World Distribution, Population Genetics, and Health Burden of the Hemoglobinopathies

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Although information about the precise world distribution and frequency of the inherited hemoglobin disorders is still limited, there is no doubt that they are going to pose an increasing burden on global health resources in the future. Their high frequency is a reflection of natural selection combined with a high frequency of consanguineous marriages in many countries, together with an epidemiological transition; whereby, as public health measures improve in the poorer countries of the world, more babies with these disorders are surviving to present for treatment.

The inherited disorders of hemoglobin are by far the most common monogenic diseases. Recent surveys suggest that between 300,000 and 400,000 babies are born with a serious hemoglobin disorder each year and that up to 90% of these births occur in low- or middle-income countries (Christianson et al. 2006). Here we will discuss the world distribution of these conditions and what is known about the mechanisms that have led to their extremely high frequency in many tropical countries.

DISTRIBUTION AND FREQUENCY OF THE HEMOGLOBIN DISORDERS

An estimate of the annual births of the important hemoglobin disorders is shown in Table 1. These figures are only a very approximate assessment and are based, in many cases, on only relatively

small samples from localized regions of different countries. It has been found recently that the distribution of all the important hemoglobin disorders is extremely heterogeneous within different countries, even within small geographical distances (Weatherall 2010). Hence, a great deal more work needs to be done to provide anything like an accurate estimate of their true frequency.

Maps showing the world distribution of the sickle cell disorders, hemoglobin (Hb)E and the different forms of thalassemia are shown in Figures 1 and 2. Sickle cell anemia occurs throughout sub-Saharan Africa and in small pockets in the Mediterranean region, the Middle East, and the Indian subcontinent. By the use of haplotype analysis, that is the pattern of single nucleotide polymorphisms in the β -globin gene cluster, it has been determined that the sickle cell

Editors: David Weatherall, Alan N. Schechter, and David G. Nathan

Additional Perspectives on Hemoglobin and Its Diseases available at www.perspectivesinmedicine.org

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Cite this article as *Cold Spring Harb Perspect Med* 2012;2:a011692

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Table 1. A breakdown of the annual number of births with the different hemoglobin disorders

Annual births with major hemoglobin disorders	
β-thalassemia major	22,989
HbE β thalassemia	19,128
HbH disease	9568
Hb Bart's hydrops (α^0/α^0)	5183
SS disease	217,331
S β thalassemia	11,074
SC disease	54,736

From available data (Modell and Darlison 2008; Weatherall 2010).

gene arose at least twice, once in Africa and once in India or the Middle East (Kulozik et al. 1986). Similar evidence suggests that the gene may have also arisen on several different occasions in sub-Saharan Africa although these data have to be reviewed with caution because it is possible that the different haplotype patterns could have resulted from gene conversion events (Flint et al. 1998). Hemoglobin SC disease is more restricted to parts of west and north Africa whereas HbS β thalassemia occurs in localized parts of sub-Saharan Africa and sporadically throughout the Middle East and Indian subcontinent. Unlike some forms of α thalassemia and HbE, which are discussed below, the gene fre-

quency for HbS rarely rises much above 20%–25% of a particular population although there are occasional exceptions.

Hemoglobin E, the other particularly common structural hemoglobin variant, occurs widely throughout the eastern half of the Indian subcontinent, Bangladesh, Myanmar, and east and southeast Asia. It occurs at varying frequencies but in some parts of Asia, notably the northern parts of Thailand and Cambodia, called the “hemoglobin E triangle,” up to 70% of the population are carriers (see Fucharoen and Weatherall 2012).

The mild forms of α thalassemia (see Higgs 2012), which result from a single α gene deletion ($-\alpha/\alpha\alpha$), occur in a broad tropical belt stretching from sub-Saharan Africa through the Mediterranean regions and Middle East to the Indian subcontinent and the whole of east and southeast Asia. In this band, they occur at a frequency of 10%–25%, although in a few localized populations such as those of north India and Papua New Guinea, they are found in up to 80% of the population and the gene appears to be going to fixation. The more severe forms of α thalassemia due to loss of both α chain genes—α⁰ thalassemia ($-\alpha\alpha$)—have a much more restricted occurrence, reaching high frequencies

Figure 1. The world distribution of the origins of hemoglobin S and hemoglobin E. (From Weatherall and Clegg 2001; reprinted, with permission, from the author.)

Figure 2. The world distribution of the origins of the α and β thalassemias. (From Weatherall and Clegg 2001; reprinted, with permission, from the author.)

only in southeast Asia and in some of the Mediterranean islands. They occur sporadically throughout other populations, however, although their true frequency has not been determined.

Although the hemoglobinopathies all occur at particularly high frequencies in these tropical regions, they have been transported to most countries of the world by population migrations over many years. For example, the sickle cell gene is extremely common in many of the Caribbean Islands and in parts of North America, and occurs in most countries to a varying degree. The same phenomenon has occurred in the case of all the common forms of thalassemia. Interestingly, there are no common hemoglobin disorders among the American Indian population, probably because these conditions were not established in Asia at the time of the

early population movements across the Bering Strait.

WHY ARE THE INHERITED DISORDERS OF HEMOGLOBIN SO COMMON?

There are several reasons why the hemoglobin disorders have reached such extraordinarily high gene frequencies in many tropical countries. First and foremost, it appears that their frequency reflects natural selection through protection of heterozygotes against severe malaria, a mechanism first suggested by Haldane (1949) and later confirmed independently in the case of sickle cell anemia by Allison (1954a,b,c). We will consider the possible mechanisms later in this work.

Natural selection is not the only mechanism involved in maintaining these high gene

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frequencies. Another important factor is the relatively high frequency of consanguineous marriages in many of the high frequency countries; this mechanism has an important effect on increasing the gene frequency of any recessively inherited disorder. Although accurate data on the frequency of consanguineous marriage are lacking, there is no doubt from such that are available that this is an important factor in helping to maintain the global health problem posed by these conditions. Another important factor is the epidemiological transition, whereby as public health and nutritional standards improve in the poorer countries, babies with these conditions who would otherwise have died in early life are now living long enough to present for diagnosis and management. As evidenced by what happened in Cyprus after it went through this transition after the Second World War, there is no doubt that this mechanism will cause a major increase in the number of patients with the more severe hemoglobin disorders in the future (Weatherall and Clegg 2001). Finally, the varying distribution of some of the hemoglobin disorders in different populations reflects strong founder effects by their original inhabitants. This mechanism is clearly illustrated in some of the Pacific Island populations (O'Shaughnessy et al. 1990).

It should be emphasized that even if some of the selective factors are reduced—the eradication of malaria, for example—it will take many generations before the frequency of these diseases starts to decline; a period during which there will be a tendency for their increase because of the epidemiological transition outlined above.

NATURAL SELECTION AND THE HEMOGLOBIN DISORDERS

During the six decades since Haldane first proposed the malaria hypothesis (Haldane 1949), evidence has steadily grown to confirm that malaria is indeed the primary force behind the high frequency of inherited hemoglobin disorders that is seen in many tropical and subtropical populations. The evidence supporting this assertion comes from four main sources: the sim-

ilarity between the distributions of malaria and specific hemoglobin disorders at local, regional, and global scales; from population genetic predictions of their historic age; from clinical studies conducted in malaria-endemic areas; and from mechanistic studies conducted both in-vitro and ex-vivo. Although such evidence is strongest for HbS and for the α thalassemias, which have been the focus of the most research, there can now be little doubt that malaria is responsible for the current distributions of all the major hemoglobin disorders. In the following sections we will review the evidence as it stands for each hemoglobin disorder individually. The proposed mechanisms for malaria protection by these conditions are summarized in Table 2. However, later in this work we will also discuss emerging data that suggest that selection for hemoglobin disorders may be competitive, and might be influenced by negative effects when inherited in combination with one another.

Hemoglobin S

The heterozygous state for hemoglobin S (HbAS) is the best described of all malaria-protective traits and is used as the classic example of balanced polymorphism in schools and colleges throughout the world. The close resemblance between the geographic distribution of HbAS and that of malaria, documented by a number of different investigators more than 60 years ago (Beet 1946, 1947; Brain 1952; Foy et al. 1952, 1954), gave the first clues. But it is Allison who first articulated the malaria hypothesis with regard to HbS most definitively (Allison 1954a,b,c). Not only, as others before him (Beet 1946, 1947; Brain 1952), did he note that “sicklers” were significantly less likely than “non-sicklers” to carry malaria parasites under conditions of natural exposure but he also showed that, when inoculated intravenously with large volumes of parasite-infected blood, sicklers were less likely to develop a clinical malaria infection. Many studies have since been conducted that put the malaria hypothesis with regard to HbS beyond reasonable doubt. First, the close correspondence between the frequencies of the β^S allele and the historic prevalence of malaria

Table 2. Summary of some proposed mechanisms of action of the malaria-resistance polymorphisms involving the inherited hemoglobin disorders

Hemoglobin disorder	Potential mechanisms for malaria protection	Key references
Sickle cell trait (HbAS)	Impairment of <i>P. falciparum</i> red cell invasion and growth under conditions of low oxygen tension	Friedman 1978; Pasvol et al. 1978; Friedman et al. 1979
	Enhanced removal of parasite-infected HbAS red blood cells	Luzzatto et al. 1970; Friedman 1978; Roth et al. 1978; Shear et al. 1993; Ayi et al. 2004
	Reduced pathogenicity of <i>P. falciparum</i> infected red blood cells because of reduced expression of PfEMP1	Cholera et al. 2008; Cyrklaff et al. 2011
	Improved acquisition of malaria-specific immunity	Edozien et al. 1960; Cornille-Brogger et al. 1979; Guggenmoos-Holzmann et al. 1981; Marsh et al. 1989; Bayoumi et al. 1990; Abu-Zeid et al. 1992; Odegbemi and Williams 1995; Le Hesran et al. 1999; Cabrera et al. 2005; Williams et al. 2005a; Verra et al. 2007b
Hemoglobin C (HbAC and HbCC)	Impairment of <i>P. falciparum</i> red cell invasion and growth under conditions of low oxygen tension	Friedman et al. 1979; Pasvol and Wilson 1982; Olson and Nagel 1986; Fairhurst et al. 2003
	Improved acquisition of malaria-specific immunity	Ringelhann et al. 1976; Verra et al. 2007b
	Reduced pathogenicity of <i>P. falciparum</i> infected red blood cells because of reduced expression of PfEMP1	Fairhurst et al. 2005; Brittain et al. 2007; Cyrklaff et al. 2011
Hemoglobin E (HbAE and HbEE)	Impairment of <i>P. falciparum</i> red cell invasion and growth	Chotivanich et al. 2002
α thalassemia	Specific protection against malaria-induced anaemia	Allen et al. 1997; Williams et al. 2005d; Wambua et al. 2006; May et al. 2007; Fowkes et al. 2008; Veenemans et al. 2008
	Reduced pathogenicity through reduced cytoadherence or rosetting	Udomsangpetch et al. 1993; Carlson et al. 1994; Cockburn et al. 2004
	Immunological priming through cross-species immunity between <i>P. vivax</i> and <i>P. falciparum</i>	Williams et al. 1996; Veenemans et al. 2011
β thalassemia	Enhanced removal of parasite-infected red blood cells	Ayi et al. 2004
	Reduced invasion and growth of <i>P. falciparum</i> parasites	Kaminsky et al. 1986; Senok et al. 1997
	Reduced pathogenicity through reduced cytoadherence or rosetting	Udomsangpetch et al. 1993; Carlson et al. 1994

has been confirmed through a growing number of surveys at both the local (Enevold et al. 2007) and global scales (Livingstone 1973, 1985; Cavalli-Sforza et al. 1994). Recently, this relationship has been quantified statistically, an analysis that found strong geographical support for the

malaria hypothesis in Africa but not in either the Americas or in Asia (Piel et al. 2010). Hemoglobin S is absent from indigenous populations in the Americas, probably because malaria did not reach the continent until relatively recently, whereas in Asia it follows a rather

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restricted distribution, being confined to a small number of tribal populations in India (Piel et al. 2010).

Direct clinical support for a protective effect of HbAS has been provided by case control, cohort, and family-based association studies conducted in multiple populations over the last 30 years (for summary, see Williams et al. 2005b; Jallow et al. 2009). In general, such studies have shown that HbAS is ~50% protective against uncomplicated and >80% protective against severe *P. falciparum* malaria. Although few individual studies have been powered to detect an effect on malaria-specific mortality, HbAS was associated with 55% protection against all-cause mortality in children 6–16 months old in a single cohort study conducted in Western Kenya (Aidoo et al. 2002). Intriguingly, HbAS has also been associated with protection against invasive bacterial infections in two studies conducted in different parts of Africa (Eeckels et al. 1967; Scott et al. 2011). This observation appears to be explained by the protective effect of HbAS against malaria and provides evidence for a causal association between malaria and bacterial infections, indicating that in malaria-endemic environments, genetic factors like HbAS may confer an additional benefit of protection against death from bacterial diseases (Scott et al. 2011). Recently, Gouagna and colleagues working in Burkina Faso, made an additional intriguing observation regarding the malaria-protective effect of HbS (Gouagna et al. 2010). Although HbAS protects against clinical malaria infections, parasite-infected blood from HbAS subjects is several times more infectious to the *Anopheles* vector than that of normal subjects (Gouagna et al. 2010). This observation, which is echoed by a similar observation from Senegal (Lawaly et al. 2010), suggests that the personal advantage of HbAS is not only balanced by the cost of potential homozygosity in offspring but also by that of increased malaria transmission to the general population.

Whereas the malaria-protective effect of HbAS is clear, the effect of the homozygous state, HbSS, on malaria risk is more controversial. Biologically, there are hypothetical reasons why subjects with HbSS might either enjoy a

greater degree of protection than those with HbAS or, conversely, might be at more increased risk than normal subjects (Williams and Obaro 2011). Few controlled studies of this question have been reported but the balance of evidence suggests that both scenarios might be true. Subjects with HbSS appear to be less susceptible than normals to developing malaria infections (Makani et al. 2010; McAuley et al. 2010) but are highly susceptible to the catastrophic consequences of malaria, particularly severe anemia, if they do become infected with the disease (Makani et al. 2010; McAuley et al. 2010; Williams and Obaro 2011). The net result is that malaria is almost certainly a major cause of premature mortality in children born with HbSS in malaria-endemic areas and that the early detection of HbSS in association with active malaria prevention could have a major impact on survival (Serjeant 2005).

The Mechanism of Malaria Protection Afforded by HbAS

Although the fact that HbAS confers malaria protection is now well established, the mechanism by which it does so remains a matter of some speculation. Through early studies, conducted soon after it became possible to grow malaria parasites in culture, investigators converged on the general hypothesis that protection resulted from impairment in the invasion and growth of *P. falciparum* parasites into HbAS red cells under conditions of low oxygen tension that were physiologically representative of in vivo conditions (Friedman 1978; Pasvol et al. 1978; Friedman et al. 1979). However, a number of alternative hypotheses have subsequently developed. Several investigators have suggested that the mechanism may relate to the enhanced removal of parasite-infected HbAS red blood cells. Some have proposed that this may relate to the fact that such cells sickle under low oxygen tension (Luzzatto et al. 1970; Friedman 1978; Roth et al. 1978) and that this leads to their premature destruction in the spleen (Friedman 1978; Shear et al. 1993), whereas Ayi and colleagues have proposed a mechanism that is generic to a number of red cell disorders

and involves the enhanced opsonization of red cells infected with ring-stage parasites through a process that involves increased oxidative stress (Ayi et al. 2004).

An alternative hypothesis has emerged more recently. Cholera and colleagues have shown that in vitro, relative to parasitized normal HbAA red blood cells, the binding of parasitized HbAS red blood cells to both microvascular endothelial cells and to blood monocytes was significantly reduced and that this correlated with altered surface display of the parasite-encoded protein *P. falciparum* Erythrocyte Protein-1 (PfEMP1) (Cholera et al. 2008). Because the PfEMP1-mediated sequestration of mature parasites in the post-capillary venules of critical tissues such as the brain have been implicated in both the pathogenesis of severe malaria and the evasion of parasite-infected red cells from immune clearance by the spleen, this provides an attractive explanation for the protective effect of HbAS. Very recently, Cyrklaff and colleagues have elaborated on this hypothesis by showing, again in vitro, that HbAS affects the trafficking system that directs PfEMP1 to the surface of infected erythrocytes. Using cryo-electron tomography they showed that within the cytoplasm of normal red blood cells the parasite proteins are transported to the surface via a parasite-generated host-derived actin cytoskeleton but that hemoglobin oxidation products disrupted this process in HbAS red cells (Cyrklaff et al. 2011).

Whereas all the hypotheses discussed so far imply that HbAS protects against malaria entirely through innate mechanisms, data from both epidemiological and clinical studies suggest that this may not be the entire story. The protective effect of HbAS in naturally exposed populations increases with age (Cornille-Brogger et al. 1979; Guggenmoos-Holzmann et al. 1981; Le Hesran et al. 1999; Williams et al. 2005a), indicating that the mechanism might not be entirely innate but might also include an acquired, immunological component. This hypothesis is supported by a number of studies that have reported enhanced malaria-specific immune responses in HbAS individuals (Edozien et al. 1960; Marsh et al. 1989; Bayoumi et al. 1990; Abu-Zeid et al. 1992; Odegbemi and

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Williams 1995; Cabrera et al. 2005; Verra et al. 2007a), and potentially by recent studies using a mouse model that suggest an immuno-modulatory mechanism mediated through hemoxygenase-1 (Ferreira et al. 2011). However, the mouse model of the sickling disorders is metabolically very different to the human sickle-cell traits. Furthermore, whereas such studies appear to support an immune component to the malaria protective effects of HbAS they are balanced by others that show no apparent differences between HbAS and normal subjects with regard to a range of immunological responses (Cornille-Brogger et al. 1979; Storey et al. 1979; Le Hesran et al. 1999; Tan et al. 2011), leaving the balance between innate and acquired mechanisms unresolved.

From the above discussion, it is clear that HbAS is associated with strong protection against all forms of clinical *P. falciparum* malaria but that the mechanism for this protection remains somewhat speculative. Although many plausible mechanisms have been proposed during the last 40 years, which (if any) provides the true explanation remains unresolved. One possibility is that there is no single mechanism for the protective effect of HbAS but that protection results from the composite of many of the mechanisms described or by different mechanisms in different populations; more work will be required, both in vitro and ex vivo, to resolve this question definitively.

Hemoglobin C

Fewer studies have focused on the malaria-protective effects of HbC than for HbS. The geographic range of HbC is considerably more limited than that of HbS, being centered on West and North-West Africa with the exception of a low-frequency corridor between West Africa and Egypt that appears to reflect patterns of human migration (FB Piel, AP Patil, RE Howes, et al., unpubl.). Although historically HbC has been restricted to malaria-endemic communities, to the best of our knowledge the relationship between the population frequency of HbC and the endemicity of malaria has not been formally tested. Early studies investigating the association

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between HbC and clinical protection were either inconclusive (Thompson 1962, 1963; Gilles et al. 1967; Guinet et al. 1997) or suggested only a marginal effect of HbC in comparison to the marked protection afforded by HbS (Ringelmann et al. 1976). This was confirmed most recently in both a large cross-sectional survey (Danquah et al. 2010) and in a birth cohort study (Kreuels et al. 2010), both conducted among children living in areas of high malaria transmission in Ghana. This may well be explained by more recent studies suggesting that protection might be specific to particular categories of strictly defined severe malaria (May et al. 2007) and that it is greater in homozygotes (with HbCC) than in heterozygotes (with HbAC) (Agarwal et al. 2000; Modiano et al. 2001; Mockenhaupt et al. 2004a). The strongest evidence for a homozygous advantage of HbC comes from a large case-control study conducted by Modiano and colleagues in Burkino Faso, in which they found a 29% reduction in the risk of clinical malaria among children with HbAC compared to a 93% reduction among children with HbCC (Modiano et al. 2001). Finally, like HbS, it appears that HbC has a marked effect on the transmissibility of malaria by the *Anopheles* vector (Gouagna et al. 2010).

Mechanistically, similar hypotheses have been pursued for HbC as for HbS. As for HbAS, early studies suggested that the protective effect of HbC might result from a reduced ability of *P. falciparum* parasites to grow and multiply in red blood cells containing HbC (Friedman et al. 1979; Pasvol and Wilson 1982; Olson and Nagel 1986; Fairhurst et al. 2003). Subsequently, however, it has been suggested that the mechanism might involve an immunological component (Ringelmann et al. 1976). This is supported by the finding of higher immune responses to PfEMP1 and various malaria antigens among children expressing the HbC allele in a low transmission urban area of Burkina Faso (Verra et al. 2007b), although no differences were found in a higher transmission rural population in the same study or in a more recent study conducted in Mali (Tan et al. 2011). As for HbAS, an alternative hypothesis has recently been developed: that HbC exerts its protection through a specific effect on cytoadherence, mediated by the altered

display of surface-expressed parasite proteins (Fairhurst et al. 2005; Brittain et al. 2007; Cyrtklaff et al. 2011).

Hemoglobin E

Much less is known about the effects of HbE on malaria than for the other common structural variants of hemoglobin. Like most of the other disorders, HbE is restricted to populations that have traditionally been endemic for malaria and there is some evidence for a correlation between the prevalence of the two conditions (Flatz et al. 1965; Kar et al. 1992; Win et al. 2005). Moreover, in one Thai population, it has recently been estimated on the basis of genetic linkage analysis that the most frequent variant, HbE $\beta 26 \text{ Glu} \rightarrow \text{lys}$, has reached its current frequency in <5000 years, a period compatible with the malaria hypothesis (Ohashi et al. 2004). Nevertheless, few clinical studies have reported the relative risk of clinical malaria in subjects with HbE. In one such study, conducted in adults with malaria who were admitted to the hospital in Thailand, the manifestations of malaria were less severe in patients with HbE trait (HbAE) (Chotivanich et al. 2002). However, in a similar study, Oo and colleagues found no significant relationship between either HbAE or HbEE and the severity of malaria in adults admitted to the hospital in Burma (Oo et al. 1995). Similarly, a small recent study found no relationship between HbE and the risk of cerebral malaria in Thai adults (Naka et al. 2008). To the best of our knowledge, the relative risk of malaria in such subjects has not been reported through case-control or cohort studies, although a single report from Sri Lanka found subjects with the clinically significant condition HbE/ β thalassemia to be at greater risk than normals from *P. vivax* malaria. This observation, which may be explained by the rapid turnover of red cells seen in patients with this condition—as *P. vivax* favors the youngest, most metabolically active red blood cells—suggests that patients with HbE/ β thalassemia should be actively protected from malaria (O'Donnell et al. 2009).

Very few studies have examined the potential mechanisms by which HbE might confer

malaria protection. In one such study, Chotivachit et al. (2002) found that compared to normal subjects, a smaller proportion of red cells from subjects with HbAE were susceptible to invasion by *P. falciparum* parasites in culture, raising the possibility that HbAE might protect against severe malaria by limiting the ability of infections to achieve high parasite densities. The degree to which HbE protects against different forms of malaria and any potential mechanisms remain, therefore, a subject for further investigation.

THE THALASSEMIAS

There is strong evidence from population data that malaria selection explains the current distribution of the thalassemias. First, at a global scale, both α and β thalassemia follow remarkably similar distribution to that of malaria (Livingstone 1973, 1985; Cavalli-Sforza et al. 1994), an observation that also holds true at a micro-epidemiological scale. For example, in early studies, Siniscalco and colleagues noted a strong correlation between the population prevalence of β thalassemia and the historic incidence of malaria among villages in Sardinia in southern Italy (Siniscalco et al. 1961), whereas Hill and colleagues drew similar conclusions in Melanesia (Hill et al. 1988). Similar observations have subsequently been made regarding the distribution of α thalassemia in South Asia (Modiano et al. 1991), Tanzania (Enevold et al. 2007), and the Pacific (Flint et al. 1986), where in some populations these conditions have virtually reached fixation (Flint et al. 1998). Second, unlike many of the other disorders of hemoglobin, the molecular defects that result in the thalassemias are extremely diverse (see Higgs 2012), having arisen separately and been locally amplified, in multiple populations throughout the malaria-endemic regions of the world. The one notable exception is South America, where in evolutionary terms malaria was introduced only relatively recently.

Despite the overwhelming epidemiological evidence for malaria selection, the protective effect of β thalassemia has been the subject of few clinical studies. Nevertheless, in one case-

control study conducted in northern Liberia, Willcox and colleagues estimated a protective effect of $\sim 50\%$ (Willcox et al. 1983). Whereas many more studies have recorded, the clinical relationship between α thalassemia and malaria, the results have not been entirely consistent. The incidence of uncomplicated clinical malaria has been lower in α thalassemic than normal subjects in some cohort studies (Wambua et al. 2006; Enevold et al. 2008), whereas in others the incidence has either been equal (Lin et al. 2010; Veenemans et al. 2011) or even higher (Williams et al. 1996; Veenemans et al. 2011). Conversely, studies focused on severe malaria have shown consistent evidence for a strongly protective effect that is generally more marked in homozygous than heterozygous subjects (Allen et al. 1997; Mockenhaupt et al. 2004b; Williams et al. 2005d; Wambua et al. 2006; May et al. 2007). Available data, therefore, provide good evidence for a protective effect of α thalassemia against severe and fatal malaria, but the data on uncomplicated malaria are somewhat perplexing. It seems likely that these observations are pointing to important clues about the mechanism by which α thalassemia protects against severe malaria.

Several studies suggest that, as opposed to protecting against all forms of clinical malaria, α thalassemia might specifically protect against the anemia that commonly complicates infections caused by *P. falciparum* malaria (Allen et al. 1997; Williams et al. 2005d; Wambua et al. 2006; May et al. 2007). Furthermore, unlike HbAS, there is little evidence that α thalassemia has any effect at the level of malaria parasite density (Allen et al. 1997; Mockenhaupt et al. 2004b; Migot-Nabias et al. 2006; Wambua et al. 2006; Enevold et al. 2008; Veenemans et al. 2008, 2011). Such clinical observations suggest that the mechanisms by which α thalassemia protects against malaria might well be different from those involved in HbAS. Two possible explanations for a specific effect against malaria-induced anemia have been put forward: first, that the higher red cell counts that are associated with α thalassemia may buffer against the development of anemia during *P. falciparum* infections (Fowkes et al. 2008), and second, that this

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protection might be immunologically mediated (Veenemans et al. 2008). With regard to the latter, Veenemans and colleagues found that in two cohorts of children in East Africa, the greatest falls in hemoglobin occurred when malaria parasitemia was associated with inflammation in the form of a raised C-reactive protein concentration in blood and that α thalassemia was strongly protective against this “inflammatory” form of the disease (Veenemans et al. 2008). A further characteristic of α -thalassemic red blood cells may provide an alternative explanation. In studies conducted in Papua New Guinea, Cockburn and colleagues noted that the expression of complement receptor-1 (CR1) is reduced on the surface of α -thalassemic red blood cells (Cockburn et al. 2004). CR1 is a ligand for rosetting in which uninfected red blood cells adhere to parasite-infected red cells in vitro (Figs. 3 and 4). Because rosetting has been associated with severe forms of malaria, including severe anemia, the reduced expression of CR1 might be relevant in the protection afforded by α thalassemia. Finally, it is also possible that immune factors might be involved. In two clinical studies, the incidence of uncomplicated clinical malaria has been paradoxically higher in the youngest α -thalassemic children (Williams et al. 1996; Veenemans et al. 2011), raising the possibility that α thalassemia might

Figure 4. A cross-sectional photograph of a rosette as shown in Figure 3. (Image supplied by D.J.P. Ferguson, Oxford University.)

be acting like a natural vaccine, boosting exposure and immunity to malaria during early childhood. As for all the hemoglobin disorders, the story is more complicated than one might have thought at one point.

EPISTATIC INTERACTIONS BETWEEN THE HEMOGLOBIN DISORDERS

If, as discussed above, malaria is responsible for the Mendelian selection of many of the inherited disorders of hemoglobin, a question remains about why they have not all become common throughout the whole of the malaria-endemic world. This is a question that has been asked particularly from the perspective of pairs of hemoglobin disorders by a number of different investigators. Studies conducted both in Kenya and in Ghana have recently shown that when inherited alone, both HbAS and α thalassemia are strongly protective against *P. falciparum* malaria but that the protective effects of each are lost when both conditions are inherited together (Williams et al. 2005c; May et al. 2007). From the perspective of HbAS, this may be explained by the changes in the intracellular concentration of HbAS that accompany the coinheritance of α thalassemia (Brittenham et al. 1980). This negative interaction between the two malaria-protective phenotypes could well explain why both are held at intermediate frequencies in

Figure 3. Three-dimensional photograph of normal red cells aggregating around a malaria-infected red cell to form a rosette. (Image supplied by D.J.P. Ferguson, Oxford University.)

populations where both occur together (Williams et al. 2005c; Hedrick 2011; Penman et al. 2011). A similar hypothesis has more recently been advanced to explain the relative frequencies of HbAS and the α and β thalassaemias within the Mediterranean region (Penman et al. 2009).

CONCLUSION

There is no doubt that Haldane's "malaria hypothesis" has been fully vindicated over the years, although his suggested mechanisms for malaria protection in thalassemia carriers, that is, the small size of their red cells, has not stood the test of time. Further work is still required toward a better understanding of the protective mechanisms, information which is of potential value not just in the field of evolutionary biology but also for its potential in directing approaches for the better prevention and management of the different forms of malaria. Similarly, further work on the remarkable epistatic interactions between various malaria-protective polymorphisms should provide invaluable information about the mechanisms for the distribution of the different forms of inherited hemoglobin disorders, in particular high-frequency populations.

ACKNOWLEDGMENTS

We are extremely grateful to Liz Rose for her help in the preparation of this manuscript. We also thank D.J.P. Ferguson of Oxford University for supplying the photographs shown in Figures 3 and 4.

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Cold Spring Harb Perspect Med 2012; doi: 10.1101/cshperspect.a011692

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