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## GENETICS OF PARASITIC INFECTIONS

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### ABSTRACT:

**Parasites cause much suffering mainly in countries of the southern hemisphere. Hundreds of millions of individuals are infected by schistosomes, leishmanias, plasmodiums, trypanosomes, and various other parasites, and severe clinical disease occurs in a sizable fraction of the infected population causing death and severe sequelae. The outcome, asymptomatic, subclinical or clinical disease, of an infection depends mostly on the parasite and on its**

**host. Several groups analyzing the genetics of human susceptibility to parasites have begun to identify the critical steps of the pathogenic mechanisms in a few parasitic infections such as malaria and schistosomiasis. The present article, which is not meant to be an exhaustive review of the field, illustrates the progresses made in this field from pioneer studies in animals to works in endemic populations using modern strategies of human genetics.**

A variety of parasites cause chronic infections that last for long periods of time in their human host without much clinical symptoms; in some subjects, however, parasites cause severe disease. These pathological disorders may become apparent after 10 to 20 years of infection as in subjects infected by *Schistosoma mansoni* or by *Trypanosoma cruzi*, or within a few weeks of infection in patients affected by *Leishmania donovani* or by *Plasmodium falciparum*. Various studies have attempted to identify the factors that cause disease to develop in only a fraction of the population exposed to parasites. Much attention has been given to the environment because parasite transmission depends markedly on environmental factors including vector density, vector distribution, and parasite virulence. Parasites, because they have a large genome, have developed very sophisticated mechanisms, like antigenic variation, to escape immune destruction. The plasticity of the parasite genome is so large that it is tempting to link the different clinical and subclinical forms caused by the infection to the existence of clones of different virulence/pathogenicity in the parasite population. This view is unlikely to apply to parasites such as *Schistosoma mansoni* that, in a given endemic area, express homogenous antigenic and pathogenic properties; it might apply, however, to infections by protozoan parasites such as plasmodium or leishmanias that are highly polymorph and multiply rapidly within their human hosts allowing for emerging variants.

The importance of host genetics in disease development has been difficult to assess because of the multiplicity of the environmental factors, including parasite heterogeneity, that may determine disease. The role of genetics was first addressed in experimental models in which environmental variables can be controlled and measured. Animal studies allowed the discovery of the most interesting *NRAMP1* gene, which likely plays an important role in innate immunity against intracellular pathogens. Studies on human genetics and susceptibility to parasitic infections began with observations of the high prevalence

of mutated alleles of the  $\beta$  globin gene in areas of malaria high endemicity, leading to the hypothesis that these alleles were protective against severe malaria. This observation was then further supported by the results of case control studies. Comparable strategies were used to demonstrate that certain HLA<sup>1</sup> haplotypes (Hill et al., 1991, 1992) and certain TNF- $\alpha$  alleles also modified host susceptibility to malaria. Recent studies in schistosome-infected population have taken advantages of the new methods of epidemiology and genetics that allow performing integrated and simultaneous evaluation of the role of environmental and host-specific factors in the control of infection and disease. This work allowed the discovery of two major loci controlling, for one, infection levels and, for the other, disease progression.

The present article will summarize the observations made in schistosome, leishmania and plasmodium infections. All three parasites are a major threat for human health in the southern hemisphere (Table 1). Hundreds of millions of individuals are infected and one to two millions die every year. This is without mentioning that these parasites also cause invalidating sequelae. Most important, no vaccines are available against these pathogens, and drugs are often inadequate either because they are too expensive, too toxic (leishmanias), or because parasites evolve rapidly to become resistant to their effects (plasmodiums). No doubt, a most important objective of genetics is the identification of the critical steps in the pathogenesis process in order to provide new targets that could be manipulated by vaccines and chemotherapy.

### Genetics of Leishmania Infections in Experimental Models

The first evidence for an important role of genetic factors in the control of infections was reported in experimental models. Studies of animals have the advantage over human studies to allow for the control of environmental factors and of the parasite (heterogeneity, size of the inoculum, etc.). In addition, genetic analysis is easier than in humans since animals can be bred. As discussed in another chapter

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<sup>1</sup> Abbreviations used are: HLA, human lymphocyte antigen; TNF, tumor necrosis factor; NRAMP, natural resistance-associated macrophage protein; iNOS, intracellular nitric-oxide synthase; ICAM, intercellular adhesion molecule; IFN, interferon.

TABLE 1

*Malaria, leishmaniasis, and schistosomiasis are parasitic diseases that are major health problems in southern countries*

Disease	At Risk	Deaths/Year	Clinical Disorders	Treatment
Malaria	>1 billion	1.5 millions	Neurological, lactic acidosis, severe anemia	Quinine, Artemeter
Schistosomiasis	500 millions	200,000	Portal blood hypertension, hydronephrosis	Praziquantel, Oxamniquine
Leishmaniasis	300 millions	100,000	Pancytopenia, mucocutaneous lesions	Antim onials Amphotericin B

of this book, earlier studies have identified a locus, *lsh*, on mouse chromosome 1 that controls early multiplication of *Leishmania donovani* in mice (Blackwell, 1982; Blackwell and Plant, 1986). *Lsh* mapped close to the *bcg* and *ity* locus (Bradley et al., 1979) that had been shown to control multiplication of *Mycobacterium bovis* and *Salmonella typhimurium* in the same mouse strains. That all three pathogens invade the macrophage phagolysosome and that resistance or susceptibility to all three pathogens was inherited as a block suggested that a single gene determined susceptibility to these pathogens. To identify this gene, considerable immunologic and genetic work was performed by several teams and allowed the identification of a new gene (Cellier et al., 1994) on mouse chromosome 1 that accounted for the *lsh*, *bcg*, and *ity* locus. This gene, "natural resistance-associated-macrophage-protein-1" (NRAMP1) is described by its inventors in another chapter of this book. It is enough to say that NRAMP1 localizes to the membrane of the phagolysosome and is a divalent cation transporter. It is thought that the effects of this protein on  $Fe^{2+}$  concentration in the vacuole influence the production of radical oxygen intermediates in the phagolysosome. In all mouse strains studied, mutations causing susceptibility to either one of *Leishmania*, *Mycobacterium*, or *Salmonella* also increase susceptibility to the two others pathogens (Malo et al., 1994). Finally, strains resistant to all three pathogens were made susceptible to all three microbes by knocking out NRAMP1 (Vidal et al., 1995). Since the important discovery of NRAMP1 in mice, this gene has been investigated in many human infections. Mutations in NRAMP1 have been associated with increased susceptibility to HIV (Marquet et al., 1999), *Mycobacterium leprae* (Blackwell et al., 1997; Abel et al., 1998) and *Mycobacterium tuberculosis* infections but not to parasitic infections, so far. Studies on murine leishmaniasis have also shown that the genetic control of infection was probably polygenic. Early studies had shown that HLA and H1 locus, in addition to *lsh* determined mice susceptibility phenotype (Roberts et al., 1989). More recent studies have confirmed this view and identify several genetic regions (Roberts et al., 1997), which contain genes that determine susceptibility to *Leishmania major* the agent of cutaneous leishmaniasis in humans. Susceptibility genes have not been identified so far. Studies of animals revealed the existence of epigenetic effects between loci (Roberts et al., 1999). Such effects will be difficult to uncover in human studies showing how useful and necessary are studies in experimental models.

### Red Blood Cell Defects in Susceptibility to Malaria

The high prevalence in certain areas of the world of deleterious alleles of a number of erythrocyte proteins have stimulated speculation as to whether these alleles might have been selected for their positive effects against infectious diseases. Since the frequency of these alleles are highest in malaria endemic areas, it has been proposed that certain of these polymorphisms increase human protection against malaria (Allison, 1969). One such polymorphism was detected in the gene of the  $\beta$  globin chain of hemoglobin (which is composed of two  $\alpha$  and two  $\beta$  chains). This mutation (noted  $\beta^s$ ) in the sixth codon of the  $\beta$  gene (GAG replaced by GTG, changing a glutamic acid into a valine), is responsible for the polymerization of hemoglo-

bin causing Sick cell anemia in homozygous subjects. Polymerization of hemoglobin in heterozygous subjects is prevented by the presence of a normal  $\beta$  chain in the tetramer. Thus, homozygosity ( $\beta^s/\beta^s$ ) is lethal whereas heterozygosity ( $\beta^A/\beta^s$ ) is not. It has been estimated that these mutations appeared 2000 to 3000 years ago in a few individuals. Since homozygosity is lethal, it was expected that the deleterious allele would have been selected against. Instead, the prevalence of  $\beta^s$  is high in certain regions of Africa. This led to the hypothesis that  $\beta^s$  may provide some advantages against certain diseases endemic in Africa such as malaria, which could exert a positive selective pressure on this allele. Indeed, case control studies showed that the frequency of  $\beta^s$  was higher in subjects with mild malaria than in subjects with severe—often lethal—malaria. The reasons for this are unclear; a current hypothesis is that the mutant  $\beta$  globin chain is less efficient in preventing generation by the cell itself or by the parasite, of radical oxygen intermediates inside the erythrocytes.

Others mutations or deletions in the genes of  $\alpha$  or  $\beta$  globin chains and of other erythrocyte proteins are frequent in regions endemic for malaria and some of them have also been (Hill et al., 1988; Clegg and Weatherall, 1999; Craig et al., 2000) associated with enhanced resistance to this infection

### Genetic Predisposition to Cerebral Malaria

The genetics of human resistance/susceptibility to infection by *Plasmodium falciparum* has been further studied by several groups using association studies to evaluate various candidate genes in the control of severe anemia and of cerebral malaria. In certain regions of Africa, up to 70% of the cases of severe malaria are coma that are associated with death in 15 to 30% of the cases depending on the rapidity and quality of the treatment. Death often occurs in subjects with respiratory distress syndrome. The choice of the candidate genes to be evaluated is based on what is known about the physiopathological mechanisms of the disease. The putative immunopathological mechanism of cerebral malaria is illustrated on Fig. 1. This figure is oversimplified to help the reader understand the roles of TNF- $\alpha$ , iNOS, and intercellular adhesion molecule 1 (ICAM-1) in the pathological process. The pathological events in cerebral malaria are thought to be initiated in the small capillaries of the brain by the adhesion of infected erythrocytes to the brain endothelial cells via ligands on the surface of infected erythrocytes that bind to the ICAM-1 (CD59) and other adhesion proteins (CD36, thrombospondin) expressed by endothelial cells (see Fig. 1). This sequestration of the infected erythrocytes, which is not unique to the brain, leads to a local concentration of parasites and to the release of parasite products (including glycosylphosphatidyl inositol-anchored surface molecules) that stimulate monocytes to produce cytokines such as TNF- $\alpha$ , IL-1, and IL-6. TNF- $\alpha$  enhances the expression of adhesion molecules on the endothelium thus increasing adhesion of infected erythrocytes. Since non-infected erythrocytes adhere to infected ones in infected subjects, it is thought that extensive red cell aggregation occurring in brain capillaries causes local thrombosis and increases local inflammation with the production of more pro-inflammatory

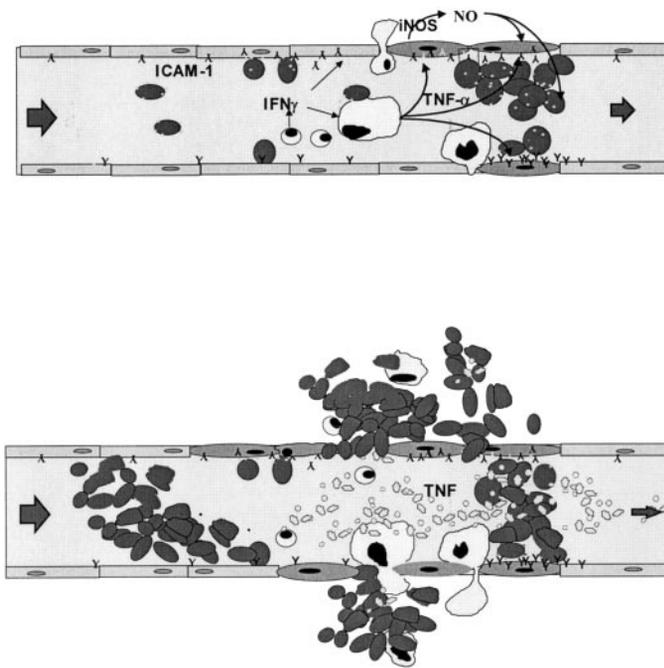


FIG. 1. Putative immunopathological mechanism for cerebral malaria.

Top panel, the adhesion of infected erythrocytes to ICAM-1 receptors on endothelium cells and the production of TNF- $\alpha$  by monocytes activated by parasite molecules or by IFN- $\gamma$  released by activated T-lymphocytes. TNF- $\alpha$  activates endothelial cells to up-regulate iNOS and ICAM-1. Arrows indicate that blood flow is decreased by the adhering infected erythrocytes. Bottom panel, TNF- $\alpha$  effects have increased inflammation and led to endothelial cell damage, migration of blood leukocytes in surrounding tissue, plasma leakage, and ring hemorrhage. Blood flow is markedly reduced. More parasites have been liberated.

cytokines such as TNF- $\alpha$ . This cytokine also increases the transcription of iNOS, which encodes the nitric-oxide synthase, an enzyme that catalyzes the transformation of arginine into nitric oxide and citrulline. Nitric oxide, when produced in large amounts, can be toxic to bystander cells including endothelial cells. It has been suggested that the products released in the inflammatory infiltrates cause endothelium damage and plasma and red cell leakage into brain tissue (Fig. 1). Such focal hemorrhages have been observed on tissue sections of the brain after death due to cerebral malaria. Based on this hypothetical pathogenesis mechanism, several candidate genes were selected; among them were the genes encoding TNF- $\alpha$ , iNOS, and ICAM-1. Polymorphisms in these three genes have been described and associated with increased (or decreased) susceptibility to malaria. The most convincing data have been reported on TNF- $\alpha$  and ICAM-1. A mutation located at -308 nucleotides relative to the transcriptional start site of the TNF- $\alpha$  gene was shown to increase transcription of the gene (Kroeger et al., 1997; Abraham and Kroeger, 1999). Because of the possible functional implication of this functional polymorphism and because of the probable role of TNF- $\alpha$  in pathogenesis of cerebral malaria, the association of this mutation with severe malaria was tested in large case control studies. The mutant allele (gene frequency 0.16) was shown to be associated with an increased relative risk of seven for cerebral malaria with death or sequelae (McGuire et al., 1994). This effect was only observed in homozygous subjects, heterozygous subjects exhibited a susceptibility to severe malaria comparable to controls. Two other mutations at position -238 and -376 have also been described, and both have been associated with increased risks of severe malaria although these effects may differ from one population to the other (Knight et al., 1999). Similar studies, performed on the ICAM-1 gene in Kenya, led to the report of an

association between a functional polymorphism located in the N-terminal domain of ICAM-1 with severe clinical malaria (Fernandez-Reyes et al., 1997; Craig et al., 2000); this polymorphism reduces binding of ICAM-1 to its parasite ligand on erythrocyte surface (Craig et al., 2000). Subjects homozygous for the mutation exhibited an enhanced susceptibility to cerebral malaria (relative risk of two).

Finally, polymorphisms in the promoter of iNOS (G-954C and polymorphisms in a microsatellite) have been reported to be associated with severity of *P. falciparum* infections in Gabon and Gambia (Levesque et al., 1999); the statistics were just significant, and the observation could not be reproduced in a Tanzanian population indicating that more work is needed to definitively demonstrate that polymorphisms in iNOS are indeed associated with severe malaria.

### Schistosomiasis: Two Major Locus in the Control of Infection and Disease

Schistosomes are trematode worms that live in the blood of their human host either in the mesenteric veins or in the vesical plexus. Female worms mate with males and lay eggs that find their way through intestinal or ureteral tissues toward the intestinal lumen or the urinary tract. Then, eggs are excreted with the feces or with the urine. In the outside world, eggs hatch and infect aquatic snails in which they undergo asexual multiplication. Sexual multiplication occurs in human hosts within 4 to 5 weeks of the infection and may continue for years. Humans become infected when snails release free-swimming larvae that are (for each snail) clones issued from a single egg.

The disease is mostly caused by eggs that are trapped in the bladder, ureter or ureteral tissues, or in the liver. These trigger an inflammation that is succeeded by a normal scar consisting of the deposition of collagen and extracellular matrix proteins. These scars normally subside after a few days to be replaced by healthy tissues. In certain subjects, the fibrotic tissue does not subside and rather accumulates around the eggs and in the portal spaces leading to massive obstruction of the blood flow in the portal system. High blood hypertension builds up in these patients who may die of bleeding (varices), co-infections, or heart failure.

### 5q31-q33: A Major Region in the Control of Susceptibility to Infections

In a study on the causes of the high infections in an endemic area of Brazil, it was observed that exposure to the parasite was not a critical limiting factor in infection, probably because exposure was quite high for most subjects (Dessein et al., 1992). No evidence was obtained in that population supporting the hypothesis of more virulent strains of parasites in subjects with the highest infections. Interestingly, however, certain subjects appeared to be predisposed to high infections whereas others always exhibited low infection in spite of high exposure (Dessein et al., 1988, 1992); this observation was made over a long period of time and after observing re-infections following several anti-helminthic treatments. This suggested that host-specific factors were important in the control of infection. The observation that high infections were rather clustered in certain families led us to postulate that these host-specific factors might be inherited factors. This hypothesis was tested using segregation analysis, which is a statistical method that evaluates whether mathematical models that incorporate a major gene effect are better than sporadic or multi-gene models to explain phenotype distribution. An interesting feature of these models is that they incorporate environmental variables and other variables such as sex and age. The analysis proceeds by steps from the least to the most restrictive model. This analysis was applied to the infection data taking into account different ages, sex, and

exposure, and showed that there was strong evidence for the control of infection by a major locus (Abel et al., 1991), also called a major gene. This locus was mapped by linkage analysis using the model provided by segregation analysis; the entire genome was scanned for linkage. The susceptibility locus (SM1) was located in the 5q31-q33 region (Marquet et al., 1996, 1999a), which contains a number of genes that encode cytokines that play an important role in the regulation of the immune response against helminth parasites. On the other hand, immunological studies performed on homozygous-susceptible and homozygous-resistant subjects showed that SM1 control is linked to the differentiation of T-helper cells into Th1 or Th2 lymphocytes (Couissinier-Paris and Dessein, 1995; Rodrigues et al., 1999). Most important, the existence of a locus of susceptibility to *S. mansoni* in 5q31-q33 was confirmed in an independent study on a Senegalese population (Muller-Myhsok et al., 1997) whereas SM1 was identified in Brazilians. Furthermore, it was also reported that blood parasitemia in *P. falciparum* infections are controlled by a locus in the same 5q31-q33 region (Garcia et al., 1998; Rihet et al., 1999). These results altogether indicate that this region is likely to play an important role in susceptibility to infectious diseases.

### Dual Control of Infection and Disease in Human Schistosomiasis

Severe disease in *S. mansoni* infections is the consequence of periportal fibrosis that develops in the hepatic periportal spaces as a consequence of the inflammation caused by eggs and worm products. Why certain subjects are unable to turnover the fibrosis that is part of a normal scar process is unknown. For a long time, it has been thought that high infections were the most important causes for severe hepatic fibrosis; more recently it became clear, however, that infected levels are only one of several factors important in disease development (Mohamed-Ali et al., 1999) suggesting that disease and infection were not necessarily regulated by the same factors. It was observed in ultrasound evaluations of 800 subjects living in an endemic area of Sudan that severe fibrosis associated with portal hypertension was more frequent in certain families and absent in others despite the fact that all families had been living for years in the same conditions of infection (Mohamed-Ali et al., 1999). Segregation analysis applied to this phenotype showed evidence for a major locus that was mapped in 6q22-q23 (Dessein et al., 1999), very close to the gene encoding the  $\alpha$ -chain of the interferon-gamma (IFN- $\gamma$ ) receptor, this chain binds IFN- $\gamma$ . This result is consistent with the well known anti-fibrogenic properties of IFN- $\gamma$ . Furthermore, a number of studies have demonstrated that polymorphisms in the genes encoding either one of the two chains of the receptor of IFN- $\gamma$  increases human susceptibility to certain infectious diseases such as tuberculosis (Pierre-Audigier et al., 1997; Roesler et al., 1999) in which the host immune response is characterized, as in schistosomiasis, by a persisting granulomatous reaction.

### Conclusion

Parasitic diseases are multifactorial and host genetic polymorphisms are not the only factors that determine infection and disease phenotypes. Dissecting the relative contribution of the environment, the parasite and the host in pathogenesis often requires large population studies that are costly and difficult to carry out. A major difficulty to be faced by the geneticists is the large genetic variability of certain parasite populations, which may complicate the detection of host genetic factors since parasite variability is not easy to evaluate. Despite these difficulties, major advances have been made in the field of genetics of parasitic diseases, including malaria and schistosomi-

asis, and provided important insights into the mechanisms of pathogenesis. It is likely that these studies will yield extremely useful information for drug and vaccine development.

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