Application potential of induced pluripotent stem cells in the research and treatment of autoimmune diseases (Review)

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Abstract. Autoimmune diseases are a group of disorders caused by the immune system mistakenly attacking the body's own tissues, including type 1 diabetes, rheumatoid arthritis and multiple sclerosis (MS). These diseases are typically accompanied by chronic inflammation and tissue damage, which markedly impact the quality of life of patients. Induced pluripotent stem cells (iPSCs), owing to their unlimited proliferative capacity and pluripotency, demonstrate unique advantages in the field of regenerative medicine. iPSCs can be induced to differentiate into various functional cells *in vitro* providing potentially important tools for disease modeling, drug screening and cell therapy. For example, iPSCs can be directed to generate cardiomyocytes, dopaminergic neurons, hepatocyte-like cells and pancreatic β-cells, highlighting their broad potential for translational applications. For treating autoimmune diseases, iPSCs can be utilized for tissue repair, replacement therapy and the induction of cells with immunoregulatory functions. The present review summarizes the latest advancements in iPSC technology and its research in various autoimmune diseases, including MS, rheumatoid arthritis, systemic lupus erythematosus, type 1 diabetes and systemic sclerosis. The present study also discusses the main challenges in the application of iPSCs, aiming to provide a theoretical basis and practical guidance for developing novel therapeutic strategies.

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Contents

1. Introduction

Autoimmune diseases represent a specific category of disorders that are characterized by the overactivation of the immune system, particularly T cells and B cells, resulting in damage to the body's own tissues. These diseases are frequently associated with chronic inflammation and tissue damage, which markedly diminishes quality of life and presents substantial health challenges for affected individuals (1). To date, 153 autoimmune diseases have been identified globally, and their diversity, complexity and intricacies pose considerable challenges to medical practice (2). A previous epidemiological study conducted in the UK in 2000-2019 reported that 978,872 out of 22,009,375 individuals were newly diagnosed with at least one autoimmune disease, with a mean age of 54 years. These diagnoses were recorded in routine primary care clinical practice, indicating that individuals were identified either when consulting physicians for symptoms suggestive of autoimmune diseases or during healthcare encounters for other medical reasons, rather than through systematic screening. Furthermore, ~63.9% of these cases were female (3). Certain autoimmune diseases exhibit seasonal and regional variations, indicating that their prevalence is influenced by external factors, such as type 1 diabetes, which shows higher incidence in winter; multiple sclerosis (MS), which is more common in populations living at higher latitudes; and systemic lupus erythematosus, which displays marked regional differences in prevalence among different ethnic groups (4).

With ongoing advancements in induced pluripotent stem cell (iPSC) technology, there is an increasing focus on its potential applications (5). Recent advancements include the development of patient-derived iPSC lines for personalized disease modeling; the generation of three-dimensional organoids from iPSCs that recapitulate human tissue architecture;

and the establishment of clinically compatible, integration-free reprogramming methods. iPSCs exhibit notable potential across various fields, including in organoids and regenerative medicine, particularly for the treatment of autoimmune diseases (6). In previous years, extensive investigations aimed at generating specific cell types from pluripotent stem cells to replace damaged tissues have been conducted (7). Because pluripotent stem cells can proliferate indefinitely and differentiate into various cell types, such as cardiomyocytes, dopaminergic neurons, hepatocyte-like cells and pancreatic β-cells, underscoring their extensive potential for translational applications ,they are considered to be ideal candidates for the research and treatment of autoimmune diseases.

At present, the first-line treatment of autoimmune diseases primarily involves non-steroidal anti-inflammatory drugs (NSAIDs) and immunosuppressants to alleviate symptoms. Emerging biological agent strategies, particularly exosome-based therapies, are under preclinical investigation for their immunomodulatory potential. Specifically, iPSC-differentiated mesenchymal-stem cell (iMSC)-derived exosomes have been shown to suppress inflammatory responses in autoimmune models, such as rheumatoid arthritis (RA) and lupus, through microRNA-mediated T-cell regulation (8,9). Notably, a previous review highlighted that exosomes derived from iMSCs demonstrate enhanced therapeutic properties in autoimmune preclinical animal models. These exosomes exhibit superior proliferative capacity and reduced immunogenicity compared with adult mesenchymal stem cell (MSC)-exosomes, enabling effective immunomodulation without triggering autoimmune rejection (9). However, these therapies typically exhibit limited efficacy and are associated with notable side effects, such as secondary immunodeficiency and resultant infections (10). Furthermore, the absence of effective *in vitro* models mimicking autoimmune diseases has further impeded research progress in this area.

By differentiating pluripotent stem cells into functional cells, such as pancreatic β-cells, neurons or immunoregulatory cells, there exists the potential that iPSCs can repair or replace tissues damaged by the immune system, thereby restoring the healthy physiological functions of tissue. In addition, utilizing iPSCs to develop disease research models may prove valuable for studying complex autoimmune conditions (11-13). However, utilizing pluripotent stem cells for the treatment of autoimmune diseases presents several challenges (14). Newly generated cells may also become targets of the immune system, meaning that strategies must be developed to safeguard these cells from immune-mediated destruction. Additionally, ensuring the safety and functionality of transplanted cells, -both in terms of maintaining the stability and viability of the induced cells and protecting patient health by minimizing potential adverse effects, such as immune rejection or tumorigenicity, coupled with their long-term survival and integration, constitutes a challenge that requires attention.

Previous reviews have outlined specific facets of iPSC applications in autoimmune diseases. A review conducted by Lee *et al* (15) first reported the generation of iPSCs by reprogramming mouse embryonic and adult fibroblast cultures with defined factors; however, this previous review did not address other important aspects, such as the broader potential of iPSCs to differentiate into multiple immune and tissue lineages, nor did it discuss the significance of preclinical studies validating these approaches. Another study by Hew *et al* (16) proposed three primary therapeutic pathways for autoimmune disease treatment using iPSCs: Immune reconstitution through cell replacement, *in vivo* immunomodulation and disease modeling. However, the study omitted concrete clinical translation strategies for iPSC applications in treating complex autoimmune conditions. Focusing on pathogenesis, Natsumoto *et al* (17) highlighted disease-specific iPSC models for polygenic autoimmune disorders but overlooked emerging technologies, such as organoids and immune-evasion tactics. A 2024 review advanced the field by synthesizing progress in various diseases, including organoid modeling and drug screening, notably for MS, inflammatory bowel disease and type 1 diabetes, but underemphasized clinical barriers (1). The present review comprehensively details recent methodological advancements and translational applications of iPSCs across major autoimmune diseases, including MS, RA, systemic lupus erythematosus (SLE), type 1 diabetes (T1D) and systemic sclerosis (SSc). The present review systematically elucidates how patient-derived iPSCs enable disease-specific modeling, facilitate high-throughput drug screening and underpin novel cell-based therapeutic strategies, including tissue regeneration and immunomodulation. Additionally, the present review methodically examines persistent translational challenges inherent to iPSC technology, such as teratoma risk, genomic instability, immunogenicity and functional maturation of differentiated cells. The present discussion provides a timely, clinically oriented framework for advancing iPSC-based approaches in autoimmune disease research and therapy development.

2. iPSCs

iPSCs are a distinct cell type that are characterized by their unlimited proliferative capacity and potential for differentiation into various cell types. In 2006, Takahashi and Yamanaka (18) successfully integrated four transcription factors, namely *Oct4, Sox2*, Kruppel-like factor 4 (*KLF4*) and *c-Myc*, collectively referred to as OSKM, into mouse embryonic and adult fibroblasts using retroviral vectors. This process effectively reprogrammed both mouse and human fibroblasts into iPSCs, thereby restoring their capacity for redifferentiation. Currently, iPSCs can be induced from adult somatic cells, which are readily obtainable from blood, urine and skin samples. However, the heterogeneity of iPSCs leads to marked variations in gene expression, differentiation potential and epigenetic status among cells derived from different somatic tissues within the same individual (3). *In vitro*, iPSCs can differentiate into various cell types encompassing endoderm, mesoderm and ectoderm lineages, such as cardiomyocytes (CMs), neurons, glial cells, pancreatic β-cells, epithelial cells and hepatocytes (Fig. 1) (19). Therefore, careful selection of iPSCs from different origins is essential for the specific desired applications of those iPSCs. For example, exfoliated renal epithelial cells, urothelial cells, smooth muscle cells and endothelial cells (ECs) can be isolated from the urine (20-23). After reprogramming, these cells possess the potential to differentiate into CMs (24), various types of functional neurons and glial cells (25).

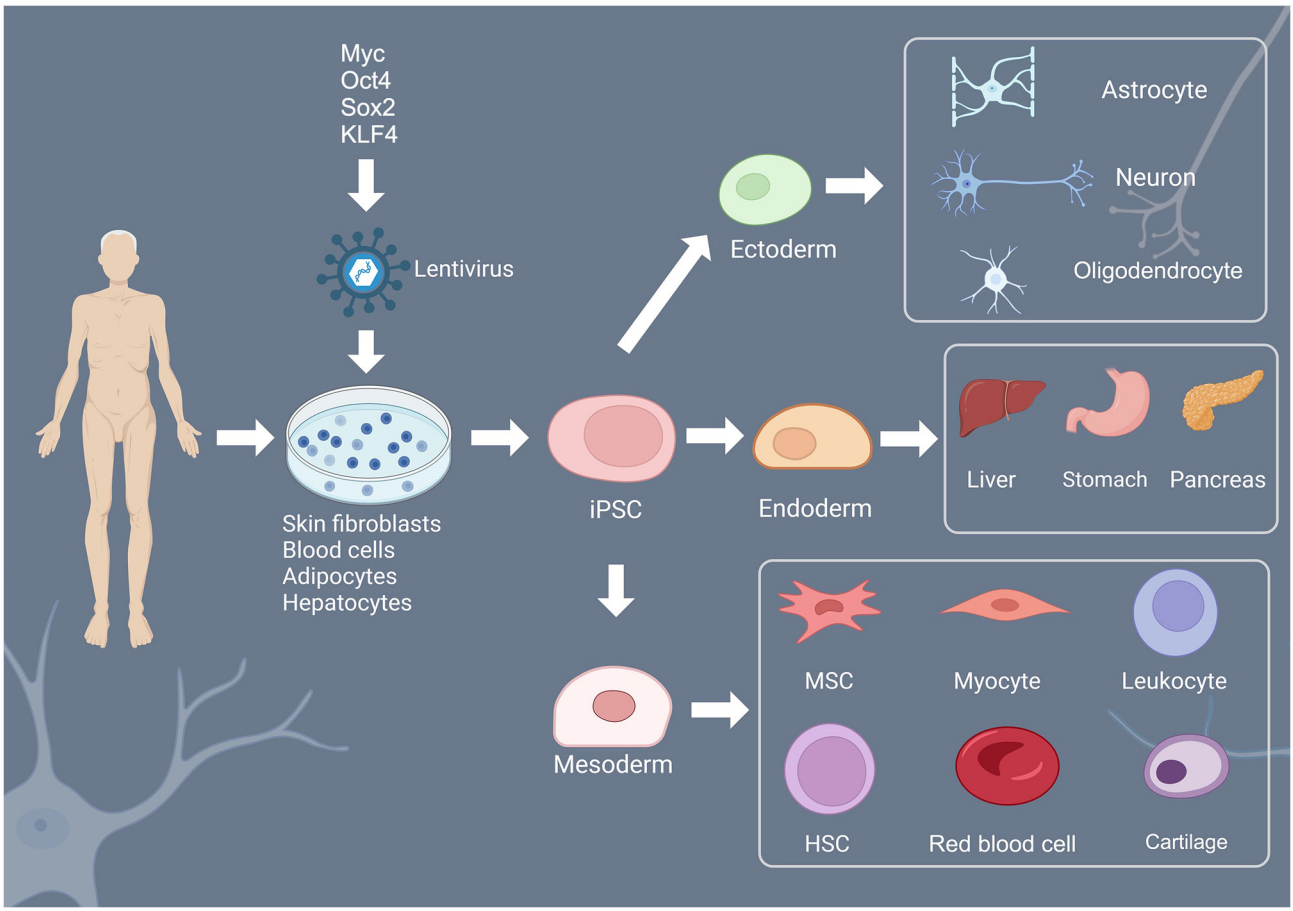

Figure 1. After obtaining patient cells, such as epidermal fibroblasts, blood cells and adipocytes from various sources (such as blood and urine), lentiviral vectors are used to retrovirally transduce the four transcription factors *Myc*, *Oct4*, *Sox2* and *KLF4* to induce iPSCs. These iPSCs can differentiate into various types of cells within the endoderm, mesoderm and ectoderm in response to specific transcription factors and compounds. Created in BioRender [Ye, Z. (2025) https://BioRender.com/3cj9ul9]. MSC, mesenchymal stem cell; HSC, hematopoietic stem cell; *KLF4*, Kruppel-like factor 4; iPSC, induced pluripotent stem cell.

Unlike iPSCs derived from different somatic tissues, the application potential of which may be influenced by their tissue of origin and differentiated cell fate, iPSCs derived from patient cells retain the genetic characteristics of the donor, facilitating the establishment of specific disease models in vitro. Patient-specific iPSCs can markedly advance disease modeling and drug discovery efforts. Patient-derived iPSCs have previously been utilized to create CM models for studying the mechanisms of heart diseases and screening new drugs (26). Furthermore, iPSCs have been used to model neurological diseases, thereby contributing to research on potential treatments for complex neurological conditions (27,28). In the context of hereditary heart diseases, iPSC technology provides novel model systems that can facilitate the understanding of the genetic basis of such conditions (29). iPSCs have also been utilized for efficient drug screening and gene correction studies in the context of liver diseases (30). These studies underscore the potential of iPSCs in personalized medicine and precision therapy, offering important tools for disease research and treatment. Information regarding iPSCs that have already entered, or are poised to enter, clinical stages is summarized in Table I and was collected from the International Clinical Trials Registry Platform of the World Health Organization (31).

Consequently, iPSCs hold notable importance for investigating autoimmune diseases, due to the limited availability of disease models and the complex mechanisms underlying these conditions. When cells from patients with autoimmune diseases are used to induce iPSCs, it becomes feasible to explore their causes and their associated intercellular mechanisms whilst conducting drug screening through *in vitro* modeling (32). Furthermore, following iPSC induction and differentiation, these cells can be transplanted into damaged areas to facilitate tissue repair or immunosuppressive therapy, potentially alleviating organ damage and persistent inflammatory responses caused by autoimmunity. Previous studies have shown that the transplantation of mouse iPSC-derived cells can elicit therapeutic effects in murine disease models. For example, in the mouse experimental autoimmune encephalomyelitis (EAE) model of MS ,transplanting mouse iPSC-derived neural precursor cells promoted LIF-mediated neuroprotection primarily through paracrine effects rather than direct neuronal replacement. In addition, in the mouse dextran sulfate sodium-induced colitis model of inflammatory bowel disease, transplanted mouse iPSC-derived intestinal epithelial-like cells enhanced intestinal barrier repair by restoring epithelial integrity and reducing inflammatory responses (33,34). These findings suggest that iPSCs also exhibit therapeutic potential for treating neurological autoimmune diseases.

Table I. iPSCs applied in clinical trials.

Trial ID	Public title	Study design	Phase	(Refs.)
ChiCTR2200062718	Treatment of SCN1A-related epilepsy with iPSC derived exosomes: a clinical exploratory study	Case-control study	Phase I	No peer-reviewed data published yet (study ongoing)
ChiCTR2400091107	Treatment of children epileptic encephalopathy with iPSC derived exosomes (GD-iExo-002): a clinical exploratory study	Parallel	Phase 0	No peer-reviewed data published yet (study ongoing)
JPRN-jRCT2091220385	Kyoto trial to evaluate the safety and efficacy of iPSC-derived dopaminergic progenitors in the treatment of Parkinson's disease	Single group	Phase III	(171)
JPRN-jRCTa032200189	Safety study of induced pluripotent stem cell-derived cardiac spheres transplantation	Single arm, active control, single group assignment	Phase 0	No peer-reviewed data published yet (study ongoing)
JPRN-jRCTa050190117	iPSC-derived platelet transfusion trial1	Single arm, historical control, single group assignment	Phase I	(172)
JPRN-jRCTa050200027	Safety study of allogenic hiPSC-retinas in retinitis pigmentosa	Single arm, single group assignment	Phase I	(173)
JPRN-UMIN000030084	Practical evaluation of PET studies with (18F)-GE180, (18F)-FDOPA and (18F)-FLT for a future clinical trial of iPSC-based cell therapy in Parkinson's disease	Single arm non-randomized	Phase I, II	No peer-reviewed data published yet (study ongoing)
JPRN-UMIN000033564	Kyoto trial to evaluate the safety and efficacy of iPSC-derived dopaminergic progenitors in the treatment of Parkinson's disease	Single arm non-randomized	Phase I, II	(171)
JPRN-UMIN000033565	Kyoto trial to evaluate the safety and efficacy of tacrolimus in the iPSC-based therapy for Parkinson's disease	Single arm non-randomized	Phase III	No peer-reviewed data published yet (study ongoing)
NCT04339764	Autologous transplantation of induced pluripotent stem cell-derived retinal pigment epithelium for geographic atrophy associated with age-related macular degeneration	Single group assignment, treatment	Phase I, II	No published data available yet (trial ongoing; first patient treated in 2022)
NCT04396899	Safety and efficacy of induced pluripotent stem cell-derived engineered human myocardium as biological ventricular assist tissue in terminal heart failure	Single group assignment, treatment	Phase I, II	(174)
NCT04744532	iPSC-based drug repurposing for ALS medicine (iDReAM) study	Single group assignment, randomized, treatment	Phase I, II	(175)
NCT04982081	Treating congestive HF with hiPSC-CMs through endocardial injection	Parallel assignment, randomized, treatment, double blind	Phase I	No peer-reviewed clinical results available yet
NCT05445063	Safety and efficacy of autologous transplantation of iPSC-RPE in the treatment of macular degeneration	Single group assignment, treatment	Phase I	No peer-reviewed data published yet (trial recruiting)

Table I. Continued.

Trial ID	Public title	Study design	Phase	(Refs.)
NCT05566600	Allogeneic iPSC-derived cardiomyocyte therapy in patients with worsening ischemic heart failure	Parallel assignment, randomized, treatment	Early phase I	No peer-reviewed data published yet (trial recruiting)
NCT05643638	A study of CYP-001 in combination with corticosteroids in adults with high-risk aGvHD	Parallel assignment, randomized, treatment, quadruple blind	Phase II	No peer-reviewed data published yet (trial recruiting)
NCT05647213	Autologous induced pluripotent stem cells of cardiac lineage for congenital heart disease	Parallel assignment, non-randomized, treatment	Phase I	No peer-reviewed data published yet (trial recruiting)
NCT05886205	Induced pluripotent stem cell derived exosomes nasal drops for the treatment of refractory focal epilepsy	Single group assignment, treatment	Early phase I	No peer-reviewed data published yet (trial recruiting)
NCT06027853	Natural killer (NK) cell therapy targeting CLL1 in acute myeloid leukemia	Single group assignment, treatment	Phase I	No peer-reviewed data published to date (trial recruiting)
NCT06367673	Natural killer (NK) cell therapy targeting CLL1 or CD33 in acute myeloid leukemia	Single group assignment, treatment	Phase I	No peer-reviewed data published to date (trial recruiting)
NCT06422208	Autologous iPSC-derived dopamine neuron transplantation for Parkinson's disease	Single group assignment, treatment	Phase I	No peer-reviewed data published to date (trial recruiting)

iPSC, induced pluripotent stem cell; CM, cardiomyocyte; hIPSC, human iPSC; SCN1A, sodium voltage-gated channel α subunit 1; PET, positron emission tomography; ALS, amyotrophic lateral sclerosis; FDOPA, 6-(18F)fluoro-L-dopa; FLT, 3'-deoxy-3'-(18F)fluorothymidine; HF, heart failure; RPE, retinal pigment epithelium; CYP, cytochrome P450; aGvHD, acute graft-versus-host disease; CLL1, C-type lectin-like molecule-1.

Furthermore, iPSC-induced regulatory T cells (Tregs) and regulatory dendritic cells (DCs) have been previously suggested as therapeutic strategies for autoimmune diseases (15). A study performed by Haque *et al* (35) detailed applying iPSCs to generate antigen-specific Tregs (Ag-Tregs) for the treatment of arthritis resulting from autoimmunity. The Ag-Tregs induced using this method were found to exhibit robust immunosuppressive activity, effectively ameliorating the progression of autoimmune characteristics in the induced arthritis models, including inflammation, joint destruction, cartilage prostaglandin depletion, osteoclast activity and Th17 production (35).

3. Limitations of iPSCs

Although iPSCs possess potential in regenerative medicine and clinical applications, their extended use is constrained by several limitations, primarily those associated with induction efficiency, cell purification and the stability of *in vitro* expansion. The induction process of iPSCs typically relies upon lentiviral transcription factors, which are influenced by numerous variables, such as cell number, cell state and viral infection efficiency (36). The classic induction method employs the aforementioned OSKM transcription factors along with their variations, such as replacing *KLF4* and *c-Myc* with *Lin28* and *NANOG* (18,37). Although these transcription factors can effectively promote cell reprogramming, they can also result in the development of oncogenic characteristics. *c-Myc* has been recognized as an oncogene that is associated with various types of cancer, including Burkitt's lymphoma, breast cancer, lung cancer and colorectal cancer, by facilitating cell proliferation whilst inhibiting differentiation during iPSC induction (38). Consequently, there have been concerns that the reactivation of c-Myc in iPSCs may lead to malignant transformation (39,40). This has prompted the exploration of low-oncogenic alternatives, such as replacing *c-Myc* with *L-Myc*, particularly in the context of non-integrating reprogramming approaches. For example, Sendai virus (a non-integrating RNA virus derived from murine respirovirus) or episomal vectors can be used, where the use of *L-Myc* instead of *c-Myc* reduces tumorigenic

risk while maintaining efficient induction (41). Furthermore, *KLF4* is known to promote cancer stemness in colon cancer cell lines (42), while *Oct4* can reinforce cancer cell stemness (43). Therefore, subsequent iPSC induction processes have instead focused on non-integrative methods, such as the use of Sendai virus and adenovirus, which has partially addressed induction efficiency issues (44-48). Plasmid systems have also been tested for use in reprogramming iPSCs, such as by utilizing the Epstein-Barr virus (EBV) nuclear antigen 1 (EBNA1) gene as a tool to maintain the stable presence of plasmids within cells (49,50). However, EBNA1 has been shown to induce malignant transformation through various mechanisms, including molecular mimicry-induced autoreactive cytotoxicity and chronic inflammation-mediated genomic instability, leading to tumor formation (51,52). In addition, Owen *et al* (53) indicated that EBNA1 is associated with the increased expression of endogenous polymerase III products induced by EBV. The purification process of iPSCs also poses a notable challenge. Incomplete induction may result in teratoma formation (54), especially when cells are implanted *in vivo*, since these implanted cells may contain incompletely reprogrammed cells. Consequently, directed differentiation *in vitro* and purification strategies for iPSCs are garnering attention, including methods such as antibody selection, to enhance the purity of iPSCs and ensure their safety (55-57).

During *in vitro* expansion, iPSCs can encounter stability issues. Common phenomena, such as chromosomal abnormalities, copy number variations and single-nucleotide mutations, all present notable challenges obstructing the clinical application of iPSCs. Previous studies have indicated that iPSCs generated *in vitro* may accumulate mutations in tumor suppressor genes, such as *TP53* (58-61), further challenging their feasibility as therapeutic tools.

Despite the aforementioned limitations, iPSCs continue to hold promising potential in the field of cell therapy.

4. iPSCs and autoimmune diseases

Autoimmune diseases are characterized by immune dysregulation, leading to the abnormal activation of self-reactive immune cells and subsequent tissue damage. Immune tolerance is established through central and peripheral mechanisms under physiological conditions. T cells undergo negative selection in the thymus to establish central immune tolerance. For self-reactive T cells that escape central tolerance, peripheral tolerance mechanisms ensure self-tolerance through clonal deletion, immune anergy and Tregs (62-64).

Autoimmune diseases arise when self-tolerance fails for various reasons, with T cells serving a notable role. Several potential causes of autoimmune diseases have been identified. The first category is genetic factors, for which multiple studies have demonstrated that mutations in a number of genes, such as *HLA*, *PTPN22*, *CTLA-4*, *STAT4* and *IL2RA*, are closely associated with certain autoimmune diseases, including SLE and T1D (65-69). The second category is environmental factors, where certain external infectious agents may continuously stimulate and excessively activate the immune system. After EBVs infect a host, various factors can continuously stimulate the host's immune response, increasing the risk of autoimmune diseases. These factors include latent reactivation, antigen similarity to the host, B-cell infection and expression of viral IL-10 homolog, which is highly homologous to human IL-10 (70-72). Additionally, autoimmune responses may be influenced by other factors, such as abnormal immune regulation and aberrant cell death (73,74).

With ongoing research into iPSCs and the resulting development of iPSC-derived therapeutic strategies, studying autoimmune diseases has become increasingly feasible and insightful. Relevant cell types from patient-derived iPSCs, such as immune cells (T cells, macrophages) and tissue-specific stromal or parenchymal cells ,can now be readily derived, allowing for a realistic simulation of the inflammatory responses occurring within the patient. Through multi-omics analysis and studies of molecular interactions, pathogenic mechanisms and therapeutic targets can also be explored with reduced difficulty. Additionally, patient-derived iPSCs can serve as *in vitro* models for targeted drug screening, further contributing to clinical applications (Fig. 2). Given the potential of patient-derived iPSCs for tissue replacement and the various immune cell types into which they can differentiate, they offer a unique opportunity for individualized therapies. For example, autologous patient-derived iPSCs may reduce the risk of immune rejection in transplantation while also providing a renewable source of disease-relevant immune cells for modeling and therapeutic testing, thereby creating considerable opportunity to exploit their use for the treatment of autoimmune diseases (75).

MS and iPSCs. MS is a neurodegenerative disease characterized by autoimmune reactions. It is caused by lymphocyte infiltration into the central nervous system (CNS), resulting in inflammation and axonal damage, typified by extensive primary demyelination, axonal transection, progressive neurodegeneration and disruption of the blood-brain barrier (BBB), ultimately causing permanent neurological damage (76-83). The pathological hallmark of MS is focal demyelination, accompanied by varying degrees of gliosis and inflammation. A 2024 meta-analysis of Chinese populations revealed a substantially lower prevalence of MS in China compared with reports from Western populations (4.08/100,000; 95% CI 3.95-4.21), with women consistently affected twice as frequently as men. In this previous meta-analysis, eight autoimmune conditions were evaluated in parallel, and MS was reported to exhibit the third-lowest prevalence among them (84).

MS can be classified based on disease progression into the following two types: Relapsing-remitting MS (RRMS) and primary progressive MS (PPMS) (85). RRMS is characterized by remission periods during which symptoms may completely disappear, making it relatively simpler to treat. Common treatments include immunomodulators and immunosuppressants, such as IFN-β, glatiramer acetate and dimethyl fumarate, which can reduce relapse frequency and slow disease progression (86). However, due to its continuous progression in contrast to RRMS, PPMS has fewer treatment options and a reduced number of drugs approved for treatment, such as ocrelizumab (87).

The etiology of MS is complex. Epidemiological studies have reported that the onset of MS is influenced by genetic factors, most notably the HLA-DRB1*15:01 allele, which confers a markedly increased risk, as well as non-HLA

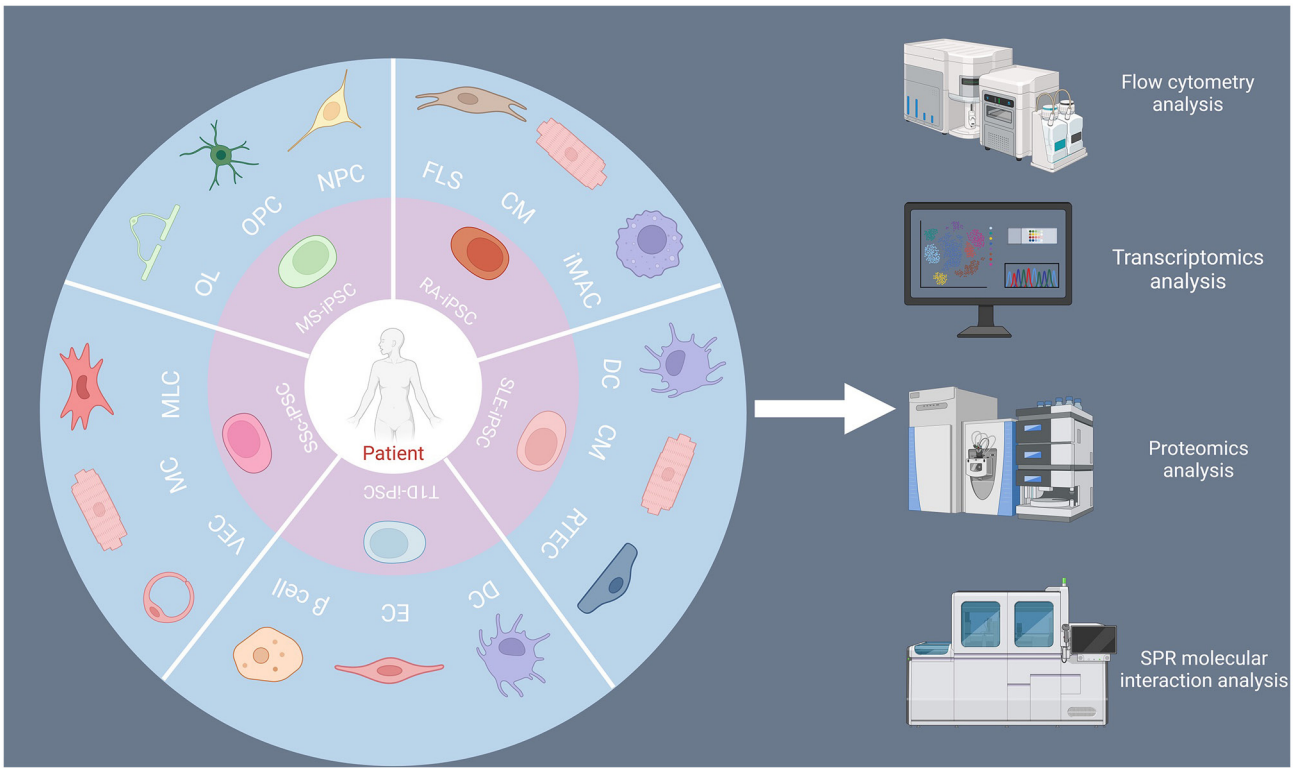

Figure 2. After inducing iPSCs from cells obtained from various sources in the patient, these derived cells are analyzed to research corresponding diseases. Flow cytometry is used to detect cell types and differences compared with normal cells. Transcriptomics and proteomics are used to analyze gene differences between patient-derived iPSCs and normal cells, aiming to identify potential pathogenic sites. Techniques such as SPR are then used to analyze interactions, to find therapeutic targets and evaluate potential drug efficacy. Created in BioRender [Ye, Z. (2025) https://BioRender.com/ulu9prm]. iPSC, induced pluripotent stem cell; MS, multiple sclerosis; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus; T1D, type 1 diabetes; SSc, systemic sclerosis; OL oligodendrocyte; OPC, oligodendrocyte progenitor cell; NPC, neural precursor cell; FLS, fibroblast-like synoviocyte; CM, cardiomyocyte; iMAC, macrophages derived from patients' iPSCs; DC, dendritic cell; RTEC, renal tubular epithelial cell; EC, endothelial cell; VEC, vascular endothelial cell; MLC, MSC-like cell; MC, mast cell; SPR, surface plasmon resonance.

variants, such as IL2RA and IL7R, which are also implicated in disease susceptibility (88,89). Furthermore, accumulating evidence suggests that inflammatory responses induced by the immune system are key factors in triggering MS. A previous study has demonstrated that the occurrence and progression of MS are associated with proinflammatory $CD4^+$ T-cell subsets, particularly Th1 and Th17 cells. These cells secrete proinflammatory cytokines, including IFN-γ, TNF-α and IL-17, which are important for the development of MS (82). In studies using the EAE mouse model for MS (90), it has been shown that mice deficient in IL-17 or its receptors, as well as those with IL-17-specific inhibition, exhibit effective alleviation of EAE symptoms. These findings indicate that Th17 cells serve a central role in the proinflammatory response within the EAE model (91,92). Another study previously suggested that patients with MS may only experience inflammatory responses after degenerative events due to the resulting defects in oligodendrocytes (OLs) and myelin (93). This suggests that the health of myelin and OLs may be key factors in determining the occurrence and severity of inflammatory responses during the development of MS. Further in-depth research into the etiology and mechanisms of MS is required for developing effective treatments.

The use of patient-derived iPSCs in MS research is of notable importance. This technology enables the reprogramming of somatic cells from patients with MS to generate iPSCs, thereby preserving the genetic background of the patient and allowing for a personalized exploration of disease characteristics. Fagiani *et al* (94) outlined the design of a method to accelerate the differentiation of iPSCs into OLs using a single transcription factor, Sox10, to establish organoid models. In these organoids, exposure to cerebrospinal fluid (CSF) from patients with MS resulted in a ~50% reduction in the number of OLs by day 6. This suggests that CSF may contain soluble mediators promoting OL death, demonstrating the value of using patient-derived iPSCs to establish organoids in MS research. In addition, Nishihara *et al* (95) described differentiating human iPSCs derived from patients with MS into brain microvascular endothelial cell (BMEC)-like cells using the defined medium method and the expanded EC culture method to model the BBB. It was found that BMEC-like cells from patients with MS exhibited impaired efflux pump activity and the upregulated expression of adhesion molecules under inflammatory conditions. Enhancing the Wnt/β-catenin signaling pathway could effectively improve the barrier function of BMECs, reducing the inflammatory phenotype and providing potential targets for BBB treatment (95). In another study by Mutukula *et al* (96), aging levels were assessed using neural progenitor cells (NPCs) derived from iPSCs obtained from patients with RRMS and PPMS. It was found that the activity of β-galactosidase and the expression levels of aging marker genes, including *p16*, *IL6*, *ATF3* and *GADD25B*, were

notably elevated in these iPSC-derived NPCs. Furthermore, aging cells could exacerbate local inflammatory responses by secreting senescence-associated secretory phenotype factors, leading to neuronal cell death and myelin loss, which in turn may affect nerve regeneration and repair capacity. These findings may be associated with the progression of MS and suggest potential therapeutic targets. In a study by Tiane *et al* (97), transcriptomic analysis of healthy and MS cells revealed that OL precursor cells (OPCs) in chronic MS lesions exhibited high levels of DNA methylation on myelin-related genes. This methylation status was notably negatively associated with the differentiation capacity of OPCs. Subsequently, CRISPR-Cas9 technology was used for epigenetic editing, utilizing iPSC-derived OPCs as a research model. Using the CRISPR-dCas9-DNA methyltransferase 3a/TET1 system, methylation and demethylation operations were conducted. These results revealed that increased methylation levels of the myelin basic protein gene may be closely associated with impaired myelin regeneration (97). These studies also demonstrated the notable research potential of MS disease models constructed from iPSCs.

In studies examining the use of iPSC-derived cells for cell therapy in MS, it has previously been reported that the differentiation capacity of OPCs is hindered during the progression of the disease, leading to impaired myelin regeneration. However, the implantation of iPSC-derived OPCs or NPCs may effectively promote functional myelin regeneration. In particular, two transcription factors, Sox10 and OL transcription factor 2, have been utilized to efficiently induce the differentiation of iPSCs into OPCs (98). When co-cultured with rat cortical neurons, OPCs can mature and differentiate into OLs, thereby facilitating axon wrapping (99). In other studies, induced OPCs were transplanted into a hypomyelinated mutant mouse model that lacks functional myelin basic protein, and thus exhibits severe neurological dysfunction. The results confirmed that OPCs exhibit myelin-wrapping effects, demonstrating their therapeutic potential (100,101).

Exogenous NPCs can also exert protective effects on endogenous neural cells by releasing cytokines or neurotrophic factors, thereby promoting myelin regeneration (102,103). Yazdi *et al* (104) implanted iPSC-derived NPCs into mouse models of chronic demyelination induced by cuprizone treatment and the mice were treated repeatedly with fingolimod. It was found that fingolimod not only exerted anti-inflammatory effects but also enhanced the differentiation of NPCs into OL lineages, thereby promoting myelin repair. These findings not only suggested that iPSC-derived NPCs can be used to treat demyelination in MS but also indicated that concurrent drug intervention is feasible (104). Additionally, in a previous study on MS, human fetal-derived glial precursor cells (hGPCs) were transplanted directly into the brains of mice, resulting in the discovery that hGPCs can effectively migrate and differentiate into myelin-forming OLs, achieving remyelination in the adult CNS (105). This suggests that iPSCs can also be differentiated to obtain GPCs for therapeutic purposes, pointing to novel directions for the application of iPSCs in treating MS through differentiation into specific cell types.

The aforementioned findings suggest that the iPSC model can not only be used to aid in understanding the genetic diversity and heterogeneity of MS, but can also serve as a tool for disease modeling and high-throughput drug screening, thereby advancing the development of novel therapies. In the future, further research using iPSC-derived organoids may continue to advance MS-related therapeutic developments.

RA and iPSCs. RA is a chronic, inflammatory, persistent and systemic autoimmune disease. An epidemiological survey analyzed the incidence of RA across 195 countries and regions globally in 1990-2017. In 2017, the age-standardized point prevalence and annual incidence rates of RA were 246.6 [95% uncertainty interval (UI), 222.4-270.8] and 14.9 (95% UI, 13.3-16.4), respectively, representing increases of 7.4% (95% UI, 5.3-9.4) and 8.2% (95% UI, 5.9-10.5) compared with 1990. The prevalence is generally higher in women compared with that in men (106). Additionally, national data from South Korea reaffirmed female predominance in RA epidemiology (107). Another systematic analysis of global epidemiological trends supported the finding that RA prevalence remains notably higher in women than in men, with this pattern persisting in studies covering data up to 2024 (108). However, with advancements in medical care, including the introduction of disease-modifying antirheumatic drugs (DMARDs) and biological therapies over the past two decades, the mortality rate of RA has decreased between 2000 and 2020 (109). The disease characteristics of RA include bone destruction, synovial inflammation and pannus formation, leading to irreversible tissue damage affecting tendons, cartilage and bones (110). On a cellular level, RA is caused by interactions between cytokines and various cell types, including osteoclasts, fibroblast-like synoviocytes (FLSs), T cells, B cells and natural killer cells.

DCs can induce the activation of T cells, B cells and FLSs. In particular, mature DCs (mDCs) can secrete cytokines that induce the activation and differentiation of T and B cells, increasing the number of inflammatory cells in joint areas to exacerbate inflammation (111). Additionally, inflammatory factors secreted by mDCs cause FLSs to release matrix metalloproteinases, which degrade joint cartilage and bone tissues. During this process, FLSs can release the receptor activator of NF-κB ligand to promote the formation, survival and activation of osteoclasts, which increases bone resorption and leads to an imbalance between osteoblast and osteoclast activity, accelerating joint damage (112). Clinical treatments for RA include NSAIDs, DMARDs and corticosteroids to alleviate RA symptoms. In cases where medication is insufficient, surgical options, such as joint fusion, tissue removal and total joint replacement, are used to treat RA (113).

At present, iPSCs in RA research are primarily used for model construction and limited cell therapy testing. In terms of the former, a number of studies have successfully established models to study RA. Lee *et al* (15), introduced a 4-in-1 lentiviral vector containing *Oct4, Sox2, Klf4* and *c-Myc* into FLSs isolated from two patients with RA and two with osteoarthritis (OA), reprogramming them into iPSCs for model construction and regenerative therapy exploration. The OSKM transcription factors have also been used for the purposes of iPSC model construction aiming to conduct drug and metabolic analyses in the context of RA (114,115). Additionally, studies have used functional CMs derived from iPSCs from patients with RA to investigate the mechanisms

of cardiovascular complications caused by RA. By analyzing the calcium-handling properties of these CMs, it has been shown that RA-iPSC-CMs exhibit notably lower amplitudes and durations of calcium transients compared with those in healthy control CMs. The contractility of RA-iPSC-CMs has also been reported to be markedly reduced, as reflected by the decreased peak tangential stress and maximum contraction rates. Consequently, it was proposed that defects in calcium handling and contraction function exist in CMs from patients with RA, which are associated with the adverse effects caused by RA (116). Furthermore, another previous study performed metabolic analyzes on patient-derived iPSCs and discovered that the expression level of nicotinamide (NAM) in RA-iPSCs was markedly higher compared with that in OA-iPSCs. It was therefore suggested that NAM may serve as an important factor for the rapid proliferation of RA-iPSCs. Upon treatment with tannic acid (TA), the expression of NAM in RA-iPSCs was notably inhibited, resulting in a marked decrease in their proliferative capacity. Therefore, the inhibitory effect of TA may influence cellular energy metabolism and proliferative capacity by reducing NAM levels, providing novel insights for the treatment of RA (117). In addition to serving as models of research, iPSC-derived cells can influence immune responses through various mechanisms, including the secretion of immunomodulatory factors, and the regulation of immune cell differentiation and function. Collins *et al* (118) used agarose hydrogels made from 3D-printed molds to encapsulate iPSCs. These iPSCs, following genetic engineering, expressed IL-1 receptor antagonist in response to inflammatory signals through a feedback mechanism driven by the C-C motif ligand 2 promoter. The hydrogel constructs were then implanted into mice for treatment. The results indicated that this method of implantation could achieve therapeutic effects in the K/BxN mouse model, a transgenic model of autoimmune arthritis via pathogenic autoantibodies against glucose-6-phosphate isomerase (51).

Furthermore, studies have also focused on utilizing iPSC-derived chondrocytes for transplantation and repair of joint damage in RA. Eremeev *et al* (119) previously evaluated iPSC-derived chondrocytes cultured *in vitro*, and found that they exhibited viable proliferation and differentiation capabilities, synthesizing abundant cartilage matrix components, such as type II collagen and proteoglycans. Additionally, Nakamura *et al* (120) combined bioprinting technology with iPSCs, utilizing Kenzan needle array technology to generate scaffolds for cartilage tissue engineering. These scaffolds demonstrated suitable mechanical properties, such as tensile strength and elasticity comparable to native cartilage, and biocompatibility, including low cytotoxicity and support for cell adhesion and proliferation, potentially serving as a therapeutic alternative for current treatments of joint damage.

Therefore, iPSCs present unique potential as a therapeutic strategy for treating RA, not only by modulating inflammation through differentiated cells but also by achieving therapeutic effects through tissue replacement.

SLE and iPSCs. SLE is a chronic, heterogeneous autoimmune disease characterized by complex and diverse immune dysregulation. According to a 2021 study on the global epidemiology of SLE, the incidence rate ranges from 1.5-11 cases per 100,000 per year, whereas the prevalence varies from 13-771.3 cases per 100,000 per year. The study noted that improvements in care quality , including earlier diagnosis, standardized treatment protocols, use of immunosuppressive and biological therapies, and comprehensive disease management strategies, have led to a decrease in the mortality rate of SLE in previous years (121). The mortality rate of SLE has continued to decline since 2021, primarily driven by increased use of targeted therapies such as JAK inhibitors and anti-B lymphocyte stimulator biologics (these target B lymphocyte stimulator, and include belimumab), which reduce organ damage and secondary infections (122). SLE affects multiple organs and systems, including the musculoskeletal system, skin and mucous membranes, heart and lungs, hematological system, nervous system, joints and kidneys (123). The disease is triggered by the erroneous response of the immune system to self-antigens, such as nucleic acids and histones. During this process, abnormalities in cell death and debris clearance can activate pathways, such as cyclic GMP-AMP synthase, leading to the release of type I IFNs. These IFNs, through antigen-presenting cells, activate T cells, causing them to lose self-tolerance and subsequently activate B cells, resulting in the production of excessive autoantibodies and the formation of immune complexes to trigger severe immune responses (124-127). In this context, the disruption of immune regulatory mechanisms leads to the expression of clinical symptoms of SLE, such as multi-organ damage and chronic inflammation, with vasculitis potentially causing ischemic damage to vital organs. Additionally, infections and cardiovascular disease are the leading causes of mortality in patients with SLE. The etiology of SLE however is complex, involving a variety of environmental factors, epigenetic factors and polygenic inheritance, making it challenging to predict clinically (64). Traditional therapies for SLE typically involve NSAIDs or antimalarials to alleviate mild SLE symptoms (127). Additionally, glucocorticoids and cytotoxic or immunosuppressive agents can be used to treat cellular involvement caused by SLE. In severe cases, interventions targeting vasculitis may require surgical procedures, such as vascular reconstruction, bypass grafting and digital sympathectomy, to improve blood flow in affected areas (128). Targeted immunotherapies have also been developed, such as the anti-B-cell activating factor antibody belimumab, which can serve as an adjunct therapy when conventional treatments are ineffective (129).

iPSC technology offers a novel perspective for SLE research. Various studies have successfully induced iPSCs from patients with SLE, which are used to derive DCs, renal tubular cells, renal tubular epithelial cells and CMs for understanding the pathogenesis of SLE (130-132). These cell types can serve as models to study the cellular changes that may reveal the underlying causes of SLE (131-133). Park *et al* (130) used Sendai virus vectors to transduce Yamanaka factors to generate two- and three-dimensional CM models from patient-derived iPSCs. The results indicated that SLE-derived CMs exhibited decreased proliferation, increased expression of fibrosis markers, such as collagen type II, and elevated levels of hypertrophy markers, including B-type natriuretic peptide. These findings suggest that the impact of SLE on the heart may exacerbate the risk of cardiovascular complications by inducing pathological changes in CMs. This provides insights

into model construction in the context of SLE-related heart disease (130).

In addition to using iPSC-derived cells directly as research models, Tang *et al* (134) has integrated multi-omics expression data from iPSCs to identify numerous differentially-expressed mRNAs, microRNAs and proteins to explore the pathogenesis and biomarkers of SLE (134). Guillet *et al* (135) conducted functional analyses using macrophages derived from human iPSCs and discovered that macrophages carrying variants of the non-receptor tyrosine kinases activated CDC42 kinase 1 (ACK1) and protein tyrosine kinase 6 (BRK) exhibited reduced phagocytic ability towards apoptotic cells and decreased regulation of proinflammatory cytokines, such as TNF and IL-1β. Combined with the observation of increased IgG deposition in the renal tubules of patients, this previous study (128) concluded that defects in ACK1 and BRK may be closely associated with the pathological characteristics of SLE.

In another study by Natsumoto *et al* (136), genetic analyses were conducted using type I IFN-secreting DCs derived from SLE-iPSCs. It was found that variations in 2'-5'-oligoadenylate synthetase-like (*OASL*) resulted in higher levels of type I IFN secretion by DCs. To further contextualize these findings, data from the ImmuNexUT database, an independent large-scale Japanese cohort of immune-mediated diseases, demonstrated that rare variations in *OASL* are present in ~6.84% of patients with SLE (137). Therefore, rare variations in the *OASL* gene may serve an important role in the pathogenesis of SLE (136). De Angelis *et al* (138) analyzed differential gene expression using iPSCs from patients with SLE with CNS involvement, before discovering notable dysregulation of multiple microRNAs. Specifically, 91 genes were uniquely expressed in CNS-SLE-derived human iPSCs (hiPSCs) compared with healthy controls, while 413 genes were expressed exclusively in CNS-SLE-derived hiPSCs compared with both healthy controls and non-CNS-SLE hiPSCs, with 67 genes confirmed to be specific to CNS-SLE. The same study subsequently confirmed the involvement of the ERK and AKT signaling pathways in the pathogenesis of SLE. Following validation with inhibitors (PD0325901 and LY294002), the participation of both pathways in cell apoptosis and immune responses was confirmed. Additionally, potential biomarkers were identified, including coiled-coil-helix-coiled-coil-helix domain containing 2, indoleamine 2,3-dioxygenase 1, S100A10, ephrin type-A receptor 4 and left-right determination factor 1, which show notable expression changes in hiPSCs derived from patients with CNS-SLE, providing a reference for future diagnosis (138).

Currently, progress in iPSC-based cell therapies for SLE remains slow, since the majority of attention is focused on using MSCs for treatment. However, whether assessing the potential of iPSCs or their ability to differentiate into MSCs, iPSCs possess the capacity for the treatment of SLE, although further research is required (1).

T1D and iPSCs. T1D is an autoimmune disease characterized by the destruction of pancreatic β-cells by autoreactive $CD8^+$ T cells, leading to insulin deficiency and persistent hyperglycemia (139). Due to the lack of insulin in the body, patients with T1D must rely on insulin injections to maintain relatively stable blood glucose levels. However, the dosage of insulin needs to be adjusted according to food intake and glucose consumption, which poses a clinical risk of hypoglycemia from insulin injections (140). Despite this, insulin remains the primary treatment for T1D. The initial symptoms of T1D are generally not immediately apparent, and by the time patients become aware of their condition, they may already be experiencing various complications associated with diabetes (141).

Epidemiological data reported in 2021 (based on data collected and analyzed in that year) indicated that ~8.4 million individuals worldwide are afflicted with T1D, including 1.5 million aged <20 years, 5.4 million between the ages of 20 and 59 years, and 1.6 million aged ≥60 years. In 2021 alone, there were 500,000 new cases of T1D, of which ~35,000 patients died within 1 year without being diagnosed. In addition, 20% of patients with T1D live in low- and lower-middle-income countries, with ~3.7 million undiagnosed cases globally in 2021 (142). These figures highlight the widespread impact of T1D and underscore the need for effective treatments.

The treatment of diabetes dates back to 1967, when Paul Lacy pioneered islet transplantation in mice, demonstrating the therapeutic potential of cell therapy for diabetes (143). A clinical trial in 2016 also achieved the treatment of T1D through human islet transplantation (144). Several studies have previously used porcine islets as donor sources for T1D treatment in mouse and monkey models, showing promising results; however, using pigs as donors requires genetic modification to avoid rejection inflammatory responses in host models (145-147).

Currently, the use of iPSC-derived pancreatic β-cells for transplantation is emerging as a therapeutic option (148). By introducing various chemical inducers and inhibitors of the Wnt and Notch pathways (such as CHIR99021 to activate Wnt signaling and DAPT to inhibit Notch signaling), iPSC-derived monohormonal β-cells, which are insulin-positive cells, can be generated (149,150). However, directly transplanted β-cells are susceptible to autoimmune destruction (151); a previous study has shown that iPSC-derived β-cells are selectively killed by T cells due to their high secretion activity, which increases their vulnerability to endoplasmic reticulum stress (152). Armitage *et al* (32), constructed an *in vitro* platform by differentiating iPSCs into DCs, macrophages, ECs and pancreatic β-cells, cultured under controlled conditions, including defined media, cytokine supplementation and co-culture ratios, with or without the use of scaffolds to facilitate cell-cell interactions, allowing these key cell types to interact directly in a controlled environment for simulation studies. The establishment of this platform has laid the foundation for developing novel therapeutic strategies and providing guidance for model construction (32).

For further studies of transplantation models, Cai *et al* (153) revealed that knocking out the *RNLS* gene in pluripotent stem cell-derived β-cells enabled them to resist autoimmune destruction, thus identifying *RNLS* to be a modifier of β-cell vulnerability and a potential therapeutic target. Structural modeling then identified pargyline, a Food and Drug Administration-approved drug, to be a potential *RNLS* inhibitor suitable for combination therapy (153). Additionally, in a new subtype of T1D, fulminant T1D, using patient-derived iPSC-derived pancreatic β-cells, downregulation of cholesterol 25-hydroxylase in these β-cells was found to reduce viral

reactivity in patients with fulminant T1D and may accelerate β-cell destruction (154). Given the safety concerns regarding transplantation, the non-integrating Sendai virus was used in another previous study to induce pancreatic progenitor cells from T1D patient-derived iPSCs, thereby avoiding the potential hazards associated with lentiviral vectors. *In vivo* mouse transplantation was then conducted, resulting in the regeneration of structures resembling human islets from transforming growth factor-iPSC-derived pancreatic progenitor cells, showcasing their potential in regenerative medicine applications (155).

For transplantation therapy, encapsulating the transplanted cells is needed to partially protect the pancreatic β-cells from immune suppression. Haller *et al* (156) encapsulated hiPSC-derived pancreatic progenitor cells in hydrophilic polytetrafluoroethylene membranes, forming microcapsules that did not hinder differentiation into β-cells. The microcapsules were shown to function in a hyperglycemic mouse model and to achieve therapeutic remission after transplantation (156). Similarly, in a study by Kasputis *et al* (157), poly(lactic-co-glycolic acid) materials were used to create a microporous scaffold that could locally and continuously release exendin-4, thereby promoting the maturation of pancreatic progenitor cells *in vitro* and supporting the transplantation of islets into the omental fat to enhance the efficacy of stem cell-derived pancreatic progenitor cell implantation. The scaffold design was proposed to have the potential to support the maturation of pancreatic progenitor cells into monohormonal insulin-secreting β-cells at non-hepatic sites, demonstrating notable potential in the use of biomaterials to treat T1D (157).

In summary, the prospects for the application of iPSC technology in T1D treatment are promising. With continuous technological advancements and in-depth research into immune protection strategies, iPSC-derived pancreatic β-cells are expected to become effective treatment options for patients with T1D.

SSc and iPSCs. SSc is a rare autoimmune connective tissue disease characterized by occlusive microvascular lesions, immune dysregulation and systemic fibrosis. Clinically, SSc can manifest as isolated Raynaud's phenomenon (RP), finger swelling, ulcers, scleroderma renal crisis and pulmonary arterial hypertension. Fibrosis may occur in the skin and can be classified as limited cutaneous SSc (lcSSc), diffuse cutaneous SSc (dcSSc) or SSc sine scleroderma (ssSSc), depending on the specific manifestations (158,159).

A previous meta-analysis showed that the overall incidence of SSc is 1.1-1.9 cases per 100,000 person-years, whilst the overall prevalence is 15.1-20.5 cases per 100,000 person-years (160). Another previous survey indicated that the prevalence of SSc is higher in Europe, North America and South America, with older patients experiencing more severe visceral involvement and faster disease progression (161). Data collected by Lescoat *et al* (162) on SSc subtypes revealed that the survival rate of patients with ssSSc (92.4%) was markedly higher compared with that in patients with lcSSc (69.4%) and dcSSc (55.5%) (162).

In clinical practice, patients with SSc are typically treated with medications targeting their symptoms, including immunosuppressants, such as cyclophosphamide and corticosteroids, to suppress inflammation (163), nintedanib for antifibrotic treatment (164), and sildenafil and bosentan for vasodilation to reduce pulmonary hypertension and RP (165). There are also biological therapies for SSc, such as rituximab, which inhibits B cells and effectively improves skin fibrosis (166). However, these treatments mainly focus on symptom relief and disease course mitigation, and do not provide a complete cure.

With the development of iPSC technology, an increasing number of studies have attempted to explore iPSCs for SSc therapeutics. Gholami *et al* (167) studied ECs and CMs derived from patients with SSc, and revealed that the expression of vascular endothelial cadherin was notably decreased in these cell types compared with in iPSC-derived ECs and CMs from healthy individuals. This decrease may lead to impaired angiogenesis in SSc-ECs, which could be strongly associated with angiogenesis dysfunction observed in patients with SSc (167). These findings may serve a role in future vascular-related diagnoses and treatments for SSc.

Furthermore, Vijayaraj *et al* (168) used multiple cell types for iPSC induction and differentiation into mesenchymal-like cells, which are important for simulating fibrosis. Some of these mesenchymal-like cells were observed to possess epithelial cell markers, whilst others exhibited markers of fibrosis-initiating cell populations or contained immune cell markers, including typical macrophage characteristics. Based on these cell profiles, a fibroblast activation (iFA) model was constructed. After conducting chemical and functional gene screening using the iFA model, it was discovered that the JAK2 inhibitor CEP-3379 and STAT5b knockout could reverse the phenotype in the iFA model. Subsequent validation confirmed that the compound AA5 could completely prevent the progression of the fibrotic phenotype in the iFA model (161). Another study by Nathan *et al* (169) utilized iPSC-derived mesenchymal cells and cultured them on hydrogels simulating wound healing, forming a 'scar-like phenotype', or iSCAR model, to replicate the fibrotic process. Through RNA-sequencing transcriptomic analysis of the iSCAR model, it was found that early scar formation genes were primarily associated with hypoxia, vascular development and glycolysis, whilst late scar formation genes were associated with cellular senescence. After screening for antifibrotic drugs, EX00015097 was reported to exhibit notable antifibrotic effects in both the early and late stages of scar formation. Therefore, the effectiveness of the iSCAR model derived from iPSCs supports its proposed use as a tool for screening antifibrotic drugs, providing insights for therapeutic development (162). Similarly, in a study by Kim *et al* (170), iPSCs were generated from the peripheral blood mononuclear cells of patients with SSc, which were subsequently differentiated into skin-related cells, including fibroblasts and keratinocytes, to construct three-dimensional skin organoids for drug screening. The results showed that selective estrogen receptor modulators, such as the osteoporosis drugs raloxifene and bazedoxifene, markedly reduced the proliferation of SSc-derived fibroblasts and extracellular matrix production, thereby alleviating fibrosis (170).

Currently, iPSC technology serves a notable role in researching the pathological mechanisms underlying SSc. It can not only compensate for the shortage of research models due to the rarity of SSc cases, but it can also allow for the high-throughput screening of targeted drugs, providing a solid foundation for future alleviation or even a cure for SSc.

5. Conclusion

In summary, iPSCs display notable potential in the medical field, where they are expected to serve an important role in various research areas in the future. Despite persisting limitations, iPSCs hold promise in cell therapy due to their ability to differentiate into various cell types, offering a number of possibilities for regenerative medicine. They are regarded as important tools in a number of applications, such as tissue repair, organ transplantation and personalized medicine, since iPSC technology can allow for the generation of specific cell types from the cells of a patient, thereby reducing the risk of immune rejection.

In addition, iPSCs can serve as viable models for studying disease mechanisms *in vitro*. They provide a platform to simulate the occurrence and development of human diseases in a controlled environment, enabling deeper insights into the pathological mechanisms underlying these conditions and facilitating the screening of potential therapeutic drugs. Although further exploration is needed to improve differentiation efficiency in iPSC induction, progress in the differentiation of various organoids continues to advance. These developments underscore the notable advantages and potential of iPSCs in model construction.

As technology evolves, the scope of iPSC applications is expected to expand, offering novel solutions to current medical challenges. Therefore, future research and exploration of iPSCs are important. Regardless of the specific research direction, iPSC technology can generate cell models that reflect the pathological states of patients, aiding in uncovering the mechanisms of disease onset and progression. The use of these models for drug screening and efficacy evaluation has the potential to markedly accelerate drug development and facilitates the exploration of underlying mechanisms of drug action.

It can therefore be anticipated that iPSCs will serve an increasingly important role in addressing autoimmune diseases and other human conditions, not only advancing research but also enabling notable improvements in treatment through their clinical applications. With continuous in-depth research and technological maturation, iPSCs are poised to become key tools for tackling complex diseases in the future, providing patients with more effective treatment options and enhancing their quality of life.

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Authors' contributions

ZY and HZ proposed the research design, conducted literature searches, drafted the original manuscript, contributed to the writing of the paper and prepared the figures. HZ and XY provided professional advice and revisions to the manuscript. All authors critically reviewed the content. Data authentication is not applicable. All authors read and approved the final manuscript.

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Competing interests

The authors declare that they have no competing interests.

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