The appendage/leg specific ABCH2 transporter mediates insecticide toxicity in the malaria vector *Anopheles coluzzii*

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ABSTRACT

Contact insecticides are primarily used for the control of *Anopheles* malaria vectors. They cross mosquitoes' legs and other appendages which represent the first barrier insecticides have to bypass to reach their neuronal targets. An ATP-Binding Cassette transporter from the insect-specific H family (ABCH2) is highly expressed in *Anopheles coluzzii* legs, especially upon insecticide exposure. RNAi-mediated silencing of the *ABCH2* caused a dramatic increase in mortality compared to control mosquitoes, indicating a role of this transporter in deltamethrin toxicity. RT-qPCR analysis and immunolocalization of the ABCH2 using specific antibodies showed that it is mainly present in legs. More specifically, the protein is expressed in the apical part of leg epidermis, underneath the cuticle. Phylogenetic analysis indicated that this transporter is orthologue with other ABCH transporters previously found to be implicated in lipid transport. However, analysis of the leg cuticular hydrocarbon (CH) content was not affected by *ABCH2* RNAi, indicating that the role of this transporter in pyrethroid toxicity is not associated with the transport of leg CHCs. We next performed protein modeling of ABCH2 based on the closest homologue available structure, the human ABCG1. *In silico* modeling, together with its functional *in vitro* expression in *Sf9* insect cells, provide clear evidence that ABCH2 half-transporter, likely physiologically adopts a homodimeric state. Concomitant protein-ligand docking analysis strongly indicate that deltamethrin could be a potential substrate of this transporter. Our findings reveal a previously undescribed mechanism of insecticide toxicity in mosquitoes, pinpointing ABCH2 as a major player of deltamethrin toxicity and potential target for vector control in the future.