Frontiers in Stem Cell and Regenerative Medicine Research

Editor:
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Bentham Books

Frontiers in Stem Cell and Regenerative Medicine Research

(*Volume 11*)

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Frontiers in Stem Cell and Regenerative Medicine Research

(Volume 11)

Editor: Shazia Anjum

ISSN (Online): 2352-7633

ISSN (Print): 2467-9593

ISBN (Online): 978-981-5238-60-0

ISBN (Print): 978-981-5238-61-7

ISBN (Paperback): 978-981-5238-62-4

First published in 2024.

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PREFACE

Stem cells and regenerative medicines have enormous potential for tissue engineering, multipotency, and self-renewal ability to address future challenges. The eleventh volume of 'Frontiers in Stem Cell and Regenerative Medicine Research' is another continuous effort to further strengthen this understanding of stem cells to show how quickly and successfully they are coming up with regenerative medicine. This field is developing leaps and bounds to a real translation into clinical practice. We welcome you to read this volume, wheres reviews are written by specialists in the key areas of stem cells and regenerative medicine, and discover more about the subject.

Remarkable studies on the beneficial effect of embryology to facilitate the understanding and application of this branch of science have widely captured the interest of scientists and physicians and encouraged students to embrace this discipline. Boroujeni *et al*. discussed recent data from several clinical trials and case reports on basic embryology with clinical practice including diagnosis and management of congenital defects and management of other diseases with the help of a developmental approach. Clinical applications and research horizons have also been discussed therein.

Another interesting report from Ahmadi *et al*., discussed the details of gene expression regulation, cellular signaling transduction and interaction, and tissue development. They showed a scheme of the gene to fetus formation in a fascinating way.

León-Campos *et al*., summarized the current understanding of the role of fundamental principles of cellular differentiation in stem cells facilitated by biomaterial compositions within hydrogel matrices and explored its potential applications in regenerative medicine.

Ture *et al*., reviewed the promising treatment of sepsis, a life-threatening syndrome through stem cell therapy. It holds the potential to significantly treat infectious diseases and has a positive influence on clinical outcomes.

Undoubtedly, stem cells hold a great promise for regenerative medicine given their ability to proliferate and differentiate into various cell types. Zongjie Wang explained the current practices of assay development to fulfill this demand . Thus the joint venture of biologists, bioengineers, veterinarians, and clinicians can confidently generate quality stem cell products to change the trajectory of tissue degeneration.

We owe our special thanks to all the contributors for their valuable impact in bringing together the eleventh volume of our book. And, we also thank the editorial staff of Bentham Science Publishers, particularly Ms. Asma Ahmed and Mr. Mahmood Alam for their relentless help and support.

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CHAPTER 1

An Introduction to the Use of Embryology in Clinical Practice

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Abstract: Embryology is a part of anatomical sciences investigating formation, differentiation, growth and development of embryos and fetuses. This science is not only limited to the definition above, but it can also be used for human adults involved in perinatology, infertility, congenital defects, cell therapy and personalized medicine. This chapter aims to introduce embryology and its role in the clinical practice of physicians. The linkage of embryology and medicine is an example of the linkage between basic and clinical medical sciences. Entering to this interdisciplinary field opens a novel door for making hypotheses for future studies.

Keywords: Embryology, anatomical sciences, clinical practice, perinatology, infertility, congenital defects, personalized medicine.

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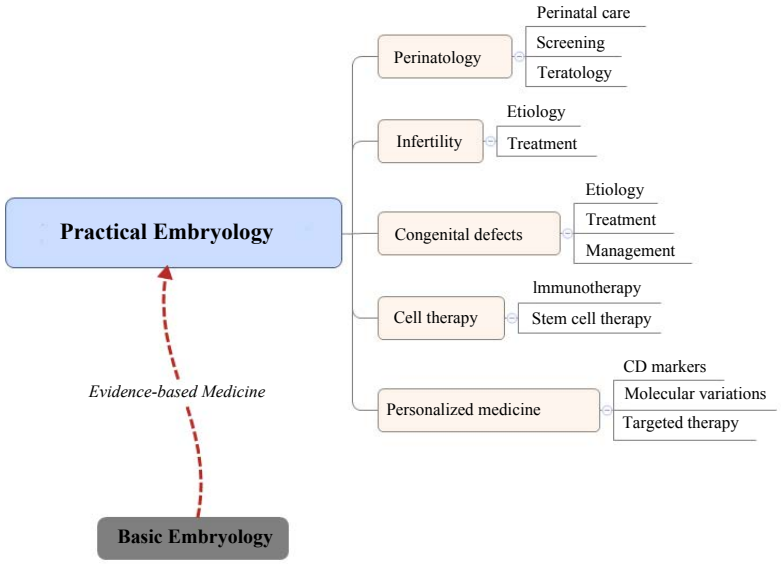
INTRODUCTION



Definitions

Embryology – sometimes called **fetology** – is a part of anatomical sciences investigating the formation, differentiation, growth, and development of embryos and fetuses. From a wider viewpoint, this science is not limited to embryos, rather it covers perinatal and even postnatal periods. In other words, embryology may be used from conception and continues until the birth of the baby, and also it is indirectly used during lifespan. Indeed, it can help physicians with the embryological basis of diseases. Nowadays, comparative and interdisciplinary approaches are used to find a developmental basis for different diseases in order to discover methods for targeted therapy and precision medicine. Both basic and practical aspects of embryology are used in this regard.

Perinatology – also known as **maternal-fetal medicine** – is a subspecialty of obstetrics and gynecology associated with maternal and fetal health from conception until a few days after the birth of the baby. However, perinatal care should start before pregnancy. **Neonatology** is a branch of pediatrics associated with neonatal care and management of neonatal diseases. The neonatal period starts from birth and ends at about one month of age (28 days).

Embryogenesis starts from the fusion of sperms and oocytes. Embryological days, weeks, and months are calculated based on this date. According to this, pregnancy is a 38-week (266-day) process in which the first 8 weeks' period is called **embryogenesis,** the first two weeks' period is called the **germinal stage**, a

period of weeks 3-8 is named the **embryonic stage**, and the next 30-week period is called the **fetal period**. In contrast to embryology, in midwifery, obstetrics and gynecology pregnancy is a 40-week (280-day) process in which the first day of pregnancy is the first day of the **last menstruation period** (LMP). In this system, days, weeks, months and trimesters are usually called "gestational" instead of "embryonic", although these terms may be used interchangeably. The rationale behind this system is that the exact day of fertilization cannot be determined based on medical history. Therefore, the first day of LMP is a day that can be remembered (Fig. **1**). The due date or **estimated date of confinement** (EDC) is calculated by adding 9 months and 7 days (about 280 days) to the first day of LMP according to Naegele's rule [1]. Since the luteal phase is usually consistent, in patients with a menstruation cycle of more than 28 days, EDC is underestimated (earlier than the real), and in patients with a menstruation cycle of less than 28 days, EDC is overestimated (later than the real); therefore, this formula should be modified patient by patient. Of course, EDC (with or without modification) is merely an estimation for normal pregnancies. In pregnancy complications such as preeclampsia, indications of pregnancy termination as well as being ready for preterm labor should be regarded to reduce fetal death and adverse pregnancy outcomes [2].

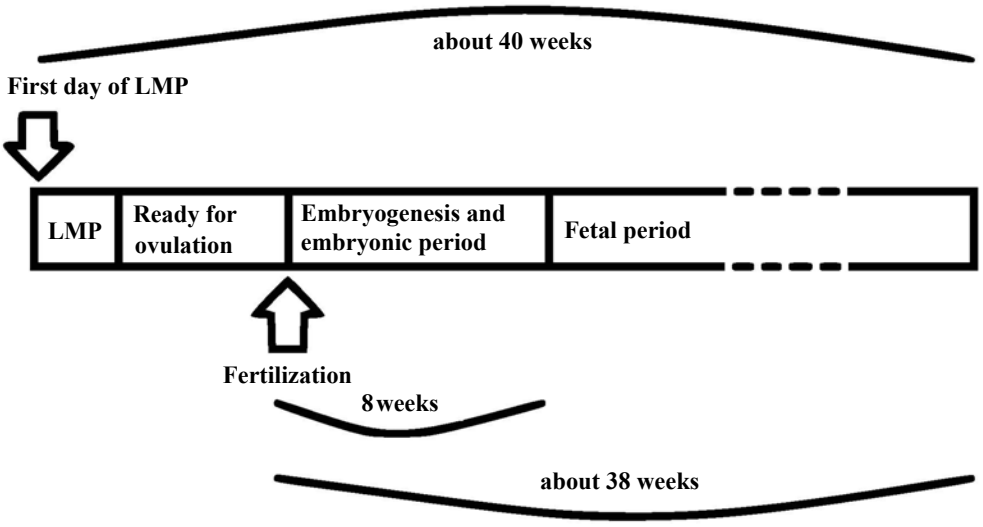


Fig. (1). Pregnancy period based on both embryology and obstetrics. If the fertilization day be 14, the exact difference between these 2 systems will be 2 weeks.

Other than natural pregnancies, some patients need assisted reproduction by **assisted reproduction technics** (ART). In pregnancies assisted with fertility

CHAPTER 2

Tissue Development: Molecular Regulation and Signaling Transduction (from Gene to Human)

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Abstract: Every human is a result of a cell formed from the fertilization of an oocyte with a sperm. This cell is called a zygote. A miracle is how just one cell can make a lot of tissues and organs. Regulation of gene expression is the first step of tissue development. Regulation of gene expression has different levels, including the genome (DNA content), transcriptome (RNA content, resulted from the transcription of DNA), and proteome (protein content, resulted from the translation of RNA) levels. The final consequence of gene expression regulation is cellular phenotype. The resulted proteins act for inter-cellular signaling transduction and tissue development. We aimed to show the details of gene expression regulation, cellular signaling transduction and interaction, and tissue development. We have shown a scheme of the gene to fetus formation.

Keywords: Tissue development, Signaling transduction, Gene expression regulation.

INTRODUCTION

Definitions

Every human is a result of a cell formed from the fertilization of an oocyte with a sperm. This cell is called a**zygote**. A miracle is how one cell can make a lot of tissues and organs. Cells resulted from the zygote up to about the fourth genera-

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tion of cell deviation (at the time of **morula** formation) are called **totipotent stem cells**. Here, totipotency means that each of these cells can *per se* create a complete human. These totipotent stem cells act as a complete genomic and epigenomic bank, having all the potential information and scripts to code all the tissues and organs of the body.

A question is that the totipotent stem cells have a common content of genetic substance, but how the resulted tissues not similar to each other. **Regulation of gene expression** (gene expression regulation) is the best answer to this question. Regulation of gene expression has different levels, including the **genome** (DNA content), **transcriptome** (RNA content, resulted from the **transcription** of DNA), and **proteome** (protein content, resulted from **translation** of RNA) levels. The final consequence of gene expression regulation is cellular **phenotype**. It should be noted that regulation of transcription mainly belongs to the genome level (not the transcriptome level) in contrast to its name, and hence regulation of translation mainly belongs to the transcriptome level (not the proteome level). Turning off or turning on each gene at the genome level (regulation of transcription), activation or inactivation of each coding RNA at transcriptome level (regulation of translation), and finally function or lack of function of proteins result in a variety of cellular **differentiations**.

Hereby, a lot of differentiation pathways are formed. In addition, they result in diversity. This process is called "**from gene to protein**". Proteome mainly consists of **membranous** and **secretory proteins**. The membranous proteins are the phenotypic proteins that may be known as **cluster of differentiation** (**CD**) markers of the cells. Of course, these **CD markers** are functional and may act as **receptors**, **enzymes** or sometimes as **ligands** (ligands are the complements of receptors which are usually soluble and sometimes connected to cell walls). The secretory or membranous proteins act for inter-cellular **signaling transduction** and **tissue development**.

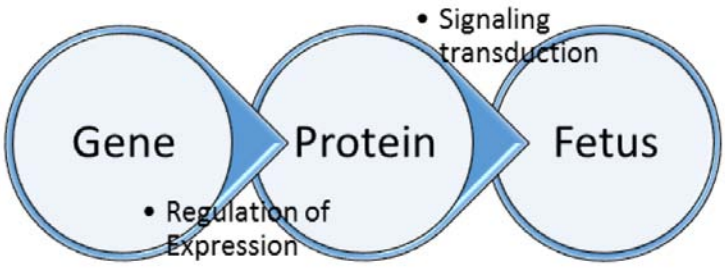

Fig. (1). A scheme of the chapter objective. This chapter consists of two parts; from gene to protein (*via* regulation of gene expression) and from protein to fetus (*via* signaling transduction).

CHAPTER OBJECTIVES

This chapter is aimed to show the details of gene expression regulation, cellular signaling transduction and interaction, and tissue development. We have shown a scheme of the gene to fetus formation Fig. (**1**).

FROM GENE TO PROTEIN

In general, the scenario from gene to protein is called gene expression regulation. In this part, we discuss different levels of gene expression regulation (Table **1**).

Table 1. Levels of gene expression regulation. Chromosomes should be converted to euchromatin. Environmental factors result in APC formation and activation. APC results in the expression of TF genes. TF, TATA box and RNA polymerase start transcription. nRNA is the first product of the genomic level. Removal of introns and alternative splicing result in the formation of isoforms. Translation of isoforms results in protein (peptide) formation. Each protein undergoes modifications to bring a phenotype. APC: activated protein complex. TF: transcriptional factor.

Level	Steps	Aim
Genome	Chromosome	Euchromatin
	Environment	APC formation
	Protein cascade	TF activation
	TF action	TATA box attach
	RNA polymerase	Transcription start
	Enhancer	Turning off/on
Transcriptome	nRNA formation	Primary RNA
	Intron removal	mRNA formation
	Alternative splicing	Isoform formation
	Other complexes	Translation
Proteome	Protein modification	Phenotype

At Genome Level

The first level of gene expression regulation is the genomic level. The goal of this level is to turn on or turn off the transcription process. DNA (gene content) is placed in a complex called chromatin. The forming unit of chromatin is the nucleosome. Each nucleosome includes a complex of eight histone proteins (4-pares) surrounded by about two rounds of DNA with a length of about 140 nucleotides. Nucleosomes are fixed to each other with another type of histone protein called H1 Fig. (**2**). In such conditions, chromatin can be compressed. If chromatin is compressed, it is called heterochromatin, and if chromatin is opened, it is called euchromatin. For the beginning of the transcription process, it is

CHAPTER 3

Cell Differentiation on Hydrogels and its Application in Regenerative Medicine

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Abstract: Cellular differentiation is a biological process in which a cell permanently alters its characteristics (phenotype), ensuring that its descendants also inherit these traits or can modify them when subjected to other differentiating stimuli. During this process, genetic changes occur within cells, leading to a commitment to a specific cell fate. Totipotent cells (stem cells) undergo differentiation based on their ultimate cell destiny, dictated by the tissue they will eventually become a part of it. A current challenge in regenerative medicine involves employing biomaterials within hydrogel matrices to induce changes in cell phenotype and functionality. Stem cells from various sources can thrive within 3D biomatrices featuring defined chemical compositions, and depending on the physical, chemical, and biological cues encountered, they can assume diverse phenotypes. The utilization of hydrogels composed of natural and synthetic polymers, as well as inorganic components, has been explored for such purposes, revealing a direct correlation between the structure and physicochemical properties of polymeric matrices and their impact on cell differentiation capacity. Consequently, the encapsulation of stem cells within these biomaterials can be tailored to enhance the effectiveness of regenerative medicine treatments, particularly in the regeneration of cardiac, dermal, epithelial, cartilaginous, and nervous tissues. This chapter aims to elucidate the fundamental principles of cellular differentiation in stem cells facilitated by biomaterial compositions within hydrogel matrices and explore its potential applications in regenerative medicine.

Keywords: Cell differentiation, Stem cell, Extracellular matrix, Protein, Polysaccharide, Polymer, Biocompatibility, Hydrogel, Tissue generation, Regenerative medicine.

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INTRODUCTION

Cell differentiation is a complex process in which stem cells, depending on their genetic or epigenetic adaptation, can develop different phenotypes characterized by specific cellular functions [1 - 3]. This process can be triggered by interactions between pluripotent cells and surfaces with defined chemical composition and physicochemical properties [2]. The high water content, modulation of mechanical behavior, and porous surface characteristics of hydrogels can be harnessed for cell differentiation strategies [1]. The hydrophobic-hydrophilic interactions that cells may experience with the polymeric matrices constituting hydrogels are of particular interest for activating specific cellular receptors related to the phenotypic change process [3]. Additionally, hydrogels enable the encapsulation of defined genetic vectors or DNA and RNA sequences that can program cellular metabolism toward a desired cellular behavior [1 - 6]. With these concepts in mind, it is noteworthy that the use of hydrogels represents a potential approach that can be leveraged for regenerative medicine strategies. The chemical and surface architecture of the hydrogel, determined by the choice of natural or synthetic polymers, governs the relationship of physicochemical and biochemical properties necessary to induce cell differentiation. In this way, stem cells can be encapsulated in hydrogel matrices to be differentiated into cells of interest in regenerative medicine. Once the hydrogel is implanted at the affected site (organ or tissue), cells programmed for specific differentiation can enhance the restoration of the affected site, offering powerful strategies in tissue regeneration (Fig. **1**). This chapter aims to introduce those interested in understanding the fundamentals of cell differentiation and the use of hydrogels to stimulate this process, as well as the key research developments in this regard.

FUNDAMENTALS OF CELL DIFFERENTIATION

The cell functions as a complex and dynamic system responsible for sustaining the overall functionality of living organisms. This functionality hinges on two essential processes: cell proliferation and differentiation. Proliferation is the mechanism through which a cell lineage increases its numbers *via* cell division. This process serves the purpose of maintaining an adequate population of viable cells within each tissue and becomes particularly crucial when a tissue sustains damage and requires repair [1].

Equally vital is the process of cell differentiation. When a cell responds to specific stimuli by choosing to differentiate, several factors come into play, driving it to specialize in a specific cell lineage. To accomplish this, the cell initiates the expression of particular genes under the regulation of transcription factors that govern distinct developmental pathways or biological events [2]. Additionally, the

cell responds to cues from its microenvironment (epigenetics) [3]. Cell differentiation is a fundamental process in biology that plays a pivotal role in the development, growth, and maintenance of multicellular organisms. At its core, differentiation refers to the transformation of unspecialized, pluripotent cells into specialized, more mature cell types with distinct structures and functions. This process is meticulously regulated and orchestrated through intricate signaling pathways and genetic programs. During embryonic development, stem cells have the remarkable ability to differentiate into various cell lineages, such as muscle cells, neurons, blood cells, and more. These specialized cells are essential for the formation of tissues and organs, each contributing to the overall functionality of the organism. Additionally, differentiation does not cease with development; it continues throughout life to replace damaged or aged cells, ensuring tissue homeostasis and repair. Understanding the mechanisms and factors that govern cell differentiation is of paramount importance in fields like regenerative medicine, cancer research, and tissue engineering, as it holds the promise of harnessing the power of differentiation to treat diseases and repair damaged tissues [3].

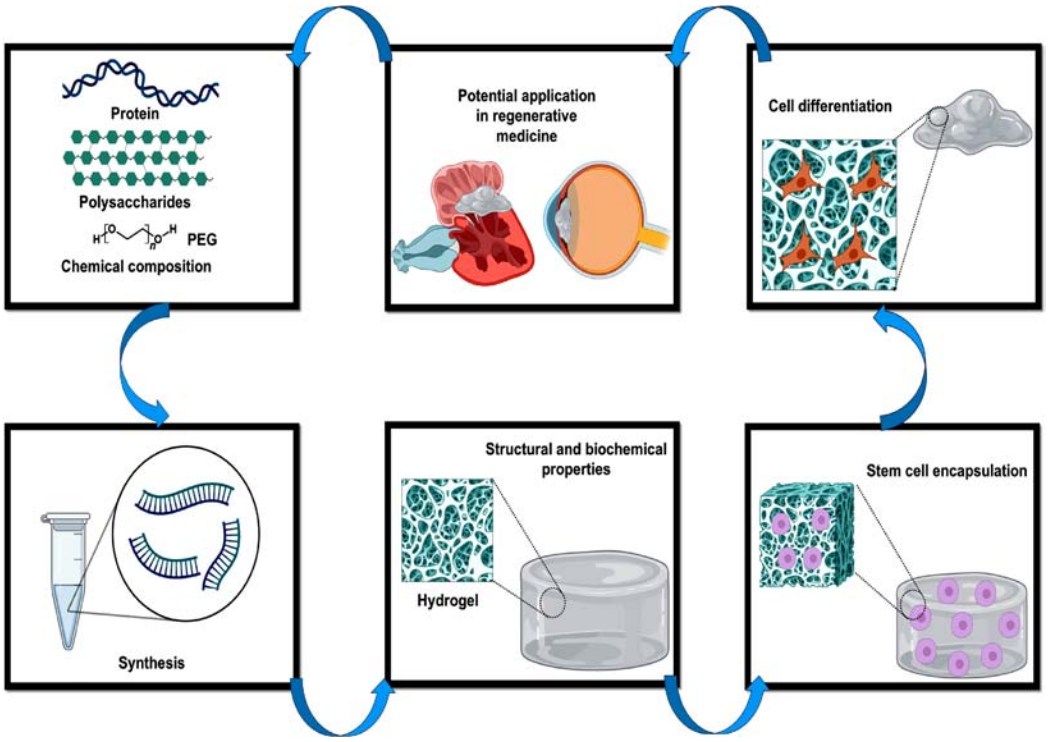

Fig. (1). Representative diagram for the use of hydrogels for cell differentiation and applications in regenerative medicine *(Own authorship).*

CHAPTER 4

The Promising Treatment of Sepsis: Stem Cell Therapy

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Abstract: Sepsis is a life-threatening syndrome that develops as a result of a dysregulated immune response caused by an infectious agent. The pathogenesis of sepsis has been better understood over the years, and new treatment protocols have been developed. In sepsis, the host immune response is equally as important as the infectious agent in the clinical presentation of sepsis and the development of shock. In the early phase of sepsis, hyperinflammation and secondary hyperinflammation occur, while in the late phase, immunosuppression is present. Sepsis treatment is based on controlling the source of infection, antimicrobial treatment and supportive treatment depending on the phase of sepsis.

Stem cells have shown great potential in recent years to become a new therapeutic option for infectious diseases. The stem cell is an undifferentiated cell that can self-renew to proliferate and differentiate into specialized cells under appropriate conditions. The following section focuses on stem cell therapy, which is an adjuvant treatment method in the treatment of sepsis. Mesenchymal stem cells (MSCs) have immunomodulatory properties through direct or paracrine interactions with immune cells involved in innate or adaptive immunity. In the treatment of sepsis, MSCs have shown promise in reducing mortality and bacteremia in experimental mouse models of sepsis. However, the number of completed clinical trials on sepsis is very limited. These studies have shown the use of MSCs to be safe at appropriate doses. Nevertheless, there may be a risk of thromboembolic events following high-dose applications. There remains a need for clinical studies on timing, dose and duration of use.

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Keywords: COVID-19, Clinical trials, Experimental sepsis, Immune response, Mesenchymal stem cells, Sepsis epidemiology, Sepsis, Stem cells, Treatment.

INTRODUCTION

Sepsis Epidemiology

The cause of sepsis is a dysregulated immunological response of the host to the infectious agent [1]. Timely diagnosis of sepsis and the application of appropriate treatments are crucial to reduce morbidity and mortality [2]. A number of rapid diagnostic criteria and treatment bundles have been developed over the years to speed up the process of diagnosis and treatment [2]. The epidemiology of sepsis differs across countries and regions. Also, the epidemiology of sepsis may vary over time in response to variables including advanced age, immunosuppression and the 2019 coronavirus (COVID-19) pandemic [3]. Each year, 49 million people worldwide are affected by sepsis, and 11 million people die as a result [4]. Approximately 1.7 million adult sepsis hospitalizations are documented annually in the largest database in the United States of America (USA), with a hospital mortality rate of 15% of events per 100 hospitalizations [5]. Furthermore, the epidemiology of sepsis can vary depending on the patient population. Sepsis incidence in post-surgical patients is approximately 2%, and the mortality rate increases 11-fold in patients who develop sepsis [5, 6]. It is reported that 13% of sepsis patients admitted to the hospital also have cancer, with a mortality rate 1.2 times higher than that of non-cancerous sepsis patients [7]. The yearly incidence of sepsis in the group of elderly patients reaches 9 per 100000, and the mortality rate increases with age [8]. The profile of the causative microorganism and the epidemiology changed with the COVID-19 pandemic [3]. SARS-CoV-2 itself is the cause of sepsis in severe COVID-19 patients, while other bacterial and fungal microorganisms can also cause sepsis during prolonged hospitalization in the ICU [3]. Considering such country-, patient- and time-dependent changes, clinicians should pay attention to early diagnosis of sepsis. A rapid diagnosis, referral to an appropriate treatment center, and prompt administration of current treatments are effective in reducing morbidity and mortality [9].

Causative Microorganisms and Risk Factors in Sepsis

The microorganisms causing sepsis vary depending on the location of the sepsis. The level of resistance of these microorganisms also differs depending on many factors, such as the site where the sepsis is acquired, the previous infection and colonization of the patient, prior use of antibiotics, and previous hemodialysis [10]. The lungs are often the focus of sepsis, followed by intra-abdominal sepsis, the bloodstream, the urinary system, and the skin's soft tissues [11]. Although gram-positive microorganisms are more commonly defined as sepsis pathogens in

community-acquired sepsis, the occurrence of gram-negative microorganisms increases in nosocomial sepsis [12]. Treating hospital-acquired sepsis is more problematic due to the high resistance of the causative microorganisms. A delay in starting appropriate treatment has an impact on costs and mortality [13].

The Role of the Immune Response in Sepsis

Pathogen identification by the immune system is the first step in the host's response to sepsis. After the onset of the inflammatory response, pathogen-associated molecular patterns (PAMPs) identify the receptors present on cell surfaces and intracellular patterns, including toll-like receptors (TLRs), C-type lectin receptors (CLRs), retinoic acid-inducible gene-like receptors (RLRs) and nucleotide-binding oligomerization domain-like receptors (NLRs). The focus of the immune response in the host has pathogen-related (virulence, microbial load, *etc.*) and patient-related (age, genetic predisposition, medical treatments, concomitant diseases, *etc.*) factors. The human proinflammatory response that occurs in sepsis begins with the release of proinflammatory mediators such as proteases, cytokines and reactive oxygen species. Such mediators are secreted by many cell types and activate the coagulation system, the complement system, and the vascular endothelium [14]. Damage-associated molecular patterns (DAMPs) or alarmins can exacerbate the proinflammatory response and trigger tissue damage following this activation. Anti-inflammatory response in sepsis is the deterioration of immune cell functions (*e.g.*, apoptosis of B cells, T cells and dendritic cells, expansion of myeloid-derived suppressor cells and regulatory T cells, depletion of T cells and decreased expression of the human leukocyte antigen-DR isotype (HLA-DR) by antigen-presenting cells (Fig. **1**). HLA-DR expression by antigen-presenting cells is reduced as a result of this dysregulation, and the production of proinflammatory cytokines and TLR signaling are reduced [14, 15]. The pathogen causes an early, excessive inflammatory and immune response in sepsis, which leads to the activation or suppression of numerous processes (immune, endothelial, bioenergetic, hormonal and metabolic processes), which, in turn, cause circulatory and metabolic changes that lead to organ dysfunction [15].

The Management of Sepsis

The treatment of sepsis has three branches that are covered by current guidelines. Hemodynamic management is one of them. The hemodynamic management includes intravenous fluid administration and the initiation of vasoactive therapies. Based on the pathophysiology of sepsis, a fluid deficit results from a decrease in fluid intake and the development of fluid leakage into the extravascular space. Whereas all patients with sepsis require intravenous

CHAPTER 5

First, Do no Harm: Current Approaches to Assess Tumorigenicity in Stem Cell-derived Therapeutic Products

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Abstract: Stem cells hold a great promise for regenerative medicine given their ability to proliferate and differentiate into various cell types. However, self-renewal and multipotency also grant a high capacity to form tumor tissues *in vivo* post-therapeutic administration. Indeed, multiple case reports have revealed the formation of stem cell-derived tumors, such as teratoma, in animal models and even in clinical applications. As a result, examination of tumorigenicity becomes one of the major considerations when assessing the safety of stem cell-derived therapeutic products. Ideally, the assessment needs to be performed in a rapid, sensitive, cost-effective, and scalable manner. In this chapter, the current practices of assay development to fulfill this demand are reviewed. Progress in animal models, soft agar culture, PCR, flow cytometry, and microfluidics are introduced and compared comprehensively. Some insights regarding the assay selection and future development are also provided as there is no one-for-all assay at this moment.

Keywords: Assay development, Biomanufacturing, Cell therapy, Cancer initiation, Quality assurance, Stem cells, Tumorigenicity.

INTRODUCTION

Stem cells are undifferentiated or partially differentiated cells that hold two essential characteristics: the ability to proliferate in a limitless manner under certain circumstances so that they can indefinitely replicate themselves, and the

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Shazia Anjum (Ed.)

potency to be differentiated into various types of cells given proper biochemical and biophysical stimulation so that they can generate other cell types. Hence, under proper conditions, in theory, stem cells can generate defined cell types indefinitely, which makes them an attractive cell source for regenerating aged or damaged tissues *in vivo* [1]. Besides, stem cells are useful tools for drug discovery [2]. Paired with high-throughput screening technology [3], stem cells can be differentiated into thousands of mini tissues, in the format of organoid [4] or organ-on-a-chip [5], to facilitate a comprehensive assessment of drug functionality and toxicity, as well as the developmental biology underneath. In addition to these two major applications, some stem cells are associated with other interesting characteristics, such as tumor homing. As a result, there are practices to engineer stem cells for cancer treatment [6].

At this moment, stem cells can be roughly categorized into two main categories, including pluripotent stem cells (PSCs) and somatic stem cells. Pluripotent stem cells are the cells that naturally occur during embryonic development. PSCs have the potential to differentiate into any of the three germ layers of the embryo: endoderm – later becoming interior stomach lining, lungs, and gastrointestinal tract, mesoderm - later differentiating into muscle, blood, bone, and urogenital, and ectoderm – later developing into neuronal systems and epidermal tissues. Therefore, PSCs hold a strong potency of differentiation. However, since the natural PSCs (also known as embryonic stem cells, ESCs) only occur in embryos, their use involves lots of ethical considerations, which significantly limits the translation of ESC-mediated therapy. In 2006, Shinya Yamanaka and co-workers showed that differentiated somatic cells (*e.g.*. fibroblasts) could convert adult cells into a pluripotent stage by transfecting four specific genes (*MYC*, *OCT3/4*, *SOX2* and *KLF4*) [7]. The birth of induced pluripotent stem cells (iPSCs) provides a simple and general approach to generate PSCs from individuals for autologous therapy. Thus far, patient-derived iPSCs have been successfully derived into more than 100 cell types [8]. Some of the differentiated cells, such as cardiomyocytes [9] and functional neurons [10], have already been involved in clinical trials [11] for curing degenerative diseases including heart failure, spinal cord injury Alzheimer's disease, and Parkinson’s disease.

Somatic stem cells (also known as adult stem cells, ASCs), unlike PSCs, are present in adults. Examples of ASCs include mesenchymal stem cells (MSCs) in bone marrow and adipose tissues [12], and hematopoietic stem cells (HSCs) from umbilical cord blood [13]. The place of origin makes the isolation of ASCs fairly straightforward and free of ethical controversy. However, ASCs can only be differentiated into limited lineages of cell types. For instance, MSCs can be robustly differentiated into adipocytes [14], osteoblasts [15], chondroblasts [16], neuroectodermal [17, 18] and hepatocytes [19]. Hence, MSCs hold great promise

for regenerating specific types of tissues but are not a one-for-all solution for organ regeneration. The translation of ASCs in the clinic varies in a type-by-type manner. The transplantation of HSCs has been approved by Food and Drug Administration (FDA) and are the gold standard for reconstructing the immunity of immunodeficiency patients [20] while the use of MSCs to treat chronic disease is still at an early stage (phase I/II trials) [21].

Despite the great promise for tissue regeneration, the use of stem cells as a therapeutic agent is accompanied by multiple possible risks, for example, graft-*versus* -host disease [22] and tumorigenicity [23]. Indeed, the self-renewal properties of stem cells are often associated with a high risk of uncontrolled proliferation and tumorigenicity. Since 2009, multiple animal models have shown that ESC or ESC-derived neural progenitor cells can develop teratoma [4] or cysts [25] in animals. In addition, a case report even highlighted that the intrathecal infusion of MSCs from unreliable resources results in glioproliferative lesions in a 66-year-old patient [26]. This tragedy attracted lots of attention worldwide [27, 28] and led the FDA to state new policy steps and enforcement efforts to ensure proper oversight of stem cell products in 2017 [29]. Since then, huge efforts have been paid to reduce or even eliminate the tumorigenic risk of stem cell products.

Some studies hypothesized that the tumorigenic risk of stem cells largely comes from remaining undifferentiated populations [30], considering that the injection of undifferentiated ESCs commonly forms teratoma, a stem-cell-derived tumor, in immunocompromised animals [31]. With this in mind, researchers devote a massive amount of effort to develop conditions to specifically remove ESC residuals while keeping ESC-derived populations highly viable. For instance, Ben-David and co-workers screened 5200 small molecules and identified ESC-specific inhibitors named PluriSIn [32]. The use of PluriSIn at the dose of 20 μM efficiently kills all undifferentiated ESCs in 24 hrs while leaving differentiated cardiomyocytes viable [33]. Similarly, other studies developed mitochondria-specific dyes [34] and doxorubicin dosage [35] that can specifically label or kill undifferentiated ESCs in cardiomyocyte populations. However, thus far, the effectiveness and toxicity of these chemicals on other ESC-derived cell populations remain undetermined. In addition, the cost of extra, small-molecul--based treatment at the manufacturing scale is not economical. Therefore, it becomes more and more acknowledged that manufacturers should run quality checks on differentiated products to determine if a specific batch would need extra treatment to reduce the risk of tumorigenicity [36].

In this chapter, I survey the common approaches to determine the tumorigenic risk of stem cell products, including animal models, soft agar culture, PCR, flow cytometry, and microfluidics. The working principle of each method is discussed

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