Functional studies of the nuclear hormone receptor NHR-8, a new therapeutic target against nematode parasites

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Context: Infections by parasitic nematodes affect nearly three billion people in the world, cause significant economic losses for livestock farmers, and greatly affect animal welfare. To control human and animal parasites, the most commonly used drugs belong to the family of macrocyclic lactones (ML) which target ion channels specific to invertebrates. However, parasites have developed resistance to MLs and there is an urgent need to improve strategies to maintain their efficacy. Genomic and transcriptomic studies have demonstrated the multi-gene nature of resistance mechanisms, which complicates the possibilities of targeting these mechanisms. Nuclear receptors, whose activity is ligand-dependent, are transcription factors regulating a large number of genes. In particular, we will focus on NHR-8, a receptor known to be involved in the regulation of drug detoxification systems.

Ongoing research in the lab: We have recently shown that targeting NHR-8 by RNA interference in the model nematode *Caenorhabditis elegans* (*C. elegans*), as well as in the parasite *Haemonchus contortus* increases their susceptibility to MLs [1]. In addition, using ML-resistant strains of *C. elegans* selected in our laboratory [2], we have also shown that NHR-8 is a key player in the ML response [1]. Inhibition of NHR-8 therefore represents an opportunity to increase the sensitivity of parasitic nematodes to MLs. However, the underlying mechanisms mediated by NHR-8 that contribute to ML resistance are poorly understood. Therefore, we are conducting molecular studies to better characterize the functions of NHR-8, mainly in the model nematode *C. elegans*. A first important issue is to identify ligands of NHR-8. For this purpose, we are currently collaborating with the Centre de Biologie Structurale (CBS) of Montpellier to solve the structure of NHR-8. In parallel, we are developing cellular assays of NHR-8 activity based on the monitoring of the luminescence of the luciferase reporter gene upon activation by the ligands.

M2 project: The M2 student will be involved in another important step to elucidate the function of NHR-8, which consists in characterizing the set of genes regulated by NHR-8 in the context of ML response. We will set up a transcriptomic study by RNA-seq using wild type, NHR-8 deficient and ML resistant strains of *C. elegans*. Then, to better understand how NHR-8 activity is regulated, we will perform a proteomic study. Using a *C. elegans* strain expressing a tagged form of NHR-8, we will perform immunoprecipitations of NHR-8 followed by a characterization of its protein partners by mass spectrometry.

Overall, this project will provide a better understanding of the physiological and ML-dependent functions of NHR-8 in nematodes. It will also allow to identify new molecular targets involved in the development of resistance to anti-parasitic drugs and to design new therapeutic treatments. The master-2 student will be involved in all or part of these studies, in the form of a mini-project to be carried out during the internship and will be supervised by Rémy Betous, INRAE researcher.

Techniques: *C.elegans* and mammalian cell culture, reporter assay, PCR, immunoprecipitation, western-blot, proteomic, RNA-seq and various bioinformatic tools.

References :

[1] The transcription factor NHR-8: A new target to increase ivermectin efficacy in nematodes. *PLoS Pathog*. 2019 Feb 13. Ménez C, Alberich M, Courtot E, Guegnard F, Blanchard A, Aguilaniu H and Lespine A.

[2] Acquired Tolerance to Ivermectin and Moxidectin after Drug Selection Pressure in the Nematode Caenorhabditis elegans. *Antimicrob Agents Chemother*. 2016 Jul 22. Ménez C, Alberich M, Kansoh D, Blanchard A and Lespine A.