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Impact of malaria infection on Cu, Fe, and Zn homeostasis revealed using elemental and isotopic analysis

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Malaria is a widespread infectious disease in tropical and subtropical regions and remains one of the leading causes of annual deaths worldwide. It is caused by *Plasmodium* parasites, which are transmitted through the bite of infected female *Anopheles* mosquitoes. When an infection occurs, these parasites infiltrate red blood cells (RBCs), multiply inside them, and eventually cause the cells to rupture, resulting in various clinical symptoms, with anemia being the most prominent.

Copper (Cu), iron (Fe), and zinc (Zn) are essential trace elements that are crucial for several biological functions and play a significant role in the development and persistence of *Plasmodium* parasites. Alterations of Fe, Zn and Cu as result of in *vivo* malaria infection and under pharmacological intervention are poorly understood, as it is presently unknown whether changes in *Plasmodium* metallomics are connected to organ-specific changes in the metal homeostasis of the host individual.

To address this gap in our knowledge on metal homeostasis, we have determined the concentrations of Fe, Cu and Zn and their isotopic composition in plasma, whole blood, purified pRBCs and liver of malaria-infected mice by ICP-tandem mass spectrometry (ICP-MS/MS) and multi-collector ICP-MS (MC-ICP-MS), respectively. Isotopic compositions of Fe, Cu and Zn showed alterations in parasitized red blood cells, suggesting that parasites are highly capable of acquiring and metabolizing essential metals from the host. To further investigate these imbalances in Fe, Cu and Zn homeostasis in a clinical context, this novel approach was extended to human blood samples from malaria-infected patients and healthy controls, providing additional insights into the alteration of metal homeostasis of essential elements during malaria infection.