Parallels between cardiac regeneration and neoplasia in zebrafish

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Regeneration and tumorigenesis both rely on cell proliferation. However, the consequences are dramatically diverging, one is reconstructing a damaged organ after injury while the second one is destructing a functional organ, potentially leading to death. Interestingly, organisms with a high regenerative ability display an increased tumorigenesis resistance. Mechanisms underlying this protection against cell transformation are still not fully understood. Here we use the zebrafish heart, which is a highly regenerative organ, to assess its susceptibility to tumor formation. Zebrafish heart regeneration is a robust process occurring by dedifferentiation and proliferation of existing cardiomyocytes (CMs) that will replace a transient scar with a new myocardium. In this project, we established a cardiac neoplasia model in adult zebrafish. Oncogenic HRAS was induced conditionally in adult cardiomyocytes using the Gal4-ERT2/UAS system. Our cardiac neoplasia model was characterized by ventricle overgrowth and abnormal histology of CM muscle fascicles. After a comparative study between oncogene-induced cardiac neoplasia and regenerating hearts, we could conclude that regenerating and oncogenic HRAS-induces hearts share similar features. Indeed, both processes display hyperproliferation of CMs, reactivation of embryonic isoform of cardiac myosin (embCMHC), inflammation response driven by leucocytes, hypoxic CMs suggesting metabolic changes, and activation of common signaling cascades such as pSmad3-dependent TGF-β pathway and TOR signaling pathway. Additionally, regenerative-responsive genes upregulated during heart regeneration display higher expression levels in oncogenic hearts. Finally, we showed that TOR pathway inhibition by Rapamycin treatment counteracts both regenerative and neoplastic growth. In conclusion, our study demonstrates that zebrafish CMs are susceptible to tumor formation and it gives a first insight of parallels between cardiac neoplasia and regeneration in adult zebrafish. Identification of different factors responsible for accurate regeneration and tumor inhibition will help to develop new therapeutical approaches in both regenerative medicine and cancer treatment.

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