# A comprehensive integrative analysis of the transcriptional network underlying the zebrafish heart regeneration

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## Background

Myocardial infarction causes irreparable damage to human heart, increasing risk of premature death and cardiac malfunction.

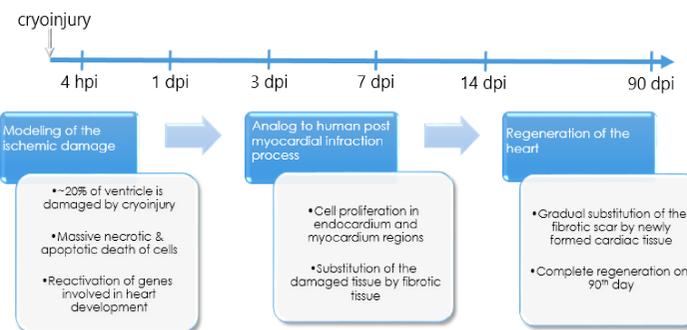Remarkably, adult zebrafish achieves complete regeneration of heart following cryoinjury.

## Objective

to characterize the transcriptional network of the zebrafish heart regeneration and underlying regulatory mechanisms

**1**

## The data

Microarray data from zebrafish cryoinjury model, containing 6 post-cryoinjury time points and 3 different Sham samples.



**2**

## Network construction

Correlation between gene expression profiles was determined by Pearson's correlation coefficient.

Each Pearson correlation value was transformed into adjacency value by soft-thresholding, resulting in weighted gene co-expression network.

| Network concept | No of edges before filtering | No of edges after filtering | Density | Centralization | Heterogeneity | Mean Clustering Coefficient | Mean scaled connectivity |
|---|---|---|---|---|---|---|---|
| Pearson's network | 6,008,311 | 436,803 | 0.074 | 0.105 | 0.498 | 0.167 | 0.412 |

**3**

## Dynamic visualization of gene expression patterns
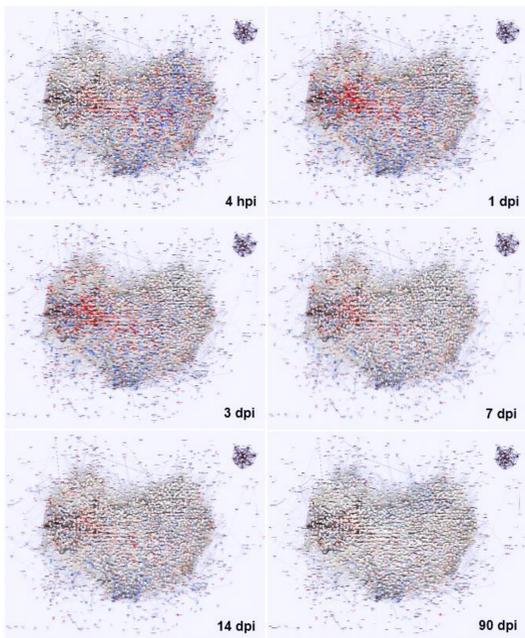


Nodes correspond to genes with colors indicating differential expression. Up-regulation is shown in gradation of red, down-regulation – in gradation of blue color. The edges denote correlation between the genes. Hpi indicates hour post injury; dpi, day post injury.
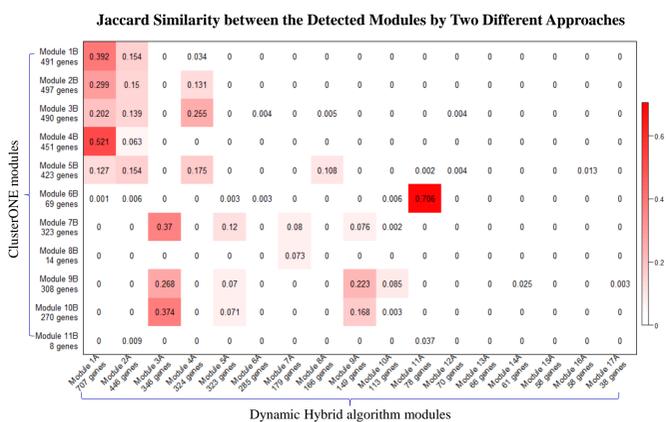
**4**

## Module detection

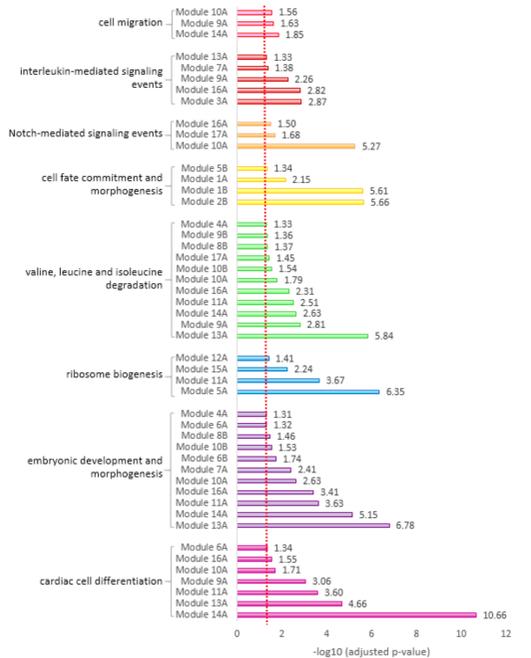A module is a group of densely interconnected nodes of the network.

*Dynamic Hybrid algorithm* (Langfelder and Horvath, 2008) detected 17 modules.

*ClusterONE* (Nepusz et al., 2012) detected 11 modules.



Jaccard Similarity between the Detected Modules by Two Different Approaches

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## Functional enrichment of the modules



The prediction of functional enrichment was obtained by Integrative Multi-species Prediction (IMP) database. The horizontal axes of the figure denote the $-\log_{10}$(adjusted p-value). The p-values were multiple test corrected by controlling FDR rate. The significance threshold for the results is presented by the red dashed line.

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## Dynamic expression patterns are linked to specific functionality
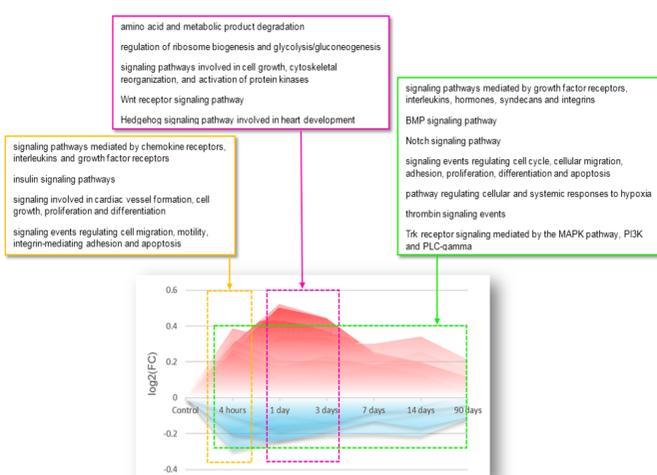


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## Regulatory hub genes

Hub genes – are potential key regulators of behavior of the modules and global network.

**Top 10 annotated hub genes detected by wiPER.** The WNC score stands for a weighted node connectivity score. p-values were adjusted by Bonferroni correction.

| Hub Genes | Module Membership | Observed WNC Score | Adjusted p-value | Expression/disease association |
|---|---|---|---|---|
| gene A | 1A, 1B, 2B, 3B, 4B, 5B | 384.71 | 0 | small cell lung cancer; rheumatoid arthritis; autoimmune disorders |
| gene B | 1A, 1B, 2B, 4B, 5B | 366.34 | 0 | end of fetal development; hemophagocytic lymphohistiocytosis |
| gene C | 1A, 1B, 2B, 3B, 4B, 5B | 364.89 | 0 | pulmonary tuberculosis |
| gene D | 1A, 1B, 2B, 3B, 4B, 5B | 362.85 | 0 | prostate cancer; intravascular atherosclerosis |
| gene E | 1A, 1B, 2B, 3B, 4B, 5B | 360.68 | 0 | Alzheimer's disease; schizophrenia |
| gene F | 3A, 6B, 9B, 10B, 11B, 12B, 13B, 14B | 357.15 | 0 | at stage of brain development; colorectal cancer; basal and squamous cell cancers |
| gene G | 2A, 4B, 5B | 351.19 | 0 | heart regeneration; heart response to chronic constant hypoxia |
| gene H | 1A, 1B, 2B, 3B, 4B, 5B | 341.01 | 0 | heart response to chronic constant hypoxia; head, neck, lung squamous cell carcinoma |
| gene I | 1A, 1B, 2B, 3B, 4B, 5B | 339.10 | 0 | - |
| gene J | 1A, 1B, 2B, 3B, 4B, 5B | 335.90 | 0 | - |

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## Conclusions

Two clustering methods are complementary and give biologically meaningful modules.

Among the top hub genes, there are potential key drivers of heart regeneration process.

Specific regeneration steps and processes are distinguished with dynamic gene expression patterns.

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