

We'll Change to Fill the Void

The developing zebrafish heart also appears to be capable of morphallaxis or transdifferentiation during regeneration. Researchers working with zebrafish larvae induced severe injury to the ventricular tissue of the larval heart by causing apoptosis of the ventricular cardiomyocytes (Zhang et al. 2013). They did so by targeting the expression of nitroreductase (NTR) in ventricular cardiomyocytes using the *ventricular myosin heavy chain* (*vmhc*) promoter and inducing cell death by administering an NTR-reactive cytotoxic prodrug. This procedure severely ablated ventricular tissue in the larval heart. What happened next was remarkable. Neighboring differentiated *atrial* cardiomyocytes responded to the injury by migrating into the damaged ventricular tissue and upregulating ventricle-specific genes such as *vmhc* (**FIGURE 1A**). Months later, fate mapping of these migrating atrial cardiomyocytes revealed that they remained in the ventricular wall, contributing to a fully regenerated and functioning ventricle and heart (**FIGURE 1B**). Zhang and colleagues went on to show that Notch-Delta signaling is highly upregulated in the atrial myocardium and is required for this atrial-mediated repair of ventricular damage (**FIGURE 1C**). Pharmacological inhibition of Notch signaling with DAPT exposure during ablation of ventricle tissue severely impairs heart regeneration (**FIGURE 1D**; Zhang et al. 2013). These results suggest that at least during larval development, cardiac myocytes are capable of undergoing transdifferentiation to support regeneration of the heart. Thus, it appears that the cells of the zebrafish heart employ multiple mechanisms to power its regeneration: blastema formation through epimorphosis, compensatory proliferation, and Notch-mediated transdifferentiation. (See **Further Development 24.11, Immune Cells to the Regeneration!**, online.)

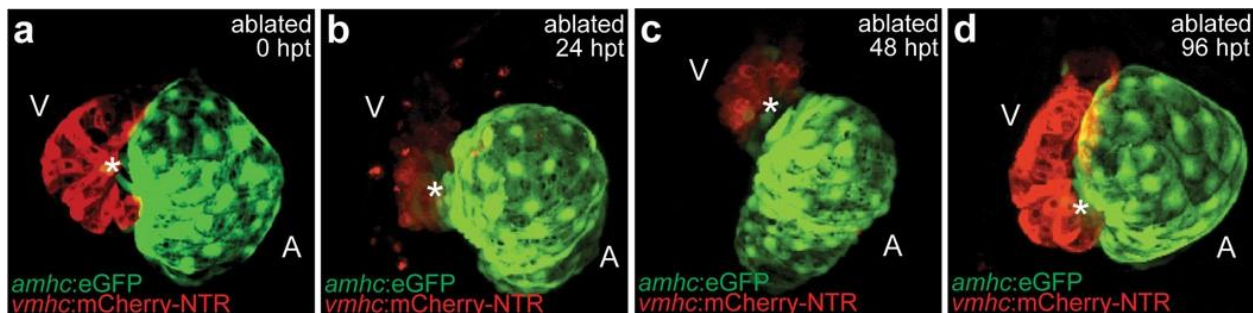


FIGURE 1 Transdifferentiation of atrial cardiomyocytes into ventricular cardiomyocytes during larval heart regeneration in the zebrafish. (A) After researchers induced apoptosis of ventricular cardiomyocytes, fate mapping of differentiated atrial cardiomyocytes (green) shows migration from the atrium to the wound area where ventricle tissue has been ablated. At the transition point during this migration, the atrial cells start expressing ventricular markers, suggesting transdifferentiation. (B) Twelve months after ablation of ventricular tissue, infiltrating atrial cardiomyocytes (green) fully differentiate into the ventricular tissue (red) and contribute to a functional adult heart. (C) Notch-Delta signaling is required for the successful regenerative contributions from atrial cardiomyocytes. Twenty-four hours after ventricular cell ablation (right photograph), *deltaD* along with other related genes (blue

stain) are highly upregulated in the atrial cardiomyocytes, particularly in those migrating toward the ventricular tissue. (D) Pharmacological inhibition of Notch signaling with DAPT exposure during ablation of ventricle tissue severely impairs heart regeneration. A, atrium; V, ventricle; AVC, atrioventricular canal; OFT, outflow tract. (D after R. Zhang et al. 2013. *Nature* 498: 497–501.)

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