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INNATE IMMUNITY TO MALARIA

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Driven by the need to develop a safe and effective malaria vaccine, research on the immunology of malaria infection has tended to focus on adaptive immunity. However, given the potential of malaria infections to kill within hours or a few days of the first appearance of parasites in the blood, there is considerable potential for innate immune mechanisms to provide immediate protection against disease and death. Using in vitro co-cultures of *P. falciparum*-infected red blood cells (iRBC) with human peripheral blood mononuclear cells, we have shown that $CD3^{-}CD56^{+}$ NK cells are major contributors to the first wave of IFN-g production, suggesting that they may be an important component of the innate defence against malarial parasitemia. Induction of IFN-γ synthesis by NK cells is dependent on (i) direct contact between the NK cell and the iRBC and (ii) a source of IL-12/IL-18. Surprisingly, this innate response is not universal among human blood donors. The donor popu-lation is extremely heterogeneous with respect to their killer immunoglobulin-like receptor (KIR) genotype and there is evidence for associations between NK receptor genotype and responsiveness to iRBC. Heterogeneity between individuals in their NK response to iRBC raises interesting questions about the functional importance of innate immune responses to malaria. Two opposing hypotheses can be proposed; rapid IFN-g production may be associated with efficient induction of IFN-g-mediated effector mechanisms and enhanced ability to control malaria infections. Alternatively, rapid innate production of IFN-g may predispose to over-production of inflammatory cytokines and increased risk of severe malaria.