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Integrating TGF-β signalling pathways and epigenetic modulations for controlling sex determination in medaka

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In stark contrast to birds and mammals, which feature extreme conservative sex-determination mechanisms across species, fish display an amazing broad range of systems and master sex-determining (SD) genes. Thus, the molecular pathways of sex-determination and differentiation must have recurrently and independently adjusted and adapted during the course of evolution. Interestingly, although being clearly subordinates of the sex-regulatory network in mammals, TGF-β family members (*Amh, Gsdf, Gdf6* or *Bmpr1bb*, *Amhr2*…) have nevertheless been the source of most of the SD genes in fish.

Facing this rolling wave of TGF-β signaling in primary SD, and taking advantage of this “evolution in action”, our aim is to decipher the key role of those TGF-β signaling pathways and their functional evolution for sex determination and maintenance of gonad sexual identity: -How is signaling specificity achieved among the different gonadal TGF-β signal transducing factors? -What are the underlying molecular mechanisms determining the sex functions of these factors? and -How do they branch into the canonical downstream sex regulatory network?

Focusing on medaka Gdf6 and Amh for approaching these conceptual questions, and using *in-vivo* and *in-vitro* approaches, combining gene editing together with transcriptomics and functional studies, we find that, in a context of sex determination:

- Amh and Gdf6 likely act through different signaling pathways and are, in a physiological manner, distinctly integrated.
- Amh and Gdf6 pathways do not necessarily branch together with the canonical sex-determining gene regulatory network for exerting their respective functions.
- Medaka Gdf6 paralogs control variations in the methylation landscape, leading to epigenetic modifications strictly regulating sex determination.

Finally, evidence is provided for an unexpected link between (i) a growth factor, (ii) transcription factors and (iii) the modulation of the methylation landscape in the context of sex determination.