

TOR signaling as a link between tumorigenesis and regeneration

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Organ regeneration is a beneficial capacity in adult vertebrates, but it may also account for an undesired predisposition for tumors. The proliferative capacity can either reconstruct or destroy the organ. A connection between the regenerative capacity and a risk for tumorigenesis is unclear for the heart. Here, we investigate whether the zebrafish adult heart, a highly regenerative organ, can also develop a tumor. To this aim, we established a tissue-specific and tamoxifen-inducible Gal4-ERT2 - UAS system in order to specifically and temporarily express the oncogenic GTPase HRas^{G12V} gene in the heart. We found that the oncogene overexpression for two weeks was sufficient to give rise to cardiac neoplasia associated with a reactivation of the embryonic cardiac program. We identified that this phenotype was partially dependent on TOR signaling, which is a downstream effector of HRas. Treatment with Rapamycin, the TOR-specific inhibitor, substantially rescued cardiac overgrowth in the oncogene expressing fish. Importantly, we found that TOR signaling is also activated during normal heart regeneration in zebrafish, without HRas overexpression. The inhibition of TOR signaling during regeneration reduced the cell-cycle entry of cardiomyocytes. Our study indicates that TOR signaling is a common mechanism that regulates cardiac cell proliferation in the adult heart during either regeneration or tumorigenesis.

In the next project, we investigated the role of heat-shock proteins in cardiac regeneration in zebrafish. Transcriptomic analysis from our lab revealed that the heat shock proteins Hsp90 and Hsp70 were upregulated in the regenerating myocardium. To investigate the role of these chaperon proteins during heart regeneration, we set up to generate three transgenic fish strains, namely a reporter line *hsp90:EGFP*, and two strains for functional assays that express either a wildtype or a dominant negative version of Hsp90 under the UAS promoter. In parallel, we applied a pharmacological approach using inhibitors against Hsp90 and Hsp70. We observed that inhibition of Hsp90 or Hsp70 reduced cardiomyocytes proliferation, resulting in impaired regeneration. Thus, we demonstrated that *hsp90* and *hsp70* are essential for heart regeneration in zebrafish.

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