

Comparison of heart regeneration between distinct fish taxa

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Humans and other mammals respond to myocardial infarction with irreversible scarring. In contrast, scarring in zebrafish is transient and functional cardiac muscle can be regenerated. However, it is unclear how common this ability is among teleost fish. Interestingly, medaka has been shown to exhibit a high rate of mortality following ventricular resection. Accordingly, it is thus far unknown whether cardiac regenerative capacity is common to various taxa of teleost fish or whether it is unique to zebrafish. In this study, we address this important evolutionary question using several fish species from distinct taxa, namely *Otophysa* and *Ovalentaria*, which phylogenetically separated more than 250 million years ago, with the aim of placing zebrafish heart regeneration research in a comprehensive phylogenetic perspective.

Using the species *P. titteya*, *D. pentazona*, *X. maculatus* and *X. hellerii* and the cryoinjury model of cardiac injury, we reveal that select fish from the taxa *Ovalentaria* exhibit a differential regenerative phenotype to zebrafish and its closer relatives, instead exhibiting an unresolved collagenous scar with little to no evidence myocardial wall closure even at 90 days post cryoinjury. A proliferation assay illustrates significant differences in the dynamics of cardiomyocyte proliferation between families; zebrafish and other regenerating species show a significantly higher cardiomyocyte proliferative index at the peri-injury zone, indicative of a regenerative blastema. However, we observe that in the less regenerative fish of the taxa *Ovalentaria*, the cardiomyocyte proliferative index is relatively consistent across the entire ventricle, indicating a different reparative response to cryoinjury. Several morphological differences were uncovered, including a lack of a compact layer and coronary vasculature in the non-regenerative species. We also reveal that key embryonic myosin isoforms, which in zebrafish become expressed in the peri-injured zone following injury and indicate dedifferentiation of cardiomyocytes, are not upregulated following injury in fish of this family. Equally, proteins known to contribute to the regenerative matrix in zebrafish such as ColXII are also differentially expressed between taxa. Further studies will be required to discover the factors that underpin these differences.

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