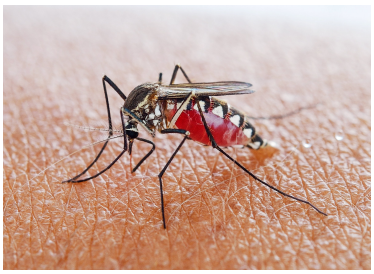
Blood-Stage Malaria Infection Suppresses Liver-Stage Development Through Interferon-Mediated Host Responses

*by Medical Writer **Alejandra Viviescas**, PhD*



Researchers at the Center for Global Infectious Disease Research, Seattle Children's Research Institute, have discovered that malaria parasites in the bloodstream suppress the development of parasites from subsequent infections. The suppression is mediated by host interferons activated by the bloodstream infection. These findings have implications for the development of live-attenuated *Plasmodium* parasite vaccines, particularly in malaria-endemic areas where concomitant infections are common.

The open-access **article**, titled "Malaria Blood Stage Infection Suppresses Liver Stage Infection Via Host-Induced Interferons But Not Hepcidin," was published in *Nature Communications* on March 7, 2024.

Malaria is a mosquito-borne disease caused by parasites of the *Plasmodium* genus. These parasites undergo two developmental stages within the human body. They initially infect and multiply inside liver cells (liver-stage). Once this development is complete, they migrate to the bloodstream, where they trigger the symptomatic phase of the disease (blood-stage).

Previous studies have suggested that blood-stage parasites could modulate the response to a subsequent infection by suppressing liver stage development. This suppression would be significant for future research aimed at enhancing malaria vaccine strategies.

Current efforts to create an effective vaccine against malaria rely on live-attenuated malaria parasites, which can grow and replicate within the liver cells of the host without migrating to the bloodstream. Therefore, any disruption of the liver stage could potentially lower the vaccine's efficacy.

The authors of the study designed a series of experiments in which they infected mouse models of malaria at two time points to observe how the blood-stage infection affected the liver-stage development of the successive infection.

They found that the blood-stage infection suppressed the liver-stage development of both live-attenuated and wild type parasites. The suppression occurred even if the *Plasmodium* species in the blood stage was different from the one in the liver stage.

The researchers investigated the host mechanism behind this suppression and determined that it was not dependent on the levels of the iron-regulating hormone **hepcidin**, contrary to previous reports. Instead, the study identified *Plamodium*-induced host interferons as the primary mediators of the suppression. The specific type of interferon driving the suppression varied depending on the species of the parasite used for the first infection. IFNγ was the main mediator of the suppression in *Plasmodium yoelii*, whereas a combination of type-I interferon and IFNγ mediated the response in *Plasmodium berghei*.

The authors concluded that the study *"*provides important mechanistic insights into the [blood-stage]-mediated suppression of [liver-stage] development. This has direct implications for understanding the outcomes of live attenuated Plasmodium parasite vaccination in malaria-endemic areas and might impact the epidemiology of natural malaria infection."

[**Nature Communications article**]

Researchers Develop Novel Metric Linking HLA Variability to Disease Outcomes in HIV-Infected Individuals

bioquicknews.com/researchers-develop-novel-metric-linking-hla-variability-to-disease-outcomes-in-hiv-infected-individuals/

by Medical Writer **Alejandra Viviescas**, PhD

Researchers at the **Frederick National Laboratory for Cancer Research** and collaborating institutions have developed a new metric to assess how HLA variants influence the effectiveness of the immune response. They applied this new metric, called "functional divergence," to HIV-infected individuals and showed that a high functional divergence correlated with reduced disease severity and reduced viral load. Functional divergence could play a role in other processes that rely on immune response, such as infection, vaccines, and immunotherapy. The study, titled "**Impact of HLA Class I Functional Divergence on HIV Control**" was published on January 18th, 2024 in ***Science***.

Human leukocyte antigens (HLA) are cell-surface proteins that present peptides, or fragments, of foreign agents, such as viruses or bacteria, to the immune cells in charge of triggering and coordinating the immune response.

These HLA proteins are highly variable–the number of described variants or alleles, is constantly expanding and is currently in the thousands. Each HLA variant can present a specific array of peptides to immune cells. Thus, an individual's response to a specific peptide can vary greatly depending on his/her unique combination of HLA alleles.

There are studies dating back over 20 years, which report that individuals who inherit two different HLA variants (heterozygous) have better disease outcomes in conditions like HIV/AIDS than individuals who inherit two copies of the same HLA variant (homozygous). It's proposed that this advantage happens because heterozygous individuals can present a wider variety of peptides to the immune cells than homozygous individuals, thus triggering more effective immune responses.

However, the authors of the current study argued that genetic-based approaches – those that focus solely on the number of HLA variants present in an individual genome as a means of predicting the array of peptides that HLA molecules can present – are simplistic. Different HLA variants, they argue, may bind very similar or radically different sets of peptides.

Therefore, the researchers developed a new metric, called “functional divergence,” to better estimate the array of peptides that a given individual can present to immune cells. Heterozygous individuals with low functional divergence have two HLA variants that present a similar array of peptides to the immune system, whereas individuals with a high functional divergence have two HLA variants that present different arrays of peptides.

The researchers tested whether functional divergence played a role in the outcomes of HIV-infected individuals and found that those with higher functional divergence showed slower disease progression and lower viral load than individuals with lower functional divergence.

Additionally, the scientists performed independent experiments with separate populations of HIV patients and found similar results, which further validates the reliability of the functional divergence metric. As the authors noted, “the peptide-centric algorithm described herein holds an advantage over genetic-based approaches and demonstrates the sizeable impact of functional divergence [for] HIV-1 infection.”

Beyond HIV, functional divergence could help researchers and clinicians better understand and predict the outcomes of other processes that rely on the immune response, such as infectious diseases, vaccination, and immunotherapy. “The metric predicts immune breadth at the peptide level rather than gene level and redefines HLA heterozygosity as a continuum differentially affecting disease outcome,” the authors concluded.

[**Science abstract**]