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Commentary

How effective are antioxidants without fetal hemoglobin in tackling oxidative stress in sickle cell disease?

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Abstract

In our previous work titled "Antioxidative potential of foetal haemoglobin in sickle cell disease", we reported that fetal hemoglobin correlated directly with antioxidative markers and inversely with markers of oxidative stress in sickle cell subjects. Based on our observations, we concluded that fetal hemoglobin contributes to the cellular antioxidant defense system by limiting the rate of production of reactive oxygen species. In this current report, we aim to highlight the synergy between fetal hemoglobin and the antioxidant defense system in modulating oxidative stress in sickle cell disease.

Keywords: Sickle cell disease, Oxidative-stress, Fetal hemoglobin, Antioxidant defense mechanism, NRF2

Introduction

Sickle cell disorder (SCD) remains a disease of public interest, accounting for a significant number of deaths, especially in low and middle-income countries in Africa [1-3]. Despite years of intensive studies, its cure remains a subject of ongoing investigation [4,5]. The clinical manifestations of this disease including oxidative stress stem from a point mutation in the beta globin gene that produces sickle hemoglobin (HbS) [6-8]. Under anorexic conditions, HbS polymerizes to form the characteristic sickle shape structure of the erythrocytes in the sickle cell subjects [7,9]. The sickle red blood cells have a short life span which accounts for the high rate of hemolysis and anemia observed in sickle cell subjects [10,11]. These clinical events are further enhanced by vascular occlusion event, which partially or completely impedes the supply of nutrients required for cell survival [12,13].

Fetal Hemoglobin and Sickle Cell Disease

Fetal hemoglobin (HbF) is the predominant hemoglobin of a fetus, synthesized by a subset of red blood cells known as F-cells [14,15]. When compared to adult hemoglobin (HbA), HbF has a higher affinity for oxygen, making it more effective in transporting oxygen to the fetus in low oxygen environments such as the womb of a pregnant mother [16-18]. The structural variation between HbF ($\alpha_2\gamma_2$) and HbA ($\alpha_2\beta_2$) accounts for their different functions. Usually, the synthesis of HbF is gradually replaced with HbA a few months after delivery [19-21]. However, some subjects with SCD still retain the ability to synthesize a high concentration of HbF as adults. This genetic alteration has been reported to be beneficial, due to its ability to neutralize HbS polymerization: which is primarily responsible for all clinical complications associated with the disease.

HbF has been reported to affect the clinical manifestation of SCD [22,23]. While some subjects suffer a milder form of the disease, others are reported to suffer a more severe form of the disease defined by several episodes of crises. Several reports have associated subjects with a milder form

of the disease possessing higher HbF concentration in their blood cells compared to those with a low HbF in their red blood cells [24-26]. Based on these findings, it has been suggested that HbF is the strongest predictor of SCD severity.

Hemoglobin Switching

During human development, different forms of hemoglobin are typically produced by a process known as hemoglobin switching. At the early stage of gestation, embryonic hemoglobin ($\alpha_2\varepsilon_2$) is the dominant hemoglobin expressed in the embryo. HbF ($\alpha_2\gamma_2$) expression soon takes over as the embryo develops into a fetus. After birth, the expression of HbF is gradually replaced by HbA ($\alpha_2\beta_2$) [27,28]. The physiological requirements of the various developmental stages are met by the expression of the various hemoglobin at their respective developmental stages [29,30]. The switching between the various hemoglobin types is genetically regulated by factors including genes, regulatory elements, and transcription factors.

Alteration in expression of transcription factors involved in the expression of HbF synthesis has been implicated in expression of abnormally high HbF concentration in some sickle cell subjects [31,32]. For instance, alteration in the expression of BCL11A, a transcription factor involved in the repression of γ-globin gene expression after birth, has been shown to cause the over-expression of γ-globin gene [33-35]. Similarly, an alteration in expression of the Krupple-like factor-1 (KLF-1) transcription factor, involved in β-globin gene expression and γ-globin gene repression, has been reported to be responsible for the over-expression of HbF [36,37]. Hence, these molecules are being viewed as potential therapeutic targets for management of SCD due to their ability to alter HbF expression [38-41].

Oxidative Stress and Sickle Cell Disease

The pathophysiology of SCD is greatly influenced by oxidative stress [42-45], which occurs as a result of imbalance in the rate of production of reactive oxygen species (ROS) and antioxidant defense mechanism of the cell [46-48]. In this state, the synthesis of critical antioxidants required to neutralize the high amount of ROS generated is either compromised or depleted. Elevated production of ROS is responsible for clinical events including hemolysis, organ damage, and damage to deoxy-ribonucleic acid (DNA). In SCD, the generation of ROS is enhanced by sickle cell hemoglobin (HbS), which easily oxidizes to form superoxide anions, that are responsible for generating ROS. Furthermore, the product of hemolysis, including free hemoglobin and heme are responsible for the generation of ROS in SCD [49,50]. Due to variations in the rate of hemolysis among subjects with SCD, the rate of ROS generation and disease severity differs among subjects with the disorder. As a result, it has been suggested that HbF, which has the ability to neutralize the polymerization of HbS and reduce the rate of hemolysis, may function as an antioxidant [51].

Nuclear Factor Erythroid 2-related Factor-2 (NRF2): The Common Regulator Involved in Expression of Foetal Hemoglobin and Antioxidants

NRF2 plays a regulatory role in the expression of antioxidants in the body. Following oxidative stress, NRF2 stimulates the expression of antioxidants to clear the free radicals generated by clinical events such as hemolysis [52-55]. NRF2 achieves this aim either by directly binding to the promoter region of genes encoding the different antioxidants to stimulate their expression or by enhancing the expression of other proteins involved in the metabolism of iron. The expression of iron-metabolizing proteins reduces the amount of iron needed for ROS synthesis [56,57]. NRF2 also regulates the expression of Glutathione; the most abundant antioxidant in the cell, by binding to and stimulating its expression [58,59]. Aside from the aforementioned roles of NRF2 in regulating the expression of antioxidants, it is also involved in the regulation of HbF expression.

NRF2 initiates the expression of HbF by binding to the promoter region of the γ-globin gene to stimulate its expression [60,61]. NRF2 also works alongside drug inducers such as simvastatin and hydroxy-urea to regulate the expression of HbF. The coordinated action of NRF2 and the drug inducers results in regulation of transcription factors which are directly involved in the expression of γ-globin gene [62,63]. For instance, studies have reported that the drugs, hydroxy-urea and simvastatin indirectly regulate the expression of the transcription factors BCL11A and KLF1, which are directly involve in regulating the expression of γ-globin gene by activating NRF2 transcription factor. Therefore, the action of NRF2 exacerbates oxidative stress in SCD by regulating the expression of antioxidants and HbF; the collective action of the two molecules greatly ameliorates the damaging effects of ROS in SCD.

Conclusion

The expression of high HbF in subjects with sickle cell disease is of immense benefit due to its ability to neutralize sickle cell hemoglobin polymerization and any other related clinical complications. The elevated rate of oxidative stress reported in subjects with low HbF concentrations compared to those with high HbF, suggests that antioxidant defense mechanism alone may be ineffective in tackling oxidative damage in SCD. Hence, a coordinated response of both antioxidants and HbF in sickle cell subject may be the best approach in tackling the elevated amount of ROS generated in SCD. Current studies are now focused on drugs that stimulate transcription factors such as NRF2, which is involved the regulation of expression of both HbF and antioxidants.

Conflict of Interest

Authors declare that no competing interests exist for any aspect of this commentary.

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