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Commentary

Haemoglobin C Promotes Distinct Membrane Properties in Heterozygous HbSC red Cells

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Sickle Cell Disease (SCD) is one of the most common severe inherited disorders. Approximately 300,000 SCD babies are born yearly, mostly in Africa, the USA and the Caribbean, but also in Northern Europe (Piel et al., 2013). In the UK, SCD patients number around 12–15,000 individuals (Hickman et al., 1999) making it a disease of considerable significance. There is no specific treatment. Nor is it understood why some patients have a more severe course of the disease, whereas others are mildly or even subclinically affected. Without this prognostic knowledge, it is not possible to instigate more aggressive therapies for children who will be most compromised later in life. For example, hydroxyurea therapy for these individuals may lessen later complications such as renal pathology and stroke.

All SCD patients have the abnormal adult haemoglobin HbS in their red cells. All the complications of SCD follow from this. HbS has a substituted amino acid at the 6th codon of the beta chain with valine replacing glutamic acid. Homozygous SCD patients (HbSS) have two copies of this altered Hb. Heterozygous HbSC individuals have a second mutated Hb in addition, HbC in which glutamic acid at the same position is replaced with lysine.

About two thirds of SCD patients are homozygous HbSS individuals but patients heterozygous for HbS and HbC (HbSC) constitute about a third of SCD cases (here termed HbSC disease), making this the second most common form of SCD (Nagel and Lawrence, 1991 & Nagel and Platt, 2001; Rees et al., 2010) and therefore representing a clinical problem of considerable impact. Although HbSC disease is common it is neglected compared to other haemoglobinopathies, such as sickle cell anaemia (HbSS) and the thalassaemias. Relatively few studies are conducted on HbSC disease, and most physiological and clinical features are inferred from studies of homozygous sickle cell anaemia (HbSS).

There is considerable evidence that the two conditions are very different. Generally HbSC is less severe than HbSS, but still results in recurrent episodes of pain and progressive organ damage, resulting in a shortening of life-expectancy by 20–30 years in the northern hemisphere. Some complications are more common in HbSC than HbSS, most notably proliferative retinopathy leading to visual loss. Laboratory measurements also demonstrate the difference between the two conditions, with higher haemoglobin and lower rates of haemolysis in HbSC, and significantly lower levels of HbF.

Cation homeostasis of red cells is critical in SCD. Red cells from patients have elevated cation permeability compared to those from normal individuals. This feature causes solute loss and shrinkage, increasing intracellular concentration of HbS. This is significant because a small rise in [HbS] will markedly promote sickling in hypoxic areas of the circulation as the lag time to HbS polymerisation is inversely proportional to a very high [HbS]. Altered cation permeability is an early event following on from HbS polymerisation and represents an important stage in pathogenesis. It is therefore important to understand red cell cation permeability in SCD.

Hannemann et al., 2015 shows important differences in cation transport comparing HbSC and HbSS patients. They indicate that conductive pathways represented by the nonspecific cation conductance (sometimes termed Psickle) and the Ca2 +-activated K+ channel (or Gardos channel) are less active in HbSC compared to HbSS. Also a lower oxygen tension is required to stimulate these pathways in red cells from HbSC patients. In contast, the coupled K+ and Cl-transporter, KCl cotransport (KCC), is increased in HbSC over HbSS. KCC activity varies markedly between patients and, critically, correlates with disease severity.

These findings represent an important breakthrough in the study of SCD in HbSC patients. They immediately suggest two possibilities which may improve patient management. First, identification of the molecular and genetic factors regulating the activity of this key transporter using modern genetic and proteomic methods may increase our understanding of the key regulatory features of this transporter. KCC is found in many tissues. This has potential relevance to various disease states, notably epithelial conditions, and is not limited to SCD. Increased understanding of this aspect of HbSC disease will facilitate rational design of specific therapies to prevent or ameliorate the deleterious sequelae of the condition. Second, these studies may also inform the establishment of biomarkers of severity. It will also allow better prognostication, with the potential for neonatal DNA testing to identify children who will follow a severe clinical course and facilitate early intervention with disease-modifying treatments.

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