Review Article

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Not all stem cells are equally great: donor single-nucleotide polymorphisms (SNP) may matter more than previously thought

Abstract

Stem cell therapy has brought new opportunities for a wide range of human diseases that currently have no cure. Stable and sustainable stem cell sources have always been a key issue for all clinical applications and regenerative properties and host-insulting nature of stem cells are determined by several factors of allogeneic or even autologous donors. Most human diseases are considered multi factorial and complex, with a degree of genetic etiologies, which may potentially influence their stem cell characteristics. This mini-review will particularly discuss how genetic traits of donors, represented by single nucleotide polymorphisms (SNPs), may have impact on the quality/suitability of stem cells for a particular disease and the clinical outcomes, and try to propose some possible solutions in light of the latest advances in genome and stem cell technologies.

Keywords: stem cell, donor, single-nucleotide polymorphisms, stem cell therapy

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Abbreviations: HSC, haematopoietic stem cells; ESC, embryonic stem cells; MSC, mesenchymal stem cells; HGP, human genome project; SNPs, single nucleotide polymorphisms; HSCT, haematopoietic stem cell transplantation; CRISPR, clustered regularly interspaced short palindromic repeats

Stem cell may provide new therapies for a wide range of human diseases

Rapid advances in stem cell research in recent decade have brought revolutionary insights into modern biology and medicine, including cell functions, development and growth, maintenance of tissue homeostasis, tissue regeneration, aging/degeneration and diseases.[1,2] Most importantly, stem cell research holds the promise of developing new therapies for a wide range of human diseases. Numerous animal and human studies indicate that stem cell therapy are very promising and especially significant for the treatment of diseases that cannot be cured with conventional medicine.[3–6] Dated on late March of 2017, the number of stem cell-based clinical trials registered in (www.ClinicalTrials.gov) has nearly reached at 6000, a number probably greater than any other single therapeutic technique or approach, whereas the majority of the trials are understandably haematopoietic stem cells (HSC) and mesenchymal stem cells (MSC) that can be harvested from various tissue sources. Knowledge of stem cell technologies and the potential clinical applications has on one hand become essential for increasing numbers of medical specialists. On the other hand, some critical issues regarding stem cell research has become prominent in order to obtain optimal outcomes in both experimental and clinical stem cell studies.

Thus far, major types of stem cells, including embryonic stem cells (ESC), induced pluripotent stem cells (iSPC) with fantastically similar properties to ESC in many aspects, adult stem cells isolated from various adult tissues, stem cells harvested from fetal and the related tissues such as umbilical cord blood, Warton's Jelly within umbilical cord, amnion and placental tissues, have comprehensively been analyzed, most of which are being clinically applied or currently studied for certain clinical conditions.[7,8] Among the adult stem cells that are extensively studied are bone marrow-derived HSC and MSC while the both stem cell types can be also isolated from other tissue origins, such as cord blood for HSC and many tissue origins for MSC. With regard to clinical transplantation, stem cell for clinical study or therapy can basically be either allogeneic or autologous, mainly depending on donor or tissue source availability as well as clinical conditions. All stem cell types harbor certain advantages over others but in the meanwhile can have some drawbacks and at present no single stem cell type reaches all criteria optimal for all clinical requirements. Therefore, a great deal of efforts in stem cell research continuously focuses on finding the most suitable stem cell types or sources for certain tissues/organs or disease types. In other words, in order to achieve the best outcomes for stem cell therapy, a number of factors and parameters should be taken into account, particularly in light of targeting the goal of Precision Medicine, an initiative and effort that aims to make advances in tailoring medical care to the individual on the genetic and molecular basis.[9]

Understanding therapeutic mechanism of stem cells following *in vivo* transplantation has been the other major issue in stem cell research in order to enhance and optimize the therapeutic efficacy while minimizing the possible adverse effects. Although it is generally thought that the major mode of stem cell actions is through direct impacts like functional and/or architectural substitution of tissue loss as well as paracrine or cellular mechanisms supporting self-restoration of the diseased tissue or organ. These mechanisms, however, are poorly

defined in any single particular stem cell- based therapy. The action mode of stem cells at the genetic and molecular level therefore have to be elucidated in order to understand the therapeutic mechanisms in sufficient depth.

The success of a stem cell based therapy may be influenced by several donor-originated factors such as age, metabolic status, disease conditions, and in some cases, the genotype matching and disease susceptibility-related genetic background, which all have become recognized to probably alter stem cell characteristics *in vivo* and *in vitro* (proliferation, differentiation, homing and paracrine) and/or insulting host response.[10–12] As a starting point, we would in this mini-review like to only focus on the brief discussion on some experimental and potential aspects of how genetic background of donors could impact on the regenerative properties of stem cells and the clinical outcomes.

Genetic traits of donors are represented in stem cells

In the past decade, the extensive wealth of information obtained from the completion of Human Genome Project (HGP) and numerous genome-wide associated studies (GWAS) has significantly enhanced our understanding of multi factorial and complex human diseases.[13–15] Particularly, thousands of single nucleotide polymorphisms (SNPs) have been identified, many of which are likely associated to various complex human diseases that were previously hypothesized to have genetic components. The resources of HGP and new genetic technologies have rapidly been evolving and its impact keeps continuously strengthening and forms the solid basis for the Prevision Medicine Initiative. We can now anticipate that as our understanding of genetic etiology of these diseases grows, future studies will further explore common or rare genetic variations contributing to diseases as well as many physiological and pathophysiological processes such as aging, tissue homeostasis and regeneration.[16,17]

Genetic studies are rapidly expanding into stem cell research and regenerative medicine models and the study of stem cell genomics has been emerging to have wide implications in biology and possible therapeutic applications of stem cells.[18,19] Genetic traits at the DNA level are reflected in stem cells originated from a donor although transcriptome and epigenome may understandable vary in different tissue and cell types. One can analyze the genomes of stem cells from different individual donors for the purpose of identifying particular genetic traits in relation to cell phenotype of different stem cell types and their derived lineages. Current technologies have gradually become mature in many mainstream institutions and extending to RNA sequencing to detect gene expression and micro RNA expression, genomic DNA methylation and transcription factor binding site localizations. The field is rapidly expanding due to the dramatic decrease in the cost of sequencing genomes. Epigenomics has been extensively focusing on the epigenetic plasticity of ESC and iPSC and gradually expanding to adult stem cells. Single cell analysis has become a major method suggested for cancer research and for research in complex diseases like Alzheimer's disease and metabolic diseases. Further steps of stem cell genome analysis will also be to combine with single cell phenotypic analysis, and the connection between the phenotype and genotype of specific stem cells.[20–22] Stem cell-based analysis of the biology of a genetic variation currently provides tools for disease mechanism study, drug screening, and in some cases for the creation of replacement cells and organs. In many instances, the analysis is conducted in patient-derived stem cells, which represent the basis for personalized therapeutics. Such strategies in areas of neurodegenerative, bone, eye, blood and cardiovascular disease, diabetes, and obesity are being tested.[23,24]

Considering the importance of SNPs in etiology of many multi factorial complex diseases, it would be highly reasonable for us to recommend that stem cells carrying with the suggested disease-causing or susceptible SNPs should NOT be transplanted onto the recipients to treat the same disease. It is just starting, however, to propose that the detection of SNPs is considered as a required indication for the selection of stem cell donors, particularly for haematological diseases (see below).

Impact of donor SNPS on the outcome of haematopoietic stem cell transplantation beyond the HLA matching

Haematopoietic stem cell transplantation (HSCT) remains the only cure for many malignant haematological diseases. HSCT could be either allogeneic or autologous.[25,26] Cryopreservation techniques now allow autologous bone marrow to be stored safely and indefinitely without catastrophic loss of stem cells on thawing. Umbilical cord blood from neonates contains substantial numbers of haematopoietic stem cells, which can be harvested at delivery, frozen, and then transplanted to patients after cell counts and virological screening are performed. Thousands of cord blood donations are normally stored in cord blood banks worldwide and information of their HLA types can be available readily for transplantation into a matched recipient without delays inherent in securing an adult donor. Similar to autologous bone marrow storage, cord blood bank also provides an opportunity, after long-term storage, for autologous cord transplantation.[27,28]

In most cases, however, allogeneic donors can be the choice only available. The most important factor affecting the outcome of allogeneic transplantation is the quality of the HLA match between donor and recipient and therefore patients subject to allogeneic HSCT will have to find a HLA-matching donor. The current mortality rate of HSCT, unfortunately, stands rather high at 30-80% although up-to-dated high-resolution HLA genotyping and matching techniques have improved the survival to a significant extent.[27,28] Despite stringent procedures to secure the best HLA matching between donors and recipients, life-threatening complications continue to occur in some cases after HSCT. Common complications post HSCT are relapse, GVHD, graft rejection and viral infection. Therefore, polymorphisms in other genes may also affect complications such as GVHD and the overall survival. In fact, numerous studies have been carried out in the past decade to suggest that a number of SNP located within genes for innate and adaptive immune responses, residual leukemia, allo-antigens, and drug metabolism, may be associated with HSCT outcomes. Studying SNPs in genes encoding co-stimulatory and other related molecules have particularly been proposed to help identify patients at risk for post-HSCT complications. SNPs within other genes have been included in the systematically analysis by different groups, such as CD274, CD40, CD154, CD28, KIR, TNFSF4, STAT4, IL-28, and VCAM, for their potential association with post-HSCT outcomes.[29–32] And, certain SNP variants do have been found to likely influence the expression level of corresponding genes. For instance, the TNFSF4C variant showed a higher affinity for the nuclear transcription factor Myb and increased percentage of TNFSF4-positive B cells after stimulation compared with CT or TT genotypes.[28]

The question now raised is: whether genetic characteristics, of stem cell donors and recipients, should be used to tailor HSCT protocols with emphasis on determining GVHD prophylaxis. In parallel, a consensus terminology of clinical outcomes should be standardized, suggested for international multicentre studies, and adopted so that each center/country uses the same grading system for complications such as GVHD and infection. What should be noted is that in different phases of GVHD, SNPs in inflammatory or anti-inflammatory genes could have different effects. In addition, these SNPs may not act in isolation but is the cumulative effect of SNP of genes that will give more precise and final patient outcome information.

Disease-causing or susceptible SNPS from donors may have impacts on regenerative properties of stem cells

There have been many examples showing that SNPs, either located in coding or non-coding region of a protein-coding gene, shows intermediate to strong associations with certain diseases. This effect may be due to the altered expression level, or more directly, the interfered function of the coded protein. In many of these diseases, the corresponding tissue homeostasis maintenance is impaired, implicating the lost or weaken tissue endogenous stem cells and their regenerative properties. In fact, tissue stem cells have now been considered as the key factor and even a target of various disease-causing factors.[33] and the potential role of particular SNP in affecting stem cell characteristics and quality should thereby be kept aware. Particularly, we should keep being cautious when autologous stem cells are used for a disease obviously associated with certain SNPs, or allogeneic stem cells from a donor carrying with disease-causing or susceptible SNPs same as recipients are transplanted.

As people live longer and whole populations become older in society, the prevalence of musculoskeletal diseases increases rapidly, including inflammation, autoimmune disorders, degeneration, trauma and malignancies in bone, cartilage and the related tissues. Thanks to the numerous GWAS in large populations completed in recent years, it has been well documented that each of most musculoskeletal diseases, such as osteoporosis, osteoarthritis and intervertebral disc degeneration, is highly associated with a number genes and their SNPs,[34] although the particular role of most of these SNPs remains to be experimentally validated in proper animal and cellular models, including stem cells.

Bone, cartilage and joint surrounding tissues all have a mesenchymal origin. By coincidence, MSC appear to be the most mature and widely used stem cell type for clinical therapy and research for bone and cartilage diseases. Among them is osteoarthritis (OA), the most common and severe degenerative disease of the joints.[35] Early pathological changes of OA most likely take place in the slow metabolism of cartilage progenitors or mesenchymal stem cells. Even small articular cartilage injury is difficult to repair by itself and may cause joint degeneration, so the restore of chondrocytes from their progenitor cells is the key to the treatment of osteoarthritis.[36] In fact, MSC transplantation has been emerging as one of the most promising methods for treating OA and has been demonstrated in several animal models.[37–39] In addition, registered in website Clinicaltrials.gov is more than 50 proof-of-concept clinical trials. Many trials revolve around the intra-articular injection of autologous bone marrow- or adipose-derived MSCs.[40] However, some studies showed that the proliferation, chondrogenic and adipogenic capacity of MSCs isolated from OA patients was significantly decreased.[41] Similar results raise suspicion that genetic background of OA patient-derived MSC may influence its therapeutic effect.[42]

The genetic architecture of OA is complex and may involve hundreds of genes. Growth differentiation factor 5 (GDF5), known to be indispensable in cartilage development and homeostasis, is the most susceptible gene thus far, based on population replication and functional studies.[43] Mutations of GDF5 lead to severe abnormal development of joints and skeletal both in mice and humans.[44] SNP (rs144383) (+104T/C), lying in 5' un translated promoter region of GDF5, is significantly associated with OA.[45] The OA-risk T allele of rs143383 was found more likely to recruit trans-acting factors Sp1, Sp3, P15 and DEAF-1, which mediate a reduction up to 27% in GDF5 expression relative to the C allele.[46,47] Subsequently, the replication experiments for different ethnic groups have confirmed the strong correlation of rs143383 with OA. About 80% of patients with OA carry the T allele, while the C allele exerts a lower risk of OA (30-40%).[48] The association and functional studies above revealed that a small but persistent imbalance of GDF5 expression throughout life renders an individual more susceptible to OA.

As MSC, either originated from bone marrow and residing within cartilage tissue, are responsible for the homeostasis and regeneration of cartilage, it is therefore assumable that the precise balance of GDF5 would bea key factor affecting the physiological function of MSC in cartilage. Therefore, even if allogeneic MSC are used for the therapy of cartilage degeneration or defects, SNP (rs143383) of the GDF5 gene might be a selection parameter for MSC donors. Currently this hypothesis is being tested in our group for the potential effects of this particular SNP on autologous and allogeneic MSC in proliferation, and chondrogenic differentiation as well as *in vivo* repair efficacy. As soon as this is experimentally validated, we would be confident to recommend that the detection of this SNP to be seriously considered when selecting MSC donors for OA patients. Furthermore, we would also like to extend this idea to any other SNPs as long as they have experimentally proved to owe a negative impact on MSC since this would throw a new light on developing new strategies to achieve optimal outcomes of stem cell therapy for diseases and injuries of cartilage.

Future perspectives

Stem cell and genomics research are two closely interplaying areas in modern biomedicine, which both can provide opportunities and perfect examples for personal therapeutics from multi aspects. Both areas advance rapidly and new technologies and facilities are becoming much accessible for most hospitals and laboratories, including new stem cell sources and their functional assay, more efficient, detailed and extensive next-generation sequencing, and gene modifications in safe and efficient manner.

For most species and cell types, the data amount has reached at the multi-Giga level and probably keeps accumulated daily in an accelerating speed rate. In order to fully take advantage of genomics research in the stem cell and regenerative medicine, the key would still be to clarify the functional significance of each of genetic variations for a particular tissue or cell types involved in a particular clinical condition. This requires both of population replication studies in more specific clinical settings and more functional assays in animal or stem cell models.[49,50] For the latter, it would be deal to establish a sort of high throughput screening assays as multiple SNPs are often

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implied in most clinical conditions. In this respect, iPSC may be selected on the basis of successful experimental systems mediating its differentiation into multiple cell line ages, and of its nature of the monoclonal growth. The latter will also be an advantage for genetic manipulation using a genome targeting technique such as the newly developed and highly efficient Clustered Regularly Interspaced Short Palindromic Repeats (CRISPR)-associated protein 9 (Cas9).[51] In fact, stem cells, particularly iPSC in combination with CRISPR/Cas9, have been currently recognized as an ideal system for validating function of a gene, or multiple genes in combination, in cell differentiation and regeneration, and utilizing the gene function to develop a new therapy.[52]

Inevitably, any formal clarification and recommendation with regards of the impact of particular SNP carried with stem cells on the outcomes of stem cell therapy will eventually require investigations in patients with design of clinical trials, just as done for HSCT. To this end, we are just starting but hopefully on the right track.

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Conflict of interest

All authors declare to have no conflict of interest.

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