Structural Parasitology of Malaria Parasites

Chi-Min Ho[1]

[1]Columbia University Irving Medical Center

ch3516@cumc.columbia.edu

While most intracellular pathogens export a limited repertoire of effector proteins to co-opt existing host-cell metabolic machineries, the Malaria-causing parasite Plasmodium falciparum exports more than 10% of its proteome into host human red blood cells, which are highly specialized for carrying hemoglobin and lack the resources to support the active growth and replication of the parasites. The hundreds of proteins in the P. falciparum exportome extensively remodel host erythrocytes, creating the infrastructure needed to import nutrients, export waste, and evade the host immune system. The complexity and breadth of its host-cell remodeling machinery make P. falciparum a rich and exciting system for the study of host-pathogen interfaces. Unfortunately, many of the molecular mechanisms underlying this parasite's ability to hijack human red blood cells remain enigmatic, as much of the P. falciparum proteome has proven recalcitrant to structural and biochemical characterization using traditional recombinant approaches. This paucity of high resolution structural and functional information is compounded by the fact that 50% of the P. falciparum proteome is novel.

To overcome these barriers to structural study of malaria parasites and address the gaps in our understanding of the molecular mechanisms underpinning host-pathogen interactions in parasite-infected red blood cells, we use a combination of CRISPR-Cas9 parasite gene editing, single particle cryoelectron microscopy (cryoEM), and in situ cryoelectron tomography (cryoET) to determine near-atomic resolution structures of previously intractable protein complexes enriched directly from endogenous P. falciparum parasites and directly visualize the host-pathogen interface in intact parasite-infected red blood cells at sub-nanometer resolutions.