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Bioinformatical Detection of Thalassemia and Bone Marrow Transplantation

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Abstract
Thalassemia is considered as a severe blood problem in which unusual type of hemoglobin produced by the body. It is a protein, present in red blood cell to transport the oxygen. Bioinformatics tools and software are used to detect, predict and visualize the mutation in a single nucleotide polymorphism including for thalassemia. Thalassemia is classified into two types as alpha thalassemia in which the properties of alpha globin altered and beta globin properties are influenced in beta thalassemia. The treatment of thalassemia depends upon the type and severity of the disease. Some of them include blood transfusion, medication and supplements, conceivable medical procedure to evacuate spleen, gall bladder and bone marrow transplantation. The transplantation of bone marrow is a clinical technique includes transplanting blood stem cells, which travel to the bone marrow where they produce fresh recruit cells and develop growth of new marrow about the extracted blood for the transplantation to analyze allogeneic bone marrow and autologous bone marrow transplantation.

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Introduction

Thalassemia is considered as one of the severe genetic disorders caused by the production of unhealthy red blood cells (RBCs) due to mutations in two major proteins namely 'alpha globin' and 'beta globin. The defect in gene helps to control the production of the protein (α globin and β globin) that can cause thalassemia, which are of three subtypes named as thalassemia major, thalassemia intermedia and thalassemia minor. Different Risk factors are responsible to cause the thalassemia disease which may leads to some major complications. The method of bone marrow transplantation is considered to treat thalassemia [1-7]. The transplantation method of bone marrow is used to overcome the abnormal functions. The excess of immature lymphocytes in bone marrow occupied a wide space in the bone marrow leading to the immature production of erythrocytes and thrombocytes. The immature RBCs lose the ability to attach with the hemoglobin resulting into thalassemia described the method of bone marrow transplantation to exchange the abnormal functioning bone marrow with healthy bone marrow. The stem cells of hematopoietic are mostly located in bone marrow while few are also present in bloodstream [8]. Hematopoietic stem cells are also present in umbilical cord blood. Various types of hematopoietic stem cells are used in bone marrow transplantation procedure depend on the medical condition of the patients.

Role of bioinformatics in the prediction of thalassemia

Bioinformatics play a major role in the prediction of genetic diseases and mutational analyses by using different bioinformatics tools and software. Bioinformatics is an interdisciplinary field for developing computational software and databases for enhancing the biological data research platform [9-11]. The bioinformatics approaches help to detect the genes involved in diseases. Thalassemia is a genetic disorder arrive inheritably which can be analyzed by using bioinformatics techniques and different methods by utilizing GenBank [12], dbSNP [13] processes, SIFT [14], ClustalW [15], PolyPhen [16]. These modern methods and techniques were used to reveal the genetic (DNA or protein) effect on an organism structurally as well as functionally [17].

In the case of thalassemia, a single nucleotide mutation or multiple amino acids deletion in *HBA1* or *HBA2* can leads to thalassemia. Bioinformatics helps a lot in the detection of thalassemia through different tools and databases [18]. After getting the mutated sequence of genes related to thalassemia from dbSNP in case of single nucleotide polymorphism, one can develop the structure of mutated protein by using bioinformatic tools and techniques help to easily visualize the structure of mutated and normal protein even a single amino acid change in protein structures. Structure evaluation and validation of proteins could be done by using bioinformatic tools such as RAMPAGE [19], ERRAT [20], VERIFY3D [21], PROCHECK [22], WHATIF. Normalization can be done using GROMACS [23], AVOGADRO [24], UCSF CHIMERA [25], PYMOL [26], Accelrys DS Visualizer software [27] to check free energy of protein (to which extent an atom can move in three-dimension freely) [28-30]. Some other tools include ligandscout [31], MODELLER [32], PatchDock [33], String [34], Stitch [35], grammX [36], MEGA [37], SwissModel [38], I-Tasser [39], mod-web [40], 3D-jigsaw [41] , ESYpred3D [42], AMBER [43], Molprobity [44], Wincoot [45], anolea [46].

Hematopoietic stem cells transplantation (HSCT)

The hematopoietic stem cell transplantation (HSCT) is derived from umbilical cord blood and bone marrow from the placenta. HSCT is used to collect the peripheral blood by the stem cells [47-50]. The transplantation depends upon the donor, known as autologous, allogeneic and syngeneic. HSCT for the most part extricated from umbilical cord blood, bone marrow and peripheral blood. The stem cells of hematopoietic have three different types for collection and harvesting.

Peripheral blood stem cells

The undifferentiated cells extracted from the donor's peripheral blood. The stems cells are also extracted from donor blood and transfer back to the donor [51]. The apheresis is a process to derive the peripheral blood stem cells for transplantation. The medicine to accelerate the stem cells injection to the donor is about 4 to 5 days before the apheresis to expand the number of stem cells in bloodstream. The large vein of the arm is used for apheresis and extracted the undifferentiated cells from the blood. Almost 4 to 6 hours are required for this process.

Bone marrow stem cells

The stem cells of bone marrow are isolated through the surgical procedure from hip bone of the patient. The isolated stem cells from the center of the bone are known as marrow and the process is known as harvesting [52]. The harvesting stem cells are collected with the help of a needle placed into the bone marrow. The effective sites used for the harvesting of bone marrow are mostly placed in the sternum and the hip bones. The donor will be anesthetized during the harvesting of the stem cells. In recuperation, the donor may encounter some pain in the area where the needle was embedded [53]. This bone marrow can be preserved and stored to retain the stem cells by a process known as cryopreservation.

Cord blood stem cells

After birth, the stem cells are collected from the umbilical cord of the newly bone baby and cut down the umbilical cord. The extracted stem cells are store to use for the next transplantation [54]. These collected stem cells have lack of nutrients and have less ability for proper matching. A much time is required to recover the blood count due to the low quantity of stem cells.

Types of bone marrow transplant

The bone marrow transplantation has been classified into autologous BMT and Allogenic BMT depending upon the medical condition of the patient (**Table 1**).

Autologous transplant

In autologous transplantation, the blood of the patient is used to extract the stem cells and the patient act as a donor. The patient's blood is used for the extraction of stem cells before the chemotherapy [55, 56]. After chemotherapy, the stem cells are utilized to generate the blood cells. After the transplantation, the stem cells produce new RBCs, white blood cells and platelets is called engraftment, usually performed after 2 to 4 weeks [57]. The autologous transplantation has a lower life threating risk, complications, graft rejection and graft-versus-host disease (GVHD).

Allogeneic transplant

In allogeneic transplantation, patients receive stem cell from another donor, including family members. Numerous complications have been reported in this procedure including the rejection of donor stem cells and develop the high risk of GVHD. ABO blood typing and Human Leukocyte Antigens (HLG) typing reduce the risks factors. HLG protein located at the cell surface types of the body [58, 59]. Moreover, HLG marker is a common protein in the blood of the patients and the donors to increase the success rate of transplantation. The donor stem cells help to destroy the unhealthy cells while the donor stem cells could also affect the healthy cells in allogeneic transplantation.

Syngeneic

In syngeneic transplantation, comparison between a host and donor is observed to check the genetical similarity and identity, often closely related individual allows to go for transplantation to inhibit an immune response. Especially identical twins are preferable for this type of transplantation.

Table 1: Comparison of Autologous BMT and Allogeneic BMT.

	Autologous BMT	Allogeneic BMT
Donor	There is no need of donor as the stem cells harvested from the blood or bone marrow of the patient	Stem cells are provided by HLA; related or unrelated donor
Tissue Matching	No need for tissue matching	Tissue matching required
GVHD	No GVHD	GVHD.
Engraftment	Faster	Slower
Immune Reconstitution	Faster	Slower
All HSCTs	57%	43%

Risk factor in thalassemia

Thalassemia is involved in some major complication as like pulmonary hypertension (PHT) associated with thalassemia, it is a disease that narrow down the blood vessel leading from heart to lungs. Some study reveals that PHT is more common in thalassemia intermedia rather than thalassemia major [60, 61]. Stem cell (graft) failure is also one of the major complications, after the stem cell infused into the body and the stem cell moves from blood to bone marrow [62-64]. The side effect may occur from chemotherapy and radiation which are the part of transplant after inducing high dose or low dose of it into the body. Other risk is donor stem cell is refused by the immune system of host body. Organ damage and disorder problems are also observed after the bone marrow transplantation include vision, dental, liver, heart, kidney and thyroid problems [65, 66].

The risks of the donor depend on the number of donated bone marrow. The use of anesthesia to the donor can lead to the serious risk and donor may have hardness, pain and tiredness for 2-3 weeks. The donor feels minimal discomfort during apheresis including light headedness, cramping in the hands, numbness around the lips and chills [67-71]. The injections given to stimulate the release of bone marrow in the bloodstream may cause pain in bones and muscles, vomiting, nausea, fatigue, headaches and sleep issues.

Conclusions

Thalassemia is a genetic disorder leads to chronic health issues. Although, bioinformatic approaches help to solve the biological problems by utilizing mathematical and statistical approaches. The bone marrow transplantation technique utilized for the treatment of thalassemia. The bone marrow of the donor removed, engrafted in the recipient bone marrow for the treatment. There are certain risks and complications observed during the bone marrow transplantation which can harm the body organs and also leads to morphological changes.

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