**Supplemental figure legends**

**Figure S1. Morphological analysis of heart regenerative process and blood clot replacement by Hematoxylin and eosin (H&E) staining.**

RCs, residual clots; sub-clot int, subcardium-clot interaction; mus-clot int, muscle-clot interaction; mus-clot com, mus-clot compartment; BV, blood vessel (encircled by dashed line); dpa, day post-amputation; Scale bar = 200 μm.

**Figure S2. Immunohistochemical detection of eight common epigenetic marks during zebrafish heart regeneration.**

Tissue samples were collected at 0dpa, 3dpa, 6dpa and 9dpa. The immunostaining intensity of each epigenetic mark in normal uncut heart (0dpa) was used as mean basal levels. The specific antibodies for the following epigenetic marks were used: DNA methylation (5-methylcytosine, 5-mC; DNA (cytosine-5)-methyltransferase 1, DNMT1), histone acetylation (H3K9Ac, H3K27Ac), histone methylation (H3K4Me3, H3K27Me3, H3K9Me3) and histone phosphorylation (H3pS10). Relative to temporal emergence of 5mC and H3K4Me3 at 3dpa in small number of light cells at intersections of epicardium-clot and muscle-clot, all new tissue cells including the clotted cells showed stable H3K27Ac expression, and global loss of H3K27Me3 and DNMT1 during heart regeneration from 3dpa to 9dpa. H3pS10 expression was detected at all stages in part of the cells, presumably in the proliferating cells. Scale bar = 100 μm.

**Figure S3. Subcellular localizations of H3K9Ac and H3K9Me3 within the transforming cells at 6dpa and 9dpa. Inlet showed magnification.**

Scale bar = 25 μm.

**Figure S4. Antagonist pretreatments altered H3K9Me3 and H3K9Ac depositions and Flk1-GFP distribution.**

Chaetocin and anacardic acid were used as specific inhibitors of the lysine-specific histone methyltransferase and histone acetyltransferase respectively. After ventricle amputation, four fish each group were soaked in 0.05% DMSO, 500 nM chaetocin or 500 nM anacardic acid. IHC was conducted at 6dpa and 9dpa. Scale bar = 50 μm.

**Figure S5. ChIP-seq identification of H3K9Ac- and H3K9Me3-specific poised enhancers**.

(A) Heatmap representation of normalized ATAC-seq signal over H3K9Ac- and H3K9Me3-specific enriched regions. The top panel shows read signal over the 8043 H3K9Ac-specific enriched regions (Class I) and the middle panel shows read signal over the 687 H3K9Me3-specific regions (Class II), while the bottom panel shows read signal over the 1286 shared regions of H3K9Ac and H3K9Me3 marks (Class III), most of which are considered to be poised enhancers. Signals within 2 Kb surrounding the region center are displayed in a descending order.

(B) Profiles of normalized tag density across a genomic window of ± 2 Kb surrounding the region center of H3K9Ac and H3K9Me3 marks.

(C) Pie chart showing the proportion of H3K9Ac and H3K9Me3 enriched sites within the indicated genomic regions: introns, exon, intergenic regions, 3’ UTR, 5’ UTR, promoters-TSS, TES and no-coding regions. Peak summit located up to 1 Kb upstream and 100 bp downstream of the TSS are determined as promoter-TSS region.

**Figure S6. Enrichments of H3K9Ac and H3K9Me3 marks at the nearest genes.**

Snapshots of the IGV genome browser showing of H3K9Ac and H3K9Me3 ChIP-seq and RNA-seq data. Peaks underlined with black bars indicate significant ChIP-seq peaks identified by MACS2.

**Figure S7. ChIP-qPCR reevaluation of the enrichment of the two histone modification marks (H3K9Me3 and H3K9Ac) at the promoters of the target genes.**

Flk1 (kdrl), alpha-SMA (acta2). \* P ≤ 0.05; \*\* P ≤ 0.01; n = not signiﬁcant.

**Figure S8. Top 10 enriched TF motifs for H3K9Ac and H3K9Me3 ChIP-seq.**

*P* values were calculated by HOMER v4.9.

**Figure S9. Localization of the Krt5 peptide in the Krt5 and/or noggin transfected PAC2 cells.**

Scale bar = 25 μm.

**Figure S10. Bafilomycin A1 (BA) pretreatment reduced tissue degradation and enhanced Flk-1 indicated angiogenesis at 6dpa.**

Bafilomycin A1 pretreatment of amputated heart reduced tissue degradation and exaggerated flk1-expressing vasculature. Bafilomycin A1 is a specific inhibitor of the vacuolar-type H(+)-ATPase (V-ATPase) in cells, and can inhibit the acidification of organelles containing this enzyme, such as lysosomes and endosomes [1]. Scale bar = 50 μm.

**Reference**

1. Klionsky, D. J.; Elazar, Z.; Seglen, P. O.; Rubinsztein, D. C., Does bafilomycin A1 block the fusion of autophagosomes with lysosomes? *Autophagy* **2008,** 4, (7), 849-50.