ZIBI Graduate School

Project description

Project Title: A novel lipid-regulated calcium homeostasis and lytic cycle of *Toxoplasma gondii*

Research Group: Metabolism and interactions between parasites and hosts

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Project Description:

The major membrane phospholipid classes, described thus far, include phosphatidylcholine, phosphatidylethanolamine, phosphatidylinositol and phosphatidylserine (PtdSer). Our recent wok has demonstrated the natural occurrence and genetic origin of an exclusive and rather abundant phospholipid, phosphatidylthreonine (PtdThr), in a widespread and clinically relevant eukaryotic model parasite *Toxoplasma gondii*. PtdThr is in fact a natural homolog of otherwise-universal and essential lipid PtdSer, which is long known to regulate membrane integrity and calcium dynamics in mammalian cells. Targeted gene disruption of phosphatidylthreonine synthase impairs the lytic cycle and virulence of the parasite due to unforeseen attenuation of the gliding motility and egress. Using a calcium biosensor, we observed that loss of PtdThr causes a dysregulation of cytosolic calcium, which in turn translates into a defective egress from mammalian host cells. In this project, we will examine the mechanistic regulation of calcium homeostasis by PtdThr and PtdSer using an approach spanning across the disciplines of biochemistry, genetic engineering, cell biology and synthetic chemistry. We will identify lipid-binding proteins involved in calcium homeostasis and lytic cycle by click-chemistry and mass spectrometry, followed by making of qualified knockouts and phenotyping of the mutants. Subcellular distribution of PtdThr and PtdSer will be monitored using synthetic probes and lipid biosensors *via* high-resolution imaging. Not least, physiological importance of the PtdThr and PtdSer species in *T. gondii* will be investigated by chemical complementation of corresponding mutants. Upon successful completion, we shall reveal lipid-mediated regulation and mediators of calcium dynamics during asexual reproduction of *T. gondii*, which can eventually be exploited to inhibit the parasite growth.