Cytokine Levels and T cell Apoptosis Associated With Cerebral Malaria Immunopathology During Plasmodium berghei Anka Infection In A Mouse Model

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Abstract:

During the course of malaria infection, a range of pro- and anti-inflammatory cytokines are produced by the host immune system. Successful recovery from malaria involves striking a balance between these counteracting cytokines. The cytokine imbalance contributes to pathological features but their exact levels have not been elucidated. The present study aimed at investigating the role played by circulating cytokines in pathophysiology of cerebral malaria. Using an experimental cerebral malaria (ECM) model, the profile of five serum cytokines was determined by employing Cytometric Bead Assay. Seventy-two BALB/c mice (7-9 week/old) were intraperitoneally inoculated with approximately 1 x 105 parasitisized red blood cells at day 0 and randomized into six groups (six mice/group). Another set of noninfected mice was included to serve as control. The mice were sacrificed at day 4, 6, 8, 11 and 20 pi. The possible role of cytokines in inducing T-cell apoptosis associated with CM was investigated using the whole genomic DNA extracted from splenic and brain lymphocytes. Significantly higher systemic levels ($P<0.05$,) of IFN-γ (mean ±S.D 210.6±133, 169.8±80.5, 203.6±91.6, 22.0±3.5 pg/ml), were observed between day 8 and 20 p.i while TNF-α levels were significant at days 4, 8 11, 14 and 20 respectively (M ±S.D 2.9 ± 0.2, 33.9±17.5, 95.5 ±17.0, 22.1±3.6 pg/ml) in BALB/c mice that survived until day 20 pi with a higher parasitemia (up to 52.6%±0.8). Significant concentrations ($P< 0.05$), of IL-4 (M ±S.D 14.6±2.5, 10.6±1.9, 9.6±1.3 pg/ml) were observed between day 4 and 8 respectively but afterwards its levels remained low throughout the course of infection. IL-5 levels (M xix ±S.D 4.1±0.7, 3.4±1.6) had significant differences at day 11 and 20 pi. The study found IL-4 to be elevated between days 11 and 20 respectively with no significant differences ($P>0.05$) being reported. T-cell pathology was revealed by fragmentation of whole genomic DNA during the infection which coincided with elevated systemic pro-inflammatory (IFN-γ and TNF-α at day six) responses which further accelerated the severity of CM. The study demonstrated a parallel link between T-cell pathology and elevated levels of Th1 cytokines concentrations in the brain and the spleen. This study revealed that elevated levels of proinflammatory cytokines induce inflammation and cellular apoptosis inhibiting parasite clearance. Thus, interventions to regulate the Th1 cytokine responses may be beneficial in the prevention of severe CM. Further work is needed on IL-2 IL-10 and IL-12 cytokines that could be involved in the pathology