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EVOLUTION OF THE NUCLEAR RECEPTOR DAF-12 IN PARASITIC NEMATODES



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INTRODUCTION

- The nematode model Caenorhabditis elegans harbours 284 Nuclear Receptor
- DAF-12 is the only C. elegans NR with known ligands, the dafachronic acids.
- DAF-12 is structurally and functionally related to the mammalian FXR
- DAF-12 controls:
 - lacksquare
 - Entry to and exit from the dauer stage (*C. elegans*), an alternative quiescent stage \bullet more resistant to degraded environments and the infective larval stage (parasitic nematodes)

OBJECTIVE: Compare DAF-12 activity and function in filarial and non-filarial nematodes



SPECIFICITIES OF FILARIAL DAF-12 ACTIVATION



MAMMALIAN SERA CONTAIN DAF-12 LIGANDS



(A) Schematic representation of the DAF-12 reporter assay. (B) Activation of DAF-12 from Dim, Bma, Hco or Cel by regular sera. (C) Dose-response curves for $\Delta 4$ -dafachronic acid and cholestenoic acid on the activation of *Dim*, *Bma*, *Hco or Cel*DAF-12.

(A) Serum charcoal stripping procedure. (B) Activation of DAF-12 from *Dim* and (C) from *Bma* by regular or charcoal-stripped sera from different mammalian species.(**D**) Concentrations of Δ 4-dafachronic acid (Δ 4-DA) and cholestenoic acid in human and mouse serum. (E) Supplementation of charcoal stripped mouse serum with cholestenoic acid (chol. ac.) or Δ 4-dafachronic acid (Δ 4-DA) at their concentrations found in mouse sera

DAF-12 ACTIVATION STIMULATES D. IMMITIS IL3 DEVELOPMENT



(A) Image of a *D. immitis* L3 in process of completely shedding its cuticle. (B) In vitro iL3 to L4 development of *D. immitis.* The iL3 larvae were collected from mosquitos and incubated in regular or charcoal-stripped FBS containing medium in the presence or absence of $\Delta 4$ -DA. The iL3 undergoing molting or which had completed the molting from iL3 to L4 were scored daily under a microscope.

DAF-12 LIGANDS BIOSYNTHESIS ENZYMES ARE DOWN-REGULATED IN THE FILARIAL NEMATODE BRUGIA MALAYI AT THE TIME OF INFECTION



CONCLUSIONS

- Filarial DAF-12s are hypersensitive to their ligands
- Host serum contains DAF-12 ligands, including $\Delta 4$ -dafachronic acid
- These DAF-12 ligands support D. immitis larval development
- The expression of genes involved in DA biosynthesis is very low during the early days of infection



(A) Schematic representation of the $\Delta 4$ -DA and $\Delta 7$ -DA synthesis pathways with known enzymes. (B) Expression levels of daf-36, dhs-16, hsd-1 and daf-9, daf-12 lit-1 in B. malayi iL3 and L3 before and after infection of Mongolian gerbils. The Yaxis represents the relative gene expression levels given in transcript per million as analyzed by Chung, M et al. (mSystems, 2019) from RNA-seq data. The variation in gene expression at time infection is highlighted in grey.

Open access RNA-seq data from Chun, al. mSystems (2019)

daf-12 may have evolved in filarial parasites to sense the host environment through its ligands and promptly trigger parasite development and growth upon infection.

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