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"EXPLORING THE ROLE OF STEM CELL THERAPIES IN HEMATOLOGIC DISORDERS"

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Abstract:

This review provides a comprehensive examination of pluripotent stem cells (PSCs) and hematopoietic stem cell transplantation (HSCT) in the context of hematological disorders. It begins by detailing the generation of PSCs, emphasizing the development of reprogramming techniques and the selection of appropriate somatic cell types for induced pluripotent stem cell (iPSC) production. The review highlights the significance of understanding factors affecting reprogramming efficiency and the impact of DNA methylation levels on iPSC differentiation. Moving forward, the review explores the role of PSCs as disease models, demonstrating their utility in elucidating disease mechanisms, drug responses, and therapeutic targets for various hematological disorders. By leveraging patient-specific iPSCs, researchers gain invaluable insights into disease pathogenesis and test novel treatment strategies. Furthermore, the review discusses the evolving landscape of HSCT across different hematological malignancies, including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), myeloproliferative disorders, myelodysplastic syndromes (MDS), chronic lymphocytic leukemia (CLL), and lymphomas. It examines advancements such as non-T-depleted haploidentical donor HSCT and the use of donor-specific molecular markers for risk assessment. In summary, this review underscores the transformative potential of PSCs in disease modeling, drug discovery, and personalized medicine, alongside the vital role of HSCT as a curative option for various hematological disorders. Through ongoing research and clinical advancements, PSCs and HSCT have the capacity to revolutionize treatment paradigms and enhance outcomes for patients with hematological diseases.

Key words: Stem cells, Hematology, Transplantation, pluripotent stem cells, hematopoietic stem cell transplantation.

Introduction:

This passage provides an insightful overview of pluripotent stem cells (PSCs), particularly embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs), emphasizing their remarkable properties such as unlimited self-renewal, proliferation, and the

ability to differentiate into various mature cell types from all three embryonic germ layers. It highlights the significant potential of PSCs in generating a clinically relevant number of cells, offering an alternative cell source for regenerative medicine applications. The passage also underscores the breakthrough achievement of generating patient-specific iPSCs through the reprogramming of adult somatic cells, bypassing previous limitations such as immunological rejection and ethical concerns associated with the use of hESCs [1-3].

Furthermore, it discusses how these patient-specific iPSCs facilitate a better understanding of various human diseases, both genetic and non-genetic, by providing a platform for disease modeling and drug discovery. Additionally, it mentions the application of genome editing technologies to correct disease-specific mutations in iPSCs, paving the way for the development of gene-corrected iPSCs for potential autologous cell-based therapies. Overall, this passage serves as a comprehensive update on cellular reprogramming in basic research and its promising applications in the field of hematological disorders, showcasing the transformative potential of PSCs in advancing regenerative medicine and personalized therapies [4-6].

Generation of Stem Cells:

OCT3/4, SOX2, KLF4, and c-MYC are examples of pluripotency-associated genes that are inserted into somatic cells during the reprogramming process. Retroviral transduction was first used for this, which sparked worries because of the possibility of insertional mutagenesis, particularly when c-MYC, a proto-oncogene, was involved. Alternative factors such as NANOG and LIN28, which provide a safer reprogramming method in place of KLF4 and c-MYC, were introduced to address safety concerns. Although lentiviral and retroviral systems were first employed due to their efficiency, there is a chance that their genomes will integrate. However, lentiviral techniques allow for transgene removal and can infect both proliferating and non-dividing cells. However, the possibility of genetic integration does not go away [7-8].

Nonintegrating delivery techniques, such as adenovirus, minicircle DNA vectors, proteins, synthetic mRNAs, Sendai virus (SeV), adenovirus, and microRNA mimics, have been developed to reduce these dangers. Every approach has benefits and drawbacks, and the decision is influenced by elements such as long-term translational objectives, footprint, and reprogramming efficiency. Though labor-intensive and less dependable than other nonintegrating approaches, mRNA-based reprogramming exhibits great efficiency, particularly for hematopoietic cells. For hematological disorders requiring red blood cell reprogramming, SeV, Epi, or Lenti techniques are recommended. Clinical translation is deemed appropriate for epi reprogramming due to its cost-effectiveness and adherence to good manufacturing procedures (cGMP) [9].

Clinical-grade reprogramming is possible using commercial kits such as CTS CytoTune-iPS 2.1 SeV, but cost is still a barrier to widespread clinical use. However, nonintegrating Epi vectors have shown safe in clinical trials, e.g., using autologous iPSCs to treat neovascular age-related macular degeneration (AMD). This thorough review emphasizes the development of reprogramming techniques, striking a balance between effectiveness and safety, and shows the strides made in the direction of iPSC-based treatments that can be used in clinical settings.

Normal starting materials for the production of patient-specific induced pluripotent stem cells (iPSCs) include somatic cells such as fibroblasts or peripheral blood mononuclear cells (PBMCs). Other somatic cell types, such as bone marrow, amniotic fluid or chorionic villus sample-derived cells from prenatal diagnostics, stomach and liver cells, brain stem cells, and endothelial cells, have also been reported for iPSC production [10].

Although these cell types provide a variety of sources for iPSC production, obtaining samples from them frequently necessitates intrusive methods. In recent times, readily available and non-invasive cell sources such as exfoliated renal epithelial cells from urine samples and keratinocytes from plucked hair have been obtained for induced pluripotent stem cell reprogramming (iPSC reprogramming), which has benefits, particularly for infants or people with bleeding disorders.

The degree of somatic cell differentiation and endogenous gene expression are two examples of variables that affect reprogramming efficiency. For example, during reprogramming, brain stem cells—which naturally express Sox2—only need Oct4 and/or Klf4. It is more effective to reprogramme hematopoietic stem cells or progenitor cells than terminally developed B cells or T cells. Because they are the easiest to isolate and reprogramme, fibroblasts and PBMCs continue to be the most widely used cell type, even if there are other options available. Hematopoietic differentiation potential, however, may be impacted by aberrant hypermethylation in undifferentiated iPSCs obtained during the reprogramming procedure. Comparing iPSCs from different parental tissues, it was discovered that those from blood cells had reduced aberrant DNA methylation and a higher ability for hematopoietic development [11].

Certain reprogramming techniques, including Epi, SeV, and retroviral techniques, can cause differences in the DNA methylation levels and ability of iPSCs to differentiate. The significance of comprehending these aspects in iPSC research and application is highlighted by the fact that choosing the right beginning cell types and reprogramming techniques is essential for producing iPSC lines appropriate for particular applications.

Pluripotent stem cells (PSCs) as disease model:

Because many transgenic animal models don't perfectly reproduce disease symptoms because of species differences, the traditional use of these models to investigate disease pathophysiology has limitations. Ex vivo growth of hematopoietic stem/progenitor cells (HSPCs) in the bone marrow is required for the research of hematological disorders affecting these cells. It has been difficult to keep HSPCs at their multipotent stage ex vivo, especially for disorders where tissue samples are hard to come by, like aplastic anemia and idiopathic myelofibrosis. Since primary bone marrow cells cannot be amplified or maintained in vivo, robust approaches for examining disease pathology frequently involve the use of peripheral blood cells, which have a limited lifespan in culture. But this restriction prevents genetic alterations, which are necessary to investigate the function of potential genes [12].

The ability to generate several disease models from patient-derived cells has transformed the study of disease mechanisms, thanks to the development of induced pluripotent stem cell (iPSC) technology. Disease-specific-iPSCs and their offspring offer important insights into

pathogenic events that may go unnoticed in primary cells during the onset and course of a disease. For the purpose of creating disease-specific-iPSCs, the right starting somatic cells with genetic or acquired mutations must be chosen. iPSCs can be produced from blood and skin biopsy (fibroblasts) for genetic blood illnesses such as X-linked chronic granulomatous disease, thalassemia, and sickle cell disease. However, disease-specificiPSCs are created from aberrant or malignant hematopoietic clones, which are normally derived from bone marrow or peripheral blood mononuclear cells, for acquired blood disorders such leukemia and myelodysplastic syndrome [13].

Next-generation sequencing is a crucial tool for characterizing cells since it can distinguish between diverse populations of normal cells, premalignant clones, and malignant clones when choosing starting cells for reprogramming. Since they lack genetic mutations, iPSCs generated from the fibroblasts of patients with acquired disorders can be utilized as controls, to produce disease-free HSPCs for autologous transplantation, or to produce immune cells for adoptive immunotherapy. To sum up, iPSC technology provides a strong platform for simulating hereditary and acquired hematological disorders, revealing prospective treatment targets and disease mechanisms [14].

Conventional drug development approaches, which depend on animal testing and cell line-based chemical screening, frequently fall short in their attempts to predict human medication responses and possible side effects. Numerous medications have been taken off the market or failed to receive approval because of unexpected side effects, mainly hepatotoxicity and cardiotoxicity, that were found in late-stage clinical trials. Technological developments in induced pluripotent stem cell (iPSC) technology present a possible way to address these issues. From a variety of patient populations, disease-specificiPSCs can be created, offering an endless supply of cells that precisely mirror the genetic and phenotypic variability of human disorders. These iPSCs have the ability to develop into disease-relevant cell types, closely resembling primary cells—which are hard to come by and have a finite capacity for proliferation. Thousands of drug libraries can be screened against in high-throughput screening assays thanks to a vast panel of disease-specific iPSCs and their derivatives. This methodology expedites the process of discovering new medicines by identifying chemicals that selectively target characteristics associated with specific diseases [15-17].

Furthermore, early in the drug development process, iPSC-derived cell types such hepatocytes and cardiomyocytes can be used to assess possible pharmacological toxicities. This not only reduces the amount of time and money needed for traditional procedures, but it also lessens the need to utilize animals in drug testing. When paired with high-content screening technologies, these iPSC-based phenotypic assays offer a novel approach to drug discovery. The potential of this method extends to a wide range of additional conditions, even though the use of disease-specific-iPSCs in drug screening has been successful to date largely in neurological diseases and metabolic liver diseases. Prolonged investigation and advancement in this field have the potential to transform drug discovery and enhance patient results [18-22].

The use of induced pluripotent stem cells (iPSCs) for disease modeling and medication screening in the context of hematological illnesses is becoming more and more common. To investigate the effectiveness of JAK kinase inhibitors, for example, iPSCs produced from individuals with JAK2-V617F mutations have been essential in the study of polycythemia vera (PV), a condition characterized by an excess of red blood cell synthesis. JAK inhibitors were applied to differentiated erythroid cells derived from iPSCs that had different JAK2 allele compositions, such as homozygous, heterozygous, and wild type. Consistent with the results of clinical trials, the study demonstrated that inhibitors such as TG101348 and INCB018424 significantly suppressed erythroid growth, although CYT387 shown less activity. This demonstrates how useful iPSCs can be in understanding medication responses and disease mechanisms, especially in conditions like PV [23-27].

In a similar vein, Diamond-Blackfan anemia (DBA), a disorder marked by impaired erythropoiesis, has been modeled using iPSCs. Researchers searched for possible treatments using iPSCs taken from DBA patients, and they found that SMER28, a tiny chemical inducer of autophagy, is one such possibility that improves erythropoiesis. This finding emphasizes how iPSC-based screening methods can be used to find new treatments for hematological diseases [28].

Furthermore, myeloid cancers such as acute myeloid leukemia (AML), myelodysplastic syndrome (MDS), and clonal hematopoiesis have all been modeled using iPSCs. Genetic analysis of iPSCs produced from patients with varying illness stages revealed subclones with diverse mutations and chromosomal abnormalities linked to myeloid neoplasms, in addition to normal clones. These disease-specificiPSCs were subsequently used to investigate the effects of small molecule inhibitors and hypomethylating drugs, among other therapeutic approaches. The research showed that iPSCs can replicate the course of a disease and offer insights into the various therapy reactions seen in myeloid cancer patients. All things considered, these instances demonstrate the revolutionary potential of iPSC technology in improving our comprehension of hematological disorders, clarifying pharmacological processes, and enabling the creation of tailored treatments [29-30].

Transplantation:

The term "hematopoietic stem cell transplantation" (HSCT) refers to techniques in which a recipient receives injections of hematopoietic stem cells from various donors and sources in an attempt to fully or partially regenerate and repopulate the hematopoietic system. Peripheral blood (PB), cord blood (CB), or bone marrow (BM) can all provide these stem cells [31-33].

There are three categories for donor classification and stem cell origins: autologous, syngeneic, and allogeneic. The latter is further divided into related and unrelated donors. Strict standards incorporating high-resolution HLA typing are used to identify an optimally matched unrelated donor (MUD), excluding closely matched related donors (such as siblings). On the other hand, an adult unrelated donor with at least one antigen or allele in their HLA profile that differs is referred to as a mismatched unrelated donor (MMUD). It should be noted that not all HLA differences are created equal. While non-permissive combinations lead to worse results,

permissive mismatches can produce results similar to those of well-matched donors. Retrospective analysis changes are now possible due to the identification of partially matched HLA donor-recipient couples as a result of improved characterization of HLA matching, particularly in situations with limited data. Nevertheless, future donor selection is not currently covered by this enhancement. Furthermore, new factors such killer cell immunoglobulin-type receptors might improve the search for more appropriate unrelated donors. The successful implementation of these criteria is contingent upon the cooperation of transplant centers and registries, as well as the creation of plans for the practical application of mismatched alternative donors (MMAD) [34-36].

The assessment of comorbidities, risk assessment prior to HSCT, the use of lower-intensity conditioning protocols in older candidates, and the choice of stem cell sources (PB vs. BM) with regard to malignant and non-malignant indications in relation to chronic graft-versus-host disease (GVHD) were all covered in detail in an earlier EBMT manuscript. It also emphasized methods for improving engraftment and the value of CB as a source of stem cells for allogeneic HSCT from MMAD. It also mentioned the growing tendency of using haploidentical family donors because of their practical benefits and how posttransplant cyclophosphamide reduces alloreactive responses. A reference to the prior EBMT indications manuscript was provided for a thorough examination [37-39].

The previous report's key finding was that transplant doctors continue to have difficulty determining the best MMAD for allogeneic HSCT candidates in the absence of well-matched donors. Though there have been discussions and developments about MMUD, CB, and haploidentical transplants, agreement on the best substitute for matched sibling donors is still elusive. Some support individualized treatment plans based on certain indications, such as CB for detecting minimal residual disease in high-risk acute myeloid leukemia (AML). Remarkably, haploidentical donor rates have increased and CB usage has decreased recently, indicating changing transplant practices driven by cost, accessibility, expertise, and research interests. Nevertheless, in the lack of strong survival information, MMAD guidelines include CB, haploidentical, and MMUD in a single group that is different from donors who are closely matched. Subsequent sections that concentrate on particular signs provide a more detailed explanation of their respective benefits [40-45].

Indications of Stem cell Transplantation

Acute Myeloid Leukemia (AML): In Europe, AML is the most common reason for allogeneic hematopoietic stem cell transplantation (HSCT), with acute lymphoblastic leukemia (ALL) coming in second. Notably, a notable development in recent times is the introduction of non-T-depleted haploidentical donor HSCT. While adult AML patients should be given serious consideration for HSCT, the choice ultimately comes down to weighing the risk of disease relapse against transplant-related mortality. Determining the risk categories for acute leukemia has advanced significantly, incorporating somatic mutations and molecular markers to enhance cytogenetics beyond white blood cell counts and response to induction therapy. Furthermore, comorbidity evaluations and risk scores have been significantly improved, which has

significantly decreased the death rate associated with transplants. Individuals who possess specific gene mutations or cytogenetic/molecular markers that indicate a favorable prognosis, like core binding factor leukemia, are now eligible for consolidation with autologous hematopoietic stem cell therapy (HSCT) in first complete remission (CR1), with allogeneic HSCT being considered in the event of measurable residual disease (MRD). The superiority of HSCT over chemotherapy in these situations is supported by data from studies and meta-analyses. The use of MUD and MMAD is increasing, which improves these patients' results even more. Guidelines are always changing, with a focus on MRD evaluation prior to allogeneic hematopoietic stem cell therapy. Allogeneic HSCT should also be explored for individuals in the favorable risk group who do not reach CR1 following initial induction treatment [46-50].

On the other hand, those who are classified as having an unfavorable risk in CR1 should have allogeneic HSCT utilizing the best donor that is available, which includes HLA-identical family members, unrelated donors, haploidentical donors, and CB, in accordance with established medical practice. In this case, autologous HSCT is not advised. With a recent upsurge in interest in autologous HSCT, intermediate-risk patients in CR1 are predominantly evaluated for allogeneic HSCT using HLA-identical sibling donors or well-matched HLA unrelated donors. Autologous HSCT is recommended for patients who achieve CR2 and MRD negative after AML M3, as the results are either comparable to or better than those of allogeneic transplantation [51-52].

Acute lymphoblastic leukemia (ALL): The use of pediatric-style chemotherapy regimens, MRD monitoring, new monoclonal antibodies, and cutting-edge cellular treatments like CAR-T cells has significantly improved the management of ALL in adults. Regarding risk classification, the majority of adult ALL patients have measurable molecular targets for MRD evaluation. It is not always advised to use allogeneic HSCT for standard-risk ALL patients, especially if they do not have MRD. In high-risk situations, such as slow remitters, resistant patients, and post-CR1 relapses, it is still a conventional procedure. Meta-analyses show that younger patients who have matched sibling donors had a higher chance of survival, particularly in terms of non-relapse mortality. For Ph+ ALL, allogeneic HSCT is still the norm, with post-transplant TKI maintenance providing extra advantages. Allogeneic HSCT is a great option for higher-risk ALL patients with persistent or relapsing MRD in CR1, as well as for those who relapse following chemotherapy and reach CR2. In certain cases of ALL, especially those with negative MRD, autologous HSCT is a possibility; nevertheless, it is generally not advised for higher-risk situations [53-56].

Even in post-allogeneic HSCT relapses, CAR-T cell treatment that targets CD19 has demonstrated encouraging results in advanced ALL patients. In order to maximize CAR-T programs, efforts are being made in the areas of accessibility, toxicity control, and efficacy assessment. To ascertain their best application in connection with HSCT—as a bridge-to-transplant or in other clinical settings—more expertise is required. Therefore, this research does not include specific recommendations about the use of CAR-T cells in ALL or other indications. Tyrosine kinase inhibitors (TKIs) have made it unnecessary to use allogeneic hematopoietic stem

cells (HSCT) as the first line of treatment for chronic myeloid leukemia (CML). Imatinib or second-generation TKIs such as dasatinib, nilotinib, or bosutinib are commonly used in first-line therapy. Remarkably, about 40% of patients who experience molecular remission after stopping their TKI treatment manage to maintain this remission even after stopping the medication. The patients' long-term curative potential is still unknown, though. When first-line therapy fails, patients should switch to second-line TKI therapy. Third-line TKIs should also be considered, depending on ABL mutation studies. When two lines of TKI fail, patients should quickly look into donor possibilities. Depending on their response and EBMT risk score, HSCT may be an option. Regardless of their EBMT risk score, patients with T315I mutations or ABL mutations resistant to third-generation TKIs are eligible for HSCT. As soon as the second chronic phase is reached, HSCT should be taken into consideration for patients in advanced stages. Outside of clinical trials, autologous HSCT is typically not advised and synthetic donors are always preferable [57-64].

Other Myeloproliferative illnesses: The only treatment that may be able to treat non-CML myeloproliferative illnesses is allogeneic hematopoietic stem cell transplantation. Generally speaking, HSCT is not necessary for polycythemia vera and essential thrombocythemia unless they develop into myelofibrosis or secondary leukemia. When it comes to primary myelofibrosis, HSCT makes sense in high-risk and intermediate II cases. In younger patients with unfavorable mutations or cytogenetics, intermediate I cases may also be taken into consideration. More research is needed to determine how JAK inhibitors affect spleen size reduction prior to transplantation. Generally speaking, autologous HSCT is not advised outside of clinical studies [65-68].

Myelodysplastic Syndromes (MDS): Allogeneic hematopoietic stem cells (HSCT) are the preferred treatment for adult MDS patients, providing a potential for long-term disease-free survival, particularly when administered prior to disease development or following chemotherapy-induced remission. The use of HSCT has increased due to expanded donor possibilities and lower-intensity training regimens. Patient assessment is aided by prognostic techniques such as IPSS, which consider factors such as somatic mutations and marrow fibrosis. An HSCT with a blast count of less than 5% at transplant improves outcomes. Although there is insufficient data to support the use of hypomethylating drugs or intense chemotherapy in patients with excess blasts in preparation for transplantation, these treatments may be used to improve post-transplant outcomes. Candidacy for HSCT is determined by patient characteristics, illness risk, and EBMT risk score [69-72].

The treatment of chronic lymphocytic leukemia (CLL) and the indications for transplantation have changed as a result of the development of signaling pathway inhibitors. Patients who respond to PI treatment for chemoimmunotherapy-resistant CLL should continue receiving PI treatment; in low-risk situations, HSCT may be considered. Patients who show resistance to both PI and chemo-immunotherapy may benefit from cellular treatments such as HSCT or CAR-T cells. In the case of CLL with histological change, autologous HSCT may be considered; otherwise, it is generally not advised [73-76].

The MED-Lymphomas Updates to standard reporting forms have improved transplant indications for lymphomas, differentiating between "true" and "post-refractoriness" CR1. Allogeneic HSCT is the preferred treatment after autograft failure, although autologous HSCT is still the norm for chemosensitive DLBCL relapse. Although CAR-T therapy shows promise, more research is necessary. Autologous HSCT consolidation in follicular lymphoma may be taken into consideration in specific high-risk situations following immunochemotherapy. The indications for transplantation in FL are essentially unchanged [77-80].

Conclusion:

In conclusion, this review provides a comprehensive overview of the applications of pluripotent stem cells (PSCs) and the indications for hematopoietic stem cell transplantation (HSCT) in various hematological disorders. The discussion begins with the generation of stem cells, highlighting the development of reprogramming techniques and the importance of selecting appropriate somatic cell types for iPSC production. It emphasizes the significance of understanding variables affecting reprogramming efficiency and the potential impact of DNA methylation levels on iPSC differentiation. The review then delves into the role of PSCs as disease models, showcasing their utility in understanding disease mechanisms, drug responses, and potential therapeutic targets. By modeling various hematological disorders using patient-specific iPSCs, researchers can gain valuable insights into disease pathogenesis and test novel treatment approaches. Furthermore, the review explores the indications for HSCT in different hematological malignancies, including acute myeloid leukemia (AML), acute lymphoblastic leukemia (ALL), chronic myeloid leukemia (CML), myeloproliferative disorders, myelodysplastic syndromes (MDS), chronic lymphocytic leukemia (CLL), and lymphomas. It discusses the evolving landscape of HSCT, incorporating advancements such as non-T-depleted haploidentical donor HSCT and the use of donor-specific molecular markers for risk assessment. Overall, this review underscores the transformative potential of PSCs in disease modeling, drug discovery, and personalized medicine, as well as the importance of HSCT as a curative option for various hematological disorders. Through continued research and clinical advancements, PSCs and HSCT have the potential to revolutionize the treatment landscape and improve outcomes for patients with hematological diseases.

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