently. The origin of cell type dictates the path to pluripotency and involves crucial events such as loss of somatic cell identity, MET (in cell types which are of non-epithelial origin), the degree to which they undergo developmental reversion, and reactivation of the pluripotency network [62]. It is very likely that other promising cell sources are still unexplored and may have a high reprogramming potential, which is still unknown due to limited knowledge on good biomarkers. For example, late-outgrowth endothelial progenitor cells ($CD34^+$ cells) derived from blood showed a 10-fold increase in reprogramming efficiency (0.22%; 10-fold more efficiently than human fibroblasts) and faster kinetics (10 days vs. 15 days for human fibroblasts) when used as a starting cell source [214].

It is also crucial that iPSCs formed have minimal or are ideally devoid of any crucial genetic mutations and chromosomal aberrations in them. Also, the epigenetic memory, which is a characteristic of the somatic cell source of origin, is required to be erased in iPSCs to avoid any impact on their differentiation potential. One of the inherent properties of iPSCs is their indefinite self-renewal and their capability to form teratoma. The presence of undifferentiated residual iPSCs during differentiation may lead to tumor formation and hence pose a serious challenge in its clinical applications. However, this can be circumvented by sorting pure populations of differentiated cells or removal of pluripotent stem cells using different strategies before transplantation [53, 215–221]. Another aspect of improving the safety of iPSCs is using integration-free reprogramming strategies instead of the commonly used integration-based approaches [7, 8, 11, 212, 213, 222]. In addition, one of the major requirements is to establish a GMP-compliant system for the derivation of clinical-grade iPSCs. To accomplish this, a fast, robust, and simple iPSC generation strategy from an ideal somatic cell source under feeder-free, serum-free, and xeno-free (ideally chemically defined culture conditions) conditions using an integration-free approach is highly desirable. Further extensive research to characterize and identify ideal somatic cell sources, which will yield genetically stable iPSCs with improved efficiency and kinetics, is crucial for biobanking and various biomedical applications. This will eventually translate this promising technology to generate patient-specific iPSCs for clinical applications.

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Declarations

Conflict of Interest The authors declare that they have no potential conflict of interest.

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