Formylglycine and an alternative maturation system regulate nematode sulfatases

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R. Sharma[I], T. Loschko[I], H. Witte[I], J. Maldung[II], M. Franz-Wachtel[II], B. Maček[II], R.J. Sommer[I], C. Igreja[I]

[I]Max Planck Institute for Biology Tübingen, Tübingen, Germany, [II]Interfaculty Institute of Cell Biology, Univeristy of Tübingen, Tübingen, Germany

Sulfatases are responsible for hydrolyzing sulfate esters during hormone regulation or the catabolism of sulfated biomolecules. Sulfatase activity resides in a cysteine (Cys) residue co-translationally modified to formylglycine (FGly) by the FGly-generating enzyme (FGE). FGly is essential for sulfatase activity across all domains of life. Mutations impairing the human FGE lead to multiple sulfatase deficiency, a fatal disorder (Previously published in: Dierks et al. (2003) Cell 113(4), 435-44). Efforts to understand desulfation in nematodes are restricted to the neuronal sulfatases *C. elegans* SUL-2 and its paralog in *Pristionchus pacificus* EUD-1. The latter acts as a switch gene controlling mouth dimorphism (Previously published in: Ragsdale et al. (2012) Cell 155(4), 922-33). The catalytic Cys is conserved in sulfatases; yet, nematodes, fungi, some algae and bacteria, lack FGE homologs and thus, a recognizable sulfatase maturation system. Here, we present our quest for the missing nematode FGE. We generated mutant worms encoding the EUD-1 enzyme lacking the signal peptide or with an active site Cys to alanine (Ala) substitution. We observed that EUD-1 endoplasmic reticulum-import and the catalytic Cys are crucial for enzyme function. To elucidate whether nematode sulfatases are modified to FGly, we expressed and purified EUD-1 in *E. coli* with a heterologous FGE. Using LC-MS/MS and chemical conjugation we reliably detect FGly in the active site of recombinant EUD-1. Immunoprecipitation of ALFA-tagged SUL-2 from extracts of wild-type or Cys to Ala edited-worms, coupled with FGly detection, shows that the catalytic Cys of endogenous nematode sulfatases is modified to FGly *in vivo*. Thus, we provide the first evidences that nematodes possess an alternative FGE that modifies to FGly the sulfatases active site. We will present our efforts to identify and characterize the unknown FGE responsible for sulfatase activation in organisms with uncharacterized maturation systems.