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Editorial

Sickle Cell Anemia: only one Single Point Mutation but Many Pathophysiological Issues

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It has been 100 years since Herrick published the first medical case report of the anemia describing abnormal shapes of red blood cells (RBCs) and gave sickle cell anemia (SCA) its name [1]. Afterwards, Vernon Ingram [2] discovered that the defect of the disease was a single aminoacid substitution in the hemoglobin (Hb) molecule ($HBB^{glu6val}$), and understanding has gradually increased since then. Even with improved knowledge of the human genome, development of new genomic tools and identification of single nucleotide polymorphisms (SNPs) associated with subphenotypes of SCA by genome-wide association studies (GWAS) [3], and more than 100 different blood and urine biomarkers have been described in SCA [4]. There is still a major challenge to combine all these variables and establish potential predictors of the SCA severity [5].

The last 60 years have resulted in an increasingly coherent detailed molecular-level description of the SCA pathophysiology [6]. Despite our precise knowledge of the molecular defect that is associated with hemoglobin S (HbS) in RBCs [7]. Furthermore, recent progress in understanding the molecular events that control polymerization of HbS and sickling of erythrocytes [8]. Nevertheless, these mechanisms are not sufficient to explain the heterogeneous phenotype found among SCA patients, such as pain episodes, acute chest syndrome, neurological complications, leg ulcers and other symptoms. In this way, despite HbS presence is indispensable for the disease establishment, several other phenomena affected by a multitude of genes other than the one directly involved (*HBB*S*) play an important role [9].

While great progress has been made in describing the basic disease process that accounts for hemolytic anemia and the obstructive events underlying vaso-occlusive events (VOE), many questions remain [6]. The simple mutation in the β6-location of globin has a profound effect on all tissues and organs in the SCA patient, and because the vasculopathy affects a large variety of physiologic mechanisms, the varied genetic background of individual patients makes prediction of the clinical severity highly complex [6]. In this way, clinical broad spectrum of SCA can be affected by a number of modifying factors including the haplotype of β-globin gene cluster [10], the coinheritance of polymorphisms associated with both clinical aspects [11] and treatment response [3], hemoglobin fetal (Hb F) levels [12], chronic inflammation and oxidative states [13, 14] as well as gender, and others [10].

Among the new evidences, oxidative stress processes have been increasingly related to the SCA pathophysiology [4]. The increased production of prooxidant elements is caused by intrinsic disease mechanisms, such as increased activity of several oxidases (NADPH oxidase and endothelial xanthine oxidase) [15, 16], HbS auto-oxidation [17], heme iron release, increased asymmetric dimethylarginine (ADMA) [18], uncoupling of nitric oxide synthase (NOS) activity, and decreased nitric oxide (NO) levels [19]. As the antioxidant defense systems in SCD are affected and/or are not sufficient to neutralize excessive production of oxidant species [20], chronic oxidative stress establishes, being a critical factor in endothelial dysfunction, inflammation and damage to multiple organs [21]. In this way, oxidative stress is directly related to both cause and consequence of inflammation, hemolysis, vasculopathy, vaso-occlusion, infection, and injury by ischemia/reperfusion, e.g. [22]. For this reason, newer therapeutic agents that can target oxidative stress may constitute valuable means for preventing or delaying the development of organ complications [23, 24]. Thus, antioxidant therapy is being a worthy, promising and increasing goal for

SCA treatment.

In this context, McCarty [25] suggested the use of comprehensive nutraceutical strategy for mitigating the contribution of oxidative stress to SCA pathogenesis, dubbed as "full-spectrum antioxidant therapy". Many recent studies, both in vitro and in vivo, have investigated different strategies as antioxidant therapy for SCA treatment [26-28]. However, paradoxical observations with regard of certain prooxidant effects of antioxidant compounds have been reported under some experimental conditions, indicating the complex interdependency among the pool of physiological relevant cellular antioxidants [29]. Therefore, more studies focusing newer and more specific oxidative stress biomarkers can be helpful to obtain better clues about effective prognostic information of SCA patients. Furthermore, it may be fundamental to the development of more efficacious therapeutic drugs in order to mitigate the devastating clinical manifestations of SCA.

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