

Abstract

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Title of Doctoral Thesis:

The role of UDP-glycosyltransferases in drug resistance in parasitic nematodes

The diseases caused by parasitic nematodes represent a serious problem, which threatens livestock's health, because pharmacotherapy is complicated by widespread anthelmintic resistance. Understanding of the mechanisms of parasite drug resistance and defense strategies is important to maintaining the effectiveness of currently used anthelmintics and developing new approaches to controlling these infections. The ability of parasites to inactivate anthelmintics through their metabolism, which is provided by biotransformation enzymes, may contribute to the development of drug resistance.

The UDP-glycosyltransferases (UGT) superfamily can protect parasites from the toxic actions of anthelmintics by modifying drugs to inactive glycoside metabolites. These metabolites have been identified in benzimidazole metabolism to an increased extent in a resistant strain of *H. contortus*, which suggests the involvement of UGTs in anthelmintic resistance.

In the genome of this parasitic nematode, 32 genes encoding UGTs divided into 15 families have been found. Further, characterization of these enzymes also revealed different transcription levels of some UGT genes in the susceptible and resistant strain during the nematode lifetime, which shows the different roles of individual UGT enzymes in *H. contortus*. Moreover, the expression of some UGT genes was induced by exposure of *H. contortus* to anthelmintic albendazole (ABZ), either under laboratory conditions or directly in a contaminated environment. Subsequently, the biotransformation of ABZ in pre-exposed nematodes resulted in increased production of metabolites that indicate a possible reason for the development of resistance associated with the presence of anthelmintic in sublethal doses in *H. contortus*. Exposition of *H. contortus* adults to the UGT inhibitor sulfinpyrazone (SP) caused a reduction in the production of ABZ-glycosides, which confirmed the involvement of UGTs in the biotransformation. In summary, the obtained results underline the association of UGTs with anthelmintic resistance in *H. contortus*.