Wild derived mice as a model for asymptomatic malaria


SIGNIFICANCE: Individuals with asymptomatic malaria are a potential reservoir of Plasmodium transmission and pose a significant threat to the control of malaria worldwide. Although commonly associated with older individuals, asymptomatic malaria can occur at all ages. Asymptomatic malaria in children who have not yet developed robust adaptive responses might be determined by differences in the immune response controlled by genetic variation of the host. There is currently no mouse model for asymptomatic malaria. We hypothesize that the wild derived mice show a diversity in disease outcome due to genetic diversity when infected with Plasmodium yoelii. They could therefore potentially be a useful mouse model for asymptomatic malaria.

OUR MODEL:

Wild derived Mus musculus domesticus

Asymptomatic Mice infected with Plasmodium yoelii XNL

Wild derived Mus musculus domesticus
• Mice captured ~20 years ago and kept as an outbred isolated population
• Have low inbreeding coefficients (low relatedness)
• Show natural mouse behavior
• Housed in SPF conditions like C57BL/6

RESULTS:

1. Wild derived mice show a greater diversity in anemia levels than B6 mice at day 19 post infection when infected with P. yoelii XNL

2. IL-10 and TNFα in the blood correlate with anemia in wild derived mice at day 19

IL-10 and TNFαs is also known to correlate with anemia in humans
• High levels of IL-10 in plasma have been associated with increased risk of developing clinical malaria in children (Kumar et al. 2019; Jagamath et al. 2013).
• TNF is associated with the development of malarial anemia via diserythropoiesis and erythropagocytosis in humans (Bouef et al. 2012).
• High levels of circulating IL-10 and TNFα have been seen in patients with severe malaria and correlated with parasitemia (Luty et al. 2000).

3. What are potential sources of IL-10 and TNFα in asymptomatic wild derived mice?

There is a negative correlation between splenic monocyte populations and the level of anemia experienced as observed in children in Eastern Uganda (Fontana et al. 2016)

TNFα is known to enhance IL-10 production in monocytes (Dautarian, et al. 1996).
• CD4 T cells may be an alternate important source of IL-10 production in asymptomatic wild derived mice.
• CD4 T cells are also major producers of IL-10 in uncomplicated malaria in humans (Peix et al. 2015).

The source of these cytokine remains to be determined

4. TNF and IL-10 correlate with hemoglobin in asymptomatic P. falciparum infections in Cameroon

Our data from the wild derived mice show similar patterns to those observed in asymptomatic humans in the Esse area of Cameroon

FUTURE DIRECTIONS:
• By depleting mice of certain cytokines and cell types we can investigate their importance in regulating malaria pathogenesis.
• Using collaborative cross mice we can start to dissect which genetic components are important to promote an asymptomatic phenotype.