Back to the Basics: Inducing Fetal Hemoglobin In Treating Sickle Cell Disease Through Regulatory Mechanisms

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Introduction

Sickle cell disease (SCD) is a group of inherited blood disorders that affect many individuals around the globe. SCD is an autosomal recessive disorder, meaning individuals must inherit the recessive allele from both parents to have SCD. Sickle cell disease can cause anemia, which is when the body fails to produce enough healthy red blood cells. In particular, SCD turns healthy, biconcave disc red blood cells into a sickle shape, which leads to a lack of oxygen in the body. SCD can cause a wide range of symptoms, with one of the most common and severe symptoms being painful episodes known as crises. Crises can last for days and cause pain in areas such as the chest, back, and legs. Additionally, due to the lack of oxygen delivery from the sickle-shaped cells, fatigue and shortness of breath are also common symptoms.

In the United States, more than 90% of individuals who have sickle cell disease are African American, as SCD occurs in about 1 of every 365 Black or African American births (CDC). Furthermore, approximately one in every thirteen Black or African-American babies is born with the sickle cell trait, meaning that they only inherit one recessive allele from a parent (CDC). While those with the sickle cell trait typically show little to no symptoms, the recessive allele can still be passed on to the next generation, potentially leading to the development of sickle cell disease in offspring. Globally, sickle-cell disease (SCD) primarily affects populations in Sub-Saharan Africa as well as those in developing countries (CDC). **Figure 1** shows the distribution of SCD worldwide in 2015, with similar rates still prevalent today (Ashorobi and Bhatt, 2019).

Sickle Cell Disease Treatments

There is only one well-known procedural cure for sickle cell disease: a bone marrow transplant. A common type is the allogeneic (or donor) transplant, which replaces diseased blood cells with healthy ones (Smith). While this process is conceptually straightforward, a bone marrow transplant is a complex and lengthy process.

The transplant process begins with chemotherapy, which destroys the patient's existing blood-forming cells—hematopoietic stem cells—including those that produce sickle-shaped blood cells. Chemotherapy also weakens the immune system, reducing the chance that the body rejects new stem cells when they are introduced (Smith). Following

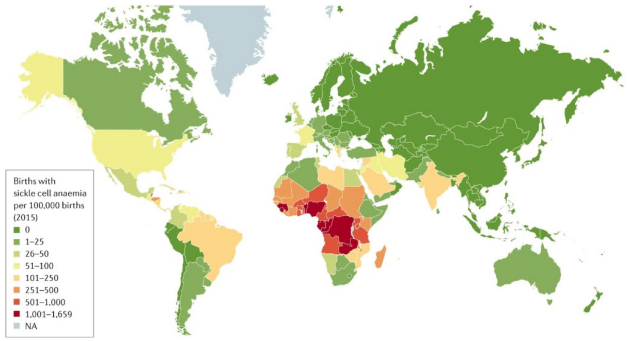

Figure 1. Global Breakdown of Sickle Cell Anemia Birth Rates (Kato, Gregory J., et al. 2015)

chemotherapy, healthy cells from a donor are injected into the patient intravenously("Sickle Cell Disease | NMDP", n.d). These donor cells travel to the bone marrow, where they begin producing healthy cells including normal red blood cells. Finally, the patient enters a recovery period, spending several weeks in the hospital before continuing to recover at home, during which they may take medication and must follow specific rules to prevent infection ("Sickle Cell Disease | NMDP"). Doctors closely monitor the pain and symptoms of the patient to ensure everything post-transplant runs smoothly. During recovery, there are risks of fever, infection, bleeding, anemia, and dietary problems for the patient.

Bone marrow transplants have demonstrated notable success rates: A transplant from a matched related donor has an 85–90% success rate, while a transplant from a sibling or family member has a 95% success rate ("Investigating Bone Marrow Transplants: A Cure for Some Sickle Cell Disease Patients"). Despite this, there are many associated risks with a bone marrow transplant. One of the most common complications is graft-versus-host disease, in which immune cells produced by the transplanted cells attack the patient's own body, potentially leading to permanent and severe health impacts ("BMT for Sickle Cell Disease"). Other associated risks include infection, rejection of the new cells, infertility post-transplant, organ damage, or even death ("Yale Medicine"). Approximately five percent of those who receive the transplant die ("Stem Cell Transplant for Sickle Cell Disease"). Given these risks, many patients rely on symptom management to alleviate the effects of SCD. Fluids, over-the-counter supplements, medical care, and nutritional supplements like zinc can help manage symptoms (Johns Hopkins Medicine).

Beyond a bone marrow transplant, the drug hydroxyurea has made significant strides in providing symptom relief for SCD patients. Hydroxyurea can help treat SCD by preventing the formation of sickle-shaped red blood cells. While primarily used as a treatment for cancer, the intake of hydroxyurea is considered safe as doctors prescribe a lower dose to treat SCD than to treat cancer (*Hydroxyurea for Sickle Cell Disease*). Hydroxyurea reduces the number of crises, episodes of acute chest syndrome, blood transfusions, and organ damage.

While this drug has made progress in the cure for sickle-cell anemia, the global impact has been mixed. Obtaining hydroxyurea in regions such as Sub-Saharan Africa may prove difficult. Barriers such as cost and the amount of hydroxyurea an individual can receive produce a paradox: hydroxyurea is life-changing, but it is not the ideal drug for sickle-cell disease. Thus, ongoing research aims to develop safer and more effective treatments for SCD.

Ongoing Research in SCD: A Case Study

Rather than focusing solely on stem cell transplants, current research is exploring how the induction of certain types of hemoglobin—a protein in red blood cells that carries oxygen from the lungs to the rest of the body—can improve SCD treatment. Fetal hemoglobin (HbF), a form of hemoglobin with a greater oxygen-binding affinity than adult hemoglobin (HbA) is one candidate for these hypothesized therapeutics (Kaufman and Lappin, 2020). Normally, adult hemoglobin completely replaces fetal hemoglobin by 12 months of age (Kaufman and Lappin, 2020). Researchers believe that inducing fetal hemoglobin in adults could be a gateway to sickle cell disease treatment due to advancements in gene editing.

Dr. Pamela Ting and her team at Novartis have pioneered a method for inducing fetal hemoglobin through the degradation of a key transcription factor known as WIZ, a repressor of HbF (Ting, et.al). Transcription factors are proteins that control whether or not a gene is expressed by binding to DNA. The inverse relationship between WIZ and fetal hemoglobin (**Fig. 2**) suggests potential for applying WIZ degradation to SCD treatments. As a result, Dr. Ting and her team began looking at cereblon (CRBN)-dependent degraders of transcription factors (Ting, et.al). The team screened 2,814 CRBNs to test for induction of fetal hemoglobin. While 7.4% of the CRBN-dependent degraders increased the fetal hemoglobin fraction, only one increased the percentage of hemoglobin dramatically while sparing

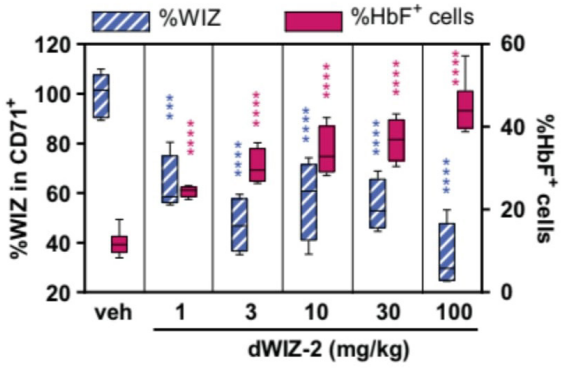

Figure 2. Inverse Relationship between WIZ and Fetal Hemoglobin (Ting et al., 2024).

erythroblast (pre-developed red blood cell) proliferation and differentiation: Compound C (Ting, et.al). Moreover, HbF induction was not observed in erythroblasts deficient in CRBN, meaning that Compound C acts through a protein degradation mechanism to induce HBF (Ting, et.al). After this finding, Compound C was renamed to DWIZ-1.

DWIZ-1 operates by degrading the WIZ transcription factor post-transcriptionally. Sequence analysis and modeling showed that WIZ is composed of 11 Zinc finger (ZF) proteins (Ting, et.al). WIZ (ZF7) is the primary ZF involved in the formation of a ternary complex, which is a direct binding mechanism of three different molecules. The researchers concluded that DWIZ-1 induces HbF expression by directly binding to CBRN and recruiting a complex of enzymes that degrade WIZ through WIZ (ZF7) (Ting, et.al). A second assay revealed that there was a high binding affinity of WIZ (ZF7) and the DWIZ-1 complex and that WIZ (ZF7) and DWIZ-1 bind through hydrogen bonding (Ting, et.al). Therefore, the researchers hypothesized that this affinity is essential to the effectiveness of DWIZ-1.

In addition to DWIZ-1, the team discovered a chemical analog, DWIZ-2, in which a methyl group of DWIZ-1 is removed. Early tests show that DWIZ-2 also works as a CRBN-dependent degrader, depleting only a small number of additional proteins. DWIZ-2 also increased fetal hemoglobin in patients with SCD from 17% to 45% of the total hemoglobin (Ting, et.al). The research team studied the in vivo activity of DWIZ-2 in human hematopoietic stem and progenitor cells (HSPCs) transplanted into mice and subsequently found that mice treated with DWIZ-2 averaged 65% WIZ degradation (Ting, et.al). Moreover, in primary human erythroblasts treated with DWIZ-2 in two different time intervals: 24 hours or seven days, in total, 407 genes were differentially expressed and 293 of these genes were upregulated, which aligns with the hypothesis that WIZ functions as a repressor (Ting, et.al). The team has further shown that WIZ degradation does not exhibit toxicity by investigating the effect of DWIZ in non-human primate models. Based on all their findings, the research team ultimately believes in the potential for WIZ degradation applications in treating human SCD.

Conclusion

Despite advancements in sickle cell disease research, researchers are still discovering ways to provide a safe and accessible cure for all those affected with SCD. Bone marrow transplants are expensive and often limit access to sickle cell disease treatment. Because sickle cell disease affects minority populations, limited access to life-saving care creates an additional barrier for these populations and leaves a detrimental impact on their health. Furthermore, access to treatment in developing countries is constrained by multiple factors including limited numbers of healthcare workers and equipment, lack of educational awareness, and poor infrastructure. However, through dedicated SCD clinics, point-of-care screening, and regional multilevel treatment guidelines, access to SCD treatments has begun to improve (Novartis). The cure for sickle cell disease is challenging at the molecular level, but the shift from stem cell transplant to new molecular modalities in research is promising. Scientists are currently focusing on in vivo gene editing— directly altering a patient's cells' genetic material inside the body—instead of ex vivo gene editing, where cells are removed from the body, treated, and then reinserted. Such an investment in new research and new technology will take time to develop. Many scientists like Dr. Ting's team are working daily to offer a holistic approach to treatment that combines scientific innovation with policy-driven accessibility. This approach will be essential in creating comprehensive solutions that benefit all individuals affected by SCD.

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