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EVOLUTION OF SOLUBLE HLA-G LEVELS DURING PREGNANCY AND INFANCY IN A BENINESE POPULATION EXPOSED TO MALARIA INFECTION

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Human Leucocyte Antigen-G is a non-classical HLA class I molecule firstly described on the surface of extravillous cytotrophoblast cells at foeto-maternal interface. HLA-G binds its inhibitory receptors present on the surface of immune cells (monocytes, NK, T,B and dendritic cells) modulating host's immune response.These immunosuppressive properties of HLA-G are crucial and benefic during pregnancy where HLA-G plays a crucial role in maternal-fetal tolerance. There are known associations between high levels of circulating soluble HLA-G (sHLA-G) and either parasite or viral infections (HIV,cytomegalovirus)and it has been suggested that the induction of sHLA-G expression could be a mechanism via which infectious agents subvert host immune defence. To explore more precisely interactions between soluble HLA-G and malaria,latent class analysis was used to test whether distinct sub-populations of children, each with distinctive soluble HLA-G evolutions may suggest the existence of groups presenting variable malaria susceptibility. This study was conducted in Benin from 2010 to 2013 and 165 children were followed from birth to12 months and soluble HLA-G was quantified by Elisa method.Three groups of children were identified: one with consistently low levels of soluble HLA-G during follow-up, a second with very high levels and a last intermediate group. In all groups, low birth weight, malaria infection and high exposure to malaria transmission were associated with high level of soluble HLA-G.Placental malaria was not. Presence of soluble HLA-G in cord blood increased the probability of belonging to the highest trajectory. These results, together with previous ones,confirm the importante role of HLA-G in the individual susceptibility to malaria. Assaying soluble HLA-G at birth could be a good indicator of newborns more fragile and at risk of infections during childhood.

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MEMORY T CELLS METABOLISM DURING CHRONIC MALARIA INFECTION

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Malaria infection kills up to 0.85 million people each year. The first generation of vaccine does not generate long-lived protection. We have shown, in *Plasmodium chabaudi* infection that CD4 effector memory T cells generated protect from parasitemia and pathology. However, the mechanisms underlying development and maintenance of this long-lived protective memory T cells (Tmem) are not well understood. Recent findings have highlighted the importance of cellular metabolism in Tmem generation. Specifically, fatty acid oxidation (FAO) has been associated with CD8 Tmem development in acute infection. Substrates for FAO in CD8 Tmem are generated through the fatty acid synthesis (FAS) pathway. However, it's not clear whether FAS pathway controls Tmem differentiation or survival. Using transcriptomic analysis, we found upregulation of FAS genes in Tmem compared to effector (Teff) in malaria-specific CD4 T cells. Interestingly, blockade of FAS pathway *in vivo* using TOFA (*Acc1-specific*), impairs Tmem development. To determine when FAS is required for Tmem differentiation, *P. chabaudi-* infected mice were treated with TOFA at the priming or contraction phase of the immune response. Preventing fatty acid synthesis during priming inhibits memory formation and reduces parasitemia. Using stable isotope tracer, memory T cells show high phospholipids synthesis. Together these data suggest that an early shift to FAS is important for CD4 Tmem differentiation and may prove crucial to development of malaria vaccine.

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IL-15 COMPLEX-STIMULATED NK CELLS PROTECT MICE FROM CEREBRAL MALARIA

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To date, no effective adjunctive therapies exist for severe malaria. *Plasmodium falciparum* is the main cause of severe malaria in humans and accounts for about 600,000 deaths per year, mainly in children in sub-Saharan Africa. Cerebral malaria (CM) is one of the most lethal complications of severe malaria. Infection of susceptible mouse strains such as C57BL/6 with *Plasmodium berghei* ANKA (PbA) induces a fatal neurological syndrome from 6-10 days post-infection (dpi). We found that prophylactic or therapeutic treatment of C57BL/6 mice with interleukin (IL)-15 complexes (IL-15C; IL-15 bound to an IL-15Rα-Fc fusion protein) prevented the development of PbA-induced CM. IL-15C treatment stimulates Natural Killer (NK) and CD8 T cells. Interestingly, adoptive transfer of IL-15C-stimulated NK cells, not CD8 T cells, prevented CM. Similar complexes formed with IL-2 (IL-2C; IL-2 bound to the anti-IL-2 S4B6 antibody) also causes robust expansion and activation of NK cells, but NK cells from mice treated with IL-2C failed to protect against CM. Comparative RNAseq analysis of IL-15C and IL-2C-treated NK cells identified novel gene expression patterns, demonstrating previously unappreciated differences between these cytokine complex signaling cascades in NK cells. Interestingly, IL-15C treatment resulted in reduced CD8 T cell activation in the brain at 6 dpi and reduced blood brain barrier breakdown, suggesting that IL-15C-stimulated NK cells limit the CD8 T cell-mediated pathology in CM. Indeed, a large subset of NK cells in the spleen, blood, and brain of IL-15C-treated, but not IL-2C-treated, mice produced the immunoregulatory cytokine IL-10 on day 3 pi. These data indicate that NK cells - which are typically involved in promoting inflammatory responses - can restrain damaging immune responses. A mechanistic understanding of CM pathogenesis and the process of cytokine complex perturbation will provide an important foundation for the identification of new therapeutic targets and aid in the development of adjunctive therapies for treating severe malaria.

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THE ROLE OF INFLAMMATION AND MICROVASCULAR DAMAGE/REPAIR IN THE PATHOGENESIS OF CEREBRAL MALARIA

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Cerebral Malaria (CM), a severe form of malaria, caused by *Plasmodium falciparum* remains a major cause of morbidity and mortality. Currently, there is no available test to predict potential CM patients, as well as mortality or recovery from the syndrome. The disease results from a combination of vascular and inflammatory immune system dysfunction. Triggering receptor expressed on myeloid cells 1 (TREM-1) has been shown to potentiate inflammatory response. A recent preliminary study has