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Transgenic mouse model in sickle cell anaemia

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DESCRIPTION

Transgenic mouse models have been created to better understand the illness's complicated biology and to test potential specific treatments in the absence of a natural animal model for sickle cell disease. The simple insertion of human globin genes to mice still expressing mouse hemoglobin resulted in the development of hemoglobin S (HbS) or HbS-related human hemoglobin in the early 1990s.To enhance the proportion of human hemoglobin and the severity of the mouse sickle cell syndrome, a combination of mice alpha- and beta-thalassemia abnormalities could be used to reduce the fraction of mouse hemoglobin, resulting in complex genotype and mild sickness. It was able to knock out all mouse adult globin genes (2alpha and 2beta) and put the human corresponding genes elsewhere in the mouse genome just after discovery of gene targeting in mouse embryonic stem cells (ES cells).Furthermore, the prenatal hemoglobin human gamma gene protected the fetus from HbS polymer formation. As a result, the adult mouse models developed in 1997 that only expressed human HbS showed severe anemia (Hb=5-6 g/dL).These "HbS-only mice" had to lower the HbS concentration in their red blood cells in order to survive.

Adding modified human gamma genes, which are still expressed in adult mice, could make the condition less severe. By homologous knock in, a final "S-only" model was developed in 2006, with human genes substituting mouse globin genes. This collection of models helps researchers better understand the role of various interacting factors in the complication of sickle cell events like red cell defects, blood flow and vaso-occlusion, hyper hemolysis, vascular tone deregulation, oxidations, inflammation, cell activation and adhesion, ischemia, and reperfusion. Furthermore, each model is excellent for evaluating experimental medicines *in vivo* and conducting preclinical studies.

To create a transgenic mouse model of sickle cell disease, researchers created beta SAD, a novel human beta-globin gene that increases the polymerization of transgenic human hemoglobin S (Hb S) *in vivo*. The beta 6Val alteration of the beta S chain, as well as two additional mutations, Antilles (beta 23Ile) and D Punjab (beta 121Gln), all enhance Hb S polymerization in humans. The beta SAD gene and the human alpha 2-globin gene were both introduced into the mouse germ line through the beta-globin locus control region (LCR). SAD-1, one of the five transgenic lines obtained, has 19 per cent human Hb SAD (alpha 2 human 1 beta 2SAD) and mouse-human hybrids in addition to mouse hemoglobin in its red blood cells. Adult SAD-1 transgenic mice were not anemic, but their erythrocytes showed aberrant characteristics and their spleens were somewhat enlarged. *In vitro* de oxygenation caused sickling in their erythrocytes. Many SAD-1 new-borns died because they were anemic. Crosses between SAD progeny and homozygous for beta-thalassemia mice were undertaken in order to develop adult mice with a more severe sickle cell condition.

In beta-thal/SAD-1 mice with abnormal erythrocyte shape and density, an enlarged spleen, and a high reticulocyte count indicating increased erythropoiesis, mortality upon hypoxia, polymerization of hem lysate similar to that seen in human homozygous sickle cell disease, and anemia and mortality during development, haemoglobin SAD was increased to 26 per cent.

Sickle cell disease is a hereditary disease characterized by the deformation of red blood cells due to haemoglobin polymerization. By mating with mice expressing the human fetal agama globin gene, the potential healing threshold of fetal haemoglobin in a transgenic SAD mouse model of sickle cell disease was evaluated *in vivo*. With increased HbF levels, Agamas mice showed significant improvements in all hematological parameters, morphological pathological features, and longevity / survival. We have established a direct therapeutic effect on fetal haemoglobin for sickle cell disease and demonstrated correction by increasing fetal haemoglobin to about 916% in this mouse model. This *in vivo* study highlights the potential of the SAD mouse model for quantitative analysis of gene therapy approaches.