Deletion of the APOBEC3B gene strongly impacts susceptibility to falciparum malaria


Abstract

APOBEC3B, a gene involved in innate response, exhibits insertion–deletion polymorphism across world populations. We observed the insertion allele to be nearly fixed in malaria endemic regions of sub-Saharan Africa as well as populations with high malaria incidence in the past. This prompted us to investigate the possible association of the polymorphism with falciparum malaria. We studied the distribution of APOBEC3B, in 25 diverse Indian populations comprising of 500 samples and 176 severe or non-severe Plasmodium falciparum patients and 174 ethnically-matched uninfected individuals from a P. falciparum endemic and a non-endemic region of India. The deletion frequencies ranged from 0% to 43% in the Indian populations. The frequency of the insertion allele strikingly correlated with the endemicity map of P. falciparum malaria in India. A strong association of the deletion allele with susceptibility to falciparum malaria in the endemic region (non-severe vs. control, Odds ratio = 4.96, P value = 9.5E-06; severe vs. control, OR = 4.36, P value = 5.7E-05) was observed. Although the frequency of deletion allele was higher in the non-endemic region, there was a significant association of the homozygous deletion genotype with malaria (OR = 3.17, 95% CI = 1.10–10.32, P value = 0.0177). Our study also presents a case for malaria as a positive selection force for the APOBEC3B insertion and suggests a major role for this gene in innate immunity against malaria.

© 2011 Elsevier B.V. All rights reserved.

1. Introduction

The role of human genetic factors in susceptibility to Plasmodium falciparum malaria infection has been the subject of many investigations (Kwiatkowski, 2005; Sirugo et al., 2008). However, most of these studies have implicated genes that affect parasite growth and survival in the blood stages and there is a dearth of information on host responses to the infection in the early pre-erythrocytic liver stage or during parasite immune clearance in the spleen. The human APOBEC family of (deoxy)cytidine deaminases play an important role in innate immunity. There has been an expansion of the APOBEC3 locus in humans with eight APOBEC3 forms (A–H) arranged in tandem and members of the human APOBEC3 family have been shown to inhibit replication of viruses as well as retrotransposition of endogenous elements (Bhattacharya et al., 2008; Bonvin and Greeve, 2008; Harris and Liddament, 2004; Stenglein and Harris, 2006). A common 29.5 kb human deletion polymorphism that removes the APOBEC3B gene has been identified and its distribution in the Human Genome Diversity Panel (HGDP) of world populations has been studied (Kidd et al., 2007). APOBEC3B has been shown to inhibit HBV replication in the hepatocytes and has been implicated as a potent innate antiviral factor (Zhang et al., 2008). In a recent report on expression profiling of mouse hepatocyte genes upon infection with the rodent parasite Plasmodium berghei a significant enhancement of
expression of a member of the APOBEC (apolipoprotein B editing complex 1) gene family was also observed in early stages of infection (Albuquerque et al., 2009). In addition, quantitative profiling of APOBEC3B has revealed significant expression in the spleen, the major site for immune clearance of erythrocytic parasites (Refsland et al., 2010).

Observations on the architecture, deletion frequency distribution and haplotype structure at the APOBEC3B locus in world populations have indicated significance of the polymorphism and revealed a weak signal of selection for the deletion (Kidd et al., 2007). The fixation of the APOBEC3B insertion allele in populations of the malaria-endemic regions of sub-Saharan Africa (Kidd et al., 2007) and the induction of APOBEC1 expression upon infection of liver cells in mice (Albuquerque et al., 2009) prompted us to investigate the possible association of the polymorphism with falciparum malaria. We thus investigated the distribution of the APOBEC3B deletion across diverse ethnic Indian populations represented in the Indian Genome Variation Consortium (IGVC) panel. The panel has previously been used to study SNP frequencies in immune response and adhesion/receptor molecules associated with susceptibility to diseases including malaria and HIV and has provided insights into the distribution of specific SNPs associated with disease susceptibility with respect to malaria endemicity (Indian Genome Variation Consortium, 2008; Sinha et al., 2008a,b). Case-control analysis with P. falciparum malaria patient samples drawn from a malaria endemic and a non-endemic region of India was also carried out. In addition, the distribution of the APOBEC3B deletion in HGD populations was analyzed in terms of the history of malaria incidence. Our analysis presents a case for malaria as a positive selection force for the APOBEC3B insertion and suggests a major role for APOBEC3B in innate immunity against malaria, possibly during the pre-erythrocytic liver stage of the infection and/or immune clearance in the spleen.

2. Methods

2.1. Populations and study subjects

The APOBEC3B insertion/deletion polymorphism study was carried out on 500 samples from 25 reference populations from the existing panel of Indian Genome Variation Consortium (IGVC). These populations encompass diverse ethnic and linguistic groups residing in different geographical regions and represent the genetic spectrum of India. The reference populations were a subset of 55 populations that had been used in Phase I analysis of the IGVC to establish genetic relatedness among the diverse populations of India (Indian Genome Variation Consortium, 2008). The populations are coded on the basis of linguistic affiliation (Indo-European; IE; Dravidian, DR; Tibeto-Burman, TB; Austro-Asiatic, AA) followed by geographical zone (North, N; South, S; East, E; West, W; Central, C; North–East NE) and ethnicity (caste LP; tribe IP; religious group, SP). Population descriptions are available in IGVC, 2008 (Indian Genome Variation Consortium, 2008). A population (OG-W-IP1) of known African descent was included as an out-group.

The APOBEC3B insertion/deletion polymorphism was analyzed in a case-control format with patients and controls drawn from falciparum malaria endemic and a non-endemic region of India. The endemic region (Antagarh, Chhattisgarh and Sundargarh, Orissa) samples primarily comprised of individuals from isolated populations of Austro-Asiatic origin while the non-endemic region (Lucknow and surrounding areas of Uttar Pradesh) samples were from populations of Indo-European lineage. Informed consent was obtained from each volunteer/guardian prior to collection. Sampling details were as described previously (Sinha et al., 2008a). Briefly, 2–5 ml of venous blood was drawn from patients of above 5 years of age diagnosed with P. falciparum malaria. Since the study aimed to include P. falciparum cases, initial screening by rapid diagnostic test (RDT) kits (Optimal/Paracheck) was done to pick up P. falciparum cases, followed by thin and thick blood smear examination for malarial parasites. In rare cases of discrepancy between the results of the two tests (positive for P. falciparum in RDT but failure to detect parasite in smear), P. falciparum infection was confirmed by a diagnostic polymerase chain reaction (PCR) specific for its 18S rRNA (Patsoula et al., 2003). Morphological forms of Plasmodium vivax are relatively easier to distinguish on smear examination than P. falciparum rings, and this was relied upon to detect P. vivax co-infections. Smear examination in our study did not suggest the possibility of mixed infection in the reported cases. The WHO guidelines (WHO, 2000) were followed to categorize severe and non-severe malaria as described in Sinha et al. (2008). Non-severe malaria patients were P. falciparum-positive, had fever and lacked symptoms that characterized severe malaria. Severe cerebral malaria was characterized by impaired consciousness (coma) with fever. Any one of the following symptoms together with a positive RDT readout and blood smear, and fever indicated severe (non-cerebral) malaria: severe anemia, acidic breathing, pulmonary edema, increased serum creatinine and increased bilirubin levels. Both cerebral malaria and severe non-cerebral malaria patients were considered under the common category of 'severe' malaria. A total of 176 P. falciparum malaria patients (91 from endemic and 85 from non-endemic region) were analyzed. Non-endemic region patients included in this study were enrolled in a referral hospital and had severe disease manifestations. Control samples were collected from ethnically-matched and unrelated individuals from the endemic (92 samples) and non-endemic (82 samples) regions. The study was approved by ethical committees of all participating institutes.

2.2. Genotyping

Genotyping of the insertion/deletion polymorphism was carried out using PCR primers described by Kidd et al. (2007). The deletion spans a 29.5 kb of segment between the fifth exon of APOBEC3A and eighth exon of APOBEC3B in chromosome 22. One pair of deletion and two pairs of insertion (insertion 1 and 2) primers were used to distinguish between the insertion and deletion alleles. The primer sequences are: Deletion_F (forward primer): TAGTGGCCACCCGGAT; Deletion_R (reverse primer): TTGACATATTTTGTGTA; Insertion1_F: TTGTGTGCTGGCC CT; Insertion1_R: TAGAGACTAGGCCCCCT; Insertion2_F: TGTGCCCTTTTACA GTTTGA; Insertion2_R: TGGACCAATTTAACTCTGAT. Deletion primers amplify a 700-bp PCR product which is specific to the deletion sequence. Insertion 1 and Insertion 2 primers are specific for the insertion and amplify 490 bp and 705 bp fragments, respectively. Insertion and deletion PCR reactions were performed separately then pooled together and visualized on a 2% agarose gel. HbAS determination was carried out by blood electrophoresis (Kohn, 1969) and confirmed by single base primer extension using SNAPsho™ (Applied Biosystems).

For evaluating population stratification, genotyping of 85 SNPs from 39 candidate genes in controls and P. falciparum patients was carried out using the Illumina genotyping platform (Illumina, SanDiego, USA). SNP genotypes were determined with the Golden Gate Assay following manufacturer’s protocol. Out of these 12 SNPs from these genes were excluded for further analysis as they were monomorphic.

In order to detect selection at the APOBEC3B locus, we genotyped 43 SNPs from a 1 Mb region encompassing the APOBEC3B locus. The SNPs had an average spacing of ~25 kb. Genotyping was performed using MALDI-TOF based chemistry on the Sequenom platform (SEQUENOM Inc., USA).
2.3. Genetic analysis

Chi-square test was performed to estimate whether populations were in Hardy–Weinberg equilibrium (HWE). $F_{ST}$ value was calculated according to the method of Nei and Chesser (1983). Odds ratio (OR) for risk assessment was estimated using EpiInfo™ version 3.4 software. We calculated an empirical $F_{ST}$ distribution of 4991 neutral SNPs spaced at 100 kb intervals from genotypes obtained in individuals from the same 25 Indian populations on the Affymetrix 50 K array. EIGENSTRAT (Price et al., 2006) was used for detection and correction of population stratification among cases and controls.

To detect possible selection at the locus we performed extended haplotype homozygosity (EHH) analysis. Haplotypes of 44 markers (43 SNPs + 1 indel) from a 1 MB region encompassing the APOBEC locus were inferred for each individual from its genotypes with fastPHASE version 1.3. The integrated haplotype scores (IHS) and XP-EHH scores (Sabeti et al., 2007) were calculated with code downloaded from the Pritchard labweb page (http://hgdp.uchicago.edu). Genotype data from the HGDP-CEPH Human Genome Diversity Panel (Cann et al., 2002; Li et al., 2008) were also included in EHH analyses.

3. Results

3.1. APOBEC3 deletion frequency differs vastly in Indian populations

The APOBEC3B insertion/deletion polymorphism demonstrated a wide spectrum of frequencies across Indian populations (Fig. 1) with the insertion allele being fixed in AA-E-IP3. Indo-European large populations from the western, eastern and northern parts of the country had the insertion allele as the major allele. In contrast, Tibeto-Burman populations residing in the North and North–East and Indo-European isolated populations of North-East and Eastern regions had the deletion allele as the major allele. Dravidian populations demonstrated considerable heterogeneity in the distribution of the deletion. OG-W-IP which is an out-group population of African ancestry also had near fixation of the insertion allele. The polymorphism was in HWE in all populations. The global $F_{ST}$ value for this locus was observed to be 0.052. Testing against a neutral set of markers this $F_{ST}$ value was in the upper 15% quartile indicative of differentiation with respect to this locus (Supplementary Table 1). However, the extent of differentiation was much lower than the HGDP panel ($F_{ST}$, 0.28).

The populations IE-E-LP4, AA-E-IP3, DR-C-IP2 and DR-S-LP2 that have low frequency of the deletion allele inhabit a region of the country where the incidence of falciparum malaria is high (Fig. 2). A comparison of the distribution of the frequency of the insertion allele with the prevalence map of $P. falciparum$ malaria in India (Hay et al., 2009) indicated a clear overlap suggestive of a correlation between the APOBEC3B polymorphism and malaria. The association between susceptibility to falciparum malaria and the APOBEC3B deletion was thus investigated.

3.2. The APOBEC3B insertion allele is strongly associated with protection from malaria

To study whether there was a relationship between the APOBEC3B insertion/deletion polymorphism and susceptibility to malaria, we genotyped cases and control samples from a $P. falciparum$ endemic and a nonendemic region of India. Malaria patients, clinically characterized as severe or non-severe, were compared with ethnically matched control samples for presence of the polymorphism. Patients diagnosed with cerebral malaria (CM) and those with symptoms of non-cerebral severe malaria (NCM) were both included under the ‘severe’ category. A significant difference in the frequency of the deletion allele was observed between cases and controls (0.11 and 0.365, respectively) in the malaria endemic region (Table 1). Strong association of the deletion allele with susceptibility to falciparum malaria was also seen in the endemic region (non-severe vs. control, OR = 4.96, $P$ value = 9.5E-06; severe vs. control, OR = 4.36, $P$ value = 5.76E-05). The higher frequency of the deletion allele was due to significant over-representation of the hemizygous genotype (ID, where I and D are the insertion and deletion allele) in both severe as well as non severe cases compared to controls ($P = 1.4 \times 10^{-5}$ and $P = 0.00$, respectively). Patients from the non-endemic region that were included in this study had severe malaria. There was no significant difference in deletion allele frequency between these severe malaria patients and controls in the non-endemic region. Separate analysis of cerebral and non-cerebral severe malaria patients also revealed strong association of the deletion allele with both categories in the endemic region (CM vs. control, OR = 3.47, $P$ value = 9.01E-04; NCM vs. control, OR = 4.96, $P$ value = 9.5E-06; CM vs. NCM, OR = 0.7, $P$ value = 0.23). No disease association was observed with the deletion allele when cerebral and non-cerebral severe patients of the non-endemic region were analyzed separately.

Comparison of genotype distribution between patient and control categories revealed significant over-representation of the
homzygous deletion genotype in cases when compared to controls in the non-endemic region [severe vs. control, DD and II, OR = 2.54, \( P = 0.064 \); DD and ID, \( P = 0.0012 \); DD and (II + ID), \( P = 0.0177 \)] (Table 2). In the endemic region, however, none of the controls was homozygous for the deletion. A strong association was observed between presence of the hemizygote (ID) and susceptibility to malaria in the endemic region with similar odds ratio values obtained for patients with severe or non-severe disease manifestation (ID and II, non-severe vs. control, OR = 1.24 [95% CI = 0.62–2.48], \( P = 0.51 \)).

Table 1

<table>
<thead>
<tr>
<th>Malaria cohort</th>
<th>Subjects</th>
<th>II</th>
<th>ID</th>
<th>DD</th>
<th>Total</th>
<th>Minor allele (D) frequency</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endemic</td>
<td>Controls Non-severe</td>
<td>73</td>
<td>19</td>
<td>0</td>
<td>92</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>21</td>
<td>42</td>
<td>5</td>
<td>68</td>
<td>0.38</td>
</tr>
<tr>
<td>Non-endemic</td>
<td>Controls</td>
<td>51</td>
<td>25</td>
<td>6</td>
<td>82</td>
<td>0.23</td>
</tr>
<tr>
<td></td>
<td>Severe</td>
<td>57</td>
<td>11</td>
<td>17</td>
<td>85</td>
<td>0.26</td>
</tr>
</tbody>
</table>

Table 2

<table>
<thead>
<tr>
<th>Malaria cohort</th>
<th>Comparisons (Fisher’s test)</th>
<th>Genotypes</th>
<th>Odds ratio (95% CI)</th>
<th>( P ) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Endemic</td>
<td>Non-severe vs. control ID &amp; II</td>
<td>7.68</td>
<td>(3.50–17.0)</td>
<td>( 1 \times 10^{-7} )</td>
</tr>
<tr>
<td></td>
<td>Severe vs. control ID &amp; II</td>
<td>8.78</td>
<td>(2.86–28.46)</td>
<td>( 5.6 \times 10^{-3} )</td>
</tr>
<tr>
<td></td>
<td>Severe vs. non-severe ID &amp; II</td>
<td>1.14</td>
<td>(0.37–3.81)</td>
<td>0.8</td>
</tr>
<tr>
<td>Non-endemic</td>
<td>Severe vs. control ID &amp; II</td>
<td>0.39</td>
<td>(0.16–0.93)</td>
<td>0.0211</td>
</tr>
<tr>
<td></td>
<td>Severe vs. control DD &amp; II</td>
<td>2.54</td>
<td>(0.86–8.42)</td>
<td>0.0064</td>
</tr>
<tr>
<td></td>
<td>Severe vs. control DD &amp; ID</td>
<td>6.44</td>
<td>(1.76–24.99)</td>
<td>0.0012</td>
</tr>
<tr>
<td></td>
<td>Severe vs. control DD &amp; (II + ID)</td>
<td>3.17</td>
<td>(1.10–10.32)</td>
<td>0.0177</td>
</tr>
</tbody>
</table>

Odds ratio (OR) for allele frequency: *Endemic, non-severe vs. control, OR = 4.96 [95% CI = 2.25–11.53], \( P = 9.5 \times 10^{-3} \); *Endemic, severe vs. control, OR = 4.36 [95% CI = 1.97–10.18], \( P = 5.76 \times 10^{-3} \). Non-Endemic, severe vs. control, OR = 1.24 [95% CI = 0.62–2.48], \( P = 0.51 \).

Fig. 2. (A) Spatial distribution of APOBEC3B deletion in Indian population. (B) P. falciparum malaria endemicity across India [map adapted from P. falciparum malaria endemicity map of the Malaria Atlas Project (MAP; www.map.ox.ac.uk); Hay et al., 2009].
3.3. APOBEC3B insertion/deletion polymorphism in world populations and malaria

In light of the strong association of the deletion allele with susceptibility to malaria, a possible role for malaria in selection at the locus was hypothesized. An overlay of the global malaria transmission risk map (WHO and UNICEF, 2005) and the APOBEC3B deletion frequency map of HGDP populations, (Kidd et al., 2007) revealed a striking correlation between disease occurrence and higher frequency of the protective insertion allele (Supplementary Fig. 2). African populations from the malarious regions of central and sub-Saharan Africa, where malaria incidence is estimated to have been high from about 4000 to 5000 years ago, were largely fixed for the insertion allele with low levels of the deletion seen in populations of North Africa. In fact, the APOBEC3B deletion allele frequencies observed for world populations seem to follow the timeline for malaria following its spread across Egypt (~4000–3500 years ago) to India (~3000 years ago) on the one hand and to the Mediterranean (2500–2000 years ago) and Northern Europe (1000–500 years ago) on the other (Sallares et al., 2004). Although malaria was largely controlled in the Mediterranean region by the late 1940s, (Gallup and Sachs, 2001; Missiroli, 1948) Italy has had a largely controlled in the Mediterranean region by the late 1940s, (Gallup and Sachs, 2001; Missiroli, 1948) Italy has had a history of falciparum malaria from ancient times (Hackett, 1937; Romi et al., 2001) possibly explaining the very low frequency/absence of the deletion in the three Italian populations of HGDP, particularly Sardinian and Tuscan. However, the high frequency of the deletion in the Melanesian (Bougainville) population and near fixation of the deletion in the non-highlander population from Papua New Guinea cannot be explained directly by the ‘selection by malaria’ hypothesis. One possible explanation can be that these Pacific Islander populations were historically subjected to extreme random genetic drift. Alternatively, epistatic effects of another locus could override the effect of the APOBEC3B insertion allele in these populations (Williams et al., 2005). Both these regions have a long history of malaria endemicity with very high incidence of P. falciparum and P. vivax malaria (Kaslow et al., 2008; Muller et al., 2003). Malaria (P. vivax) was probably introduced to The New World (South America) only at the end of the 15th century AD and P. falciparum probably reached Central America through the African slaves brought by the Spanish colonizers (Patrick Schlagenhauw-Lawlor, 2001). Malaria spread to North America in the 18th century. This relatively recent exposure of the Americas to the malaria parasite is reflected in the higher frequency of the APOBEC3B deletion in HGDP populations from Brazil, Colombia and Mexico. Since presence of APOBEC3B may also result in hypermutations a deletion of this gene might have beneficial effects in the absence of infection as proposed by Kidd et al. (2007). Therefore, the overall global distribution of the APOBEC3B insertion/deletion polymorphism may reflect a balance between the advantages of the insertion allele, for instance in viral infections or malaria, or the deletion which could lower the risk of hyper-mutation.

In order to determine whether the APOBEC3B locus was under selection we carried out XP-EHH and IHS analysis in these populations. Strong signals of positive selection based on the current data were not observed. The extent of Linkage disequilibrium (LD) in this gene region was weak across majority of the populations of IGV and HGDP-CEPH panels indicating the presence of recombination hotspots which could lead to a breakdown of LD on the core haplotype and a low EHH (Supplementary Fig. 3). The power of EHH-based methods could be compromised in case of LD decays quickly and haplotype homozygosity could not extend to long range in case natural selection occurred in genes with recombination hotspots (Supplementary Fig. 4).

4. Discussion

The APOBEC3B deletion, which results in the loss of at least one copy of the unique coding portion of APOBEC3B, ranges in frequency from 0% to 43% in Indian populations with low deletion frequency observed in populations inhabiting malaria endemic regions of India. The deletion allele was strongly associated with susceptibility to falciparum malaria in an endemic region and the homozygous deletion genotype was over-represented in cases when compared to controls in a non-endemic region. Strong association of the deletion allele with manifestation of falciparum malaria indicates a possible role for APOBEC3B in innate immunity against malaria. The distribution of the deletion in HGDP populations reported by Kidd et al. (2007) suggests selection of the protective insertion allele in regions with high malaria incidence.

Kidd et al. (2007) reported clinal increase in deletion frequency in HGDP populations as one moves eastward from Africa, following the route of human migration. However, pairwise FST estimates in their study differentiated Amerindian, Oceanic and some East Asian populations from other populations based on the frequency of the deletion in comparison to other ins/del polymorphisms and SNPs. This indicated that the pattern of distribution of the APOBEC3B deletion is not the result of demographic history alone (Kidd et al., 2007). Our results on Indian populations and the association study suggest a role for malaria as a selection force for the protective insertion allele. However, these results would need to be corroborated in a larger clinical study in different geographical settings before the functional role of APOBEC3B in malaria can be established. As we did not observe high linkage disequilibrium in the vicinity of APOBEC3 locus, the involvement of a closely linked locus that may confer differences in malaria susceptibility seems unlikely.

APOBEC3B is among the innate immune response genes that are induced during the acute stage of HIV infection but returns to baseline levels in the asymptomatic stage (Li et al., 2009). The protein also inhibits infectivity of wild-type HIV-1 (Doehle et al., 2005) and recently an association of the APOBEC3B ins/del polymorphism with risk of HIV acquisition has been reported (An et al., 2009). The interaction between HIV and malaria that may fuel the spread of both infections, particularly in Sub Saharan Africa and parts of Asia, is a public health concern. It has been speculated that HIV immune suppression increases the risk of malaria infection and malaria infection provokes a transient increase in the viral load in HIV infected individuals (Abudu et al., 2006; bu-Raddad et al., 2006; Kublin et al., 2005). Both malaria and HIV pathogenesis is influenced by a range of factors including host genetics, parasite strain, parasite exposure and treatment. Cell based immune responses to HIV and malaria provides an explanation for the observed interaction between the virus and the protozoan (Renia and Potter, 2006). If basal or induced levels of APOBEC3B in the human host differ between the insertion homozygote and the hemizygote carrying a deletion allele, host innate immunity to both HIV and malaria may be influenced and both the infections may play a role in selection of the protective insertion allele in affected populations.

APOBEC3 proteins in humans are a family of cytidine deaminases that mediate C→U or dC→dU conversion in mRNA or DNA, respectively (Cullen, 2006). These proteins cause hypermutations in hepatitis B virus DNA and APOBEC3B, 3F and 3G, which are expressed in the liver and up-regulated by IFN-γ in hepatocytes have been shown to contribute to the non-cytolytic clearance of HBV (Bonvin et al., 2006). APOBEC3A is expressed predominantly in the nucleus but is seen in the cytoplasm in association with viral particles in HBV-infected cells (Bonvin et al., 2006). There has been an expansion of the APOBEC3 gene family in humans such that eight APOBEC3 genes (A–H) are tandemly arranged on human
chr22q13.1 (Bhattacharya et al., 2008; Harris and Liddament, 2004). Quantitative estimates of APOBEC3B levels in human tissues have revealed significantly higher expression in the lungs and spleen (Refslund et al., 2010).

A recent study on expression profiling of the rodent parasite P. berghei-infected and non-infected hepatoma cells had shown significant induction of the related APOBEC1 gene in the first 6–12 h after infection (Albuquerque et al., 2009). The mouse genome encodes only one APOBEC3 gene on chr15 as compared to the expanded APOBEC3 locus on chr22 in humans. It is tempting to hypothesize that the role of APOBEC3 genes as innate immune response genes in the liver may influence the growth of the malaria parasite in the pre-erythrocytic stages and impact upon subsequent parasite release and invasion of erythrocytes. Further, the higher expression of APOBEC3B in the human spleen is suggestive of a possible role of this protein in immune clearance of the parasites. Although the mechanism for the protective role of APOBEC3B remains to be elucidated, a direct action on parasite replication or growth may require its import into the parasite through the uptake mechanisms used by Plasmodium in infected liver cells (Bano et al., 2007).

The results reported here are for P. falciparum alone and the effect of the APOBEC3 deletion on P. vivax cases, and P. falciparum and P. vivax co-infections remains to be investigated. While our study indicates a strong association of the APOBEC3 deletion with susceptibility to falciparum malaria, the functional effects of the polymorphism on basal and induced levels of APOBEC3B, Plasmodium replication and growth in the liver and erythrocytic stages as well as HIV-1 and HBV replication remain to be ascertained.

Acknowledgments

We are grateful to all donors and their families. We thank Dr. Prajesh Tyagi and Dr. G.N. Jha for help with sample collection. The project was supported by funding from the Council of Scientific and Industrial Research (CMM-0016 to MM and SH, and SIP006 to MM) and from the Department of Biotechnology to SH and VV (BT/PR6065/MED/14/738/2005). Senior Research Fellowship to PJ from MM) and from the Department of Biotechnology to SH and VV (BT/PR6065/MED/14/738/2005). Senior Research Fellowship to PJ from the Council of Scientific

References


A recent study on expression profiling of the rodent parasite P. berghei-infected and non-infected hepatoma cells had shown significant induction of the related APOBEC1 gene in the first 6–12 h after infection (Albuquerque et al., 2009). The mouse genome encodes only one APOBEC3 gene on chr15 as compared to the expanded APOBEC3 locus on chr22 in humans. It is tempting to hypothesize that the role of APOBEC3 genes as innate immune response genes in the liver may influence the growth of the malaria parasite in the pre-erythrocytic stages and impact upon subsequent parasite release and invasion of erythrocytes. Further, the higher expression of APOBEC3B in the human spleen is suggestive of a possible role of this protein in immune clearance of the parasites. Although the mechanism for the protective role of APOBEC3B remains to be elucidated, a direct action on parasite replication or growth may require its import into the parasite through the uptake mechanisms used by Plasmodium in infected liver cells (Bano et al., 2007).

The results reported here are for P. falciparum alone and the effect of the APOBEC3 deletion on P. vivax cases, and P. falciparum and P. vivax co-infections remains to be investigated. While our study indicates a strong association of the APOBEC3 deletion with susceptibility to falciparum malaria, the functional effects of the polymorphism on basal and induced levels of APOBEC3B, Plasmodium replication and growth in the liver and erythrocytic stages as well as HIV-1 and HBV replication remain to be ascertained.

Acknowledgments

We are grateful to all donors and their families. We thank Dr. Prajesh Tyagi and Dr. G.N. Jha for help with sample collection. The project was supported by funding from the Council of Scientific and Industrial Research (CMM-0016 to MM and SH, and SIP006 to MM) and from the Department of Biotechnology to SH and VV (BT/PR6065/MED/14/738/2005). Senior Research Fellowship to PJ from CSIR is duly acknowledged. This is CDRI communication number 7857.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.meegid.2011.11.001.

