Simon Bradbrook

PARASITOLOGY

The *Plasmodium* stage manager

The phosphorylation of eukaryotic translation initiation factor 2α (eIF2α) regulates the conversion of *Plasmodium* spp. salivary gland sporozoites into liver-stage sporozoites, according to a new report by Min Zhang and colleagues in the *Journal of Experimental Medicine*.

In eukaryotes, phosphorylation of eIF2α downregulates protein synthesis and is carried out by eIF2α kinases, which are also found in protozoan parasites, including *Plasmodium* spp. These parasites infect humans through the bite of an infected female mosquito, which releases sporozoites from the salivary glands into the mammalian host. The sporozoites migrate from the skin to the liver, where they infect hepatocytes and undergo a replicative cycle that results in the release of merozoites that can infect erythrocytes, causing the clinical signs and symptoms of malaria. In contrast to the blood and liver stages, sporozoites in the mosquito salivary glands are quiescent and undergo few developmental changes, a phenomenon Zhang and co-workers refer to as 'latency'.

Three eIF2α kinases have been identified in *Plasmodium* spp., and Zhang *et al.* were interested in investigating the role of one of these kinases, IK2, in sporozoite latency. The levels of *IK2* transcripts were followed throughout the *Plasmodium berghei* life cycle using real-time PCR, and it was shown that *IK2* is mainly transcribed by sporozoites in the salivary glands. Analysis of eIF2α in wild-type sporozoites in the mosquito midgut, haemocoel and salivary glands revealed that the level of eIF2α phosphorylation was highest in the salivary glands. In *IK2*-knockout sporozoites, this phosphorylation was absent and translation was enhanced.

Is this phosphorylation maintained after the sporozoites are injected into a mammalian host? Immunoblot analysis revealed that eIF2α became dephosphorylated after 30–60 minutes at 37 °C. The addition of a selective inhibitor of eIF2α dephosphorylation increased eIF2α phosphorylation and the infectivity of wild-type sporozoites. The authors concluded that IK2 phosphorylates eIF2α in salivary gland sporozoites and that phosphorylated eIF2α is dephosphorylated in the mammalian host by an unidentified phosphatase. Finally, comparing transcriptional profiles in salivary gland sporozoites showed that ~8% of the *P. berghei* genes examined were upregulated in *IK2*-defective mutants compared with levels in wild type, and this group was enriched for genes encoding proteins that are typically associated with the liver stage. The authors speculate that this upsurge in transcription might be caused by the relief of translational repression of a transcription factor that is crucial for the expression of liver-stage genes. Moreover, in *IK2*-defective salivary gland sporozoites, Western blot analysis revealed the accumulation of known liver-stage proteins.

So, IK2 and an unknown phosphatase control the stage conversion of *Plasmodium* spp. sporozoites. IK2 maintains salivary gland sporozoites in a latent state, in which the transcripts of proteins that are required for the liver stage can accumulate but are not translated. On injection into the mammalian host, this translational repression is relieved by the phosphatase, allowing translation of the liver-stage transcripts to proceed, readying the sporozoites for the liver stage.

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ORIGINAL RESEARCH PAPER Zhang, M. *et al.* The *Plasmodium* eukaryotic initiation factor-2α kinase IK2 controls the latency of sporozoites in the mosquito salivary glands. *J. Exp. Med.* **207**, 1465–1474 (2010)