

Project:

The role of host cell factors in full development of the malaria parasite inside hepatocytes

Plasmodium is the causative agent of malaria, one of the most prevalent and severe human infectious diseases. Anopheles mosquitoes inject sporozoites into the host, which rapidly migrate to the liver, invade hepatocytes and develop into merozoites that are released to the blood stream initiating the clinical phase of infection. Because liver infection is the first obligatory step of infection, hepatocyte-Plasmodium interactions crucial for the establishment of infection, constitute an ideal target for potential anti-malarial vaccines or preventive treatments.

Sporozoites traverse the cytosol of several hepatocytes before the final infection. During this migration, Plasmodium sporozoites disrupt the host plasma membranes. Our recent results show that host cell wounding by sporozoite migration induces the secretion of hepatocyte growth factor (HGF), which through its receptor MET, renders hepatocytes susceptible to infection. These results strongly suggest that the host cell has an important role on the success of infection. Additionally, Plasmodium sporozoites are able to enter any type of cell tested so far but only fully develop inside hepatocytes indicating a crucial role of the host cell in sustaining the growth and development of Plasmodium. This specificity is thought to be mediated by the unique ability of hepatocytes to provide an adequate environment for sporozoite development. The reason, however, why Plasmodium sporozoites are only able to develop within hepatocytes remains unknown. We propose to determine the host cell molecules and mechanisms required for proper parasite development inside hepatocytes. On one hand, we will focus on mechanisms that might be involved on the HGF/MET signaling. On the other hand, we will use two general methodologies to identify novel host cell factors crucial for infection. We expect to provide a significant contribution to the understanding of the mechanisms mediating Plasmodium/hepatocyte interactions, which might have important implications in the prophylaxis and/or treatment of malaria.

Comments:

This project tackles cellular aspects of host-parasite interactions, required for efficiently fighting malaria. This proposal has a strong chance of yielding new therapeutic agents. In addition to a major impact in the field, this project will have broader impact, in particular in the area of pathogen interactions in the liver.

She is an excellent scientist who has made major breakthroughs in the understanding of malaria parasite infection in humans. She is established as a group leader and has already high-impact publications from her own group.

This proposal studies the role of hepatocytes in the infection cycle of the malaria parasite, an aspect that was neglected in the past. The completion of the project will have a major impact on our understanding of how host cells react to the malaria parasite, using state-of-the-art technology in an intelligent and thought-through manner.

The candidate is moving to a new institute of molecular medicine, which has already attracted young, leading experts in molecular biology. The major strengths of the host institution are in cell biology and infection, which will provide all the required support for the success of this project.

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