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SICKLE CELL DISEASE: TREATMENT ON MOLECULAR LEVEL

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ABSTRACT

Sickle cell disease is one of most common hereditary disorder that affects millions of people over the world wide. It is autosomal dominant. It is a monogenic disorder caused by an point mutation in B chain of haemolysis that causes polymerization of deoxygenated Sickle haemoglobin. (HbS). SCD the most common problem analogous with SCD is Vaso- occlusion and haemolysis. In spite of latest advances in understandind this disorder a molecular level, few therapeutic Strategies are available. Hydroxyurea is recently approved by the USFDA for the SCD. But this drug has crucial side effects and ineffectiveness in some patients. So, however, new therapeutic strategies are under research to discover new drug to treat SCD.

KEYWORDS: Sickle cell Disease. Haemoglobinopathy gamma globin, Fetal Hemoglobin drug discovery.

INTRODUCTION

Sickle cell anaemia is also called Haemoglobinopathic haemolytic anemia. Sickle cell disease is a global public disorder that affects millions of people across the world. It is a monogenic disorder caused by A-to-T point mutation in the B globin gene that produces abnormal haemoglobin (HbS) which makes the RBC'S rigid, Sticky so these cells can get stuck in small blood vessels. Which can slow or block blood flow and oxygen to parts of the body. in this condition Haemoglobins of "S" type instead of normal haemoglobin "A". Haemoglobin "S" is peculiarly sensitive to a lowered oxygen supply. Sickle cell disease (SCD) was first reported by Herrick in 1910 even though reports suggest prior.[5,6]

Description of the disorder[1]; it is the result of homozygous and compound heterozygote

inheritance of a mutation in the _-globin gene. A single base-pair point mutation (GAG to GTG) results in the substitution of the amino acid glutamic acid (hydrophilic) to Valine (hydrophobic) in the 6th position of the _-chain of haemoglobin referred to as haemoglobin S (HbS).[2]

Phenotypic variation in clinical presentation is a unique feature of SCD despite a well-defined Mendelian inheritance, the first to be molecularly characterised as described by Pauling.[3] and confirmed to be due to a single amino acid substitution by Ingram[3] almost 70 years ago. SCD is a multi-organ, multi-system disorder with both acute and chronic complications presenting when foetal haemoglobin (HbF) drops towards the adult level by five to six months of age.[4]

Symptoms of SCD are

1. Anaemia
2. Episodes of pain
3. Swelling of hands and feet
4. Frequent infections delays growth of puberty
5. Vision Problem
6. Osteonecrosis. Osteoarthritis, Osteomyelitis.
7. Dizziness
8. Priapism
9. Acute chest syndrome

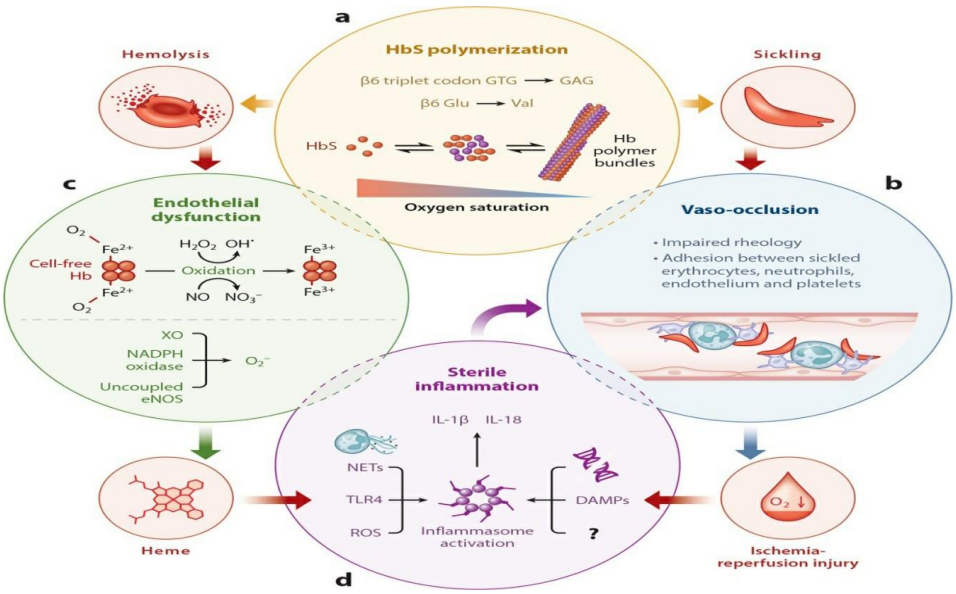

Fig: Pathophysiology of SCD.

Molecular Pathophysiology of Sickle Cell Disease

(a) A single-nucleotide polymorphism in the β-globin gene leads to substitution of valine for glutamic acid at the sixth position in the β-globin chain. Following deoxygenation, the mutated hemoglobin (HbS) molecules polymerize to form bundles. The polymer bundles result in erythrocyte sickling (clockwise), which in turn results in **(b)** impaired rheology of the blood and aggregation of sickle erythrocytes with neutrophils, platelets, and endothelial cells to promote stasis of blood flow, referred to as vaso-occlusion. Vaso-occlusion promotes ischemia- reperfusion (I-R) injury (clockwise).[12] **(a)** Hemoglobin (Hb) polymer bundles also promote hemolysis or lysis of erythrocytes (counterclockwise), which **(c)** releases cell-free Hb into the blood circulation. Oxygenated Hb (Fe^{2+}) promotes endothelial dysfunction by depleting endothelial nitric oxide (NO) reserves to form nitrate (NO^{-}) and methemoglobin ($Fe3^{+}$). Alternatively, Hb can also react with H2O2 through the Fenton reaction to form hydroxyl free radical ($OH^{\bullet}$) and methemoglobin (Fe^{3+}). Also, NADPH oxidase, xanthine oxidase (XO), and uncoupled endothelial NO synthase (eNOS) generate oxygen free radicals to promote endothelial dysfunction. Methemoglobin (Fe^{3+}) degrades to release cell-free heme (counterclockwise), which is a major erythrocyte damage-associated molecular pattern (DAMP). **(d)** Reactive oxygen species (ROS) generation, Toll-like receptor 4 (TLR4) activation, neutrophil extracellular trap (NET) generation, release of tissue or cell-derived DAMPs, DNA, and other unknown factors (?) triggered by cell-free heme or I-R injury can contribute to sterile inflammation by activating the inflammasome pathway in vascular and inflammatory cells to release IL-1β. Finally, sterile inflammation further promotes vaso-occlusion through a feedback loop by promoting adhesiveness of neutrophils, platelets, and endothelial cells.[7,8,9,10,11,13]

Main Complications of SCD By Organ System[18-21,23,27]

Sr. No.	Name of System	Complications
1.	Central Nervous System	Stroke Cognitive Impairment
2.	Cardiopulmonary System	Pulmonary hypertension Acute chest syndrome Restrictive lung disease
3.	Genitourinary System	Priapism Chronic kidney disease Papillary necrosis of the kidney
4.	Hepatic system	Hepatic sequestration Hepatic crisis and intrahepatic cholestasis

Current and Future Therapies Targeting Molecular Pathobiology of Sickle Cell Disease

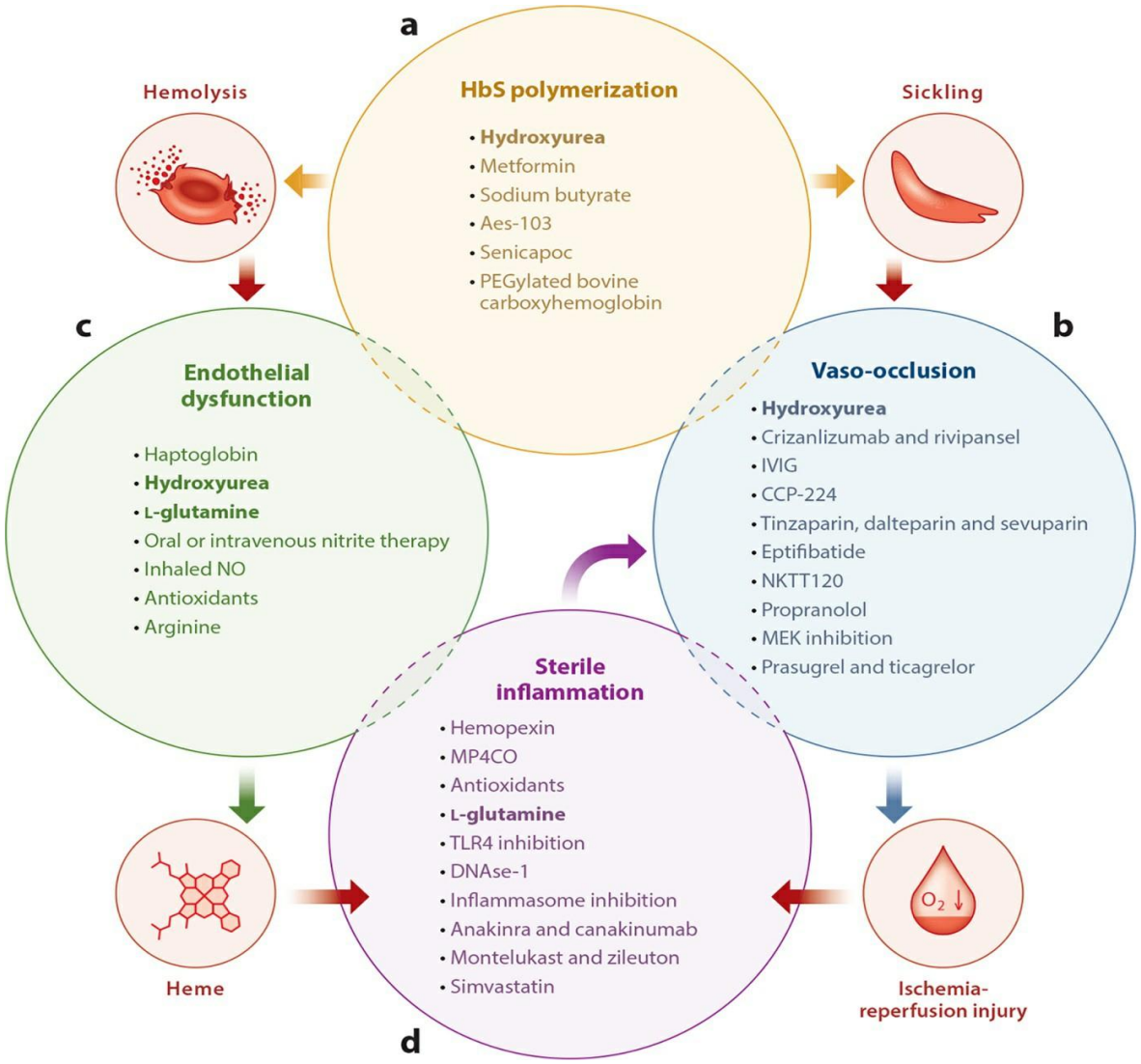

Fig: Current and future therapies targeting molecular pathobiology of sickle cell disease.

(a) Drugs capable of modulating hemoglobin (Hb) polymerization, erythrocyte dehydration, and Hb oxygen affinity. (b) Drugs capable of preventing vaso-occlusion by inhibiting adhesive interactions between leukocytes, platelets, or endothelial cells and erythrocytes. (c) Drugs capable of preventing endothelial dysfunction by scavenging Hb and reactive oxygen species (ROS) or promoting nitric oxide (NO) synthesis. (d) Drugs capable of preventing sterile inflammation by scavenging heme and ROS, digesting neutrophil extracellular traps (NETs), inhibiting Toll-like receptor 4 (TLR4) or inflammasome activation, and inhibiting IL-1β-dependent innate immune signaling. Drugs approved by the US Food and Drug Administration (hydroxyurea and L-glutamine) are shown in bold font.[14,16,17,22]

As shown in (Figure-2a) some of the approved or potential therapies prevent HbS polymerization and rescue erythrocyte deformability by inducing HbF production

(hydroxyurea, metformin, and sodium butyrate), allosterically modifying HbS oxygen affinity (5-hydoxymethyl-2-furfural or Aes-103), preventing erythrocyte dehydration (senicapoc), or serving as carbon monoxide (CO) donors (PEGylated bovine carboxyhemoglobin).[24] In addition to antipolymerization or antisickling therapies, several antiadhesion therapies are approved or being tested that seek to inhibit the multicellular adhesion cascade of vaso-occlusion (Figure- 2b). These targeted therapies are variously directed at P-selectin (crizanlizumab), E-selectin (rivipansel), Mac-1 (intravenous immunoglobulin), platelet glycoprotein Ibα (CCP-224), or mitogen-activated-protein-kinase inhibitors (MEK inhibitors) to prevent erythrocyte adhesion. Other proposed or FDA-approved therapies may prevent endothelial dysfunction by scavenging cell-free Hb (haptoglobin), promoting NO production (hydroxyurea, oral or IV nitrite, inhaled NO, and oral arginine), or reducing oxidative stress (L-glutamine and antioxidants). The emerging role of sterile inflammation in SCD-associated morbidity suggests that anti-inflammatory approaches, such as therapies that induce heme degradation enzyme hemeoxygenase-1 (MP4CO), scavenge ROS (antioxidants and L-glutamine), inhibit TLR4 signaling, degrade NETs (DNase-1), inhibit leukotrienes, or inhibit inflammasome- or IL-1β-dependent signaling, could be beneficial in SCD.[24,25] Interestingly, IL-1RA-blocking Ab (anakinra) and IL-1β-blocking Ab (canakinumab) are already FDA approved as anti-inflammatory biologics for the treatment of rheumatoid arthritis[26] and NLRP3-inflammasome-mediated cryopyrin-associated periodic syndrome (CAPS)[26], respectively. The existing evidence justifies the need for clinical trials to test the safety and efficacy of repurposing these drugs for SCD and also highlights the need for more studies to refine our understanding of the role of inflammasome pathways in SCD.

CONCLUSIONS

Sickle cell disease is one of the most prevalent hemoglobinopathies worldwide. Clinical proof- of principle that substantial total hemoglobin increases can be produced by non-cytotoxic inhibition of specific epigenetic enzymes, to shift RBC Precursor hemoglobin manufacturing from HbS to HbF, and by chemical modification of hemoglobin to promote the high oxygen affinity ‘R’ quaternary structure of the hemoglobin molecule, has already been generated in SCD patients. Clinical evaluation to determine the long term safety, the impact on symptoms and multi-organ pathophysiology, and the durability of any benefits, is ongoing. There is hope that one or more of the small molecules being evaluated will pass rigorous scrutiny and culminate in practical, accessible, cost-effective, safe and potent disease – modifying therapy for SCD patients worldwide.

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