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Artemisinin resistance in malaria parasites elucidated

Hamburg / Nijmegen, 3 January 2020 – Tobias Spielmann and his team at the Bernhard Nocht Institute for Tropical Medicine (BNITM) together with their cooperation partners from Radboud University in the Netherlands have identified the mechanism responsible for resistance to artemisinin, currently the most important malaria drug. The parasite protein Kelch13 plays a key role in this process. These important findings, were published today in the journal *Science* (Birnbaum & Scharf *et al.* 2020).

Plasmodium falciparum, the parasite causing severe forms of malaria, is one of the most important human pathogens responsible for more than 200 million new infections every year and more than 400,000 deaths. In order to treat malaria, combination therapies containing artemisinin are primarily used.

However, the success of this treatment is increasingly threatened by resistance of the parasite to this drug. Previous observations have shown that there is a correlation between mutations in the parasite protein "Kelch13" and the occurrence of artemisinin resistance. Until now the function of Kelch13 in the parasite and how Kelch13 mutations cause resistance were unclear.

Malaria parasites proliferate in red blood cells and feed by uptake and digestion of hemoglobin, the major content of red blood cells. With the help of sophisticated cell biological investigations and the use of elaborately produced, genetically modified parasites, the Spielmann group and the team of Richárd Bártfai at Radboud University have now been able to show that Kelch13 interacts with proteins that are responsible for the uptake of hemoglobin into the parasite. "It was the identification of Kelch13 partner proteins that gave us the decisive clue which function Kelch13 could have in the parasite", said Spielmann describing the work of his group. "Confirming this idea, the targeted inactivation of Kelch13 indeed led to a reduced uptake of hemoglobin".

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Less is more: Kelch13 mutants have an advantage when exposed to artemisinin

In order to exert its toxic effect, artemisinin has to be activated after absorption into the parasite. The malaria parasite takes up hemoglobin, digests it as a nutrient source and thereby produces hemoglobin degradation products. These degradation products activate artemisinin, killing the parasite.

In further experiments, the Hamburg scientists showed that the known Kelch13 mutations reduce hemoglobin uptake by the parasite. This results in lower amounts of hemoglobin degradation products and artemisinin is no longer sufficiently activated to kill the parasite.

"Actually, arteminisin resistance is a very subtle balance between food intake and artemisinin activation," Spielmann summarizes the results. "On the one hand, the parasite still has to consume enough hemoglobin to survive, but on the other hand the uptake of hemoglobin has to be restricted to a level that artemisinin is no longer sufficiently activated," explains the group leader. “These findings do not provide an immediate solution to artemisinin resistance - adds Bártfai - but knowing the mechanism of resistance might help developing improved antimalarial drugs in order to counteract the increasing resistance of the parasite to artemisinin”.

3.197 Characters (with spaces)

BNITM comprises the National Reference Centre for Tropical Pathogens and the WHO Collaborating Centre for Arbovirus and Haemorrhagic Fever Reference and Research.

Together with the Ghanaian Ministry of Health and the University of Kumasi, it runs a modern research and training centre in the West African rainforest, which is also available to external research groups.

Radboud University – Radboud Institute for Molecular Life Sciences

Radboud Institute for Molecular Life Sciences (RIMLS) – a leading research institute that focuses on the molecular mechanisms of disease – brings together research groups from the Radboud university medical center (Radboudumc) and the Faculty of Science (FNWI) of the Radboud University. Clinical and fundamental scientists who specialize in diverse areas of the life sciences work closely together to understand the underlying molecular causes of disease. By integrating fundamental and clinical research, we obtain multifaceted knowledge of (patho)physiolofical processes.

We aim to improve clinical practice and public health by:

1) generating basic knowledge in the molecular medical science

2) translating our gained knowledge into clinical applications, and into diagnostic, therapeutic and personalized treatment strategies

3) training and exposing researchers of all levels to societal-relevant multidisciplinary research questions.