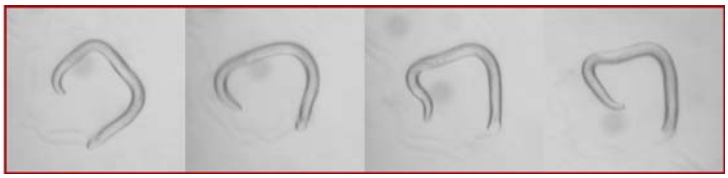
FACULTY OF SCIENCE
University of South Bohemia
České Budějovice

Ph.D. Thesis

Functional analysis of the nuclear receptor NHR-25 during *C. elegans* development



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Cover image: Movement series of a *C. elegans* male that carries *rol-6(su1006)* mutation.

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Annotation:

This thesis introduces a study of a conserved nuclear receptor NHR-25 and of its role during development of the nematode *Caenorhabditis elegans*. To address the function of NHR-25 in certain developmental processes, several approaches of genetic, cellular and molecular biology have been used. This work reveals an indispensable role of NHR-25 in asymmetric cell division and cell fate decision of the epidermal stem cells, seam cells. The results represent one of the first direct implications of any nuclear receptor being required for cell fate determination. It demonstrates a genetic *in vivo* interaction between NHR-25 and the Wnt/β-catenin asymmetry pathway, which is essential for proper seam cell differentiation. Remarkably, NHR-25 is shown to modulate Wnt signaling in either synergistic or antagonistic manner, depending on cellular context. This finding provides a novel insight to the crosstalk between nuclear receptors and Wnt signaling. Moreover, it sheds light on our understanding how interacting signaling pathways control differentiation of multiple tissues in multicellular organisms.

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Declaration:

I hereby declare that I did all the work, presented in this thesis, by myself or in collaboration with the co-authors of the published article.

Further, I declare that in accordance with the Czech legal code § 47b law No. 111/1998 in its valid version, I consent to the publication of my Ph.D. thesis (in an edition made by removing marked parts archived by the Faculty of Science) in an electronic way in the public access to the STAG database run by the University of South Bohemia in České Budějovice on its web pages.

České Budějovice, June 16, 2009 Martina Hajdušková

Author contributions

As the first author of the paper accepted by *Journal of Cell Science* (see chapter "Research article"), I designed many experiments and did the vast majority of the bench work. This included generation and phenotypic analyses of transgenic *C. elegans* strains for tissue-specific *nhr-25* RNAi, phenotypic analyses of the male tail morphology, and examination of T cell polarity defects by means of direct lineage analysis of the T cell progeny and by using dye-filling techniques in *nhr-25* mutant and RNAi worms. I discovered a synergistic genetic interaction of NHR-25 with the Wnt/β-catenin asymmetry pathway and with the parallel RUNX signaling during the T cell differentiation. I evaluated the data and interpreted them in a complete manuscript draft that I wrote by myself, including preparation of the figures. Dr. M. Asahina, besides designing and supervising the project, contributed experiments showing ectopic expression of the Hox gene *mab-5* in *nhr-25* mutant male tails. Prof. M. Herman taught me how to perform the lineaging and dye-filling experiments in his lab. Dr. M. Jindra served as a scientific advisor and helped with writing of the paper. I also did most of the work described in "Unpublished preliminary results" except where stated otherwise directly in the thesis chapter.

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Contents

Abstract

Asymmetric cell divisions produce new cell types during animal development. Studies in *Caenorhabditis elegans* have identified major signal transduction pathways that determine the polarity of cell divisions. How these relatively few conserved pathways interact and what modulates them to ensure the diversity of multiple tissue types is an open question. The Wnt/β-catenin asymmetry pathway governs polarity of the epidermal cell T in the *C. elegans* tail. Here, we show that the asymmetry of T cell division and morphogenesis of the male sensory rays require NHR-25, an evolutionarily conserved nuclear receptor. NHR-25 ensures the neural fate of the T cell descendants in cooperation with the Wnt/β-catenin asymmetry pathway. Loss of NHR-25 enhances the impact of mutated nuclear effectors of this pathway, POP-1/TCF and SYS-1/β-catenin, on the T cell polarity, while it suppresses the effect of the same mutations on asymmetric division of the somatic gonad precursor cells. Therefore, NHR-25 can either synergize with, or antagonize the Wnt/β-catenin asymmetry pathway depending on the tissue context. Our findings define NHR-25 as a versatile modulator of Wnt/β-catenin-dependent cell fate decisions.