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Heart Preconditioning and Regeneration, Müller Glia-mediated Retina Regeneration and Autistic Behavior in Adult Zebrafish

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A small freshwater fish called zebrafish (*Danio rerio*) has become one of the favorite model organisms in science. It has also been recognized as a powerful model in regenerative biology. After injuries, this fish can faithfully restore many organs such as the heart, the fin, and the retina. Furthermore, this vertebrate can also be used various topics such as systemic preconditioning and autism disorder. This thesis gathers several projects related to diverse biological aspects of adult zebrafish.
In a first part were investigated the molecular mechanisms leading to preconditioning; a way to enhance the resilience of tissue after exposure to peripheral injuries. Chest incision was found to be sufficient to trigger pro-regenerative program in the intact heart. Transcriptomic analysis of stimulated hearts identified Ciliary neurotrophic factor (CNTF) as a molecular player of preconditioning. In a second part, a method of intrathoracic injection was established for delivery of a small amount of CNTF directly into the pericardial cavity. Loss of function (LoF) mutant lines were established using the CRISPR-Cas9 technology. This project revealed that *cntf* is required for heart preconditioning. Moreover, *cntf* function was tested during regeneration of the fin, the heart and the retina. This experiment revealed that *cntf* might be required for heart regeneration only as regeneration is altered in *cntf* loss of function.
In the second project, heart regeneration after multiple injuries was investigated. This could establish that zebrafish had the capacity to regenerate their heart after up to six successive injuries, despite an increased fibrosis.
In the third project, a common regulatory sequence expressed in regenerating myocardium and fin called the *careg* element was investigated during retina regeneration. The *careg* element was found to be activated in Müller glia (MG) during regeneration. Cre-lox cell lineage analysis identified *careg* expression in regenerating MG. scRNAseq analysis of regenerating retinas of *careg:GFP* fish established the transcriptome of *careg* expressing cells.
In the fourth project, the involvement of Parvalbumin (*Pvalb*) in autism spectrum disorder (ASD) was investigated. *pvalb6 and pvalb7* LoF zebrafish were generated with CRISPR/Cas9 and social behavior of the double mutant adult fish was tracked. The obtained results revealed impaired social capabilities of *pvalb* mutant fish, reminiscent of the ASD phenotype.

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