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Induced Pluripotent Stem Cells for the Treatment of Hemophilia A

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Abstract

Factor VIII, one of the most complex proteins known, plays a major role in blood coagulation pathway. Defects in factor VIII protein result in hemophilia A, a severe bleeding disorder. Plasma derived factor VIII or recombinant factor VIII has been used extensively for treating hemophilia A patients. Number of attempts at gene therapy for hemophilia A has failed for various unknown/not much studied reasons including immune rejection. Here, the progress that has been made in establishing iPSC-based disease models and the potentials of iPSC technology for personalized medicine and cell therapy for hemophilia A are reviewed. The challenges of iPSC technology are also briefly discussed.

Introduction

Hemophilia A is one of the most common genetic coagulation disorders arising due to the deficiency of factor VIII protein. It is estimated that 1 in 5,000 males are affected by hemophilia A [1]. It is caused by several genetic mutations, which include deletions, insertions, inversions and point mutations in the factor VIII gene (Haemophilia A Mutation, Structure, Test and Resource Site; http://hadb.org.uk). According to the severity of bleeding and time taken for clotting, hemophilia A can be characterized as severe, moderate or mild [1]. Currently, there is no cure for hemophilia A. The only available treatment for this disease is the infusion of or administration of recombinant factor VIII. However, the treatment with recombinant factor VIII is limited due the formation of factor VIII inactivating antibodies, exorbitant cost and requirement of frequent injections.

After the introduction of gene therapy, it is found that gene therapy is a promising option for the treatment of hemophilia A. Natwani et al. has used the adeno-associated virus vector (AAV) to deliver factor IX cDNA to correct hemophilia B. This method of delivery could not be used for hemophilia A patients since the size of full length factor VIII cDNA is too large and AAV cannot accommodate the large size of factor VIII cDNA. Besides, gene therapy is ideally used to correct genetic defects rather than to deliver a functional gene.

Usage of iPSC in hemophilia A

Another promising option for the treatment of hemophilia A is the introduction of patient-derived induced pluripotent stem cells (iPSCs). The defective gene can be corrected in iPSCs by using programmable nucleases like zinc ginger nucleases (ZFNs) [2-5], transcription activator-like effector nucleases [6-8] and clusters of regularly interspaced palindromic repeats [9-16]. In case of these programmable nucleases they cleave the chromosomal DNA in a targeted manner and produce DNA double stranded breaks. The nick will be repaired by endogenous mechanisms known as homologous recombination or non-homologous end-joining. Finally, it will result in the correction mutagenesis such as deletions [17,18], duplications and inversion [19]. These gene-corrected iPSCs are then allowed to differentiate into appropriate somatic cells before delivery to patients to ensure the expression of the functional gene.

Challenges of the technology

iPSCs have their own merits and demerits. Though iPSCs are mentioned to be the cells that will rule the future medical industry to provide patient-specific stem cells [20-22], there are controversies over its application to human subjects [23,24]. Challenges are encountered with the recent advancements which can harness its true activity for biomedical research to successfully formulate effective therapeutic approach [25]. It is worth to estimate the potentials of iPSCs as they are quite prominent being the readily accessible such as skin or blood which are enough to generate the disease-specific models. Existing challenges include the kinetics of disease onset and progression and also the spatial localization of the disease to create disease models which are commented can be tackled with advanced strategies such as gene modification, biomaterials, reprogramming etc. [26]. Researchers have been already working to correlate hemophilia A using patient-specific iPSCs because of its unlimited self-renewal and differentiation capabilities [27-31].

Conclusion

Approaches to generate an effective mechanism involving iPSCs are noteworthy to clearly define the potentials to tackle Hemophilia A and with priority attention over this much needed technology will play an eminent role in therapeutic scenario.

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