Personalized Regenerative Medicine

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Abstract- Personalized medicine as a novel field of medicine refers to the prescription of specific therapeutics procedure for an individual. This approach has established based on pharmacogenetic and pharmacogenomic information and data. The terms precision and personalized medicines are sometimes applied interchangeably. However, there has been a shift from "personalized medicine" towards "precision medicine". Although personalized medicine emerged from pharmacogenetics, nowadays it covers many fields of healthcare. Accordingly, regenerative medicine and cellular therapy as the new fields of medicine use cell-based products in order to develop personalized treatments. Different sources of stem cells including mesenchymal stem cells, embryonic stem cells and induced pluripotent stem cells (iPSCs) have been considered in targeted therapies which could give many advantages. iPSCs as the novel and individual pluripotent stem cells have been introduced as the appropriate candidates for personalized cell therapies. Cellular therapies can provide a personalized approach. Because of person-to-person and population differences in the result of stem cell therapy, individualized cellular therapy must be adjusted according to the patient specific profile, in order to achieve best therapeutic results and outcomes. Several factors should be considered to achieve personalized stem cells therapy such as, recipient factors, donor factors, and the overall body environment in which the stem cells could be active and functional. In addition to these factors, the source of stem cells must be carefully chosen based on functional and physical criteria that lead to optimal outcomes.

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Introduction

Personalized medicine as an emerging field of medicine refers to the prescription of a specific therapeutic procedure for an individual based on the pharmacogenomics information. The term, "personalized medicine" first appeared in published works in 1999 with the creation of the core concepts in the early 1960s (1). Several technologies as molecular diagnostic tools have played a crucial role in the development of medicament of personalized medicine in order to identify specific `biological markers that have achieved the best medical treatment for each patient. Many patients who do not respond to conventional therapies or experience treatment side effects are considered as a candidate for modern approaches applied in personalized medicine for cancer therapy according to their genotype-based selection of patients. Although personalized therapy is an expensive technology, it is financially feasible due to reducing the costs of drug development by shortening the development cycle (1-4). Moreover, progresses in personalized medicine have given rise to the implementation of more powerful tools for genetic profiling of various cancer types. On the other hand, molecular diagnostic pathways as a key component of personalized medicine could improve the prediction and determination of appropriate treatment approaches

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and facilitated monitoring of possible undesirable side effects (5,6). Due to benefits of personalized medicine mentioned above, it has penetrated many fields of healthcare. To expedite finding more efficient diagnostic methods, "precision medicine" has emerged as a newly introduced medical model described as an individualized treatment using novel molecular diagnostic technologies and appropriate treatment according to genetic, biomarkers, phenotypic, or psychosocial characteristics of each patient. Since precision medicine and personalized medicine seems broadly similar, some scientists prefer to change the name from personalized medicine to precision medicine after the US National Research Council published their report named "Toward Precision Medicine: Building a knowledge network for biomedical research and a new taxonomy of disease" in 2011 (7). Because there are lots of overlaps between these two terms, the terms precision and personalized medicines are sometimes applied interchangeably. The misinterpreting of personalized medicine as treatments and preventions especially developed for each individual is a matter of concern to scientists. An accurate description of precision medicine is to identify various effective approaches based on genetic, environmental, and lifestyle factors (8,9). Accordingly, there are some considerable differences between precision medicine and personalized medicine; 1) precision medicine try to put people into particular sub-groups according to their susceptibility to some diseases, biological characteristics,and prognosis of those diseases, or in their responses to a specific medication (10); 2) in terms of pharmaceutical and medical research, precision medicine is an novel approach to discover the biological realities of concepts of diseases applying both clinical and molecular information, and to develop medical products and provide the high-quality outcomes for patients. Thus, precision medicine concentrates on the research and development patterns that will enable more patient-centered clinical practices, including treatment decision-making based on genetic and other related information of each individual. In contrast to personalized medicine, precision medicine is a more research-based knowledge. Furthermore, in practice, personalized medicine usually refers to the stratification of apparently clinically uniform patients into subpopulations with distinguishable clinical prognosis or response to treatment (11). The unique properties of stem cells, which allow scientists to potentially isolate, repair, and implant desired cells for each patient, mark a turning point in personalized medicine. Therefore the discovery and characterization of stem cells with self-renewal and differentiation capacities, also accelerate development of this field, making regenerative medicine as a new independent discipline (12). The majority of currently in use treatments are straightened towards the general population. In contrast to precision medicine, personalized medicine is based on targeted therapeutic approaches that allow patient specific care in order to maximize the therapeutic efficacy while reducing the risk of unwanted adverse effects (13). A large body of evidence state that stem cell research and regenerative medicine could be considered as a therapeutic revolution to reshape conventional medicine. Moreover, regenerative medicine and cellular therapy are believed as a personalized method, since treatment efficacy is inevitably influenced by the complex interactions between donor and host. Therefore, to achieve the great potential of stem cell therapy in regenerative medicine, the profile information of each patient should be precisely determined and further stem cell therapeutic strategies should be in accordance with particular characteristics of each individual (12,14). In this regard, precision medicine proposes therapeutic strategies according to individual differences in people's genes, microbiomes, environments, family history, and lifestyles (11,15). The current concepts of regenerative medicine and stem cell therapy, as well as a different source for stem cell therapy, will be discussed in detail in subsequent sections.

Regenerative medicine

Regenerative medicine refers to a multidisciplinary field that develops methods to regenerate, repair, improve or replace cells, organs, and tissues that have been damaged due to aging, diseases, chronic diseases or congenital abnormalities. Regenerative medicine aims to develop new therapies in order to heal structure and biological function following tissue injury and delay the progression of the diseases. This field presents novel treatment approaches including tissue engineering, cell biology, and biomaterials (16-20). Regenerative medicine involves the use of stem cells from different sources. The study of these isolated stem cells compromises the foundation of regenerative medicine which contributing cellular therapy (18,21-24). Stem cells are characterized by self-renewal ability and generation of undifferentiated cells that make them a potentially unique option for clinical practice.The advancement in stem cell-based treatment strategy

resulted in using stem cells for treatment of different types of diseases, so tissue engineering technology and stem cells culture into a 3D scaffold which closely mimics an in vivo environment could be considered as a promising method to be applied for personalized applications (21). Although variation in donor characteristics and stem cells processing unavoidably influence stem cell characterization in the personalized application, regenerative medicine approaches could implement stem cell-based product to develop the personalized medicine (19).

Stem cell therapy

Cellular therapy offers promising approaches the field of regenerative medicine that can be focused on a substitute for destroyed cells. Personalized stem cell therapies with allogeneic or autologous stem cells have become increasingly popular in the areas of medical expertise for potential treatment of a wide range of diseases including cancers, cardiovascular, neurological, autoimmune (Type 1 diabetes, multiple sclerosis, Crohn's disease), ophthalmologic, renal, liver and skeletal (osteoarthritis) diseases, arthritis, heart disease, etc. (25-27). According to current cell therapy reports, experimental and clinical studies have been carried out in patients suffering from neurodegenerative diseases, like Parkinson's disease, amyotrophic lateral sclerosis, multiple sclerosis, epilepsy, stroke, and spinal cord injury (28-31). It has been demonstrated that there are a variety of sources for multipotent and pluripotent stem cells used in regenerative medicine. Multipotent progenitor cells differentiate into specialized cells with specific functions derived from a single germ layer, whereas pluripotent stem cells are capable of differentiating into all the 3 germ layers, consisted of embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) (32,33). Today, two main categories of stem cells are recognized for treatments: autologous and allogeneic stem cell therapies in which autologous stem cells (the host's cells) offer safer treatment that avoids the problem of tissue rejection and taking immunosuppressant drugs (20). So, autologous stem cell therapy can be considered as one of the safe and effective personalized medicine strategies.

Autologous stem cell therapy

Personalized autologous stem cell therapy has shown great advantages in the field of cellular therapy. Immune responses following autologous and allogeneic transplantation are different. Autologous stem cell therapy may be a type of personalized medicine which could give many advantages such as the elimination of immunosuppressants drug used to graft versus host disease (GVHD). Additionally, increased availability is the other benefit of autologous stem cell transplantation (34). Autologous transplantation avoids stimulating immune responses and GVHD, so reduce its ethical issues. Autologous stem cell therapy has found the most success as the main therapy in several hematological disorders, such as multiple myeloma and malignant lymphoma. In the autologous transplantation, the host stems cells are harvested and cryopreserved prior to chemotherapy.Then re-administered and led to damage prevention of the host stem cell pool. An extensive understanding of mechanisms involved in induction or avoidance of GVHD by specific stem cell is essential to find out transplantation principles that could be implemented as a form of personalized medicine (35,36). The significant global effort has been made to assess the safety and unknown risks of stem cell therapy by determination of the optimum source of stem cells, development of feasible clinical grade raw materials, large-scale expansion of desired stem cells, and well-controlled clinical trials under standard conditions. This accurate assessment performed to evaluate cell-based therapies safety lead to warranty its efficacy and safety and will promise a bright future for treatment of incurable diseases (37). Human adipose-derived stem cells (ADSCs) are the most appropriate sources for autologous stem cells used in personalized cell-based therapies. ADSCs appear to be an ideal population of stem cells for practical regenerative medicine because of immune privilege and modulatory properties and availability with minimal ethical considerations. It has been revealed that ADSCs as a kind of progenitor adult stem cells could undergo osteogenic, chondrogenic, neurogenic, and myogenic differentiation in vitro (37,38). The minimally invasive procedure of multipotent autologous ADSCs harvesting makes them a promising candidate for regenerative therapy (39). Consequently, ADSCs banking seems valuable in order tomake a great potential toward the development and implementation of regenerative and personalized medicine procedure. ADSCs may soon substitutes bone marrow mesenchymal stem cells as the recommended alternative source for most regenerative and personalized medicine applications (19,40). Furthermore, autologous stem cell would eschew the problem of transplant rejection, although it could have potential implications for the cost of patient care, as it

would not involve off-the-shelf product (37).

Embryonic stem cells

ESCs have enormous potential in the field of regenerative medicine as they hold the capacity to yield each type of cell and tissue in the body. Applying of ESCs in personalized therapy must defeat important deterrent. One of the most apparent challenges is the immunogenicity in the scope of personalized therapy which can cause implanted cells rejection due to major histocompatibility complex (MHC) expression (41). Moreover, the application of ESCs in personalized medicine raises ethical issues (42). In order to find an appropriate alternative stem cell source for ESCs, scientists introduced the idea of using reprogrammed adult somatic cells which being induced to enter a pluripotent state. With regard to the application of large-scale precision medicine initiative, human iPSCs technology plays the key role to develop seemingly limitless regenerative medicine which is discussed in the next section (43-45).

Induced pluripotent stem cells (iPSCs)

IPSCs are pluripotent stem cells generated from adult cells by reprogramming to an embryonic stem cell-like with functional similarities to ESCs. This novel technology was innovated by Shinya Yamanaka's lab in Kyoto, Japan. He has demonstrated that four specific genes encoding specific transcription factors are responsible for a successfully reprogramming process which leads to conversion of adult cells into pluripotent stem cells (46). This engineering process on available cells does not develop through the blastocyst stage allows derivation of patient-specific iPSCs enabled to differentiate towards specific cell types (43-45). The generation of iPSCs from somatic cells by retrovirus transfection genes including Oct4,Sox2, cMyc, and Klf4 resulted in an important landmark in the field of stem cell biology and created the establishment of patient-specific pluripotent cells (47). Since the advent of human iPSCs technology, tireless efforts have been made in order to fulfill the therapeutic potential of human ESCs. Adding to the possibility of generating an unlimited amount of any cell type of interest, human iPSCs technology now enables the derivation of cells with patient-specific phenotypes. As the reprogramming of a variety of somatic cell types has been achieved, it seems that iPSCs technology has huge potential to develop medical therapy by personalizing regenerative medicine and creating novel human disease models for research and therapeutic trials (43,48,49).

Conclusion

Despite therecent advancement of personalized medicine which is based on targeted therapeutic approaches focus on patient-specific characteristics, the most common treatments are population-based approaches (13). Accordingly, personalized medicine not only has improvedthe quality of life and health care but also has reduced the costs of ineffective therapies which consequently help authorities in health issues to control the health care cost. The goal of personalized medicine is to establish the highest quality treatment approaches and to maximize the therapeutic potential of health interventions while lowering the risks and side effects of the conventional medications (35,50). Drastic improvement in personalized medicine, as an innovative medical approach, has given rise to the implementation of powerful tools for genetic profiling of different types of cancer. Molecular diagnostics help the development of prediction of response and determination of appropriate treatment, facilitating the monitoring of the efficacy of therapeutic effect on a wide range of diseases, considered as a key component of personalized medicine (2,5,6). On the other hand, cellular therapies need a personalized approach due to interactions between donor and host that can influence treatment outcomes (51). Therefore, because of differences between members of the population in terms of the result of stem cell therapy, individualized cellular therapy must be coordinated with a patient specific profile, in order to achieve the best therapeutic strategy (33). Accordingly, several factors should be considered in the field of personalized stem cells therapies including; recipient specification, donor characteristics, and the overall environment in which the stem cells lay their roles. In addition, the source of stem cells must be carefully chosen based on functional and physical criteria that lead to optimal outcomes (52,53). Therefore, personalized medicine as the most promising method to customize health care in order to improve the quality of medical services can shed light on the treatment of patients according to individual differences.

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