CXCR4 regulates Plasmodium development in mouse and human hepatocytes

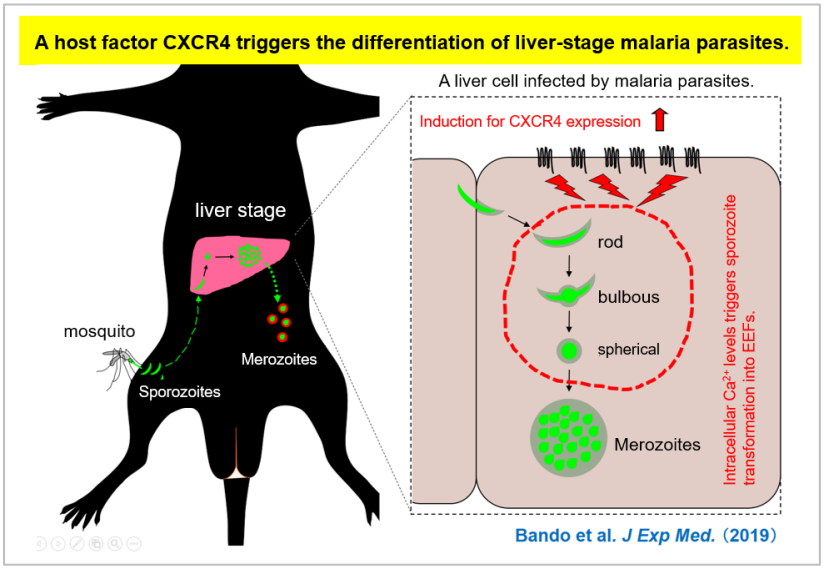
Points

1. In hepatocytes, the host CXCR4 causes morphological changes in malaria parasites.
2. Enhanced CXCR4 expression increases calcium ion concentration in hepatocytes, and malaria parasites differentiate into erythroid phase.
3. CXCR4 inhibitors that have been used are expected to be new preventive agents for malaria.

The liver stage of the etiological agent of malaria, Plasmodium, is obligatory for successful infection of its various mammalian hosts. Differentiation of the rod-shaped sporozoites of Plasmodium into spherical exoerythrocytic forms (EEFs) via bulbous expansion is essential for parasite development in the liver. However, little is known about the host factors regulating the morphological transformation of Plasmodium sporozoites in this organ.

The research group of Masahiro Yamamoto (Immunoparasitology, IFReC/RIMD, Osaka University) showed that sporozoite differentiation into EEFs in the liver involves protein kinase C ζ-mediated NF-κB activation, which robustly induces the expression of C-X-C chemokine receptor type 4 (CXCR4) in hepatocytes and subsequently elevates intracellular Ca2+ levels, thereby triggering sporozoite transformation into EEFs.

Blocking CXCR4 expression by genetic or pharmacological intervention profoundly inhibited the liver stage development of the P. berghei rodent malaria parasite and the human P. falciparum parasite also. Collectively, our experiments show that CXCR4 is a key host factor for Plasmodium development in the liver, and CXCR4 warrants further investigation for malaria prophylaxis.



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