Hemoglobinopathy for malaria protection

Redcellsandanaemia: Whatevidenceexists tosupportthehypothesis thathaemoglobinopathies conferprotectionagainstmalaria?

Introduction

Haemoglobinopathies can be divided into two areas, abnormal haemoglobin synthesis and decreased haemoglobin synthesis. Abnormal haemoglobin synthesis is usually a result of genetic defects, caused by amino acid substitutions in the Î± or Î² chains of the haemoglobin molecule. Decreased haemoglobin synthesis is also caused by genetic disorders and arise from gene deletions of either Î± or Î² globin chains. This group of diseases is called thalassemia.

Malaria is a parasite infection caused by the Plasmodium genus. There are 4 types that affect humans, Plasmodium falciparum (P. falciparam), Plasmodium vivax (P. vivax), Plasmodium malariae (P. malariae) and Plasmodium ovale (P. ovale). The most common form is P. falciparam, which is responsible for 80% of all cases and 90% of deaths. Malaria affects between 300-500 million people each year and is prevalent in tropical areas where mosquitoes act as vectors for the parasite. Hence, much of research undertaken to date focuses primarily on P. falciparam infection. Upon entering the body the Plasmodium parasite migrates to the liver. After multiplication, they are released into the blood as merozoites. The merozoites then bind to and enter the red blood cell.

The hypothesis that haemoglobin disorders confer protection against malaria can be evaluated by reviewing the evidence in support of malarial

protection. However, evidence showing that these disorders do not confer protection should not be ignored.

Sickle cell disease

The protective effect of Sickle cell disease (SCD) against malaria was first described over 60 years ago (Beet, 1946). SCD is an inherited disease, caused by the production of abnormal haemoglobin, HbS. The gene for sickle haemoglobin (HbS) substitutes valine for glutamic acid at the sixth position from the amino terminus of the Î² chain (Serjeant). Under low oxygen tension, the HbS polymerises resulting in sickling of the red blood cell (haem mal 4).

Homozygous individuals for HbS carry the genotype HbSS, inheriting abnormal genes for Î²-globin from both parents. Without adequate treatment, this form of the disease is fatal in early life. However, heterozygous individuals who inherit one abnormal and one normal Î²-globin gene are asymptomatic and carry the genotype HbAS. This genotype is known as Sickle cell trait, which various studies claim confers protection against malaria (Allison, 1964, Freidman, 1978) (ref 10&11, haem mal4).

The mechanism by which HbAS prevents malaria is unclear and is an area that requires greater research. However, there have been many suggested mechanisms over the years. These mechanisms involve the interactions between red blood cells and parasites, without excluding the role of the immune system.

A study conducted by Cholera 2008 examined the role of cytoadherence of parasite and red blood cells. The findings showed that parasite infected HbAS red blood cells showed reduced binding capability to endothelial cells and blood monocytes when compared to parasitized normal Hb red blood cells. This impairment caused by HbAS is caused by a reduced expression of P. falciparam erythrocyte membrane protein 1 (PfEMP1), responsible for cytoadherence of infected red blood cells to critical tissues such as the brain.

The role of the immune system in resisting parasite infection has also been explored. Increased phagocytosis of infected HbAS erythrocytes in comparison with normal infected erythrocytes was observed (ref smith et al 2002, akide et al 2003, Roberts Williams 2003 etc Haem mal). Further evidence showing the central role of the immune system has been illustrated by increased protection with age, strengthening the importance of immunological responses to parasite infection.

Other mechanisms include the inhibition of parasite growth within erythrocytes by HbS polymerisation caused by low oxygen tension (Haem mal).

Haemoglobin C

Haemoglobin C is found in west Africa, and in its homozygous state, referred to as HbCC, causes haemolysis and splenomegaly. Heterozygotes are asymptomatic and display the genotype HbAC. Haemoglobin C arises from a point mutation where glutamate is replaced by lysine at the sixth position of the Î²-globin chain. Acquired immunity against P. falciparum was reported in HbC and HbS due to abnormal display of PfEMP1 (Verra et al, 2007).

However, studies on HbC malarial protection have produced contradictory results. Some studies claimed homozygous HbCC individuals were protected from developing severe malaria(haem mal) and were also at a reduced risk of malarial infections (modiano et al, 2001, haem mal).

Î±-Thalassemia

Î±-thalassemia is caused by decreased synthesis of Î±-globin. It is caused by deletion of Î±-globin genes on chromosome 16 (Yuthavong & Wilairat 1993, haem mal). Î±-thalassemia results in mild anaemia, and lower levels of haemoglobin in red blood cells. Population genetics have shown Î±-thalassemia to protect against malaria, but similar to SCD, there is no consensus on the mechanism of action.

Studies have shown Î±-thalassemia protects against severe and fatal malaria, whereas parasiteamia is unaffected (72-78, haem mal 3). A reduction in complement receptor 1 (CR1) expression caused by Î±-thalassemia has been proposed as a possible mechanism of protection. CR1 deficient erythrocytes reduce rosetting of cells, which is associated with severe malaria (Cockburn 2004). This rosetting of cells mediated by CR1 can potentially obstruct capillaries (Stoute, 2011).

Î²-Thalassemia

Î²-thalassemia results in either no or little Î²-globin production, caused by mutations on chromosome 11. Heterozygotes experience mild anaemia and ineffective erythropoiesis whereas homozygotes suffer from severe anaemia and leads to death without proper treatment (Weatherall, 2000, haem mal).

Protection in early life from malaria was seen in Î²-thalassemia carriers as a result of foetal haemoglobin levels declining more slowly than usual (Pasvol 1978). Other researchers reported P. falciparam growth inhibition in vitro (Brockleman 1978) and higher phagocytosis of Î²-thalassemia infected erythrocytes compared to normal erythrocytes.

Like Î±-thalassemia and SCD, there is not yet a definitive mechanism by which Î²-thalassemia protects against malaria and suggested mechanisms put forward until now require greater research.

Conclusion

By examining the evidence, haemoglobinopathies do confer protection against malaria. However, the protection varies from one disorder to the next as does the level of protection from malarial infection and parasite progression. The protection revolves around the red blood cell which is central to the life cycle of the malaria parasite. The different haemoglobin abnormalities disrupt parasite and red blood cell interactions in diverse pathways, resulting in differing mechanisms of protection and subsequently different levels of protection. The lack of consensus regarding mechanisms involved highlights the necessity for further research. In addition to the possible protection pathways mentioned earlier, the analysis of population genetics cannot be ignored. The haemoglobinopathies discussed have a higher prevalence in malaria endemic regions due to the protection conferred from this lethal parasite.