Ex vivo hematopoietic stem cells gene therapy against thalassemia

地中海貧血的體外造血幹細胞基因療法開發

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Being one of the malaria endemic areas historically, Hong Kong has more than 8% of the total population carrying the genetic defects of thalassemia, since people with thalassemia traits are more resistant to malaria. Most thalassemia patients suffer from mild or moderate anemia, lacking enough red blood cells (RBCs), while thalassemia major patients require life-long blood transfusion and other therapies. Only a few thalassemia major patients are lucky enough to receive hematopoietic stem and progenitor cell (HSPC) transplantation, but they might be borne with severe side effects. The increased blood transfusion demands for thalassemia patients stress the public blood transfusion service. In Hong Kong, it is estimated that more than 30% of blood supply will be consumed by thalassemia patients by 2024. Therefore, there is an urgent need to develop new therapies against thalassemia.

Imbalance expression of hemoglobin in thalassemia

One hemoglobin molecule is composed of two alpha hemoglobin chains and two non- alpha hemoglobin chains. In thalassemia, erythroid progenitors fail to maintain the balance between alpha and beta hemoglobin, which is one type of non-alpha hemoglobin, due to genetic defects, leading to excess expression of alpha or beta hemoglobin. Interestingly, patients with beta thalassemia have normal RBCs with fetal hemoglobin in fetus, because fetal hemoglobin is composed of alpha and gamma hemoglobin, instead of alpha and beta hemoglobin. The transition from gamma to beta hemoglobin happens six months to one-year post-birth, when the onset of beta thalassemia initiates. Therefore, switching back to fetal hemoglobin could be a therapy against beta thalassemia. Actually beta thalassemia patients with high expression of fetal hemoglobin have moderate anemia comparing to those with low fetal hemoglobin.

The switch of gamma to beta hemoglobin is controlled by a transcription factor B-cell lymphoma/leukemia 11A (BCL11A). Depletion of BCL11A triggers the expression of gamma globin, and increases the production of fetal hemoglobin in mice and human primary HSPCs.

Therapy development against thalassemia

Many effects have contributed to thalassemia therapy development. Bluebird develops a technology called LentiGlobin to treat beta thalassemia. The technology introduces the genomic integration of mutated beta globin into HSPCs by lentivirus ex vivo. Targeting BCL11A is also an attractive strategy to treat thalassemia. Many therapies have been developed to deplete BCL11A to rescue the expression of gamma globin in beta thalassemia and other beta hemoglobinopathies including sickle anemia.

Drawbacks on drug development against thalassemia

Current treatment requires patient preconditioning and ex vivo manipulation of HSPCs, which demands complex medical equipment, and induces additional adverse effects. therefore, an in vivo therapy development for thalassemia is urgently needed**.**

We have recently developed a novel strategy for RNA drug delivery based on human red blood cell extracellular vesicles (RBCEVs). Therefore, we propose to deliver RNA drug against BCL11a to HSPC ex vivo using RBCEV.

Milestone 1: We will synthesize Cas9 mRNA and sgRNA targeting Bcl11a ex vivo and incorporate them into RBCEVs by electroporation.

Milestone 2: We will infuse engineered HSPC into the mouse model of beta thalassemia. And the mice should have improved RBC parameters.

The success of our project will pave the road to therapy development against beta thalassemia.