Potential long-term treatment of hemophilia A by neonatal co-transplantation of cord blood-derived endothelial colony-forming cells and placental mesenchymal stromal cells.

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Public Summary:
Hemophilia A (HA) is an X-linked recessive disorder caused by mutations in the Factor VIII (FVIII) gene leading to deficient blood coagulation. As a monogenic disorder, HA is an ideal target for cell-based gene therapy, but successful treatment has been hampered by insufficient engraftment of potential therapeutic cells.In this study, we sought to determine whether co-transplantation of endothelial colony-forming cells (ECFCs) and placenta-derived mesenchymal stromal cells (PMSCs) can achieve long-term engraftment and FVIII expression. ECFCs and PMSCs were transduced with a B domain deleted factor VIII (BDD-FVIII) expressing lentiviral vector and luciferase, green fluorescent protein or Td-Tomato containing lentiviral tracking vectors. They were transplanted intramuscularly into neonatal or adult immunodeficient mice.In vivo bioluminescence imaging showed that the ECFC only and the co-transplantation groups but not the PMSCs only group achieved long-term engraftment for at least 26 weeks, and the co-transplantation group showed a higher engraftment than the ECFC only group at 16 and 20 weeks post-transplantation. In addition, cell transplantation at the neonatal age achieved higher engraftment than at the adult age. Immunohistochemical analyses further showed that the engrafted ECFCs expressed FVIII, maintained endothelial phenotype, and generated functional vasculature. Next, co-transplantation of ECFCs and PMSCs into F8 knock-out HA mice reduced the blood loss volume from 562.13 ± 19.84 μl to 155.78 ± 44.93 μl in a tail-clip assay.This work demonstrated that co-transplantation of ECFCs with PMSCs at the neonatal age is a potential strategy to achieve stable, long-term engraftment, and thus holds great promise for cell-based treatment of HA.

Scientific Abstract:
BACKGROUND: Hemophilia A (HA) is an X-linked recessive disorder caused by mutations in the Factor VIII (FVIII) gene leading to deficient blood coagulation. As a monogenic disorder, HA is an ideal target for cell-based gene therapy, but successful treatment has been hampered by insufficient engraftment of potential therapeutic cells. METHODS: In this study, we sought to determine whether co-transplantation of endothelial colony-forming cells (ECFCs) and placenta-derived mesenchymal stromal cells (PMSCs) can achieve long-term engraftment and FVIII expression. ECFCs and PMSCs were transduced with a B domain deleted factor VIII (BDD-FVIII) expressing lentiviral vector and luciferase, green fluorescent protein or Td-Tomato containing lentiviral tracking vectors. They were transplanted intramuscularly into neonatal or adult immunodeficient mice. RESULTS: In vivo bioluminescence imaging showed that the ECFC only and the co-transplantation groups but not the PMSCs only group achieved long-term engraftment for at least 26 weeks, and the co-transplantation group showed a higher engraftment than the ECFC only group at 16 and 20 weeks post-transplantation. In addition, cell transplantation at the neonatal age achieved higher engraftment than at the adult age. Immunohistochemical analyses further showed that the engrafted ECFCs expressed FVIII, maintained endothelial phenotype, and generated functional vasculature. Next, co-transplantation of ECFCs and PMSCs into F8 knock-out HA mice reduced the blood loss volume from 562.13 +/- 19.84 mul to 155.78 +/- 44.93 mul in a tail-clip assay. CONCLUSIONS: This work demonstrated that co-transplantation of ECFCs with PMSCs at the neonatal age is a potential strategy to achieve stable, long-term engraftment, and thus holds great promise for cell-based treatment of HA.