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Editorial

Sickle Cell Disease -Related Pathophysiology of Vasoocclusion and Hemolysis : Remaining Challenges

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Editorial

Sickle Cell Anemia (SCA) is the most common hemoglobinopathy, which induces a structural transformation of the normal (i.e. "donut-like shape") Red Blood Cells (RBCs) into intravascular sickle RBCs (i.e. "croissant-like shape") [1,2]. This blood pathology is characterized by a point mutation (i.e. single nucleotide substitution [β6Glu (GAG) →Val (GTG)]) in the normal β-globin gene (HBB) [1,2]. SCA is transmitted over the generations following an autosomal recessive Mendelian pattern. Interestingly, in spite of its monogenic basis, it is a systemic disorder with broad phenotypic and sub-phenotypic heterogeneity [1,2]. Clinical features such as stroke, acute chest syndrome, vaso-occlusive episodes, a vascular necrosis, leg ulcers, priapism and retinopathy accounts for this disease heterogeneity [1,2]. The first description of sickle cells was made in 1910 by Herrick and in 1949, Pauling and colleagues discovered the pathological hemoglobin S (HbS), which led to the first demonstration that the production of an abnormal protein could be the cause of a genetic disorder [1,2]. Now a day's, Sickle Cell Diseases (SCD) in general and SCA in particular, represent a topic of great concernment and scientific interest.

Sick led red cells, the hallmark of the disease, would be due to helical polymerization of hemoglobin S (HbS) that form long bundles (or aggregates) under hypoxia, reduced pH and/or increased temperature [1,3,4]. These bundles lead to membrane lesion and alteration in cationic content alongside with water loss, which consequently cause reduction in deoxyhemoglobin solubility [1,5]. Furthermore, there is increasing evidence that, in addition to the rheological features and endothelium adhesiveness displayed by the irreversibly sick led cells, the SCA-related pathophysiology of vaso-occlusion and hemolysis involves other interacting factors. Indeed, it has been shown that HbS polymerization and its downstream events are influenced by the interaction of hemoglobin structural variants [1,2,6,7]. Besides, endothelium activation in response to inflammatory response [8-10], impairment in Nitric Oxide (NO) homeostasis [11], and altered expression of adhesion molecules such as P-selectin [12], E-selectin [13], Inter Cellular Adhesion Molecule-1 (ICAM-1) and Vascular Cell Adhesion Molecule-1 (VCAM-1) [14] are involved in the SCA disease complexity. Even more intricate, angiogenesis promoting molecules, namely angiotensin-1 (Ang-1) and -2 (Ang-2) as well as Vascular Endothelial Growth Factor (VEGF), and how they interact with each other and with other factors in the bloodstream may be involved in the equilibrium between prolife ration and regression/infarction of neovascular formations, such as seen in retinopathy [15].

Hemoglobin C (HbC) is frequently found in heterozygosis with HbS, and this condition (HbSC) shows a diverse profile from SCA (HbSS), with systemic outcome relatively benign, but more likely to be affected by retinopathy, thromboembolic complications and renal papillary necrosis [16]. The reasons for HbSC patients being more likely to exhibit ocular manifestations than patients with HbSS are not clear. It is postulated that there may be a relation to the rate of sickling [17], blood viscosity and hematocrit [18].

Ongoing research studies, including Genome-Wide Association Studies (GWAS), are expected, and should lead to: (i) the identification of differential factors involved in SCA complications different worldwide populations, which could be useful for personalized the ranostic medicine; (ii) the design and development of safer and more efficient drugs than HU, the current orphan FDA-approved drug despite its potential DNA-damaging effects.

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