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Fixing a Broken Heart: A Look at Heart Regeneration in Zebrafish



Abstract

Time heals all wounds they say, but not damage to cardiac muscles. Heart tissues respond to injury not by replacing damaged or lost tissues but by creating scars which remain as non-contractile dead zones. However, recent studies of zebrafish have shown that two months after 20% of the heart has been amputated, heart regeneration does occur. Indeed, histological sections of hearts examined at different time points exhibited robust proliferation of cardiomyocytes where the heart was sectioned. A proposed mechanism for heart regeneration involves the reentry of differentiated cardiomyocytes into the cell cycle followed by proliferation to replace the amputated tissue. BrdU was used to label cells undergoing mitosis, and significant accumulation was observed in cardiomyocytes surrounding the damaged area. Furthermore, temperature-sensitive mutants of the cell cycle regulator *Mps1* failed to regenerate and instead formed scars. Analysis of gene expression through *in situ* hybridization revealed that components of the Notch pathway and the *Msx* family of transcription factors are upregulated early on in heart regeneration, although the exact roles they play remain to be elucidated. Interestingly, none of these genes are found to be expressed in developing hearts. This indicates that a specific genetic program is executed in regeneration instead of a simple recapitulation of the original developmental program. In a separate study, microarray analysis revealed three gene clusters expressed in a sequential pattern that function in wound response, wound healing, and finally tissue remodeling. Another pathway, the PDGF signaling pathway, has been implicated in cardiomyocyte proliferation, although its mechanisms in heart regeneration, along with the other factors identified through microarray analysis, have yet to be determined. An understanding of the molecular mechanisms of heart regeneration in zebrafish may shed light on possible therapeutic approaches to address human cardiac injuries.

Keywords: heart regeneration, Notch, Msx, PDGF signaling, cardiomyocyte proliferation

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Abstract

Time heals all wounds they say, but not damage to cardiac muscles. Heart tissues respond to injury not by replacing damaged or lost tissues but by creating scars which remain as non-contractile dead zones. However, recent studies have shown that in zebrafish, heart regeneration does occur, within two months, after around 20% of the heart has been amputated. Indeed, histological sections of hearts examined at different time points exhibited robust proliferation of cardiomyocytes where the heart was sectioned. A proposed mechanism for heart regeneration involves the reentry of differentiated cardiomyocytes into the cell cycle followed by proliferation to replace the amputated tissue. BrdU was used to label cells undergoing mitosis, and significant accumulation was observed in cardiomyocytes surrounding the damaged area. Furthermore, temperature-sensitive mutants of the cell cycle regulator Mps1 failed to regenerate and instead formed scars. Microarray analysis revealed three gene clusters expressed in a sequential pattern that function in wound response, wound healing, and finally tissue remodeling. *In situ* hybridization revealed that components of the Notch pathway and the *Msx* family of transcription factors are upregulated early on in heart regeneration, although the exact roles they play remain to be elucidated. Interestingly, none of these genes are found to be expressed in developing hearts, indicating that a specific genetic program is executed in regeneration instead of simply calling upon the original developmental program. Another pathway, the PDGF signaling pathway, has been implicated in cardiomyocyte proliferation, although its mechanisms in heart regeneration, along with the other factors identified through microarray analysis, have yet to be determined. An understanding of the molecular mechanisms of heart regeneration in zebrafish may shed light on possible therapeutic approaches to address human cardiac injuries.

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