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Malaria: a new route of access to the heart of the parasite

Scientists have just identified an Achilles heel in the parasite that causes malaria, by showing that its optimum development is dependent on its ability to expropriate RNA molecules in infected cells – a host-pathogen interaction that had never previously been observed. Although the precise function of this deviation remains mysterious, these findings open new perspectives for the targeted delivery of therapeutic agents within the parasite. This study, performed by the CNRS Architecture et Réactivité de l'ARN laboratory (Strasbourg), in collaboration with the Malaria Infection and Immunity Unit at Institut Pasteur (Paris), is published in *PNAS* the week of 11 April 2016.

Single-cell parasites in the *Plasmodium* genus are the infective agents responsible for malaria and constitute one of the principal threats to human health and development in southern hemisphere countries[1]. The life cycle of this parasite occurs partly in the *Anopheles* mosquito (digestive tract, salivary glands) and partly in humans or other mammals (liver, blood cells).

During this study, the biologists identified a protein (tRip) localized on the parasite's surface and capable of of importing host tRNA into the parasite (tRNAs are key molecules involved in protein production). This is the first time that the import into cells of exogenous tRNA has been demonstrated. The scientists also demonstrated that if tRip were not present, the parasite no longer imported tRNA, its protein synthesis was reduced, and its development was markedly slowed down in the blood cells of infected mice.

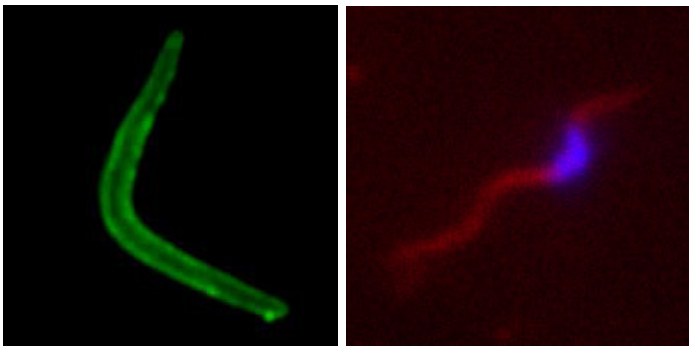
But what is the function of this tRNA expropriation by *Plasmodium*? While most eukaryote[2] genomes contain several copies of each tRNA gene, the *Plasmodium* genome codes for a minimum number of these genes. Thus the parasite may need supplementary tRNA to complete the synthesis of the proteins necessary for its development. According to another hypothesis, host tRNA may act as small regulatory RNA and modulate expression of the parasite's genes.

From a medical point of view, the discovery of this mechanism means that it may be possible to develop methods to enable the targeted entry of therapeutic molecules into the parasite, so as to improve the

[1] *The WHO recorded 214 million cases of malaria in 2015, 80% of them in sub-Saharan Africa.*

[2] *Eukaryotes means all organisms whose cells contain a nucleus holding genetic material (unlike prokaryotes, which contain bacteria and Archaea).*

efficacy of treatments. Particularly since the tRip protein – and thus, perhaps, this import mechanism – is seen in other parasites in the *Plasmodium* family, the *Apicomplexa*, which include the human pathogens *Toxoplasma* and *Cryptosporidium*.



Left: detection of the tRIP protein at the periphery of a Plasmodium *parasite at the sporozoite stage (infective form present in the salivary glands of an infected mosquito). Right: detection of the entry of an exogenous tRNA (red) into a* Plasmodium *parasite at the sporozoite stage, whose nucleus is labeled in blue.*

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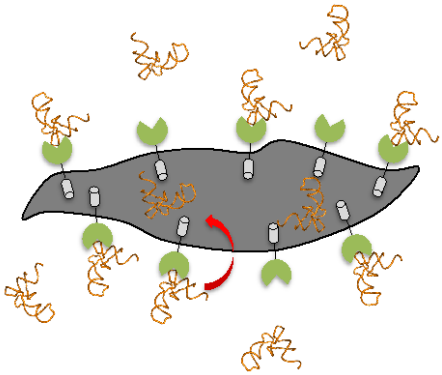

The tRIP protein, expressed on the parasite's surface, binds exogenous tRNA (via its tRNA binding site, in green) and permits their entry into the parasite.

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Bibliography

Apicomplexa-specific tRip facilitates import of exogenous tRNAs into malaria parasites, Tania Bour*, Nassira Mahmoudi*, Delphine Kapps*, Sabine Thiberge, Daniel Bargieri, Robert Ménard & Magali Frugier. *PNAS*, online the week of 11 Avril 2016. DOI : 10.1073/pnas.1600476113
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