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## **Sex Determination in Medaka (*Oryzias latipes*): When Epigenetics Overrides Genetic Determinants**

Alexandra Depincé<sup>1</sup>, Florent Murat<sup>1</sup>, Violette Thermes<sup>1</sup>, Aurélien Brionne<sup>1</sup>,  
Manfred Scharl<sup>2</sup> and Amaury Herpin<sup>1</sup>

[alexandra.depince@inrae.fr](mailto:alexandra.depince@inrae.fr)

<sup>1</sup> INRAE, UR1037 Fish Physiology and Genomics, Rennes F-35000, France.

<sup>2</sup> Department of Physiological Chemistry, University of Würzburg, D-97074 Würzburg, Germany.

Fish exhibit a wide range of sex determination mechanisms, along with a high turnover of master sex-determining genes (MSD). As a result, the downstream molecular pathways and regulatory processes governing sex determination and differentiation have undergone iterative adaptations throughout evolution. Interestingly, genes related to transforming growth factor- $\beta$  (TGF- $\beta$ ) signaling are frequently selected as MSD genes in various teleost fishes.

Studying how members of the TGF- $\beta$  family might influence gonadal commitment, we discovered that the Gdf6 signaling is able to override the already established genetic sex determination system of medaka controlling an unexpected and heritable epigenetic modulating mechanism.

Hence, while the loss of Gdf6 function results in XY male-to-female sex-reversal, we could show that this gonadal reversion is associated with specific alterations in the whole epigenetic landscape, including transposable elements and hypermethylation of specific regions on the existing Y-chromosome. Interestingly, this sex-reversal is abolished when embryos are either treated with the DNA demethylating compound 5-azacytidine or subjected to targeted CRISPR-dCas9-TET1 epigenetic editing, suggesting that the observed sex-reversal is indeed driven and propagated through specific epigenetic alterations. Consistent with these findings, overexpression of Gdf6b in a Medaka cell line resulted in the de-localization of DNMT1 and UHRF1 - two proteins known to be crucial for maintaining the overall DNA methylation landscape- from the nucleus to the cytoplasm.

Altogether, our data clearly support the idea that in medaka, GDF6 signaling is physiologically integrated by safeguarding the methylation states of specific loci within the genome for guarantying the correct sequential activation and execution of the gonadal gene regulatory network led by its master sex determining gene, Dmrt1bY.

Challenging the traditional view of medaka sex determination being a process strictly controlled by strong genetic factors, our results also reveal that epigenetic mechanisms/modulations play a pivotal role in sex determination. Overriding the action of established genetic determiners, GDF6 factors, functioning as epigenetic modifiers, obviously influence plastic gene regulatory networks and might facilitate the high turnover and frequent transition of sex determination systems and mechanisms observed in fish.