Human host genetic factors and cytokine responses associated with the pathogenesis of plasmodium falciparum malarial disease

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Abstract:

Host and parasite genetic factors, among may other contributory factors of immunologic and pathologic basis, have been thought to play a central role in determining the outcome if severe Plasmodium Falciparum malarial disease. There is recent evidence to show that immunological mechanisms of the human host too would combine with its genetic factors in regulating the severe malaria pathogenesis. Thus the importance of immunopathological investigations conducted in the context of human genetics has been highlighted in the field of malariology. Based on this background, in the present study, a selected set of human genetic factors and cytokine secretory responses of the human host was investigated with respect to the severe malarial disease in a same set of patients, in an integrated manner. Specifically, in the present study, investigations were conducted on human TNFa and ßpolymorphisms and their associations with several aspects and conditions of P. Falciparum malaria; nature of the disease status/outcome of severe disease, TNFa IL-10, IFN-? And IL-6 secretory responses and heir cross regulations, fever response of malaria patients operate as heredity factors and asymptomatic nature of the disease, TNF polymorphisms were also studied in yet another set of patients (named as severe non-malarious) who were recognized as having malaria-like symptoms but infected with infectious agents other than malaria. Thus the current study was planned to study the human genetics with their relationships with immunologic mechanisms and also their relationships with malarious and non-malarious disease. The results of these studies indicated that the frequency of TNFa*2 allele was significantly higher in both categories of severe/complicated (SC) and severe non-malarious (SN) groups compared to the uncomplicated (UC) and healthy control (HC) groups tested. Further, the genotype frequency of TNFa*1, *2 and TNFa*2,*2 were found to be significantly higher in the SC and SN groups than HC. The frequencies of TNFa*1, *2 in SC and TNFa*2, *2 genotypes in SN were also significantly higher when compared to the UC category. The presence of TNFa*1, *2 genotype increases the risk up to 6-15 fold and TNFa*1,*2 genotype increases the risk up to 2-3 fold in severe disease compared to HC. Such associations of either allele of genotype frequency on TNFß genes were

not found among the tested similar categories of individuals. However, the results further showed that when TNFß*1*2 genotype in combination with either TNFa*1,*2 and TNFa*2,*2 genotype, increases the risk of having severe disease up to 11-14 fold as found in the SC and SN categories of patients compared to HC. These results may point to the fact that the single allele/genotype or the combinations of certain alleles/genotypes of TNFa and ßgenes (which are tandemly arranged in the human MHC complex genes) may up-regulate the mechanisms which determine the status of malarial disease outcome to varying degrees. The results also showed that TNFa allele and its associated alleles/genotypes may also regulate the disease outcome of infectious diseases (as found in the SN group) other than malaria indicating common genetic/immunopathalogical severe disease mechanisms triggered in the human host regardless of the differences among infectious agents. The investigations on TNFa /ß polymorphisms and cytokine secretory responses of the patients indicated that only the plasma cytokine level of TNFa and IL-6 compared to IL-10 and IFN-? of SC patients (compared to UC) were with a significantly higher elevation in the presence of TNFa*2 and TNFß*2 alleles, when tested separately. Moreover, in the CM (cerebral malaria) and MODS (multiple organ dysfunction syndrome) categories of patients (when analysed separately), only elevation of TNFa was observed in the presence of TNFa*2 and TNFß*2 allele. In addition, an increase of IL-10 in the MODS and IL-6 levels in the CM groups were observed in the presence of TNFß*2 allele. A genotype analysis also demonstrated that humans with TNFa*1,*2 and ß*1,*2 genotype combination was susceptible to have the severe malarial disease outcome associated with the increased secretion of TNFa cytokine and TNFa*1,*1 and ß*2,*2 genotype combination in human led to the severe disease through increased secretion of IL-6. These results indicate a complex cross-regulatory pattern of mechanisms operating based on TNF a/ß polymorphism and cytokine responses to determine the status of malarial disease. Yet another observation for this cytokine cross-regulation was that the general presence of TNFa*2 in individuals comprising all of UC, SC categories, TNFa cytokine levels were positively correlated with IL-10 whereas it was negatively correlated with IFN-?. In the presence of TNFß*2 allele as well, TNFa levels were positively correlated with IL-10 in all of tested patients. The investigations on TNFa/ß polymorphisms and cytokine secretory responses and non-clinical parameters indicated an increased secretion of TNF-? in the endemic patients than non-endemic patients. Specifically, in the endemic patients, a positive correlation between IL-10 and TNFa levels with the presence of TNFa*2 was noted. This simultaneous presence TNFa IL-10 may be regulating exposure related immunity shown by the endemic patients. These results demonstrated that the exposure related immunity (which is different in non-endemic and endemic patients) also has associations with cytokine cross-regulatory mechanisms and TNFa/ß genetic polymorphisms. These results suggests that, the presence of TNFa*2 allele in both its heterozygous and homozygous status in humans would be responsible for generating predominantly severe malaria and severe non-malarious conditions to a certain extent. Further, the combinations of particular TNFa and ß alleles would be associated with cytokine cross-regulatory mechanisms and non-clinical parameters associated with exposure related host immunity determining the status of malarial disease outcome. TNF allele polymorphisms were also investigated in a Sri Lankan population where it was previously shown that there are heritable components associated with fever responses of the malaria patients. Considering our own findings on the presence of TNFa*2 allele and TNFa secretion and their associations with

the malarial disease, the current study attempted to see whether these heritable factors are actually related with TNF genes/alleles. The results demonstrated in this study that the presence of TNFa*1, *2 genotype is significantly associated with the high fever response in tested patients. Futher, there was a more significantly higher proportion of carriers of the combination of the TNFa*1, *2 allele and TNFß*2 allele in the high fever response group of patients. These results are suggestive of the involvement of TNFa and ß genes with the heredity components influencing the presentation of fever responses in malaria patients.However no any signigicant association was found between the TNFa/ß genes and their polymorphisms and asymptomatic nature of the malaria patients. Thus, the current study generated information to view the associations between certain TNFa and ß genes/alleles and malarial disease outcome, related cytokine secretion and relevant cytokine cross regulations to determine the disease outcome and heritable components operating as fever generating factors in
malaria patients in Sri Lanka.

Key Words : Malaria, falciparum / Malaria-genetics