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OPINION REVIEW

Applications of artificial intelligence in stem cell therapy

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Abstract

Stem cell therapy holds great promise for the regeneration and repair of damaged tissues and organs. Stem cell therapy has been successfully applied to treat diseases that cannot be cured with conventional medicine. A careful evaluation of the outcomes is required for successful implementation of stem cell therapy. Recently, artificial intelligence (AI) has opened new avenues for research in the stem cell therapy field. The integration of AI can assist in evaluating the quality, efficiency and safety of stem cells by analyzing available data. It has the potential to improve and accelerate progress in various aspects of stem cell research and therapeutic applications. AI is still in its infancy and has certain limitations, such as algorithm validation problems, inadequate data availability, poor data quality, and ethical considerations. Considering the potential of AI to improve stem cell research and therapeutics, this review aims to explore applications of AI in understanding stem cell behavior, identification and characterization, optimization of the delivery methods, stem cell modeling and prediction of mortality risk. In addition, this review highlights the role of AI, machine learning, deep learning, and other subtypes in advancing stem cell biology research. This review also discusses the current limitations, ethical considerations, and future prospective of use of AI in stem cell research and therapeutic applications.

Key Words: Artificial intelligence; Neural network; Machine learning; Stem cell therapy; Regenerative potential

Core Tip: Stem cell therapy can repair and regenerate tissues and organs, and it has been successfully applied to treat diseases that cannot be cured with traditional medicine. The integration of artificial intelligence (AI) with stem cell therapy has the potential to transform the field of regenerative medicine. AI can analyze data to evaluate quality, efficiency, and safety of stem cells. It can accelerate the progress of stem cell research and medicine. However, the AI field is still new and has challenges, including algorithm validation, data availability, poor data quality, and ethical concerns.

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INTRODUCTION

Stem cells have self-renewal potential and the ability to develop into various types of specialized cells. These characteristics make stem cells ideal candidates for regeneration and repair of lost or damaged tissues and organs. Stem cell-based therapies are rapidly evolving as treatment modalities for diseases that cannot be treated with conventional medicine. The outcomes of previously registered stem cell-based clinical trials are promising and provide hope for patients suffering from a wide range of diseases or conditions, including cardiovascular diseases, spinal cord injuries, neurological disorders, diabetes, skin disorders, and blood disorders. However, before stem cells are fully applied in clinical settings, certain limitations, including optimized delivery methods, quality control of stem cells, ethical considerations, and risk prediction for stem cell transplantation, need to be considered. In addition, developing an effective stem cell-based therapy requires the ability to analyze substantial amounts of complex data. This is where artificial intelligence (AI) can make significant contributions to advancing stem cell-based therapies[1,2].

AI is a subfield of computer science that aims to develop computer systems to mimic human intelligence, such as reasoning, decision making, and learning[3]. AI technology was developed with a goal to widely apply it to many fields, including industry, science and technology, and even in routine activities. In 1956, the computer scientist John McCarthy described AI as the engineering and scientific process of making intelligent machines, particularly intelligent computer programs[4]. As technology evolves daily, the emergence of AI has gained popularity in the scientific world, where the aim of AI is to develop an intelligent machine that can think like humans and imitate human behaviors, including reasoning, perception, planning, learning, and prediction. AI researchers have integrated a broad range of problem-solving techniques, including machine learning (ML), artificial neural networks (ANNs), mathematical optimizations, and other methods, such as Bayesian networks (BNs), based on statistics and operations research to facilitate working processes[5,6]. Furthermore, the ability to analyze sophisticated medical data and the potential to make use of meaningful connections within a dataset not only contribute to diagnosis and treatment, but also to outcome prediction in a variety of clinical scenarios, thereby confirming the importance of AI in the healthcare industry. The increase in complex diseases has produced numerous opportunities to use AI technology to implement more targeted, effective, and significant interventions in patient care[4].

AI and stem cell therapeutics are two rapidly developing fields with numerous connections. AI is a powerful tool for stem cell therapy[7], as it can help researchers discover new insights by analyzing large amount of data and identifying new patterns. AI algorithms can help choose the best stem cells for each patient based on their genetic information and medical history, leading to more successful treatment outcomes. AI can inform cell therapy by providing optimal conditions for cell growth and quality control. The delivery of stem cells to a particular target site is also very important for stem cell therapy. AI can help by optimizing the route of administration to ensure that cells successfully reach the target site. Moreover, AI can optimize the dose and timing of cell delivery to enhance therapeutic outcomes. AI can open up new opportunities for investigating, diagnosing, and treating many diseases by combining the power of regeneration and power of computation[7]. In this review, we aim to highlight the AI applications, such as ML, deep learning (DL), and their subtypes, in stem cell therapy and discuss their future impact on regenerative medicine.

REGENERATIVE POTENTIAL OF STEM CELLS

Stem cells are undifferentiated cells that can self-renew and develop into various cell types[8]. They are categorized into four major types: Embryonic stem cells (ESCs), adult stem cells (ASCs), induced pluripotent stem cells (iPSCs), and neonatal stem cells. These four types of stem cells have distinct regenerative characteristics in terms of proliferation and differentiation into three germ layers (mesoderm, endoderm and ectoderm). ESCs and iPSCs can develop into cells from all three germ layers but cannot make extra-embryonic structures. ESCs are isolated from the inner cell mass of a 3-5 day-old embryo, while iPSCs are artificially reprogrammed somatic cells that form pluripotent cell lineages unique to each patient and capable of treating human model diseases[9]. ASCs are multipotent stem cells that can differentiate into multiple tissue-specific stem cells and are found throughout the entire body in ASC niches. The discovery of multipotent stem cells in the bone marrow in 1961 marked the beginning of stem cell research. Neonatal stem cells are found in birth-related tissues, such as cord blood, cord tissue, Wharton's jelly, *etc.* These cells are also multipotent-like ASCs.

Multipotent stem cells are currently the focus of research due to their ability to treat hematological disorders, such as myeloma, lymphoma, and leukemia[9]. After several decades, human pluripotent stem cells were employed in pre-clinical research. The research entailed isolating cells, determining their functions, and conducting preclinical trials. There has been a recent significant increase in stem cell research, particularly in its progression to clinical phases. This progress has been made possible by advances in technology, which eventually lead to the initiation of human clinical trials[10].

Stem cells are ideal candidates for tissue regeneration due to their potential to generate every tissue in the human body. Due to the success of preclinical and clinical trials, the potential applications of stem cells continue to expand, offering new perspectives for regenerative medicine. These innovative treatments have addressed a range of disorders characterized by abnormal cell development or function, such as congenital disabilities, cardiovascular diseases, neurodegenerative diseases, and retinal degeneration[11]. Despite the tremendous promise of stem cells in regenerative medicine, stem cells developed for patient treatment have encountered several challenges. These challenges include the inability to analyze complex data, challenges in identifying optimal cells for individual patients, difficulties in drug discovery, and disease modeling, limited understanding of stem cell behavior, challenges in delivering stem cells, costly and time-consuming experiments involving stem cell culture and differentiation, and the ability to predict mortality risk. AI can make substantial contributions in these domains. The most common applications of AI in stem cell-based therapies include the use of computational algorithms based on ML and ANNs for performing automated cell handling, predicting the most optimal cell types by analyzing patient's medical history and genetic information, cell culture optimization and differentiation, tissue engineering, disease diagnosis, drug development, use of robotic systems to rapidly design scaffolds for regenerative medicine and tissue engineering applications, and analysis of cellular images and large datasets [1,12].

AI

The field of AI has gained popularity both inside and outside the scientific community in the last 10 years. The subject of AI has been extensively covered in both non-technology and technology-based studies. There are many subtypes of AI, including ML and DL. However, there is a lot of misconception regarding AI, ML, and DL. Despite their strong association, these terms cannot be used interchangeably. The key differences between AI, ML, and DL are shown in Table 1. AI fundamentally involves the incorporation of human intelligence into machines through a particular set of algorithms[13]. ML is a subset of AI and is the process that allows a computer system to learn automatically on its own from past events and improve without the need for explicit programming. The emphasis of ML is on the development of a system that can obtain data and use it for its own purposes. The whole procedure makes observations on data to recognize potential patterns and make better decisions based on the examples provided. The basic objective of ML is to enable computers to autonomously learn knowledge through experience, devoid of human involvement or assistance[13,14]. DL is a specific subclass of ML that employs neural networks. DL neural networks mimic the ability of the human brain to recognize patterns, learn from experience, and make decisions. These neural networks function analogously to neurons in the human brain, which receive input (information), process and transmit signals (data), learn from experiences (training data), and adapt to new situations (improve performance). In contrast to ML, DL functions on larger datasets, with predictive algorithms autonomously maintained by the machines[13,14]. Figure 1 depicts the differences between ML and DL.

ML

The terms "machine learning" and "artificial intelligence" can be used interchangeably. However, ML is a subfield of AI. Samuel[15] coined the term "machine learning" and defined it as the capacity of computers to learn without specific modifications. This principle necessitates that humans provide machines with the necessary information for learning, which enables them to perform tasks or make decisions without the need for programming. A ML system is intelligent if it can compute a prediction based on the best chances and is prepared to learn from past mistakes. Supervised, unsupervised, and reinforcement learning are the three types of ML. Supervised learning addresses the challenges of guided learning, which involves label samples in the training data. The labeled samples will facilitate the prediction and classification of the test samples with the underlying mathematical model, which will optimize its parameters. Unsupervised learning is a category of ML that does not require labeled samples with class identifiers. Reinforcement learning is not completely unsupervised. Because this method lacks label examples for training, it also cannot be considered supervised learning. Instead of relying on manual adjustments to previously defined processing steps or parameters, ML studies the processing rules from model examples. ML is superior to traditional image processing systems, as it can handle complex multi-dimensional data evaluation problems[9].

DL

DL is a popular subfield of ML that computationally models the learning process and learns from data. Data processing, understanding human speech, and visual object perception are all accomplished using algorithms. Face identification, speech recognition, and computer vision have all been areas where AI has struggled throughout the years. However, DL has overcome these challenges. The development of DL is based on neural networks. Neural networks is a popular method that attempts to mimic the way a living thing learns. Neural networks are inspired by the brain's exceptional capacity for complex, parallel, and non-linear computations; they have demonstrated that with an adequate number of neurons in their hidden layers, they can approximate any function with arbitrary precision, functioning as universal function approximators. It is common practice for DL models to employ hierarchical structures to link all of its layers. The

Table 1 Key differences in artificial intelligence, machine learning and deep learning

Feature	AI	ML	DL	Ref.
Definition	It involves incorporating human intelligence into machines using algorithms and a set of rules	Enables computer systems to learn automatically from past events and improve accordingly without explicit programming	Use neural networks to learn from data	[9,13-15]
Subset relationship	A broader field encompassing ML and DL	A subset of AI	A subset of M	[9,13-15]
Functionality	Employs decision-making to exhibit intelligence	Uses algorithms to evaluate data, detect patterns, and make predictions. The system learns from data and improves over time	Analyzes data using multi-layered neural networks, producing output based on deep pattern recognition	[9,13-15]
Learning approach	Can be data-driven, knowledge-based, or rule-based	Relies on data-driven learning. Includes supervised, unsupervised, and reinforcement learning	Employs neural networks with hierarchical layers. Transforms simple features into abstract representations for better feature extraction	[9,13-15]
Human intervention	Requires human-defined rules and logic	Some human intervention is needed for data labeling and training	Minimal human intervention. Relies on self-managed learning processes	[9,13-15]
Data dependency	Can work with smaller datasets and predefined rules	Needs a moderate amount of structured data to learn effectively	Requires enormous volumes of labeled data for training	[9,13-15]
Processing power	Involves complicated arithmetic, search trees, and reasoning techniques	Involves complex algorithms and mathematical models	Requires high computational power due to deep neural networks	[9,13-15]
Efficiency	Efficiency is determined by the effectiveness of ML and DL components	More efficient than AI alone but less efficient than DL in handling large datasets	Highly efficient for processing large datasets due to automated feature extraction	[9,13-15]
Applications	Encompasses diverse subfields including natural language processing, computer vision, and robotics	Used in applications such as recommendation systems, and predictive analysis	Best suited for tasks like image recognition, speech recognition, and autonomous driving	[9,13-15]

AI: Artificial intelligence; ML: Machine learning; DL: Deep learning.

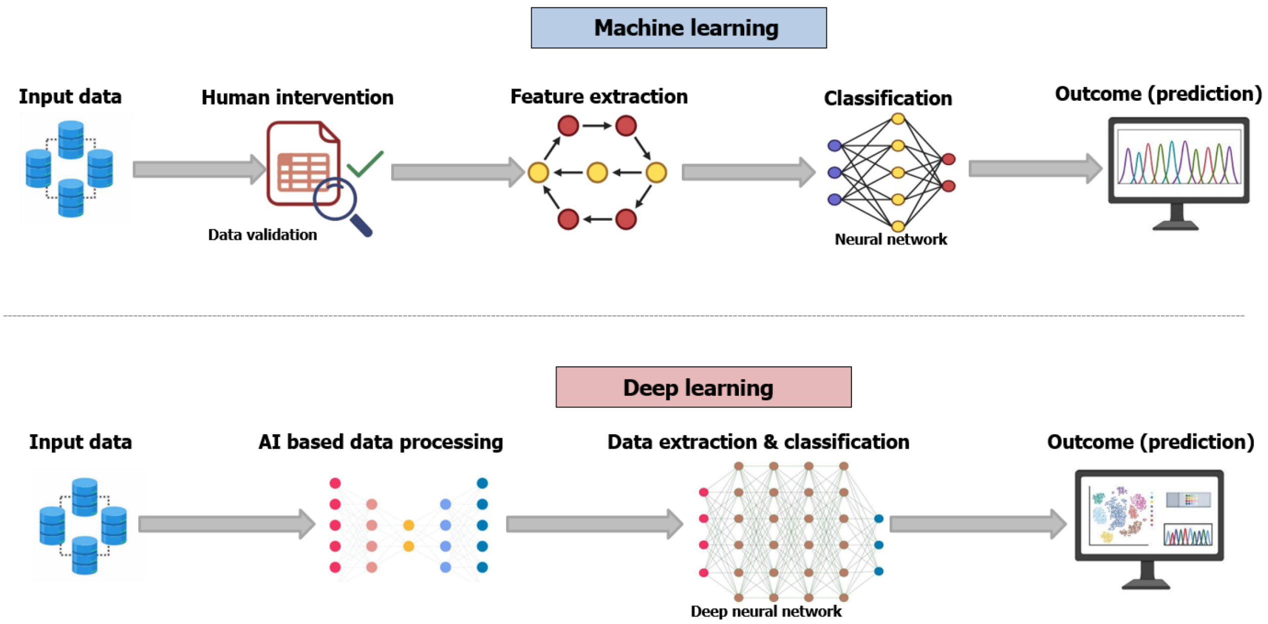

Figure 1 Machine learning *vs* deep learning. This figure illustrates the differences between machine learning and deep learning. Data is collected and stored in databases. In machine learning, human intervention is required for data validation and feature extraction before classification using a neural network. In contrast, deep learning automates feature extraction using deep neural networks, eliminating the need for manual input. Deep learning is more data-intensive but enhances accuracy and efficiency in predictions. AI: Artificial intelligence.

output data from lower levels serves as input data for higher layers. This property allows DL models to transform simple data features into more abstract ones, which improves their feature representation compared to other shallow ML models like improving and support vector machines (SVMs). In contrast to traditional ML methods that depend on user experience, DL relies on data, which reduces the need for operation users. Rapid advancements in computing power, storage capacity, and accessibility have been associated with the sudden rise of DL as a crucial method for ML[9].

SUBTYPES OF AI

Various subtypes of AI, ML, and DL play unique roles in the field. We have focused on discussing those subtypes and algorithms that hold significant importance in stem cell applications, offering valuable insights for researcher in the fields. These include natural language processing (NLP), random forests, SVMs, convolutional neural networks (CNNs), ANNs, logistic regression (LR), k-nearest neighbors (k-NNs), BNs and decision trees.

CNN

CNN is a common DL method that directly learns from the input, thus eliminating the requirement for extraction of human features. CNNs are widely used for object recognition, picture similarity-based aggregation, and image classification. Initially, CNNs were widely employed in object identification. However, they are now used in a variety of applications, including visual labeling, action identification, object detection, and recognition. CNNs generate hierarchical and a high-level visualization of features by processing multiple levels of input images[9]. Neocognitron was the first self-organizing neural network model developed in 1980 for a pattern recognition mechanism[16]. LeNet, an ANN with multiple layers, was developed by LeCun in 1998 and significantly contributed to the development of CNNs[17]. LeNet can identify patterns in the input images and categorize handwritten digits without any modification. Difficulties of this model stemmed from insufficient training data and lack of computational power, preventing this model from properly working in a complex environment. Many of the errors in annotation made during the large-scale image classification were easily managed by the subsequent construction of AlexNet CNN mode[18]. This model, which consisted of five convolution layers and three fully linked layers, brought significant breakthroughs in image classification with the aid of advanced technology. AlexNet is now considered an innovative milestone achievement in computer vision[9].

Convolution and pooling layers comprise the feature extraction portion of the CNN framework, whereas fully linked layers comprise the classification portion. A picture is first run through a sequence of convolution layers, followed by feature extraction by pooling layers and classification by fully connected layers. Feature maps of varying sizes are generated by the convolution layers. These maps are subsequently reduced by the pooling layers and passed on to the following layers. The more complicated structures in the image are detected by the neurons in the deeper layers, while the simpler ones, including edges, blobs, and lines, are identified by the preliminary layers. The CNN is required to undergo a training phase to determine the optimal weights for the images to generate high-quality results. Due to transmission of the error signal obtained by the loss function, which enhances the feature extraction portion, the CNN provides a better picture representation[9]. CNNs are widely utilized in NLP, visual identification, image segmentation, and medical image analysis because they are specifically designed to handle a diverse range of two-dimensional shapes. It is more powerful than a standard network because it can automatically extract important features from the input without requiring human intervention. Depending on their capacity for learning, a number of CNN variations can be applied in different application domains in healthcare, such as NLP, image classification, image analysis, and diagnosis [19].

ANNs

The ANN is a subtype of ML that is built using interconnected nodes. The information in these nodes is processed like the natural human nervous system. The primary component of ANN is its unique structure, which gives it the ability to process information with great power. Its structure is made up of several interconnected information processing units or neurons that work together to solve specific problems. Like human neural systems, ANNs learn and gain knowledge through pictures. ANNs are intricately designed to use learning process to solve particular problems[20]. Every artificial neuron takes in information from other linked neurons, processes it, and then transmits the results to other neurons in the network. Each neuron’s output is determined by an activation function, which is a non-stationary function of the combined value of its inputs. The “signal” is an actual number. A weight that changes as the learning process progresses determines the signal strength at each connection. The typical arrangement of neurons is in layers, and it is possible for inputs to be differentially transformed by distinct levels. Signals can pass through more than one hidden layer on their route from the input layer to the output layer. A network with two or more hidden layers is called a deep neural network. Predictive modeling, adaptive control, and AI problem solving are just a few of the many applications of ANNs. They are capable of learning from their mistakes and drawing inferences from apparently unconnected pieces of data[15].

BNs

A BN is a graphical model with probabilities that can be utilized to construct models based on data or expert opinion. They can be employed for a variety of functions including investigations, reasoning, decision making in the presence of malfunction detection, forecasts, and even automatic insight and others. A brute force algorithm to create a graph model consists of building a directed acyclic graph that defines the network structure and a probability distribution over the vertices, or nodes, in the network. For example, the BN model can encapsulate the essential characteristics of cell differentiation without the need to consider artificial boundaries of experimental conditions and intricate interactions between genes. BNs often allows a biologist to systematically investigate all possible ways for various cell types and patients undergoing gene therapy by linking probabilistic, domain, and biological data[21].

NLP

NLP is a branch of AI and is the simulation of human conversation through a computer. NLP employs ML and DL language processing in tandem with computational linguistics rule-based modeling. The combination of these technologies permits automatic processing of documents or data in the form of speech, particularly when it comes from a human. When employed in medical notes, it is possible to improve hospital triage systems, forecast outcomes of patients, and build algorithms for the diagnostic detection of diseases in patient records. NLP is capable of natural language generating in addition to natural language understanding, giving patients access to relevant information and ask questions from a chatbot[22].

SVMs

SVMs are supervised learning models capable of handling regression tasks and performing classification. Therefore, the domains of biological data categorization, regression, and cluster analysis have made extensive use of computational tools and algorithms. The main goal of classification analysis is to train a classification model using labeled data. New data is then classified based on the trained model. Biological databanks are growing at a rate that makes it imperative to automate the classification process with computer systems. Currently, SVMs are the most effective computer systems for making predictions. These machines are designed to maximize the margin between two classes so that the trained model will generalize well on unobserved data. Most other computer programs use the minimization of training error to create a classifier, which results in less effective generalization. Therefore, SVMs have been extensively used in various bioinformatics domains such as gene expression, transcription start site prediction, protease functional site recognition, and prediction of protein function[23].

Random forests

Random forest is a popular tree-based ML method that can handle "large p, small n" issues, is highly data adaptable and can consider for interaction as well as correlation among features. "p" represents number of predictors or features (variables), and "n" represents the number of observations or samples (data points). Random forests are very effective in the study of high-dimensional genomic data. It randomly selects a subset of potential predictor variables (*e.g.*, genes) and subset of training data cases. Each tree is then built using the variables and sampled data. The collection of decision trees is then used to classify new data[24,25].

Decision trees

Decision trees are among the most successful supervised learning methods for regression and classification applications. A decision tree is constructed with a hierarchical structure, featuring terminal nodes assigned class names, branches designating test results, and internal nodes representing attribute assessments. It is built by constantly dividing the training data into smaller subgroups based on attribute values until a specific stopping criterion, such as the minimum number of samples or the maximum depth of the tree required to divide a node, is met[26,27].

LR

LR is a type of supervised learning commonly used for classification purposes, predicting the probability of an observation being classified into a specific category. This statistical method analyzes the association between a group of binary dependent variables and a set of independent factors. It is an effective tool for making decisions. Biomedical data typically consist of few samples and many variables. It is difficult to mine such high dimensional data with current classifiers, and the results are frequently erroneous. LR is a popular method for making predictions. Nevertheless, when employing LR, it is challenging to incorporate prior biological knowledge into the study. Almost every biomedical domain has linked domain knowledge. Building predictive models with the ability to incorporate such new knowledge would be beneficial. When attempting to develop a model for categorization and prediction of a given disease, it would be beneficial to utilize information such as the identification of a predictor variable as a biomarker. The computational efficiency of Bayesian LR is high and the method can integrate prior knowledge[28].

K-NNs

K-NN is one of the most basic yet useful categorization methods in ML. It is a member of the supervised learning domain that is extensively used in data mining intrusion detection and pattern recognition. K-NN classifiers are widely utilized in a variety of fields including medicine. It identifies class membership of an unlabeled sample based on class membership of k-labeled samples that are closest to the unlabeled samples, known as nearest neighbors[26,29].

APPLICATIONS OF AI IN STEM CELL MANUFACTURING AND THERAPEUTICS

The automation of AI can help improve stem cell manufacturing (Figures 2 and 3). AI uses mathematical models including data mining, DL algorithms, ML algorithms, and other subtypes to study how stem cells grow, migrate, interact, and adapt to different conditions. These technological developments have assisted in maintaining stem cell quality, identifying a reliable framework for colony classification, characterization of stem cells, identification of cellular

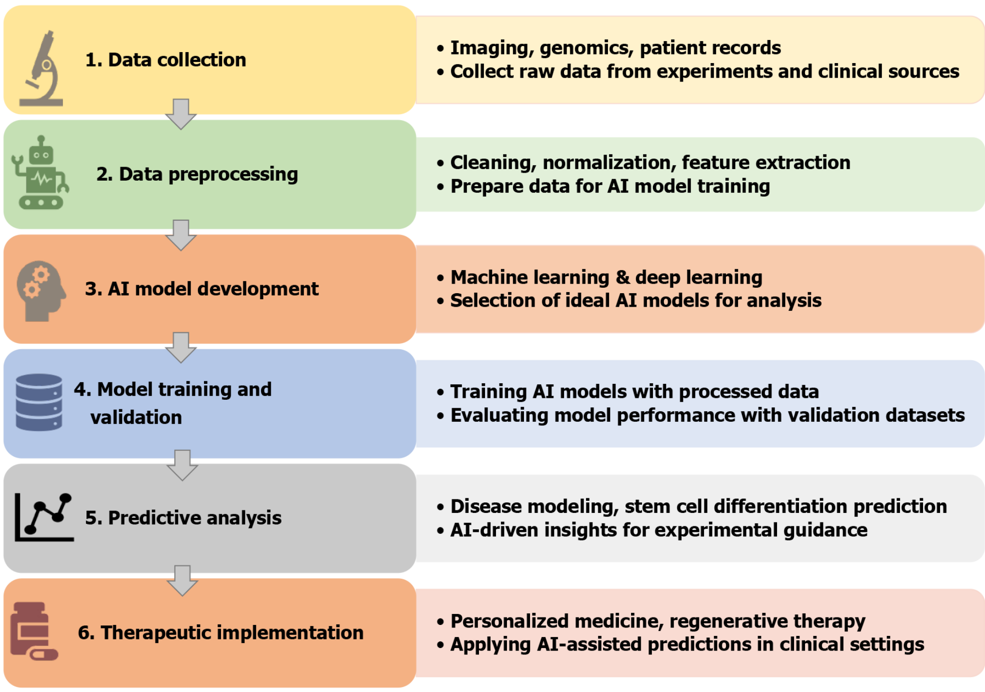

Figure 2 Development of artificial intelligence-driven stem cells-based therapeutics. Image, genetic, and patient record data from clinical and experimental sources are collected. The collected data undergo cleaning, normalization, and feature extraction to prepare it for artificial intelligence (AI) model training. Machine learning and deep learning algorithms for analysis are chosen and implemented during AI model construction. AI models are trained with processed data and validated using validation datasets. Predictive analysis uses AI to model diseases, predict stem cell differentiation, and direct experiments. Clinicians use AI-assisted predictions to promote personalized medicine and regenerative therapies. AI: Artificial intelligence.

morphology and prediction of risks and outcomes of drugs[12]. All stem cell types, including mesenchymal stem cells (MSCs), and iPSCs can be used in combination with AI to enhance their use in research and therapy[12,30]. The quantitative modeling of stem cells with AI support is a potential improvement due to its promising accuracy. Using AI to create quantitative stem cell models has the potential to improve our understanding and use of these cells[12,30,31]. Stem cells have greater therapeutic success because of their immunomodulatory roles, effective homing capacity to injured sites, anti-inflammatory effects, and multipotentiality. However, stem cell potency and pharmacological effectiveness vary according to the tissue origins, method of harvest, culture expansion, stem cell handling, dosage and delivery route[32]. Therefore, it is challenging to standardize and optimize stem cells for clinical use. AI technologies such as DL and ML can overcome these limitations by providing quantitative methods to analyze stem cells. These technologies can be utilized to extract significant features from stem cells such as surface markers, morphology, differentiation potential, secretome, and gene expression. Researchers can gain a better understanding of stem cell behavior, function, and potential by understanding these features. As outlined in Table 2, this can lead to improved methods for: (1) Behavior and characterization of stem cells; (2) Stem cell culture and differentiation; (3) Prediction of mortality risk; (4) Stem cell imaging-based classification; (5) Stem cell modeling; (6) Drug discovery; and (7) Optimization of delivery methods. AI can also help reduce the time and cost required for the development and testing of MSC, as well as MSC translation from bench to bedside[31]. Researchers and doctors can gain new insights of stem cell biology and function by using AI to model stem cells and to increase their quality and consistency for therapeutic applications.

Evaluating stem cell behavior and characterization

Stem cells replace damaged or lost tissues and generate new cells in the body and can differentiate into various cell types. Controlling and understanding stem cell behavior is an essential step in stem cell-based treatments. AI can provide a deeper understanding of cellular and molecular pathways, allowing for the development of more effective and safe stem cell therapies. AI combines data from various sources, such as cellular images, epigenetic markers, and gene expression profiles to create a comprehensive understanding of stem cell behavior. AI uses ML algorithms to identify correlations and patterns within the data, revealing complex relationships between stem cell behavior and various factors. It also helps in the identification of ideal conditions and parameters influencing stem cell behavior, such as type of culture media, environmental conditions (temperature and pH) and type and concentration of growth factors. AI uses NLP to understand and analyze the vast amounts of available research data available in the literature related to stem cell biology [33].

One of the limitations of stem cell therapy is identifying the most effective type of stem cells for a specific disease or injury. There are many types of stem cells, including MSCs, ESCs, iPSCs, *etc*., each with its own unique characteristics and functions. AI can assist physicians in finding the most promising type of stem cells for a specific disease by analyzing patient's medical history and genetic information[7,34]. The success of stem cell therapy is largely dependent on the characterization of stem cells, which is a complex and multifaceted process. Stem cell characterization involves various

Table 2 Artificial intelligence tools and methods in stem cell therapy

Application in stem cell therapy	AI tools or methods
Behavior and characterization of stem cells	Deep learning, natural language processing and machine learning
Stem cell culture and differentiation	Convolutional neural networks and random forests
Prediction of mortality risk	Artificial neural networks, k-nearest neighbors, logistic regression, and decision trees
Stem cells imaging based classification	Deep learning and convolutional neural networks
Stem cell modeling	Machine learning algorithms
Drug discovery	DeltaVina, neural graph fingerprint, AtomNet, and DeepTox have been used in drug discovery
Optimization of the delivery method	Convolutional neural network

AI: Artificial intelligence.

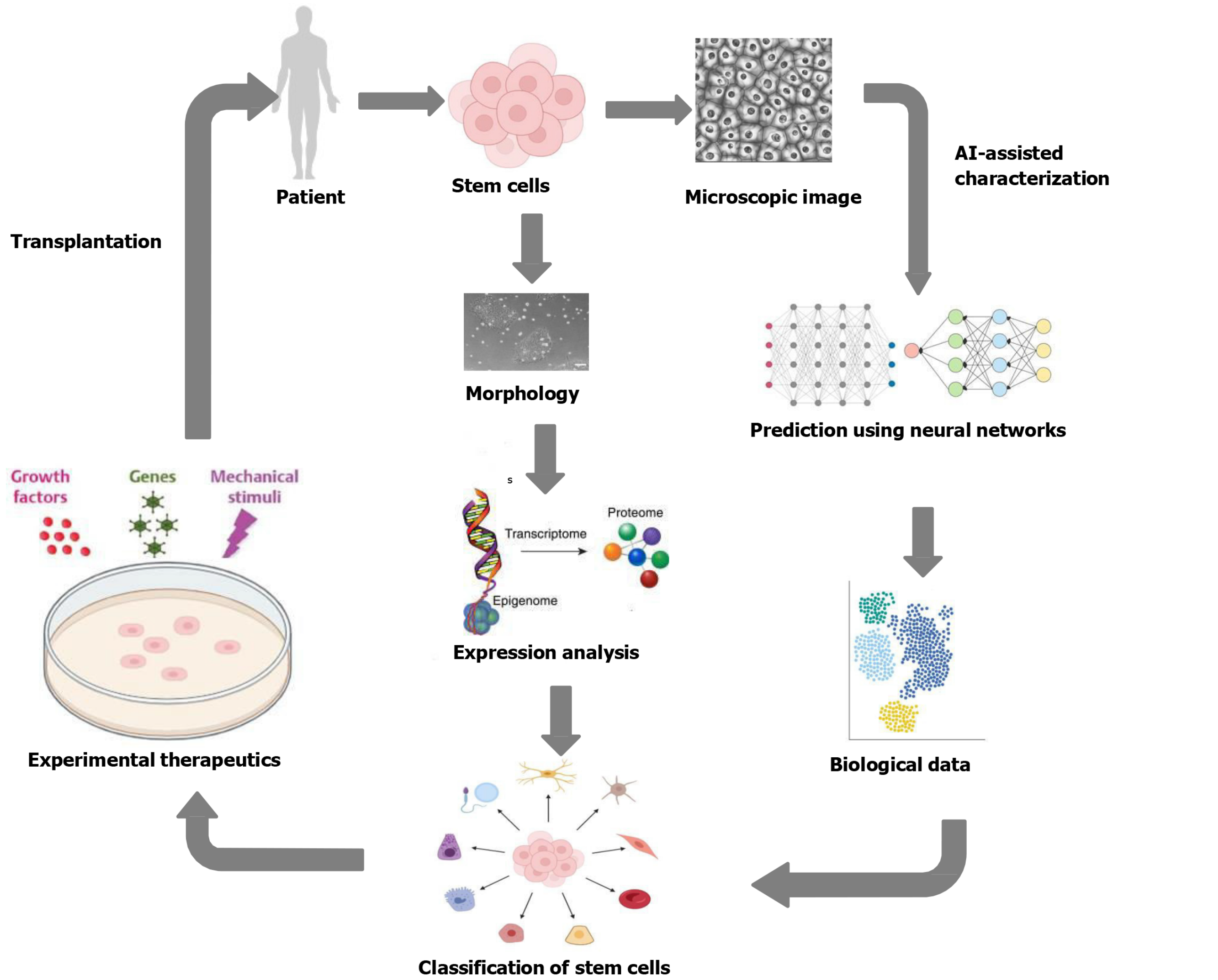

Figure 3 Representative image of artificial intelligence-supported stem cell treatment. Patient stem cells are isolated. An image of a stem cell is captured with the use of a microscope. Artificial neural networks, genetic algorithms, and Bayesian networks analyze stem cell characteristics. Deep learning, natural language processing, and machine learning predict stem cell morphology and behavior. Stem cell types are classified using convolutional neural networks, support vector machines, and random forests based on this biological data and expression. Stem cells are modified using growth hormones, genes, and mechanical stimulation for clinical use. Therapeutic stem cells are then administered to the patient. AI: Artificial intelligence.

types of data, including protein expression profiles, gene expression patterns, metabolic activity, electrophysiological properties, and epigenetic modifications. These diverse data types make stem cell characterization a challenging task, requiring advanced analytical techniques to integrate and interpret the information. Various AI approaches, including BNs and ANNs, are employed based on various parameters of metabolic networks, gene regulatory networks, and signaling pathways[35].

Stem cell culture and differentiation

Stem cell differentiation is thought to be initiated by changes at the genetic level. These genetic changes allow stem cells to undergo differentiation, ultimately defining their fate. Computer simulation and mathematical modeling assist in understanding the process of self-renewal and differentiation properties of stem cells by simulating the entire cell population rather than focusing on individual cells[12]. Pluripotent stem cells have a significant function in regenerative medicine, disease modeling, and drug testing because they can transform into diverse cell types in an organism. ESCs and iPSCs are two unique types of pluripotent stem cells. ESCs are formed in the initial stages of embryo development, whereas iPSCs are produced through the reprogramming of genes, which involves reversing the specialization of somatic cells to a pluripotent state. iPSC-derived cells provide a focused investigation of cellular physiology, making them highly helpful for tasks such as disease research, drug screening, and regenerative medicine[36]. Moreover, the application of fully developed endothelial cells, obtained from iPSCs through the process of differentiation, has the capacity to be used for disease simulation and organ growth. Nevertheless, the presence of highly skilled researchers in consistently maintaining iPSCs and performing differentiation studies to obtain specific cell types requires substantial time and financial resources[37]. Scientists have developed a CNN algorithm called Resnet50 to accurately differentiate slight variations in stem cell morphology, such as changes in shape, size, and texture, specifically ESCs and iPSCs, when subjected to various growth conditions. The experimental conditions included three media formulations, including one with leukemia inhibitory factor to maintain stem cell pluripotency, another without leukemia inhibitory factor, and a third with insulin/transferrin/selenium to induce differentiation. The research employed transmitted light microscopy to monitor cell morphology changes over 24 hours. Notably, the algorithm attained an accuracy rate of 95% in recognizing culture conditions and cell types exclusively based on cellular shape[38].

Prediction of mortality risk

A very powerful feature of AI in stem cell therapy is its prediction of mortality risk because it requires estimating the risks and outcomes of stem cell transplantation with the help of cell dose, disease condition, patient factors, cell source and delivery route. These parameters can be useful in predicting patient survival and mortality outcomes over the stem cell transplanted for different types of injuries or diseases. Unquestionably, AI can help improve research objectives by using ANNs, LR, and decision trees methods to process images, medical files, and lab tests. This enables better patient selection and treatment planning[31]. For example, Shouval *et al*[39] developed a ML model using an alternating decision tree to predict the 100-day mortality rate after hematopoietic stem cell transplantation. The model, built using data mining methodology and validated on a large dataset, demonstrated excellent calibration. This model can help assess and stratify transplantation risk before the procedure, inform patient counseling during consent sessions, and guide personalized transplantation regimens or alternative treatment recommendations based on individual risk profiles. On the 100th day, the overall mortality rate was 13.9%. The data mining technique has demonstrated its ability to predict the overall death rate within 100 days and has further expanded this prediction to a maximum of 2 years[39].

Stem cell imaging-based classification

Microscopes are a vital instrument in the field of medicine, facilitating the detailed examination of cellular morphology and detection of unusual cell characteristics. In biological research, maintaining healthy cell cultures and accurately recognizing specific cell types are important for reliable results. Nevertheless, this process is labor-intensive and susceptible to mistakes. DL can overcome these limitations by effectively processing large quantities of data. CNNs can detect small alterations in cell morphology caused by cell culture media and conditions, which are not noticeable to the naked eye. It is worth investigating the feasibility of classifying the required neuronal cells exclusively using cell pictures, by comparing their morphology to that of well-characterized stem cells. The goal of image-based cell classification is to identify whether cellular differentiation can be detected at an early stage or if distinct cell types can be recognized during the initial phases of differentiation. If effective, the exclusive utilization of early differentiating cell pictures could substantially decrease the overall time and expense associated with differentiation tests. The precision of CNN predictions can be validated by annotating stem cells and their corresponding differentiated cell types and viewing them with a confocal microscope. Additionally, the expression of genes relevant to stem cells and differentiation can be evaluated by real-time polymerase chain reaction assays. The precision and efficiency of CNN relies on the quantity of images and classes, and the specific CNN model selected for image analysis.

Stem cell modeling

Modeling can help inform the fundamental principles and mechanisms of stem cell biology, as well as in optimization of parameters and experimental designs for manipulation of stem cells. AI may assist in the construction and refinement of these models by using ML algorithms to learn from experimental data and provide hypotheses or predictions. Researcher have developed an AI framework that can model the gene regulatory network of human ESCs using single-cell RNA sequencing data[40]. This methodology can help infer gene-to-gene causal relationships and identify essential regulators of human ESCs pluripotency[40]. Network-based screening using AI tools is a powerful method for modeling iPSCs. AI can be used to generate complex tissue structures with multiple cell types in the culture and maintenance of iPSCs, which is necessary for organoid formation. These complex structures, which display the three-dimensional organization of tissues, offer more profound understanding of disease causes compared to simpler single-cell models[41].

Optimization of the delivery method

The method of stem cell delivery is another important aspect of the success of stem cell therapy. Stem cells can be delivered to sites of injury *via* infusion, injection, and direct transplantation. AI can assist clinicians in optimizing the delivery method by analyzing medical imaging scans. Two main AI applications are being developed to enhance stem cell distribution and performance. The primary impact is on the streamlining of stem cell production through the automation of AI-powered simulation and model-building processes. Secondly, mathematical modeling can be used to identify relationships between cellular features and their microenvironments; this can improve the efficiency of tissue production while keeping cell therapy safe. By utilizing this technology to enhance picture evaluation and processing, researchers were able to study stem cell shape, distinguish between healthy and diseased cells, and determine the different roles played by pluripotent stem cells. The current standard for validating monoclonality involves operating a microscope by hand, which is labor-intensive, expensive, and dependent on the operator's skill set. Therefore, the basic idea is that an automated method can overcome observer bias[1]. One study that established the importance of this finding used human iPSC-derived cardiomyocytes to establish cell culture quality standards[42].

Drug discovery

The process of stem cell-related drug discovery involves the identification of molecules or other therapeutic agents that can stimulate tissue regeneration and facilitate the restoration of normal function. The molecular space contains an immense quantity of molecules, which offers both possibilities and difficulties in the field of drug discovery and development. Current drug development methods of stem cells are time-consuming and costly, as they require the synthesis and testing of a significant number of chemicals to find ideal drug candidates. Their advancement in drug development is limited by the lack of sophisticated technologies to test drug efficacy and safety. AI can overcome these problems by analyzing large datasets of chemical compounds to predict the most effective drug candidate for specific diseases. Various AI-based models such as DeltaVina, neural graph fingerprint, AtomNet, and DeepTox have been employed in drug discovery[7]. These models have improved drug discovery for stem cell-based therapies using pre-trained models for predicting and analyzing the binding affinities between proteins and ligands, screening large chemical databases, predicting compound characteristics, and evaluating drug toxicity[43,44].

By leveraging AI, researchers can gain valuable insights into the functionality and potential efficacy of therapeutic targets, saving significant time and resources. Early detection of potential safety issues during drug research reduces the likelihood of unfavorable outcomes. AI can aid in the development of novel molecules tailored to specific therapeutic objectives. The integration of AI with iPSC technology in drug research and development has gained popularity, leading to innovative methods for patient evaluation and drug discovery. This collaboration extends beyond image analysis to include genomic data analysis and disease studies. These advances enable rapid selection and analysis of new drug candidates using virtual screening methodologies, transforming iPSC drug discovery research by enhancing understanding of their interactions and effectiveness. A groundbreaking study in 2015 utilized iPSC-derived cardiomyocytes to assess drug cardiotoxicity. ML differentiated between regular and irregular contractions and changes in membrane depolarization voltage following exposure to cardioactive drugs, achieving an accuracy rate above 80%[45]. Another study subsequently found that computational techniques are effective in predicting treatment responses and identifying internal changes after treatment with specific drugs and pharmaceutical toxicity in iPSC and organoid models[46]. Presently, AI technology is being utilized to create efficient, non-labeled drug screening devices with enormous capacity.

ETHICAL CONSIDERATIONS

The term "artificial intelligence ethics" refers to a set of values, principles, and techniques that use widely recognized norms of wrong and right to guide ethical behavior in the development and use of AI technologies[47]. AI systems have the potential to create a wide range of problems for people and society as a whole because of their abuse, poor design, or unanticipated negative effects. The creation and implementation of AI systems in healthcare can be guided by specific medically based ethical guidelines that already exist in the fields of medicine and research. The ethical development of technology in the scientific and computational areas, as well as decision-making in health care, are guided by these concepts. Transparency, bias mitigation, and patient privacy are guaranteed by professional codes of ethics specifically designed for AI applications, which must be adhered to by all individuals, including clinicians and ML model developers. Organizations should encourage stakeholders to increase trust and sustainability by establishing strong rules and transparent processes that ensure ethical conduct both internally and in partnerships. Even though regulations for medical AI are still in their early stages, it is imperative that regulatory agencies take the lead in monitoring the ethical standards of AI in healthcare and making sure that these technologies put patients' needs first[48].

The use of human ESCs has been the subject of ongoing ethical debates because their derivation typically involves the destruction of human embryos, raising concerns about the moral status of embryonic life. In contrast, iPSCs, which are generated by reprogramming adult cells, do not involve embryos and therefore pose minimal ethical concerns. The incorporation of AI-driven technologies in stem cell therapy raises other crucial ethical concerns that require careful examination. Data privacy and security is a major issue. AI systems frequently depend on large volumes of private data, such as health records and genetic information. This prompts critical inquiries regarding consent, ownership, and the susceptibility of personal data to misuse. The protection of individual rights and the preservation of public trust necessitate the establishment of strong regulations and open data handling practices[49]. Ensuring patient privacy and data security is vital when using AI in healthcare, as it involves handling sensitive personal information, raising concerns about potential data breaches and unauthorized access. Moreover, the transparency and explainability of AI algorithms, known as the "black box" issue, pose significant challenges in healthcare settings. It is crucial to ensure that AI systems perform fairly and without bias for them to function ethically. When data is collected, prepared, or analyzed in a method that is systematically inaccurate or significantly deviates from its real value, this is known as bias in data science. Various factors, including incomplete data, skewed sampling methodologies, or defects in data recording, can contribute to this phenomenon. Prejudiced results and healthcare choices might result from AI algorithms that are educated on biased data and then perpetuate these mistakes. AI models can be skewed for using biased data; developing models with the wrong AI algorithms; or having users interact with the model in a way that does not represent their actual needs. Data can reflect social prejudices (such as racism, bigotry, and classism) and historical biases that influence medical practice and health care delivery, making the use of data to train algorithms an ever-present difficulty. The data sets utilized to train AI models are a common source of bias in these algorithms. These datasets could unwittingly incorporate prejudices that mirror past injustices or systematic unfairness that was present throughout data collecting. Because of inequalities in health care access or differences in the diagnosis of specific diseases across populations, diagnostic algorithms trained on past patient data in electronic health records may unfairly include particular demographic groups (*e.g.*, gender, race, socioeconomic status, religion, or disability) over others. The creation and use of algorithms are additional potential entry points for bias in AI models. Unintentionally reinforcing biases in the training data might occur because of algorithmic design decisions like feature selection or model weights. Once implemented in practical settings, this phenomenon, which is referred to as algorithmic bias, has the potential to maintain and worsen preexisting inequalities. Several factors can lead to biased medical data. Patients' medical records are often incomplete or missing important details because they may have visited or tested at more than one location. Patient portals may not be completely utilized or results may not be appropriately reported by patients with poorer health or information technology literacy, which can further contribute to incomplete data. Recognizing and addressing possible unfairness in training data, validation, model creation, and deployment is crucial in addressing bias in AI models[48,49]. Lack of transparency can erode trust and dependability, particularly when evaluating the viability, efficacy, and safety of stem cell therapies. Healthcare professionals must prioritize patient welfare, acting as moral agents to ensure AI systems adhere to ethical standards, including the respect for human dignity, accountability, and sustainability[48,50,51].

Utilizing diverse datasets and continuous monitoring to mitigate bias is crucial for designing AI systems with fairness in mind. It will be essential to establish ethical guidelines and regulatory frameworks to navigate these intricate issues and guarantee that advances are consistent with societal values. Ultimately, it is imperative that we evaluate the societal implications of AI and its broader implications. It is critical that we guarantee that the advantages of these technologies are shared fairly and do not worsen inequalities, even though they may revolutionize healthcare and agriculture. Promoting the public good through AI applications requires involving a wide range of people, such as ethicists, policy-makers, and community leaders[49].

LIMITATIONS AND FUTURE DIRECTIONS

Stem cell therapy holds significant potential for improving patient outcomes and expediting recovery. Nevertheless, several limitations remain, including inefficient production processes, high costs, complex procedures, and human errors. Understanding the genetic factors that influence tissue and organ development, including morphogenesis and patterning is crucial. Although some studies have identified key gene regulators in various regenerative contexts, the intricate processes governing organ formation remain poorly understood. AI-driven approaches and constructive algorithms offer considerable promise for elucidating these mechanisms, streamlining stem cell-based therapy development, and reducing human error. However, the absence of international standards for ensuring dataset quality and reliability poses a notable challenge. Restrictions on dataset access, incomplete reporting of findings, and inadequate methodology descriptions hinder reproducibility. The application of AI in stem cell biology encompasses diverse empirical methods, but these approaches often lack robust theoretical foundations. Advances in AI technology and high-quality data availability are expanding the potential to enhance and tailor AI algorithms for regenerative medicine. Integrating AI with nanotechnology, genome editing, and three-dimensional bio-printing may lead to groundbreaking advancements in personalized regenerative medicines[52-54].

Establishing rigorous benchmarking standards and criteria is crucial for effectively designing and evaluating AI systems. Standardized reporting methods will significantly enhance research quality in AI applications. It is essential that AI systems are validated to identify the best stem cell treatments and predict results. AI models need to be built with the ability to precisely evaluate treatment-related risks. It is crucial that regulatory agencies such as the food and development authority conduct thorough clinical trials on AI-assisted therapeutic choices to ensure that they are supported by strong data. In addition, there are security and privacy concerns regarding the massive volumes of patient data that will need to be collected and analyzed for AI. AI should not replace human judgment simply because it can handle massive quantities of data and make complicated predictions. In the decision-making process, medical professionals must continue to be a critical component, utilizing their expertise to interpret AI recommendations and make the ultimate treatment decisions. With a topic as complex and individualized as stem cell biology, it is crucial that AI works in tandem with healthcare professionals rather than taking their jobs. There will be concerns about responsibility as AI becomes more integrated into healthcare decision-making. Who is to blame if a choice made by an AI system has unintended consequences? Who is responsible for this: The designers, the doctors, or the AI? Making sure that accountability is established and that responsibility for clinical decisions is clearly defined requires the development of clear guidelines. Although it is still in its infancy, the collaboration between AI and stem cell research holds tremendous promise. More accurate and efficient treatments for many diseases will be possible as AI continues to develos and reveals more about stem cell biology. With AI at the forefront of implementing these advancements in healthcare, stem cell therapies guided by the technology might soon be standard practice, providing individuals with individualized, regenerative treatments that have the potential to increase their longevity and enhance their quality of life[34,55]. In the near future, we can anticipate the emergence of numerous algorithms and tools that will assist in developing regenerative therapies and predicting outcomes, providing decision support for healthcare providers.

CONCLUSION

When combined, stem cell medicine and AI have the potential to treat diseases that were previously incurable. This could lead to a significant transformation of healthcare. Their combined strength holds the prospect of accelerating scientific advancement and bringing in a new era of regenerative and personalized medicine. Utilization of AI in stem cell therapeutics is a highly beneficial approach and can offer unique opportunity for improving stem cell quality, understanding stem cell behavior, characterizing stem cell types, culture and differentiation, predicting mortality risk, stem cell-based image classification, drug discovery, and optimization of the delivery methods. However, because AI is at its primitive stage, there is need to streamline the processes and define standard criteria for evaluating the quality and reliability of datasets while maintaining patient privacy and confidentiality. We can expect more tools soon that can improve the frontiers of regenerative medicine and assist in predicting treatment outcomes and providing decision support to healthcare providers.

FOOTNOTES

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