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## Review Article

### SICKLE CELL DISEASE: TARGETED PATHWAYS OF ANTISICKLING PRODUCTS

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#### ABSTRACT

We present in this study a theoretical review of Sickle Cell Disease (SCD), highlighting on the pathophysiology and targeted pathways of antisickling products. Sickle cell disease (SCD) is one of the most common genetic disorders worldwide. It is caused by a point mutation that changes glutamic acid (Glu6) to valine (Val6) in the  $\beta$  chain of hemoglobin. This change has many damages: polymerization of abnormal haemoglobin HbS when oxygen tension decreases; red blood cell membrane deformability and cell-to-cell adherence, adhesion of sickle red blood cells to the endothelium, high production of reactive oxygen species (ROS), decreasing lactate dehydrogenase activity and  $Fe^{2+}/Fe^{3+}$  ratio of HbS. Understanding polymerization and pathophysiological of SCD constitute a therapeutic strategy base in the pharmacology research of this molecular disease.

**Keywords:** Sickle cell disease, Pathophysiology, Targeted pathways, Antisickling products.

#### INTRODUCTION

Sickle cell disease (SCD) is one of the most prevalent hemoglobinopathies worldwide. It has been hypothesized that this disease originated millions of years ago, in the sub-Saharan countries in mid-western Africa, eastern Asia, and some regions of India (Weatherall, 2008).<sup>1</sup> Today, SCD is not restricted to Africa and parts of India, but is found in the America and Europe, mainly as a result of migration and racial intermingling. In the United States, the disease afflicts approximately 1:500 Afro-American and 1:4000 Hispanic-American neonates (Bonds, 2005).<sup>2</sup> Sickle haemoglobin (HbS) shows peculiar biochemical properties, which lead to it polymerising when deoxygenated. HbS polymerisation is associated with a blood cell membrane deformability and cell-to-cell adherence, adhesion of sickle red blood cells to the endothelium, high production of reactive

oxygen species (ROS), decreasing lactate dehydrogenase activity and increasing  $Fe^{2+}/Fe^{3+}$  ratio of HbS (Bunn and Forget, 1986; Hebbel, 1997; Stuart and Nagel, 2004; Shalev and Hebbel, 1996; Nwaoguikpe and Uwakwe, 2005; Dahmani *et al.*, 2009).<sup>3-8</sup> Antisickling agents are nutrients, drugs, phytochemicals and ions which by their actions inhibit polymerization of sickle red blood cells or the pathophysiological mechanisms leading to sickling in the vasculature. These agents nonetheless exhibit pharmacokinetic and pharmacodynamic properties (Nwaoguikpe, 1993).<sup>9</sup> However understanding polymerization and pathophysiological of SCD constitute a therapeutic strategy base in the pharmacology research of this molecular disease.

#### Polymerization of HbS

The hemoglobin molecule is made up of four polypeptide chains (globins): two alpha chains

of 141 amino acid residues each and two beta chains of 146 amino acid residues each. The alpha and beta chains have different sequences of amino acids but fold up to form similar three-dimensional structures. Normal hemoglobin (HbA) is formed by two type  $\alpha$  and two type  $\beta$  polypeptide chains. In sickle cell hemoglobin (HbS), the normal sequence of Valine-Histidine-Leucine-Threonine-Proline-Glutamic acid-Glutamic acid-Lysine is changed to Valine-Histidine-Leucine-Threonine-Proline-Valine-Glutamic acid-Lysine, with the amino acid valine substituting for the glutamic acid in the  $\beta 6$  (codon 6) site (Maciaszek *et al.*, 2011).<sup>10</sup> The gene defect is a known mutation of a single nucleotide of the  $\beta$ -globin gene and hemoglobin with this mutation is referred to as hemoglobin S (HbS) as opposed to the more normal adult hemoglobin A (HbA). In HbS, replacement of the hydrophilic glutamic acid at position 6 in the  $\beta$ -globin chain by the hydrophobic valine residue makes that this last one establishes hydrophobic interactions with other hydrophobic residues on the  $\beta$ -globin chain of another deoxy-HbS molecule (Bunn and Forget, 1986; Edelstein *et al.*, 1973).<sup>3,11</sup> This process needs a certain time to be primed, the so-called "delay time", which is inversely proportional to the intracellular concentration of HbS. This imperfectly formed mutant forms an imperfect bond which limits its function as an oxygen-carrier. Hence, when there is a low concentration of oxygen, the hemoglobin HbS molecules polymerizes and can stick together in long, rigid chains inside the red blood cells. When this occurs, the red cells are forced to change from its usual disc-like shape to a banana or sickle shape. At low oxygen pressure, deoxy-HbS polymerises and gets organised in long polymer fibres that deform, stiffen, and weaken the red blood cell. This process represents the basic mechanisms leading to haemolytic anaemia and to vaso-occlusive events in the microcirculation (Labbie and Elion, 1999).<sup>12</sup> During the sixties-seventies, the first coherent pathophysiological scheme based on the abnormal polymerization of

deoxy-HbS was elaborated (Bunn and Forget, 1986).<sup>3</sup>

### **Membrane Alterations in the Sickle Red Blood Cell and Cell-To-Cell Adherence**

#### *Membrane Alterations in the Sickle Red Blood Cell*

Red cells from patients have elevated cation permeability compared to those from normal individuals. Formation of the deoxy-HbS polymer fibres triggers a whole series of changes of the red blood cell membrane. This feature causes solute loss and shrinkage, increasing intracellular concentration of HbS. In fact due to polymerization of the sickled cells, peroxidation of membrane lipids produced secondary lipid peroxidation products such as malondialdehyde which can damage membrane structure, alter water permeability and decrease cell deformability. The disruption of membrane phospholipids exposes phosphatidylserine (PS) on the outer cell surface. Macrophages recognized these Erythrocytes that have PS exposed on the outer surface engulfed and degrade them (Carrell *et al.*, 1975; Hebbel, 1985; Nur *et al.*, 2011).<sup>13-15</sup> The red cell membrane loses its functional abilities which results in loss of potassium and water and a corresponding gain of sodium ion. Increased intracellular free calcium occurs during sickling, resulting in a loss of potassium with accompanying movements of chloride and water (Brugnara *et al.*, 1993).<sup>16</sup> Ion channels are affected and their dysfunction is responsible for a cellular dehydration which, in a vicious circle, favours deoxy-HbS polymerization. Hemichromes are released and lead, in particular, to the formation of protein band 3 aggregates on which anti-band 3 IgGs accumulate. The liberation of heme and  $\text{Fe}^{3+}$  favours an oxidizing microenvironment. Exposure of anionic phosphatidylserines at the external side of the membrane creates a procoagulant surface. Finally, microparticles are released. Dysregulation of cation homeostasis noted resulting from the activation of some ion channels, such as the K-Cl co-transport system and the Ca-dependent K-channel (Gardos channel) in particular, leads to a loss of

potassium and cellular dehydration which, in turn, by increasing the intracellular Hb concentration, favours deoxy-HbS polymerization (Stuart and Nagel, 2004).<sup>5</sup>

### *Cell-to-Cell Adherence*

Heterogeneity of sickle red blood cells (RBCs) adhesion in relation to cellular deformability has been suggested. A polymer forms and lengthens in helical fibres which, grouped together, stiffen, and induce the characteristic SS-RBCs shape change, classically in the shape of a sickle (Mohandas and Evans, 1985).<sup>17</sup>

### **Adhesion of Sickle Red Blood Cells to The Endothelium**

In the eighties and nineties the teams of Hebbel and of Mohandas showed the existence an increased adhesion of the SS-RBCs to the endothelium (Hebbel,1997; Mohandas and Evans, 1984).<sup>4,18</sup> Unexpectedly, it turned out that rather than the distorted RBCs, the main actors of this abnormal adhesion process are a population of young RBCs, referred to as “stress reticulocytes”. These stress reticulocytes, coming out prematurely from the bone marrow because of the anaemic stress, express on their surface adhesion proteins that do normally maintain them in the marrow. Thus vaso-occlusive crises seem to be composed of two consecutive steps. The first one involves adhesion of the stress reticulocytes to the endothelium of post-capillary veinules, slowing down the blood flow and thereby inducing and propagating sickling of mature SS-RBCs that are maintained for a longer time in a hypoxic environment. This first step leads to a second one which corresponds to the entrapment of irreversible sickle cells and to the complete occlusion of the micro-vessels (Bunn, 1997).<sup>19</sup> The first molecular partners identified as actors of these abnormal interactions on RBCs were the  $\alpha 4\beta 1$  integrin or very late antigen-4 (VLA-4) which directly binds to the vascular cell adhesion molecule-1 (VCAM-1) on the endothelial surface, and CD36 which interacts with another CD36 molecule on the endothelium through a molecular bridge formed by a molecule of

plasmatic thrombospondin (TSP) (Figure 1) (Hebbel, 2008).<sup>20</sup> The result is the production of proinflammatory cytokines that maintain a state of generalized cell activation. Furthermore, haemolysis leads to the liberation of free iron from the heme which is at the origin of an oxidative stress which in turn, via the activation of transcription factors such as nuclear factor-kappa  $\beta$  (NF $\kappa$  $\beta$ ) and activator protein-1 (AP-1), participates into the endothelial expression of VCAM-1, inter-cellular adhesion molecule-1 (ICAM-1), and E-selectin (gene expression in endothelial cells), all proteins that are involved in the adhesion of stress reticulocytes and in leukocytes recruitment (Pauling *et al.*, 1949).<sup>21</sup> Consequently we assist to NO bioavailability decrease and an increasing hemolysis in furthering blood cell adherence (Space and *et al.*, 2000).<sup>22</sup> Vaso-occlusive crises are caused by sickled red blood cells that obstruct capillaries and restrict blood flow to an organ. Vaso-occlusive pain is the most common problem experienced by patients with SCD and the most frequent reason for emergency department and hospital admission (Adachi and Asakura, 1979).<sup>23</sup>

### **Oxidative Stress**

SCD is characterised by a pro-oxidant environment due to high production of reactive oxygen species (ROS) related to increased levels of free iron and haem groups associated with a reduction in antioxidant systems such as GSH (Shalev and Hebbel, 1996).<sup>6</sup> Molecular oxygen has the ability to form highly reactive metabolites such as superoxide anion radical ( $O_2^{\circ}$ ), hydrogen peroxide ( $H_2O_2$ ), and hydroxyl radical ( $^{\circ}OH$ ). These reduced metabolites of oxygen are referred to as “reactive oxygen species”. ROS can induce oxidative damage to the cell and can form a very stable structure by extracting electrons from other sources.  $H_2O_2$  has the ability to form the more damaging  $^{\circ}OH$ , through a combination of the Fenton and Haber-Weiss reactions (Kohen and Nyska, 2002).<sup>24</sup> The inhibition of the mitochondrial electron transport chain activity can lead to ROS generation by inducing a leak of electrons from complex I

(Prabhakar and *et al.*, 2007).<sup>25</sup> Major ROS defense mechanisms include enzymatic and non-enzymatic systems are saturated. The ROS which are not neutralized can target biological molecules such as DNA, lipids, proteins, and carbohydrates, which can result in cell dysfunction or cell death. The chronically elevated oxidative stress in SCD might play a significant role in the development of SCD related organ complications (Xu *et al.*, 2004).<sup>26</sup>

### Lactate Dehydrogenase Activity

Lactate dehydrogenase (LDH) is one of the enzymes of the glycolytic pathway that catalyzes the conversion of pyruvate to lactate with concurrent conversion of NADH to NAD<sup>+</sup>. It is a ubiquitous enzyme found in all tissues. Serum LDH exists in 5 separable isoenzymes numbered 1-5 according to their electrophoretic mobility (Neely *et al.*, 1969).<sup>27</sup> The distribution of the 5 isoenzymes is not uniform across body tissues. LDH1 and LDH2 are found primarily in RBCs and heart muscle; LDH3 is highest in the lungs; LDH4 is highest in the kidneys, placenta, and pancreas; and LDH5 is highest in skeletal muscle and liver. The routine determination of serum LDH includes all of its isoenzymes (Pincus *et al.*, 2011).<sup>28</sup> Along with reticulocyte count, indirect bilirubin level, and serum haptoglobin, LDH has been used as a marker of hemolysis. Serum LDH is usually elevated in sickle cell anemia in the steady state (SS) (Karayalcin *et al.*, 1981).<sup>29</sup> During painful vasoocclusive crises (VOCs), the LDH may increase further in some patients because of hyperhemolysis, as shown by RBC survival studies (Ballas and Marcolina 2006).<sup>30</sup> In fact when oxygenation is insufficient at the sickle cells patients, pyruvate is reduced in lactic acid which acidifies the medium, thus causes sickle cells hemolysis (Hamadah *et al.*, 2010).<sup>31</sup> LDH is a sensitive indicator of haemolysis and its level in sickle cell blood determines the severity of crises (Nwaoguikwe and Uwakwe, 2005).<sup>7</sup>

### Fe<sup>2+</sup>/Fe<sup>3+</sup> Ratio of HbS in Sickle Cell Disease

About 65% to 70% total body iron is found in heme group of hemoglobin. A heme group

consists of iron (Fe<sup>2+</sup>) ion held in a heterocyclic ring, known as a porphyrin. Even though carbon dioxide is also carried by hemoglobin, it does not compete with oxygen for the iron-binding positions, but is actually bound to the protein chains of the structure. The iron ion may be either in the Fe<sup>2+</sup> or in the Fe<sup>3+</sup> state, but ferrihemoglobin also called methemoglobin (Fe<sup>3+</sup>) cannot bind oxygen. In binding, oxygen temporarily and reversibly oxidizes (Fe<sup>2+</sup>) to (Fe<sup>3+</sup>) while oxygen temporarily turns into superoxide, thus iron must exist in the +2 oxidation state to bind oxygen (Linberg *et al.*, 1998).<sup>32</sup> Substitution in the chain  $\beta$  of the glutamic acid in position 6 by valin involves the precipitation of hemoglobin in the red blood with falcification supporting the oxidation of the ferro-iron (Fe<sup>2+</sup>) to ferri-iron (Fe<sup>3+</sup>) which cannot banding O<sub>2</sub> (anorexia) any more. Methemoglobin is when the iron atom in the heme group of hemoglobin is oxidized to the +3 state. In this oxidation state, the heme group is unable to carry oxygen and Fe<sup>2+</sup>/Fe<sup>3+</sup> ratio decrease (Dahmani *et al.*, 2009).<sup>8</sup>

### Therapies Target in Sickle Cell Disease

Sickle cell crises have been investigated in top priority by researchers all around the world in order to explore effective therapy towards solving the sickle cell disease problem. Even though people with sickle cell disease suffer from several pain crises every year, there is no cure for the majority of them. However, some researchers tend to treat people with sickle cell disease with therapeutics treatments, which means different options that available under health care professionals, such as preventive measures, symptomatic treatment, bone-marrow transplantation (BMT) and some products having targeted pathways. All these kind of treatments aimed to reduce the number of pain crises in a year expect bone marrow transplant, which aimed to cure from sickle cell disease.

### Preventive Measures

The preventive measures include continued community education programmes for areas with high prevalence of the disease by creating and

strengthening the national sickle-cell disease control programmes, setting up sickle-cell screening and genetic counselling programmes. The disease should be identified during the prenatal period or at birth as part of a routine screening programme. Use of prophylactic drugs and vaccines, provision of primary health care (access of sickle cell children to health centers), improved standard of living and better feeding for patients with SCD (Wethers, 2000).<sup>35</sup>

### **Symptomatic Treatment**

It concern to treat painful crises; acute chest crises and blood transfusion. Blood transfusion is widely used in the treatment of sickle cell anemia. It is estimated that 50% of all patients receive a red cell transfusion at some point in their lives and that 5% receive chronic transfusions (Rosse *et al.*, 1990). Red cell transfusion can help to deliver oxygen to the body and unblock blood vessels, which means prevention from sickle cell crises and its complications.

### **Bone-Marrow Transplantation (BMT)**

A bone marrow transplant is a procedure to replace damaged or destroyed bone marrow with healthy bone marrow stem cells from a donor. BMT is considered the only curative therapy available to date. The goal is to eliminate the sickle erythrocyte and its cellular progenitors and replace them with donor hematopoietic pluripotent stem cells that give rise to erythrocytes that express no sickle hemoglobin (HbS), thereby reducing HbS levels to those associated with the trait condition (Parkman, 1986).<sup>37</sup>

### **Products Having Targeted Pathways**

Several strategies and products can be explored for the treatment of SCD. Among these, we include: the induction of HbF synthesis; hemoglobin modifiers; membrane stabilization agents of sickle red blood cell; the inhibition of erythrocyte dehydration; the inhibition of cellular adhesion; anti-oxidant agents; the enzymatic inhibition and chelating agents.

*Agents Capable to Increase Foetal Haemoglobin Concentration; Induction of HbF Synthesis*

The induction of HbF synthesis is a promising strategy for the treatment of SCD. The elevated levels of HbS and low levels of HbF in patients with SCD are related to the clinical severity of the disease and the early mortality of the patients (Steinberg, 2001; Pace, 2006).<sup>38,39</sup>

### *Inhibitor of Sickle Cell Polymerization Agents: Hemoglobin Modifiers*

Polymerization of hemoglobin S is the central event in the pathophysiology of sickle cell disease (SCD) (Bunn, 1997).<sup>19</sup> The hemoglobin modifiers are classified as either covalent or noncovalent. Although noncovalent modifiers have shown interesting activities, their use is still limited (Waterman *et al.*, 1974).<sup>40</sup> The modification of hemoglobin by covalent modifiers reduces erythrocyte sickling by two possible mechanisms: by increasing HbS solubility and/or by increasing its affinity for oxygen (Ueno, 1989).<sup>41</sup>

### *Membrane Stabilization Agents of Sickle Red Blood Cell*

Under low oxygen tension, deoxy-HbS molecules polymerize, causing the formation of rigid and sickled erythrocytes. The deformity of the sickled erythrocyte results in their shortened survival since they become vulnerable to lysis as they penetrate the interstices of the splenic sinusoids and hence severe hemolytic anemia ensues with hemoglobin values ranging from 6 to 10 g/L (Martins, 1981; Karayakin, 1971).<sup>42,43</sup> Membrane stabilization is a process of maintaining the integrity of biological membranes such as erythrocyte and lysosomal membranes against osmotic and heat-induced lyses (Sadique *et al.*, 1989; Oyedapo *et al.*, 2004).<sup>44,45</sup>

### *Gardos Channel Inhibitors to Prevent of Sickle Red Cell Dehydration*

Strategies that prevent cellular dehydration should be explored for the treatment of SCD. The inhibition of potassium–chloride cotransport, in which potassium causes the movement of chloride ions and water, produces an osmotic imbalance and causes dehydration, with further polymerization of HbS (Flatman, 2004).<sup>46</sup> The calcium-activated potassium channel known as

the Gardos channel is also present on sickle erythrocytes and could be inhibited to promote an adequate osmotic balance (Lew, 2005).<sup>47</sup>

#### *Agents Which Reduce Sickle Cell-Endothelial Adhesive Events*

The adhesion of sickle cells to the vascular endothelium involves various mediators, including integrin  $\alpha 4\beta 1$ , CD36, and ICAM-4, which are responsible for the cellular interaction with the endothelium directly through E-selectin, P-selectin, integrins, and VCAM-1, or indirectly through molecules such as thrombospondin and von Willebrand factor (Embury, 2004; Matsui, 2002).<sup>48,49</sup> Several compounds have demonstrated a capacity to inhibit cellular adhesion.

#### *Anti-Oxidant Agents*

Reactive oxygen species (ROS) are considered to play a crucial role in the pathogenesis of sickle cell anemia. Under normal physiological conditions antioxidant defense system, balance the ROS and prevents or limits oxidative damage. Intracellular metabolism is the generator of ROS such as superoxide ( $\cdot O_2^-$ ), hydrogen peroxide ( $H_2O_2$ ), and hydroxyl radical ( $\cdot OH$ ), oxidative stress occur due to imbalance between oxidants and antioxidants because of increased pro-oxidants and/or decreased antioxidants trigger a cascade of oxidative reactions (Malowany *et al.*, 2011).<sup>50</sup> Oxidative stress is a major cause of anemia and have role in complicating anemia with other infectious diseases (Wellems *et al.*, 2009).<sup>51</sup> Antioxidants are most important and vital in lowering or preventing the disease crisis by eradicating oxidative stress.

#### *Enzymatic Inhibition*

It is the case of Lactate dehydrogenase activity (LDH). The inhibition of enzyme (LDH) gives

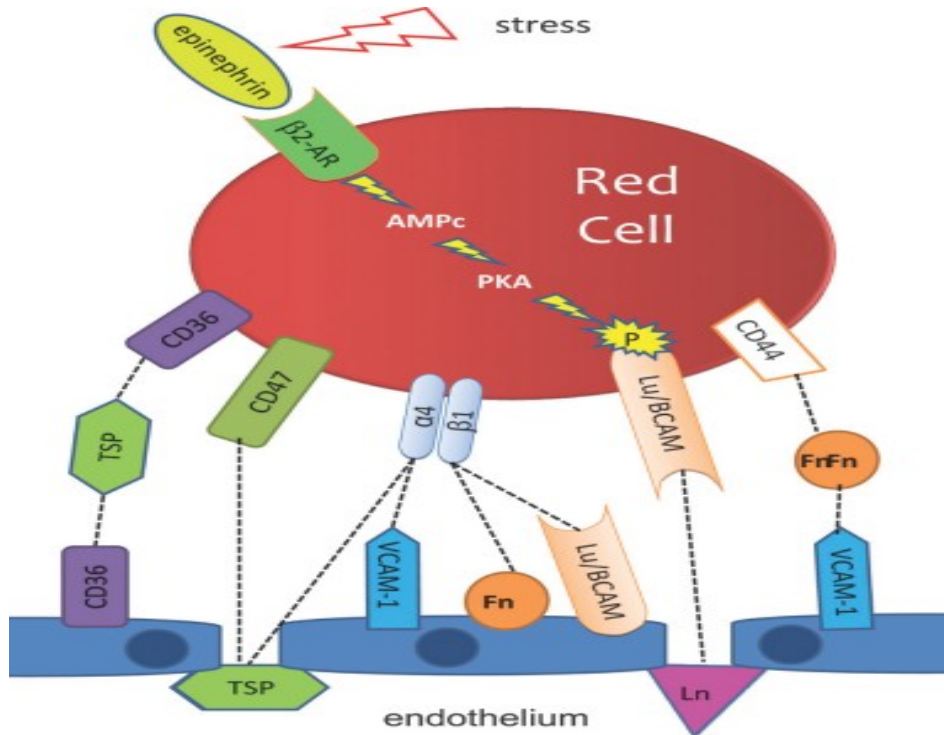
the possibility of decreasing the production of lactate. This situation stabilizes the sickle cells thus reducing to their destruction with a significant improvement of anemia among sickle cells patients, and a better red blood oxygenation (Kotue T.C., 2014).<sup>52</sup>

#### *Fe<sup>2+</sup>/Fe<sup>3+</sup>: Chelating Agents*

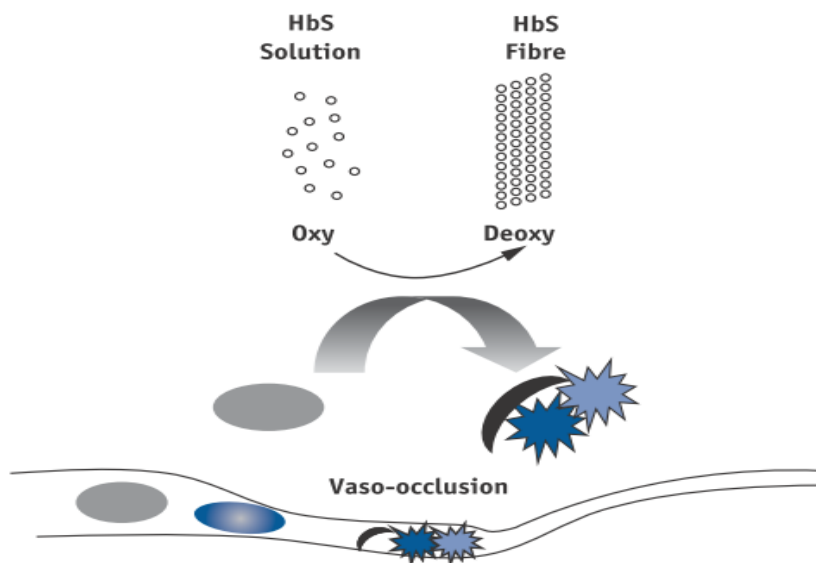
Under normal physiological conditions iron homeostasis is tightly regulated by complex mechanisms which avoid cellular injury. It is done by the structure of hemoglobin. Iron-containing heme is placed in hydrophobic globin pocket that limits the reactivity of iron by shielding the heme from most of external solutes. Therefore heme tends to bind reversibly with oxygen in the ferrous ( $Fe^{2+}$ ) state rather than the ferric ( $Fe^{3+}$ ) state<sup>53</sup> (McCord, 2004). Iron-chelation therapies have been used to control iron overload in patients who have received several blood transfusions to reduce disease complications (Wanko, 2005).

## **CONCLUSION**

Sickle cell disease (SCD) is one of the most prevalent hemoglobinopathies worldwide. Apart from preventive measures, symptomatic treatment, bone-marrow transplantation (BMT), the emerging picture for the treatment of SCD is that abnormalities ranging from the induction of HbF synthesis; hemoglobin modifiers; membrane stabilization agents of sickle red blood cell; the inhibition of erythrocyte dehydration; the inhibition of cellular adhesion; anti-oxidant agents; the enzymatic inhibition or chelating agents, may constitute new pharmacological targets for treating SCD. Prospective therapies for SCD need to combine molecules with different pharmacological targets in order to increase their therapeutic efficacy.



**Figure 1:** Adhesion of sickle red blood cells to the endothelium and cell activation (Elion *et al.*, 2010).<sup>33</sup>



**Figure 2:** Schematic diagram of pathogenesis of sickle cell disease (Eaton and Hofrichter, 1990).<sup>34</sup>

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