

The Role of HbF in Retarding Deoxy-HbS Polymerization

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Fetal hemoglobin (HbF) is the dominant form of hemoglobin that acts as the main oxygen carrier protein in the human fetus during gestation. Although the level of HbF remains high in babies, it starts reducing immediately after birth, reaching almost insignificant levels when an infant is about six months (Paikari & Sheehan, 2017). Between six months and one year, the child assumes adult forms of hemoglobin. Sickle cell anemia is a condition that mainly affects the adult forms of hemoglobin, whereby the patient possesses atypical hemoglobin molecules called hemoglobin S (HbS). The HbS molecules polymerize to form fibers that can distort red blood cells and make them less flexible, thereby reducing their capacity to deliver oxygen to all parts of the body effectively (Eaton, Bunn, 2017). Consequently, inhibiting the polymerization of HbS has been largely explored and used as a method of treating sickle cell anemia.

Fetal hemoglobin (HbF) has been identified to be effective at inhibiting the deoxygenation-induced polymerization of HbS, which is responsible for the development of sickle cell disease (Steinberg, Chui, Dover, Sebastiani & Alsultan, 2014). HbF hinders polymerization because it leads to reduction of the mean cell HbS concentration, which is a crucial factor in catalyzing the process of formation of fibers (Eaton & Bunn, 2017). Additionally, both the HbF and its mixed hybrid tetramer cannot enter the deoxy-HbS polymer formation, which slows the process of polymerization (Steinberg et al., 2014). HbF's functioning explains why symptoms of sickle cell disease are less evident in infants and young children, who have higher levels of HbF when compared to adults. Moreover, studies have shown that adult patients who have high levels of HbF are associated with a milder risk of disease (Sokolova, Mararenko, Rozin, Podrumar & Gotlieb, 2019). Therefore, regulation of HbF levels in sickle cell disease patients has been one of the major techniques that have been used to manage the illness.

HbF IN RETARDING DEOXY-HbS POLYMERIZATION

3

Due to the role of HbF in inhibiting deoxy-HbS polymerization, induction of high levels of HbF in patients with sickle cell anemia has been used in pharmacologic treatment of sickle cell anemia (Ferrone, 2018). However, if HbF levels are below 30%, the total HbF or F-cell percentages do not necessarily indicate how severe the disease is in an individual because not all F-cells have sufficient levels of HbF to protect against polymer-induced damage. Studies have been ongoing to find out how HbF levels can be increased to the necessary degree. For example, targeting BCL11A has shown reasonable promise. BCL11A has been found to be a strong repressor of gamma-globin, which makes it a highly suitable target for HbF, thereby limiting the ability of HbF to prevent HbS polymerization (Sokolova et al., 2019). Therefore, inactivating BCL11A leads to higher levels of HbF, thereby enhancing the ability of HbF to retard deoxy-HbS polymerization. Hence, any strategies that will lead to the levels of HbF above 30% will increase the rate of inhibiting deoxy-HbS polymerization, and have better results in sickle cell patients.

References

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