

A close-up photograph of a laboratory setting. A pipette is positioned above a multi-well plate, with a single drop of red liquid about to fall into one of the wells. The plate is filled with many other wells, each containing a similar amount of red liquid. The background is a soft, out-of-focus light blue.

STEM CELLS IN CLINICAL APPLICATION AND PRODUCTIZATION

Editor:
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Stem Cells in Clinical Application and Productization

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Stem Cells in Clinical Application and Productization

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FOREWORD

Stem cells possess self-renewal and multi-lineage differentiation potential, which are capable of differentiating into more than 200 types of functional cells in vitro and thus hold promising applications in regenerative medicine. Generally, stem cells can be divided into four types: totipotent stem cells (*e.g.*, zygotes), pluripotent stem cells (*e.g.*, embryonic stem cells, induced pluripotent stem cells), multipotent stem cells (*e.g.*, mesenchymal stem/stromal cells, neural stem cells), and unipotent stem cells (*e.g.*, amniotic epithelial stem cells, hematopoietic stem cells).

State-of-the-art renewal has indicated the combination of biomaterials (*e.g.*, hydrogels, hydroxyapatites, nano-materials, scaffolds) with mesenchymal stem/stromal cells (MSCs), which are heterogeneous populations with unique hematopoietic-supporting and immunoregulatory properties for tissue engineering purposes. For decades, we and other investigators have demonstrated the promising prospects of MSC-based tissue engineering in regenerative medicine, and in particular, for the administration of recurrent and refractory disease. Very recently, a number of talented experts took advantage of the biomaterial/MSC composite or scaffolds for applications in osteoarthritis, burn wounds, and refractory wounds associated with diabetic foot as well. Strikingly, the composite or scaffold showed superiority in the continuous improvement of the biological functions of the injured areas over biomaterials or MSCs, respectively. Therewith, stem cells, and biomaterials are recognized as “seeds” and “soils”, which are of equal importance for tissue engineering. Collectively, stem cell and biomaterial-based tissue engineering is a core frontier area for disease remodeling and the accompanied regenerative medicine in the future.

Therewith, in this book, Professor Leisheng Zhang in our team and the coauthors have summarized the latest updates of biomaterial/stem cell composites in tissue engineering and put forward the hotspot issues in the future including 3D printing, biomaterial/MSC-exosomes in preclinical and clinical applications.

Zhongchao Han

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PREFACE

Stem cells with self-renewal and multi-lineage differentiation potential have highlighted regenerative medicine for diverse refractory and recurrent disease administration. This book mainly focuses on the landscape of the biological properties and translational research of representative types of stem cells, including hematopoietic stem cells (HSCs), neural stem cells (NSCs), and mesenchymal stem/stromal cells (MSCs). Meanwhile, we are aiming to introduce the latest updates and development prospects of stem cells alone or in combination with advanced biomaterials and technological innovations toward large-scale standardization and productization. Collectively, the content will help enlighten the understanding and further development of stem cell-based innovative medicine and healthcare.

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CHAPTER 1

The Historical Overview of Stem Cells

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Abstract: Stem cells of hierarchical clustering have emerged as alternative and promising sources for tissue engineering and regenerative medicine. Owing to the unique self-renewal and multi-lineage differentiation attributes, stem cell-based cytotherapy has evoked great expectations in handling numerous refractory and recurrent diseases. Of note, quality control (QC), good manufacturing practice (GMP), and guidelines for stem cells and the derivations are prerequisites for evaluating the safety and efficacy of stem cell-based remedies. In this book, we principally focus on the definition, classification, signatures and functions, safety and efficacy of stem cells, together with the core concerns upon stem cell-based clinical applications and investigational new drug (IND) and new drug application (NDA). Collectively, this

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book will effectively benefit the novel stem cell-based tissue engineering and regenerative medicine.

Keywords: Amniotic stem cells, Constitutive microenvironment, Embryonic stem cells, Exosomes and small microvesicles, Hematopoietic stem cells, Hematopoietic-supporting effect, Immunomodulation, Immunoregulatory property, Induced pluripotent stem cells, Investigational new drug, Mesenchymal stem/stromal cells, Multipotent stem cells, Neural stem cells, Pluripotent stem cells, Refractory and recurrent disease, Regenerative medicine, Stem cells, Tissue engineering, Totipotent stem cells, Uni-potent stem cells.

INTRODUCTION

Stem cells are unique cell types of undifferentiated population, which are characterized by self-renewal and multi-lineage differentiation features, and thus hold promising prospects in tissue engineering and regenerative medicine [1]. State-of-the-art renewal has indicated the involvement of stem cells in a variety of physiological and pathological processes. On the one hand, numerous preclinical and clinical investigations have highlighted the therapeutic prospects in multiple refractory and recurrent disease administration, including hematological and circulatory diseases (*e.g.*, acquired aplastic anemia, acute lymphoblastic leukemia, graft-versus-host disease, acute myocardial infarction) [2 - 5], urogenital diseases (*e.g.*, premature ovarian failure, Turner's syndrome, intrauterine adhesion, thin endometrium, male erectile dysfunction, female stress urinary incontinence, interstitial cystitis) [6 - 10], neurological disorders (*e.g.*, Parkinson's disease, Alzheimer's disease, cerebral stroke, infantile cerebral palsy, spinal cord injury) [11 - 16], motor system diseases (*e.g.*, osteoarthritis, meniscus injury, osteonecrosis of the femoral head, critical limb ischemia) [17 - 19], respiratory diseases (*e.g.*, bronchopneumonia, chronic obstructive pulmonary disease, anaphylactic rhinitis, and even COVID-19-induced acute lung injury and acute respiratory distress syndrome) [20 - 24], cutaneous diseases (*e.g.*, decubitus, refractory wounds, allergic dermatitis) [25 - 27], immune diseases (*e.g.*, systemic sclerosis, systemic lupus erythematosus, rheumatoid arthritis) [28 - 32], endocrine and metabolic diseases (*e.g.*, diabetes and complications, osteoporosis, hyperuricemia and gout) [33 - 36], and digestive diseases (*e.g.*, decompensated liver cirrhosis, acute colitis, chronic acute liver failure, Crohn's disease, ulcerative colitis) [37 - 44]. On the other hand, we and other investigators in the field have also devoted to dissecting the potential pathogenicity of stem cells *via* secretion, dysimmunomodulation, and providing a constitutive microenvironment [20, 38, 45]. For instance, we recently reported the multifaceted variations in the biological phenotypes and transcriptomic features of bone marrow-derived mesenchymal

stem/stromal cells (BM-MSCs) in patients with acquired aplastic anemia and acute myeloid leukemia [45, 46].

Despite the detailed information of the mode of action of stem cells is still far from satisfaction, yet the overall ways of function have been extensively described, including direct-differentiation, trans-differentiation, dedifferentiation, autocrine and paracrine (*e.g.*, exosomes, small microvesicles, cytokines, anti-inflammatory factors), bidirectional immunomodulation, and constitutive microenvironments [1, 13, 47 - 49]. For instance, Yuan *et al.* put forward the therapeutic applications and the concomitant “SMART” principles (including self-renewal, multi-lineage differentiation, apoptosis, rest, and trafficking) of hematopoietic stem cells (HSCs) for hematologic malignancy administration [50]. Instead, Zhao *et al.* highlighted the underlying mechanism of HSC-based cytotherapy for continuous blood cell generation *via* orchestrating cell proliferation, self-renewal, and cell differentiation in the microenvironment [51]. As to MSC-based remedies, we and the colleagues also verify the way of action such as differentiation, secretion, hematopoietic-supporting effect and bidirectional immunoregulation [4, 18, 20].

In this chapter, we mainly focus on the multifaceted characterization of the definition, classification, and the features of stem cells, which will supply overwhelming new references for further understanding the historical overview as well as dissecting the fundamental and clinical investigation of stem cell-based tissue engineering and regenerative medicine.

THE DEFINITION AND HISTORY OF STEM CELLS

In 1868, Ernst Haeckel and the colleagues originally put forward the definition of “Stammzelle” (stem cells) for the description of the ancestor unicellular organisms for the evolvement of all multicellular organisms, who were also the pioneering proponent of the “Anthropozoic Age” concept [52, 53]. In 1902, hematopoietic progenitor cells (HPCs) were identified from bone marrow, and HPC-based transplantation was accomplished for aplastic anemia treatment in 1939 [54]. In 1957, E. Donnall Thomas reported the first allogeneic transplantation of hematopoietic stem cell transplantation (HSCT) by combining the unfractionated mononuclear population with immune suppressive regimens [55 - 57]. In 1968, Friendenstein and the collaborators verified the distinctions between HSCs and stromal cells in the bone marrow environment, which were further named “mesenchymal stem/stromal cells” by Arnold I Caplan *et al* in 1991 [58, 59]. In 1990s and 2000s, pluripotent stem cells (PSCs) including embryonic stem cells (ESCs) and induced PSCs (iPSCs) were identified with the aid of OSKM factor (also known as “Yamanaka factors”, including OCT4, SOX2,

Biomaterials and Stem Cells

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Abstract: Longitudinal studies have indicated the involvement and performance of multitudinous biomaterials for stem cell-based cytototherapy and regenerative medicine largely attribute to their specific biocompatibility. Currently, stem cells and biomaterial scaffolds have been considered as the two essential elements of the cornerstone of tissue engineering. On the one hand, biomaterials are beneficial to provide suitable microenvironments for enhancing the cellular vitality and therapeutic effect of stem cells. On the other hand, biomaterial-induced fibrosis and inflammation remain a prominent challenge in designing and synthesizing appropriate materials to facilitate tissue repair and organ regeneration. In this book chapter, we summarize the classifica-

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tion and physicochemical properties of the indicated biomaterials, and appraise the latest literatures of biomaterial and stem cell composite for broad biomedical applications in tissue engineering and regenerative medicine. Collectively, we retrospect the current advancement of biomaterial engineering and science, and highlight the multifaceted biomaterial-assisted stem cell-based tissue engineering and regenerative medicine, and in particular, the biomaterial-based composites with mesenchymal stem/stromal cells (MSCs) and the derivatives (*e.g.*, exosomes, small microvesicles) for intractable disease administration.

Keywords: Biomaterials, Biocompatibility, Clinical trials, Cancer immunotherapy, Exosomes, Hyaluronic acid, Hydrogels, Immunomodulation, Mesenchymal stem/stromal cells, Microenvironment, Nanomaterials, Organ regeneration, Physicochemical properties, Preclinical applications, Regenerative medicine, Stem cells, Small microvesicles, Scaffold, Tissue engineering, Three-dimensional printing.

INTRODUCTION

State-of-the-art renewal has indicated the superiority of biocompatible and biodegradable biomaterials in facilitating the ameliorative or therapeutic effect of stem cells upon numerous intractable diseases as well as enhancing immune cell manifestations during anti-cancer immunity [1 - 3]. Generally, biomaterials play an ancillary role with the objective of endowing the special ability of encapsulated constituents such as stem cells, immune cells, and derivatives (*e.g.*, exosomes). For example, the orientation and conformation of the proteins in dendritic cell-derived exosomes (DC-exo) can be altered and thus form “biomaterial-associated molecular patterns (BAMPs)” with the adsorbed biomaterial surfaces [4]. As to the immunogenicity problem, Jiang *et al.* reviewed alternative solutions with the aid of genetically modified cell-based biomaterials carrying particular immunomodulatory genes [5]. Even though, the intrinsic shortcomings of the current genetically modified stem cell-based or immune cell-based biomaterials remain to be overcome, such as nonspecific effects, uncertain biosecurity, and overlooked personalization [5]. In addition to that, we foresee that the next generation of biomaterials for tissue engineering and regenerative purposes will entail more effective interactions with the encapsulated cells including stem cells and the derivatives.

In this chapter, we are principally concerned with the latest updates in stem cell-based cytotherapy and tissue engineering by combining stem cells or derivatives with well-established biomaterials such as hyaluronic acid (HA) and nanomaterials, which will supply new references and benefit the development of stem cell-based biomaterials and biomedicine.

HYDROGEL/STEM CELL COMPOSITE

Current studies have suggested the cell-laden hydrogels as a tissue-engineering platform with promising prospects for reinforcing the biological properties and biofunctions of the encapsulated objectives [6]. Of them, gelatin and hyaluronic acid (HA) have been recognized as the two major components of the extracellular matrix in various tissues, which are appealing for the generation of compatible hybrid hydrogels *via* orchestrating the scaffold structure, specific composition, and physico-chemical property [7]. For example, Madhusudanan *et al.* considered hydrogels rather than relative scaffolds as excellent candidates for the preparation of neural cells and the resultant neural tissue engineering (NTE) attributed to their intrinsic properties in orchestrating immune microenvironment and secreting the antagonists of neural growth inhibitors, neurotrophic factors, and relative neural growth-promoting agents [8]. Meanwhile, Xiao *et al.* and Celikkin *et al.* reviewed the Gelatin methacrylate-based hydrogels in tissue engineering applications based on the biofunctionality and mechanical tenability (*e.g.*, chemical properties, physical strength, porosity, and conductivity) [9, 10].

Of note, state-of-the-art renewal has also highlighted the gelatin methacrylate-based hydrogels with controlled microstructures and excellent 3D scaffolds for facilitating cellular vitality and tissue engineering, including microfibers, microspheres, microgrooves, microridges, microchannels, microwells, and micropillars [11]. For instance, Khayambashi *et al.* figured out hydrogel encapsulation in enhancing the maintenance of the biological activity and controlling the release of paracrine factors from MSCs and MSC-exos [12]. Similarly, Tang *et al.* and Han *et al.* discussed the exosome-loaded thermosensitive hydrogels and 3D-cultured MSC-exo/hydrogel hybrid patch for corneal epithelium regeneration and spinal cord repair, respectively [13, 14].

Of note, current studies have also indicated that cryogels and other tissue equivalents could also act as good carriers for stem cells [15, 16]. As a specific hydrogel, cryogels are a category of macroporous and interconnective hydrogels that can polymerize at sub-zero temperatures, and thus form mechanically robust and elastic networks [17]. For stem cells, cryogels and the concomitant cryogelation are adequate to provide a unique and sponge-like structure for cell cultivation and the resultant tissue regeneration [18, 19].

Overall, a variety of hydrogel/stem cell composites have been continuously developed for regenerative purposes, including MSCs/thermosensitive hydroxypropyl chitin hydrogel (HPCH), ϵ -caprolactone (PCL)/nano-hydroxyapatite (nHA) scaffold, injectable chitosan hydrogel, and PCL/nHA + HPCH hybrid scaffolds [20, 21].

CHAPTER 3

Hematopoietic Stem Cells in Regenerative Medicine

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Abstract: Hematopoietic stem cells (HSCs) are a common origin of blood cells and the intermediate progenitor cells and precursor cells including the myeloid or lymphoid lineages, which are the footstones of short-term and long-term blood regeneration. HSCs are precisely orchestrated by the constituents in the hematopoietic microenvironment in the bone marrow niches such as stromal cells, immune cells, and cytokines. The dysfunction and genetic variations of HSCs might lead to hematopoietic abnormality, haematopoietic equilibrium and even hematologic malignancies. Meanwhile, the cellular and molecular mechanisms of HSC maintenance and differentiation according to the niche are of great importance for disease administration via hematopoietic stem cell transplantation (HSCT). In the chapter, we mainly focus on

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the works of literature on the definition, biological phenotypes, preclinical investigation and clinical trials of HSCs, which will collectively facilitate the clinical application of HSCT and the relative regenerative medicine for hematological diseases and immune diseases in future.

Keywords: Acute myeloid leukemia, Acute lymphocytic leukemia, Biological phenotypes, Bone marrow microenvironment, Biological features, Classification, Chronic lymphocytic leukemia, Chronic myeloid leukemia, Hematopoietic diseases, Hematopoietic stem cells, Hematopoietic stem cell transplantation, Homeostasis, Hematogenesis, Hematologic malignancies, Hematopoietic progenitors, Immune diseases, Molecular mechanisms, Regenerative medicine, Safety and efficacy, Stem cells.

INTRODUCTION

Hematopoietic stem cells (HSCs) are rare and unique cell populations with remarkable features of self-renewal and lineage differentiation potential towards differentiated hematological cell lineages [1, 2]. HSCs can be divided into the quiescent subpopulation and the activated subset, which are elaborately orchestrated by the hematopoietic microenvironment in the bone marrow [3]. HSCs reside in the microenvironment and are modulated by stromal cells and relative constitutive elements in the niches, which thus determine the quiescence of HSCs and the differentiation of hierarchy of blood cells [4, 5]. On the basis of the specific properties, HSCs sustain the lifelong generation of blood precursor cells and functional blood cells, together with immune cells at various stages of differentiation and maturation [6, 7]. Therewith, HSCs play a crucial role in both physiologic and pathological hematogenesis, and the concomitant HSCT [8].

In this chapter, we mainly summarize the state-of-the-art renewal and the challenges of HSCs from the aspects of definition, biological phenotype, hematopoietic microenvironment, regulation of hematopoiesis in physiologic hematopoiesis and pathological hematologic malignancies. Taken together, the contents in this chapter will help boost our understanding of HSC-based cytotherapy, and in particular, hematopoietic stem cell transplantation (HSCT) for blood production and hematopoietic reconstitution *via* the hierarchical organization of HSCs and their progenies including progenitor cells and precursor cells, which will collectively benefit HSC-based investigations for regenerative purposes.

THE OVERVIEW OF HEMATOPOIETIC STEM CELLS (HSCS)

HSCs present at the apex of the hematopoietic hierarchy of progeny cells and blood cells. As mentioned above, the typical property of quiescent HSCs is that

they principally maintain in the interphase of cell cycle (the G₀ stage) and divide infrequently as well, while the activated HSCs are adequate to program into differentiated progeny and sustain the hematopoietic homeostasis [4, 9].

The maintenance of HSC pool and the derivatives is modulated by a complex network of stromal cells, endothelial cells, extracellular matrix, cell cycle proteins, nutrients, transcriptional factors, and microenvironment in an orchestrated fashion [10 - 12]. Nowadays, aging has been considered to show a broad impact upon the biofunction of hematopoietic system, and in particular, the heterogeneous HSC population [13]. Interestingly, mounting evidences have indicated the diversity and multi-layered hierarchy of the hematopoietic system, which will supply new insights into hematogenesis and facilitate *ex vivo* preparation of engraftable and functional multi-lineage blood cells [14].

Despite the widely application for HSCT and gene therapy, the amount of HSCs for large-scale treatments is still unavailable due to the deficiency in *ex vivo* preparation. For the purpose, numerous talents are devoted themselves to improving the yield and maturation of HSCs by utilizing small-molecule compound- or cytokine cocktail-based programming, and the direct-differentiation from human pluripotent stem cells (hPSCs) including human embryonic stem cells (hESCs) and the induced pluripotent stem cells (hiPSCs). Even though, the efficient procedures for expansion, purification and generation of HSCs are still urgently needed to be resolved in future [2].

THE ORIGINS AND DEVELOPMENT OF HSCS

State-of-the-art renewal in mice has challenged the current paradigm of single long-term HSCs for regenerating all the constituents of the mammalian immune system [15]. Of note, there are more and more studies upon the origins and the development of HSCs *via* dissecting the epigenetic and transcriptional signatures of HSCs and the progeny [4, 16]. To date, over 80 common gene expression modules have been involved in the assessment of distinct populations at various sub-stages of HSC differentiation [17]. For example, studies have shown the hierarchy within acute myeloid leukemia (AML), including the CD34⁺CD38⁻ fraction in leukemic stem cells (LSCs), CD34⁺CD38⁺ leukemia progenitor cells, and CD34⁻ leukemic blasts [18 - 20]. At the meantime, the specific and differentiated hematopoietic microenvironment further complicates our understanding of the resident HSCs [21]. Very recently, Bigas and the colleagues highlighted the latest updates and the feasibility of using PSCs for further dissecting the normal and abnormal hematopoietic development, which were supposed to recapitulate the leukemic transformation processes *in vitro* and served as a promising model for the hematopoietic and leukemia development [22]. Even

Neural Stem Cells in Tissue Engineering

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Abstract: Neural stem cells (NSCs) are unique subsets of stem cells with self-renewal and multiple lineage differentiation potential, which are considered promising cell sources for neuron generation and complex cognitive and sensory functions, and the resultant NSC-based cryotherapy for regenerative purposes. Of them, distinguished from the small amount of activated subset, most of the NSCs are maintained in the quiescent state and reveal a low level of metabolic activity but a high sensitivity to the environment. The dynamic balance between quiescence and the activity of NSCs determines both the efficiency of neurogenesis and the long-term maintenance and self-renewal of the NSC pool as well as the neurogenic capacity of the brain. In this chapter, we mainly review the classification and biofunction of NSCs, and introduce the significant progress in the understanding of NSC-based applications and the underlying molecular mechanism for NSC quiescence, the dysfunction in neurogenesis, and the pathogenesis of neurological disorders. Collectively, these data will facilitate

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the development of NSC-based cytotherapy for a broad spectrum of refractory and recurrent diseases in the future.

Keywords: Alzheimer's disease, Amyotrophic lateral sclerosis, Biological features, Cerebral palsy, Classification, Definition, Fetal alcohol spectrum disorders, Human pluripotent stem cells, Microenvironment, Multiple lineage differentiation, Multiple sclerosis, Neural stem cells, Neurodegenerative diseases, Parkinson's disease, Peripheral arterial disease, Psychiatric illnesses, Safety and efficacy, Self-renewal, Stroke, Spinal cord injury.

INTRODUCTION

Neural stem cells (NSCs) have been recognized as tumor-tropic cells with self-renewal and multi-lineage differentiation properties towards all types of nerve cells and the concomitant complex nervous system [1, 2]. Two decades ago, NSCs were first identified in the adult brain with the capacity to produce new neurons for the repair of impaired nervous system [3]. Nowadays, it is well-known that the cell sources of NSCs are diverse from embryonic origins to adult origins, including human embryonic stem cells (hESCs), human induced pluripotent stem cells (hiPSCs), direct reprogrammed astrocytes, and neural stem /progenitor cells (NSPCs) derived from fetal brain [4]. Of note, recent works of literature have also indicated the variations in the NSC microenvironment, which is also known as NSC niche heterogeneity for the modulation of NSC differentiation potential towards specific nerve cells [5, 6]. Otherwise, the dysregulation of NSCs by the components in the niche usually leads to neurodegenerative diseases [7].

The stem cell niche, also known as the stem cell environment, is adequate to circumscribe and regulate stem cell fate in the naive state, which thus provides a complex contribution and impact to stem cells in various biological processes [6]. The development of NSCs and the progeny is precisely modulated by the close-knit and synchronized interactions between the enteric NSCs and the niche [8]. To date, NSCs and neuron progenitors have been employed for the treatment of various neurodegenerative diseases [9, 10]. For example, NSC-based transplantation (NSCT) for spinal cord injury (SCI) is recognized as one of the most promising and representative therapeutic remedies in pre-clinical practice [11]. Meanwhile, talented investigators in the field also turned to transcriptional analyses for the dissection of the genetic characteristics and gene expression profiling in NSCs during embryonic and adult neurogenesis [3, 12, 13].

In this chapter, we aim to review the basic knowledge of NSCs or neural stem/progenitor cells (NSPCs) and the concomitant NSCT, including the

conception, biological properties, origins and treatment of neurological diseases, and the underlying molecular mechanism as well. Collectively, the content in this chapter will benefit the development of novel remedies for neurodegenerative diseases and NSC-based regenerative medicine strategies for combating the central nervous system (CNS) injury in future.

THE OVERVIEW OF NEURAL STEM CELLS (NSCS)

Neural stem cells (NSCs) are a category of stem cells for neurogenesis, which are the origins of glia and neurons and possess the capacity for generating all kinds of differentiated neural cells via producing intermediate precursors, NSC secretomes according to neurodevelopment [14 - 16]. However, the failure or disorder in the regulation of NSCs might cause impaired memory and learning, brain malformation, neurodegenerative diseases, and tumor development [4, 17].

Therefore, the precise and dynamic control of NSC proliferation, migration and differentiation is very crucial and essential for the spatio-temporal development and biofunction of human brain [16, 18]. For example Kageyama *et al.* discussed the biofunction of basic helix-loop-helix (bHLH) family members (*e.g.*, *Ascl1*, *Hes1*, and *Olig2*) in the dynamic control of NSC vitality and cell-fate determination including the maintenance and proliferation, and in particular, the *Hes5*-mediated the switching of NSC competency and the development of the nervous system [19]. Furthermore, Ming *et al.* and Zhu *et al.* highlighted the emerging principles for NSC-based neurobiology, disease remodeling, electrical stimulation, and neural plasticity during adult neurogenesis in the brain [20, 21]. Currently, numerous literatures have indicated the promising perspectives of NSC-based cythotherapy for neurodegenerative disease management both preclinically and clinically such as Huntington's disease (HD), Alzheimer's disease (AD), stroke, glioblastoma multiforme, and amyotrophic lateral sclerosis (ALS) [10, 22 - 24].

THE ORIGINS AND DEVELOPMENT OF NSCS

State-of-the-art updates have elucidated the generation of NSCs with inherent plasticity from the neuroepithelium in the neural tube, which further develops into radial glial cells, and followed by receding at later developmental stages committed to the neural lineages and biofunctional nerve cells [25 - 27]. During the past decades, numerous procedures of neurogenesis have been established and various molecular biomarkers have been identified for the exploration of embryonic or adult NSCs [17]. NSCs are known to persevere in the postnatal brain and result in the generation of neurons and neuroglia [5, 17].

Therewith, NSCs can be enriched from both embryonic and adult brains, and new

Biomaterials and Mesenchymal Stem Cells

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Abstract: Mesenchymal stem/stromal cells are splendid cell sources for tissue engineering and regenerative medicine attributed to the unique hematopoietic-support and immunomodulatory properties as well as the multi-dimensional differentiation potential towards adipocytes, osteoblasts, and chondrocytes *in vitro* and *in vivo*. To date, MSCs have been identified from various approaches, such as perinatal tissues, and adult tissues, and even derived from human pluripotent stem cells (hPSCs). Longitudinal studies have indicated the ameliorative effect and therapeutic efficacy upon a variety of refractory and recurrent disorders such as acute-on-chronic liver failure (ACLF), acute myeloid leukemia (AML), premature ovarian failure (POF), and intractable wounds. To date, MSCs have been found to have various origins, including mesoderm, endoderm and ectoderm. In this chapter, we mainly focus on the concepts, and biological and therapeutic properties of MSCs, together with the standardizations for industrial transformation. Overall, the descriptions would help promote a better

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understanding of MSCs in disease pathogenesis and management and benefit the preclinical and clinical applications in the future.

Keywords: Adipocytes, Biological features, Chondrocytes, Classification, Cytotherapy, Definition, Human pluripotent stem cells, Immunomodulation, Industrialization, Molecular mechanism, Multi-dimensional differentiation, Osteoblasts, Preclinical and clinical applications, Refractory and recurrent disorders, Regenerative medicine, Safety and efficacy, Secretion, Standardization, Stem cells, Tissue engineering.

INTRODUCTION

Mesenchymal stem/stromal cells (MSCs) were first identified from clinical samples of patients, which were different from the well-established hematopoietic stem cells (HSCs). In detail, Friedenstein *et al.* reported the first identification of MSCs from bone marrow (BM-MSCs) with long-spindle morphology in 19681. After that, MSCs of different origins have been isolated from various tissues such as adult tissues (*e.g.*, adipocyte tissue, dental pulp, bone marrow, tendon, smooth muscle) and perinatal tissues (*e.g.*, umbilical cord, amniotic membrane, placenta)², and even derived from PSCs including ESCs and iPSCs³⁻⁷. Of them, BM-MSCs and the perinatal tissue-derived MSCs are considered with the most extensive applications in clinical trials and the most robust *in vitro* proliferation capacity, respectively [8 - 11].

Nowadays, MSCs and their derivatives including exosomes and small extracellular vesicles (MSC-exo, MSC-sEVs) have been extensively explored as the key component in the microenvironment by both preclinical and clinical investigations for the pathogenesis of hematologic malignancies and the development of novel cytotherapy for relapse and recurrent disorders [12]. Interestingly, Zhang *et al.* verified that the outcomes of rats with acute liver failure (ALF) were various due to the alterations of transplanted MSCs, whereas Zhao *et al.* found that UC-MSCs at various passages (passages 3, 6, 15) revealed diversity in the efficacy upon mice with acute graft-*versus*-host disease (aGvHD) [11, 13].

In this chapter, we aim to present the latest updates of MSCs and the concomitant MSC-based tissue engineering, their definition, the historical overview, biological and molecular properties, their origin and development, and the standardizations and industrialization, which will benefit further investigation of MSCs with respect to the pathogenesis and the concomitant regenerative medicine in future.

THE BIOLOGICAL PROPERTIES OF MSCS

Mesenchymal stem cells (MSCs), also known as mesenchymal stromal cells, multipotent stem cells, and medicinal signaling cells, are a heterogeneous population and have been regarded as advantaged cell sources with unique immunomodulatory and hematopoietic-supporting properties, together with tri-lineage differentiation potential towards adipocytes, osteoblasts, and chondrocytes [3, 11, 14].

For a long period, there were many definitions of MSCs due to the lack of unified understanding or consensus on MSCs. In 2005, the first version of the golden criteria for MSC clarification was published by the International Society for Cellular Therapy (ISCT). According to the documents, there are three contents including (1) fibroblast-like and plastic-adherent morphology; (2) the population with a high proportion of mesenchymal-associated surface markers over 95% (CD73, CD90, CD105) but the percentage with minimal hematopoietic- or immune-associated surface markers less than 5% (*e.g.*, CD34, CD45, HLA-DR); (3) The population revealed multi-lineage differentiation capacity towards adipocytes, osteoblasts and chondrocytes under indicated stimulations [15]. However, it is still noteworthy that the detailed information on MSCs contributing to the microenvironment and further classification of the subpopulations with specific properties are still pivotal and lack clarification as well.

To date, a series of functional experiments *in vitro* and *in vivo* have been explored to test the multifaceted biofunctions of MSCs. As mentioned above, besides the classical tests upon the immunophenotype and multi-dimensional differentiation, the relative experiments such as mixed lymphocyte culture (MLC), hematopoietic colony formation unit (CFU), Transwell assay, co-culture of mono-nuclear cells (MNCs) with MSCs, cobblestone area-forming cell (CAFC) test, Matrigel assay for angiogenesis evaluation, and immunohistological examination of subcutaneous tumorigenesis have been carried out [2, 11, 16, 17].

THE ORIGINS AND DEVELOPMENT OF MSCS

MSCs have been identified with heterogeneity, which are partially ascribed to the diverse origins with inherent properties of the origin areas [4, 18, 19]. For instance, the adipose tissue-derived MSCs (AD-MSCs) showed superiority in adipogenic differentiation potential over those derived from other counterparts such as bone marrow, dental pulp, and umbilical cord [20, 21]. Instead, bone marrow-derived MSCs (BM-MSCs) and dental pulp-derived MSCs (DPSCs) displayed preferable osteogenic differentiation potential and teeth repair capacity, respectively [22 - 24]. Of them, umbilical cord-derived MSCs (UC-MSCs), placenta-derived MSCs (P-MSCs), and pluripotent stem cell-derived MSCs (PSC-

Stem Cells-Based Technological Innovation in Tissue Engineering

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Abstract: Stem cells are a category of cells with self-renewal and multi-lineage differentiation capacity, which have been recognized as advantaged sources for tissue engineering and regenerative medicine. To date, stem cells and their derivatives alone or combined with biomaterials have aroused extensive and sustained attention to investigations in the field of fundamental research and clinical practice. In recent years, a series of novel technologies have been involved in stem cell-based cytotherapy, such as three-dimensional (3D) printing, organoid research, and multitudinous kinds of gene-editing technologies, which collectively facilitate the development of tissue engineering for disease administration. In this chapter, we summarized the rudimentary knowledge of the aforementioned new technologies, together with the promising perspective and the concomitant challenges, which would help increase the cognition of technological innovation for stem cell-based investigations and remedies in the future.

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Keywords: Bioprinting products, CRISPR/Cas9, CAR-T, Deoxyribonucleic acid, Gene knock-out, Gene knock-in, Human embryonic stem cells, Human induced pluripotent stem cells, *In vivo* organogenesis, Kidney organoid, Lipid nanoparticles, Modeling diseases, Molecular mechanisms, Organoids, Single-cell transcriptomics, Stem cells, Scaffolds, TALENs, Three-dimensional printing, Tissue engineering.

INTRODUCTION

Stem cells of various origins in the niche, including those from the embryonic stage and the adult tissues, are a unique cell population with self-renewal and multi-lineage differentiation [1, 2]. Due to the abovementioned properties, stem cells can be divided into pluripotent stem cells (PSCs, including embryonic stem cells and induced PSCs), perinatal stem cells (*e.g.*, umbilical cord-, amniotic membrane-, amniotic fluid-, and placenta tissue-derived stem cells), and adult stem cells (*e.g.*, dental pulp-, apical papilla-, adipose tissue-, bone marrow-, and muscle tendon-derived stem cells) [3 - 5]. Of them, hematopoietic stem cells (HSCs) and mesenchymal stem/stromal cells (MSCs) function critically in hematogenesis and immunomodulation, respectively, which have been explored with the widest range of clinical applications for numerous refractory and recurrent disease management, such as hematologic disorders and malignancies (*e.g.*, acute myeloid leukemia, acquired aplastic anemia, multiple myeloma, myelodysplastic syndrome, acute lymphocytic leukemia), degenerative diseases (*e.g.*, Parkinson's disease, Alzheimer's disease, osteoarthritis, meniscus injury), and diseases associated with immune abnormalities (*e.g.*, rheumatoid arthritis, systemic lupus erythematosus, allergic asthma, graft-versus-host disease) [6 - 11].

In recent years, novel stem cell-based technologies have continuously emerged and further accelerated the development of concomitant cytotherapy and regenerative medicine [12 - 14]. To date, we and other investigators in the field are devoted to developing a variety of advanced technologies, including organoid, gene editing, three-dimensional (3D) printing, *in vivo* fluorescence tracer, and single cell sequencing, which conformably reveal promising prospective and vastly facilitate tissue engineering in combination with stem cells [15 - 20]. For example, Kim and colleagues summarized the application of 3D stem cell systems for tissue repair and regeneration, including the 3D stem cell spheroids and the 3D stem cell organoids for mimicking the *in vivo* environments [15]. In the chapter, we described the concepts and the instances of the aforementioned revolutionary technology in stem cell-based approaches for regenerative purposes.

THREE-DIMENSIONAL (3D) PRINTING

3D printing has emerged as an exciting branch of manufacturing technology by fusing single or varied materials together in a layer-by-layer manner for the construction of an integrated 3D product [21 - 23]. Therefore, compared with the traditional manufacturing process, 3D printing based on stem cells and appropriate biomaterials offers high flexibility in the design and preparation of personalized and off-the-shelf medical production that accommodate the needs of patients, which thus transforms the way of stem cell-based tissue engineering [18, 23]. For instance, 3D bioprinting products including the instrumentation and implants have indicated transformative bone and cartilage restoration procedures for treating inpatients with varying degrees of musculoskeletal injuries by combining orthopaedic surgery with stem cell-based medicine [23].

During the past decades, 3D bioprinting and additive manufacturing have achieved rapid development with decreasing costs due to the progress in new common printing methods, material synthesis, and education of patients and trainees [24, 25]. For example, the injectable conductive hydrogels have been considered an ideal biomaterial for 3D bioprinting and tissue engineering scaffolds, which are adequate to facilitate the communication of specific electrical signals among cells and thus simulate the physiological or pathological microenvironment of electroactive tissues [18]. To date, 3D bioprinting has been involved in a variety of refractory and recurrent disease management as well as multifaceted regenerative purposes, such as otorhinolaryngology, urology, spine surgery, the retina, minimally invasive cardiac surgery, orbital diseases, the reconstruction of congenital defects, orbital trauma, cardiovascular diseases, and tumor resection [22, 24, 26 - 29]. Collectively, 3D bioprinting has been employed in a series of surgical and medical specialties for the improvement of advanced resident physician training and the concomitant patient care [30].

ORGANOID

Organoids are three-dimensional (3D) *ex vivo* culture systems generated from self-organizing stem cells, which are 3D structures comprised of diverse cell types and self-organized to recapitulate and mimic the spatio-temporal processes of embryonic and tissue development *in vitro* [31 - 33]. Different from the two-dimensional (2D) culture methods, the 3D organoids with favorable architecture and microenvironment reveal multifaceted advantages of stem cell maintenance and differentiation, conducting high-throughput pharmaceutical screening, as well as mirroring architecture, functionality, and geometric properties of tissues *in vivo* [32]. Generally, organoids can be derived from various kinds of stem cells including human embryonic stem cells (hESCs) and patient-derived human

MSCs as Biological Drugs: From Manufacturing to Commercialization

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Abstract: Mesenchymal stem/stromal cells (MSCs) can be used as a therapeutic agent in regenerative medicine, owing to their unique self-renewal, multi-lineage differentiation, and immunoregulation properties. The manufacturing of authorized MSC products should depend on good manufacturing practices (GMP), Good Laboratory Practice (GLP), and Good Clinical Practice (GCP). Until now, many biotech companies have invested in developing the clinical application of MSC product all over the world. Meanwhile, the application of MSC products for human use must comply with regulations and guidance for a biotech company. In this chapter, we discuss the process and development of MSC products from production-manufacturing to commercialization.

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INTRODUCTION

Mesenchymal stem/stromal cells (MSCs) are a cohort of heterogeneous populations with multifaceted biological properties such as splendid hematopoietic-supporting effects, immunological tolerance, and multi-lineage differentiation potential [1, 2]. Since the 1960s, MSCs have been isolated and identified from adult tissues (*e.g.*, adipose tissue, bone marrow), perinatal tissues (*e.g.*, placenta, umbilical cord), and so forth [3]. Until now (~2023 years), there are more than 1400 MSCs clinical trials underway worldwide, as well as over sixty thousand scientific publications published about MSCs from 2013 to 2023 years. Currently, MSC products and the derivatives must be manufactured under Good Manufacturing Practice (GMP) conditions according to investigational new drug (IND) regulations, in other words, identification and assessment of critical quality attributes (purity, potency, and safety) for release criteria as early as the process development stage would ensure product consistency during commercial manufacturing [4, 5]. Meanwhile, the pharmaceutical Non-clinical Trial of MSC products should comply with the “Good Laboratory Practice” (GLP). Subsequently, the researchers should follow the requirements of the “Good Clinical Practice” (GCP) in the phase of clinical trials. There is an increasing need to understand the regulatory issues that have led to the development of the MSC as a medical drug product. For example, in the European Union, the development and authorization of MSCs-based products and derivatives are regulated by the European Medicines Agency (EMA), which is in charge of the certification and evaluation procedures of MSCs [6]. In Korea, the development and authorization of MSCs-based product is regulated by the Ministry of Food and Drug Safety (MFDS) and the Pharmaceutical Affairs Act (PAA), which governs the release or commercial launch of cell and gene therapy products [7]. Meanwhile, in China, the development and authorization of MSCs-based products are regulated by the National Center of Drug Evaluation (CDE) on the basis of the National Medical Products Administration (NMPA) regulations [8]. Therewith, in this chapter, we mainly describe a route for scientists, biotech companies, and clinical trial investigators toward the successful development of MSC-based therapeutic products.

PROCESS DEVELOPMENT OF MESENCHYMAL STEM CELLS PRODUCTS

In general, the process of approval for MSCs-based products is developed following a rigorous procedure as shown in Fig. (1). (1) The basic research stage:

it mainly includes cell isolation, expansion, processing, formulation, and mechanisms of action (MOA). (2) The CMC stage: it mainly includes chemistry manufacturing control (CMC), product testing and releasing, stability programs, and so forth. (3) The non-clinical stage: it mainly includes pharmacology and toxicology. (4) The IND stages: these stages mainly include pre-IND meetings, IND applications, and submission. (5) The clinical trials stage: these mainly include exploratory and confirmatory clinical trials.

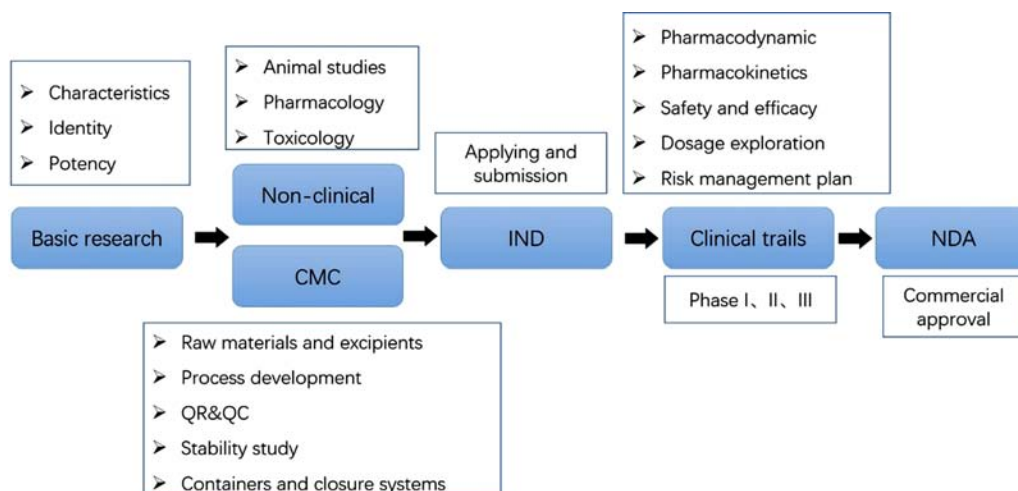


Fig. (1). Process for the generation of MSC-based clinical product in compliance with regulatory requirements of CFDA.

CHEMISTRY, MANUFACTURING, AND CONTROLS (GMP)

Stem cell products that are developed and registered as pharmaceutical products are subject to the supervision of the State Drug Administration (NMPA) and comply with the requirements of the Drug Administration Law of the People's Republic of China, the Administrative Measures for Drug Registration, and the Pharmacopoeia of the People's Republic of China and other relevant laws and regulations. The whole production process of stem cell products for human use should comply with the basic principles and relevant requirements of the Good Manufacturing Practice (GMP). The quality assurance system should supervise all production activities, from the control of raw materials, processing, testing, staff, equipment, labeling, check of production records, error detection and correction, and authorization for the final release of the product [9, 10].

Raw Materials and Excipients

Materials for production include all raw materials and excipients used in the production of MSCs products. Raw materials include starting materials

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