The integrated analysis of the dynamic transcriptional network of heart regeneration in the zebrafish: Biological insights and connections to mammals

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Abstract

Background: The zebrafish has the capacity to fully regenerate its heart following severe cardiac injury. The dynamic, systems-based modeling of the transcriptional events underlying heart regeneration in the zebrafish offers opportunities for fundamental and translational biomedical research. This may potentially result in novel therapeutic strategies to induce and boost this regenerative capability in humans who suffer from heart attacks.

Methods: We implemented an *in vivo* (cryoinjury) model of heart damage in the zebrafish. We recovered heart samples at different critical times during heart regeneration as well as samples from control hearts, and performed microarray experiments. Based on these data, we created a dynamic co-expression network that characterizes each stage of the regeneration process. We investigated relevant network properties and linked them to biological function in the zebrafish. We examined biologically-meaningful associations between these predictions and genes with experimentally-validated regulatory roles in heart regeneration in three mammal organisms.

Results: The heart regeneration network is organized into interconnected modules of highly co-expressed genes. A diversity of cellular processes relevant to heart regeneration are significantly activated in a time-specific manner and at the level of network modules. We identified network hubs that are candidate regulators or mediators of the regeneration process. Among the hubs, we found genes that have been previously shown as relevant to heart regeneration or to cardiac damage response in different model organisms. Hubs are also detected as such in an independent network of heart regeneration in the zebrafish. We also show that hubs are significantly conserved in mammals, including humans. Many of their homologs are targets of miRNAs known to induce heart regeneration in mammals.

Conclusion: This study provides the first comprehensive, network-based characterization of the heart regeneration process in zebrafish at the transcriptional level. We identified network hubs of relevance to regulatory control of the heart regeneration program in zebrafish and mammals.