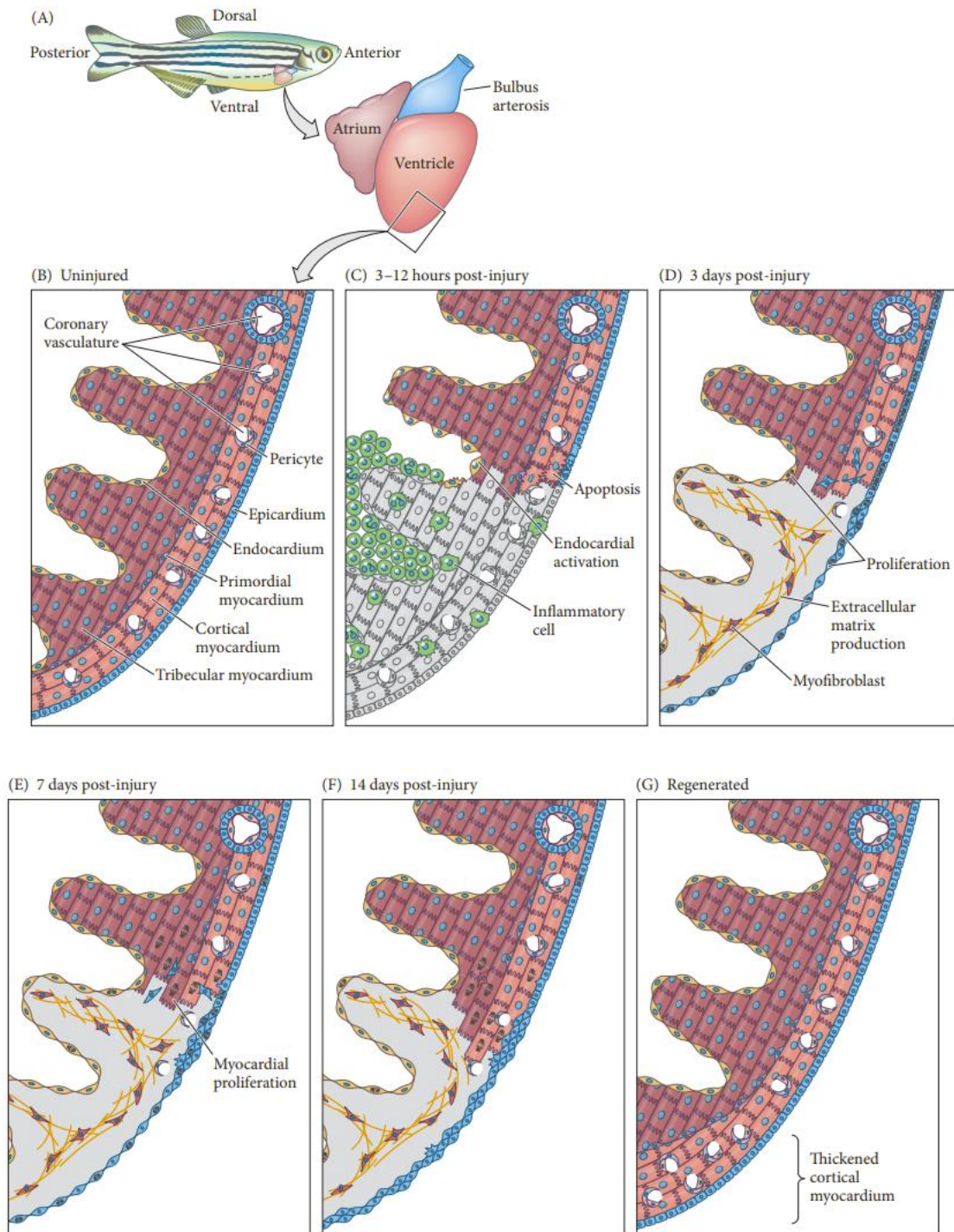


The “heart” of the matter: epimorphosis, compensation, and transdifferentiation

The zebrafish has a relatively simple tubular heart. Venous blood enters the sinus venosus, passes into the single atrium, is pumped into the single ventricle, and leaves the heart through the bulbus arteriosus. Several different injury models—including surgical removal of pieces of the myocardium, cryoinjury, and genetically induced tissue-specific ablation—have been adopted to study regeneration of heart tissues in zebrafish (reviewed in Shi et al. 2015; Mokalled and Poss 2018).

The zebrafish heart retains the ability to regenerate throughout the life of the fish, in part due to the sustained mitotic capacity of the cardiac myocytes (heart muscle cells) that constitute a majority of the heart tissue (Poss et al. 2002). It is clear that a major contribution to regeneration of the adult heart comes directly from preexisting myocytes. Indeed, use of the “zebrabow” transgenic system for tracing the lineage of cells under the control of heart-specific promoters demonstrated that previously differentiated cardiac myocytes give rise to clones of different types of regenerated cells. These studies and work described in Further Development online entries demonstrate that the zebrafish uses dedifferentiation, transdifferentiation, blastema formation, and compensatory proliferation to regenerate the heart (González-Rosa et al. 2017).

The stages of zebrafish heart regeneration are summarized below and in [FIGURE 24.37](#).



Early responses (Figure 24.37B)

Injury by amputation, freezing, or other means induces an inflammatory response required for regeneration to proceed. Macrophages, neutrophils, and other cells invade the site of injury. Localized apoptosis occurs near the edges of the injury.

The normally tightly adherent endocardial cells lining the heart chambers ball up and start to express both embryonic and cytokine genes.

The regeneration scaffold (Figure 24.37C)

The endocardial cells and the epicardial cells lining the heart proliferate and migrate over the inner and outer surfaces of the injured tissue.

Myofibroblasts and extracellular matrix components increase within the injured area, creating fibrotic, scarlike tissue.

The cardiac blastema (Figure 24.37D)

The myocardium at the edge of the injury undergoes significant proliferation.

Compensatory proliferation and revascularization (Figure 24.37E)

New coronary vessels rapidly form. This revascularization is necessary for complete regeneration.

Proliferation of cardiomyocytes increases throughout the heart.

Fibrotic tissue (the meshwork of fibroblasts covering the wound site) is progressively lost over the course of regeneration.

Integration (Figure 24.37F)

The fibrotic scar is completely removed and replaced with a slightly thicker myocardium than that of an uninjured heart.

The regenerated myocardium becomes functionally integrated into the rest of the heart.

(See WATCH DEVELOPMENT 24.1, **Dr. Neil Chi and Zebrafish Heart Regeneration**, online.)

FIGURE 24.36 Preexisting cardiomyocytes contribute to ventricular regeneration in zebrafish.

(A) Double-transgenic zebrafish were used to produce multicolor clonal labeling only in cardiomyocytes, as controlled by the *cmhc2* promoter for Cre expression. The “ER” in CreER denotes its estrogen-responsive control, which enables researchers to use the drug tamoxifen to induce recombination at any time. This image is of a 6-week-postfertilization heart ventricle following recombination at 4 days postfertilization. Patches of distinct colors can be seen, indicating that the heart is derived from only several dozen cardiac progenitors. (B) These preexisting clonally labeled cardiac myocytes are seen contributing to a majority of the regenerated ventricular tissue. Arrowheads and arrows indicate the primordial (Pr) and cortical layers (Cor), respectively.

24.36 PHOTO CREDITS

A,B from V. Gupta and K. D. Poss. 2012. *Nature* 484: 479–484

FIGURE 24.37 (A) Lateral view of an adult zebrafish and the parts of the heart; the boxed portion of the ventricle wall is shown to the right, magnified and in cross section. (B–F) Stages of zebrafish heart regeneration. Detailed descriptions are given in the text. (After J. González-Rosa et al. 2017. *Regeneration* 4: 105–123/CC BY 4.0.)

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