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Dissertations-Kurzfassung

Medaka Wnt8a1 regulates posterior axis formation independently of the Wnt/β-catenin pathway

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Comparative studies analyze evolutionarily distant but morphologically similar animal species to uncover species-specific and conserved gene functions. We are investigating the genetic hierarchies underlying posterior axis formation in the medakafish, a teleost distantly related to the more widely known zebrafish. ENU-mutagenesis screens are possibly one of the most unbiased approaches to identify novel genes and their functions. Random point mutations are introduced into the genome allowing researchers to screen for resulting morphological alterations and the subsequent identification of the mutated gene.

We have isolated a medaka mutant named "*köpfchen*" *(kfn)* carrying a recessive lethal mutation resulting in the absence of all structures posterior to the embryonic head. We identified the gene mutated in *kfn* as the *Wnt8a1* gene. Like in all other teleosts analyzed, the medaka genome contains two *Wnt8a* paralogues. Given that these paralogues have redundant functions in zebrafish, it is intriguing that a point mutation in one medaka *Wnt8a* gene causes the dramatic phenotype. We show that the medaka *Wnt8a1* gene is crucially involved not only in embryonic patterning but also in morphogenetic cell movements during early steps of the gastrulating embryo. This dual role of *Wnt8a1* in medaka may explain the dramatic phenotype caused by its absence. While currently *Wnt8* genes are thought to activate the Wnt/beta-catenin pathway, we have collected evidences from experiments in medaka, zebrafish and Xenopus that medaka *Wnt8a1* functions mainly through a non-canonical Wnt pathway. Over-activation of *Wnt8a1* in wild type embryos does not result in phenotypes characteristic for canonical Wnt signaling. Furthermore, the *kfn* mutant phenotype can only be rescued with downstream components of the PCP pathway, but not the β-catenin pathway.

Our investigations are consistent with a novel concept, which postulates that medaka utilises a *Wnt8a1* mediated genetic cascade different to zebrafish and Xenopus to develop the posterior axis. This cascade regulates both patterning and morphogenesis in the gastrulating embryo.