Using the hemoglobin switch for the treatment of sickle cell disease

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Sickle cell disease is one of the most common monogenic disorders worldwide, and is the most common genetic disease in Africa, the Caribbean, the Americas, the Middle East, and India.[1] Sickle cell disease is an autosomal recessive disorder caused by mutations in the hemoglobin beta (HBB) gene, the hemoglobin gene that is specifically used after birth.[1] In the fetus, the hemoglobin gamma genes (HBG1 and HBG2) are expressed, and two hemoglobin alpha chains together with two hemoglobin gamma chains constitute fetal hemoglobin (HbF). After birth, the switch to adult hemoglobin (HbA) takes place, with only a tiny fraction of HbF remaining in adults. The normal adult hemoglobin tetramer consists of two hemoglobin alpha chains and two hemoglobin beta chains. Mutations in the hemoglobin beta (HBB) gene cause sickle cell anemia. Absence of the hemoglobin beta chain causes beta-zero-thalassemia, while reduced amounts of hemoglobin beta causes beta-plus-thalassemia.

As is clear from its name, sickle cell disease is characterized by the presence of sickle shaped rigid red blood cells, caused by the hemoglobin gene/protein defect. Individuals with sickle cell disease have an increased risk of a variety of complications and a shortened life expectancy. Clinical management of sickle-cell disease is still no more than basic and no drugs have been developed that specifically target the cause of this disease, while allogeneic stem cell transplantation remains an option.[1,2] Although it is a monogenic disorder caused by a clear defect in one gene, the phenotypic expression and severity vary greatly from one patient to another.[3]

Sickle cell disease is thus caused by mutations in the hemoglobin beta gene that only become apparent after the switch from fetal hemoglobin (using the gamma gene) to adult hemoglobin (using the beta gene). Reactivation of the fetal form of the complex could potentially solve or decrease the 'sickle problem', since the fetal hemoglobin gamma could replace the mutated hemoglobin beta. Indeed, it has previously been shown that persistent expression of fetal hemoglobin (HbF) can ameliorate the phenotype of sickle cell disease, and this occurs in the normal population as a consequence of genetic variation.[1] Many studies have identified genetic variants controlling HbF levels in adults, and there is compelling evidence that both BCL11A and KLF1, a key erythroid transcriptional regulator that regulates BCL11A expression, are important for gamma to beta globin gene switching.[4-6] There is, however, no *in vivo* evidence to demonstrate the potential of these factors as therapeutic targets for sickle cell disease.

In a study published in the November 18 issue of Science, Xu and colleagues[7] used a sickle cell disease mouse model to demonstrate that interference with BCL11A function *in vivo* in the mouse could increase fetal hemoglobin levels, and thereby reduce the severity of the disease in that model.[7] Since BCL11A null mice are postnatally lethal, Xu *et al.* used a conditional knock-out strategy targeting BCL11A in an erythroid specific manner. In this way, the authors obtained a sustained increase in HbF expression through adult life, with minimal effects on red blood cell production. Most importantly, improvement of hematologic parameters was observed in two mouse models for sickle cell disease, with correction of red blood cells counts, hemoglobin levels and the disappearance of sickle cells. These data nicely demonstrate the potential of *in vivo* targeting of the transcription factor BCL11A for the treatment of sickle cell disease and open new perspectives for the treatment of this disease.

References

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