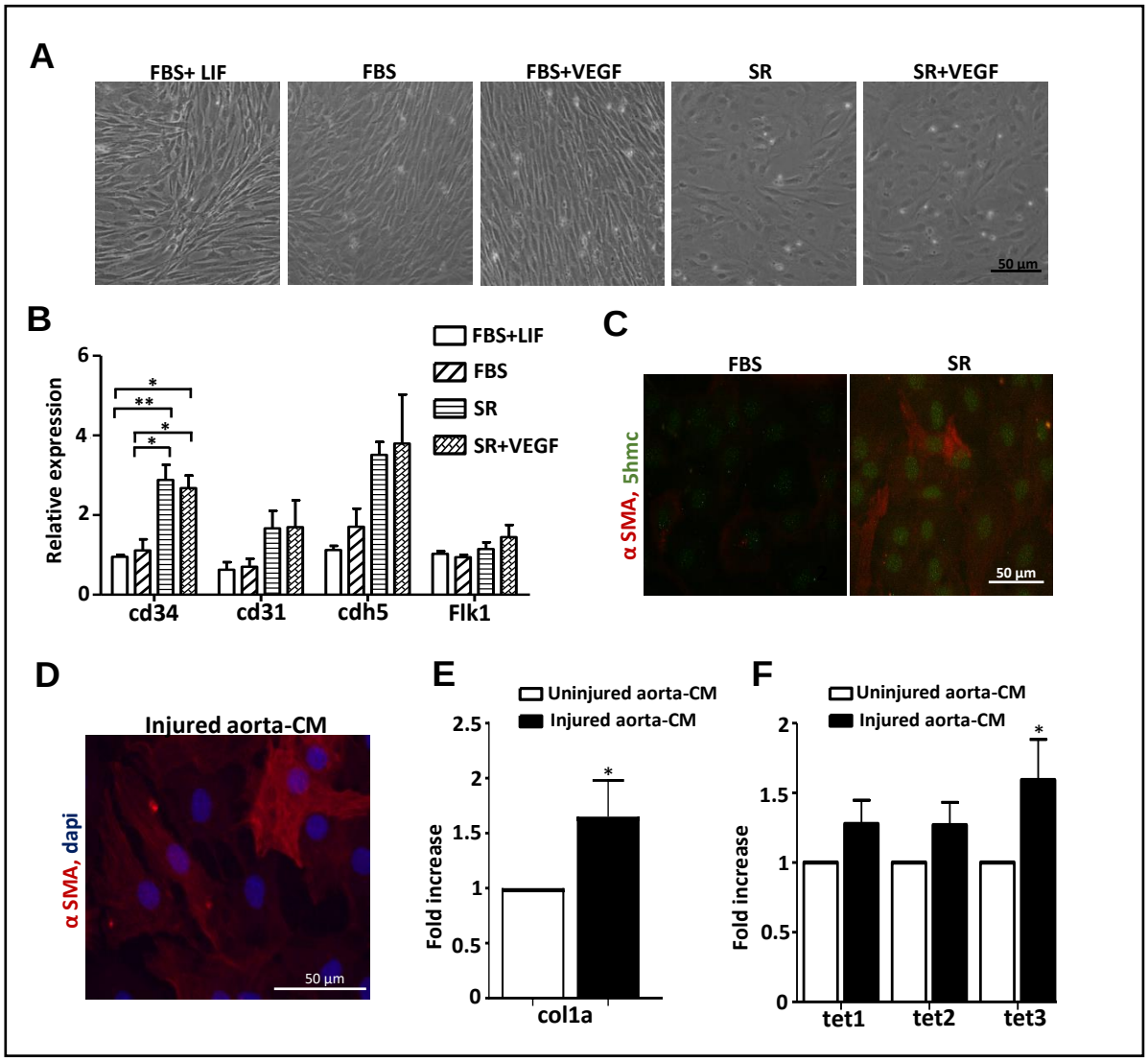

Figure I. AdvSca1 cells differentiate into SMC/mesenchymal cells and undergo epigenetic changes *in vitro* and *ex vivo* in response to vascular injury. **A,** Morphology of AdvSca1 cells cultured for 3 days in stem cell medium supplemented with FBS+LIF, FBS, FBS+VEGF, or differentiation medium SR, or SR+VEGF. No typical EC cobblestone morphology was observed in any conditions. **B,** Quantitative RT PCR analysis of EC genes expression in AdvSca1 cells cultured in different conditions (experiment performed in triplicate,*p<0.05,**p<0.01, data representative of 2 independent experiments). **C**, Immunofluorescence staining of AdvSca1 cells cultured in FBS or SR for αSMA (red) or 5hmc (green) showed the correlation between increased DNA hydroxymethylation and SMC/mesenchymal differentiation. Mouse AdvSca1 cells were cultured for 5 days in presence of conditioned media (CM) from uninjured or injured sections of the same rat artery **D,** Higher magnification of immunofluorescence staining for αSMA (red) of AdvSca1 cells treated with injured aorta CM shows the stress fiber organization. Quantitative RT PCR shows increase in (**E**) col1a expression and **(F)** Tet3 expression (n=9 arteries, *p<0.05 versus non injured aorta-CM).

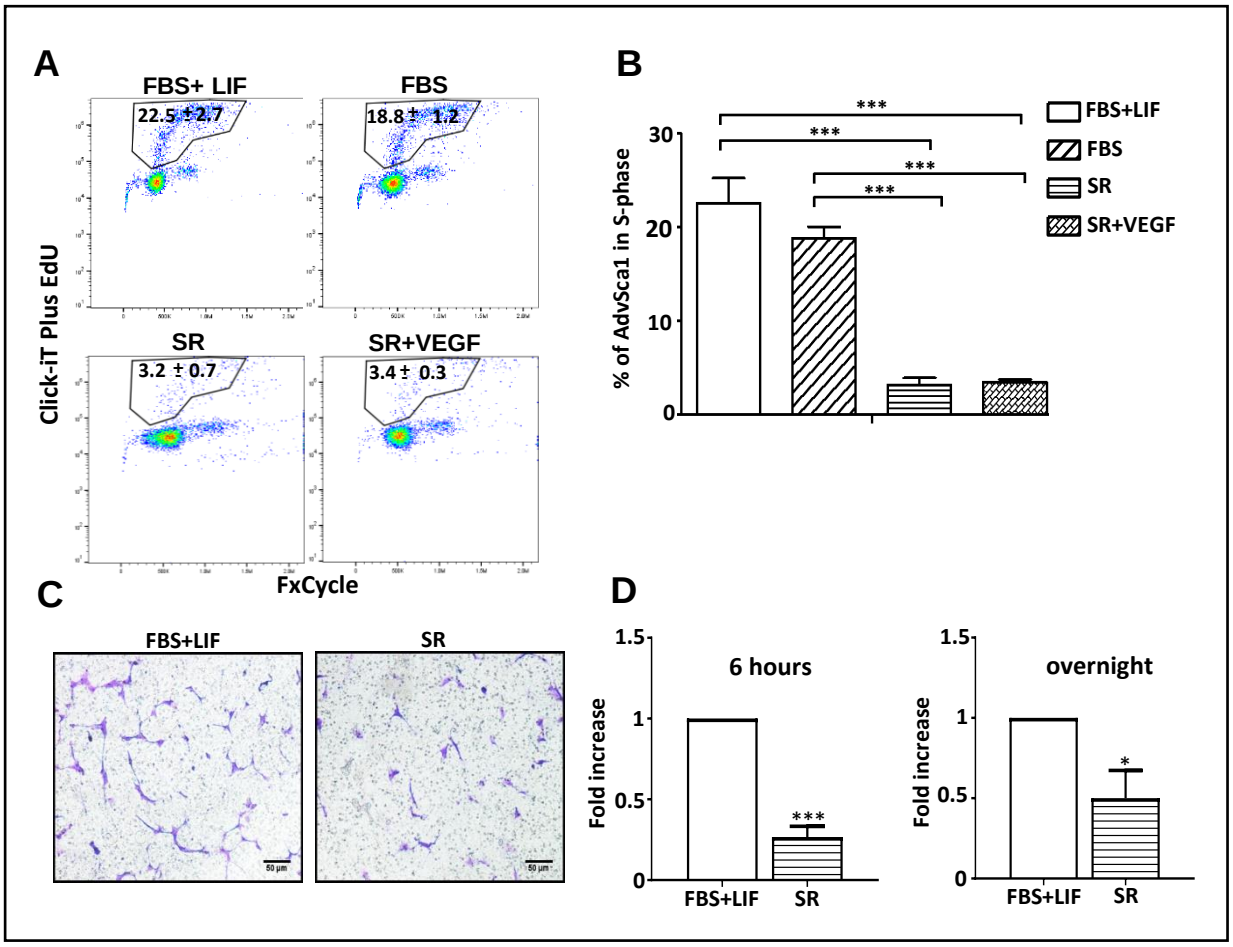

Figure II. AdvSca1 cells cultured in different conditions show changes in their proliferation and migration properties. **A**, Representative pictures of flow cytometry analysis for Edu and cell cycle distribution of AdvSca1 cells cultured for 3 days in FBS+LIF, FBS, SR and SR+VEGF. **B,** Percentage of AdvSca1 cells in S-phase for the different groups (***p<0.001, n=3, data representative of 2 independent experiments). AdvSca1 cells were cultured for 5 days in FBS+LIF or SR and then assessed for migration ability by transwell assay **C,** x10 magnification images of the transwell inserts of the overnight migrated AdvSca1. **D,** Quantification of transwell migration assay after 6h and overnight. 5 fields at x10 magnification of each insert for each condition were considered for quantification of cell migration (*p<0.05 , ***p<0.001 n=3).

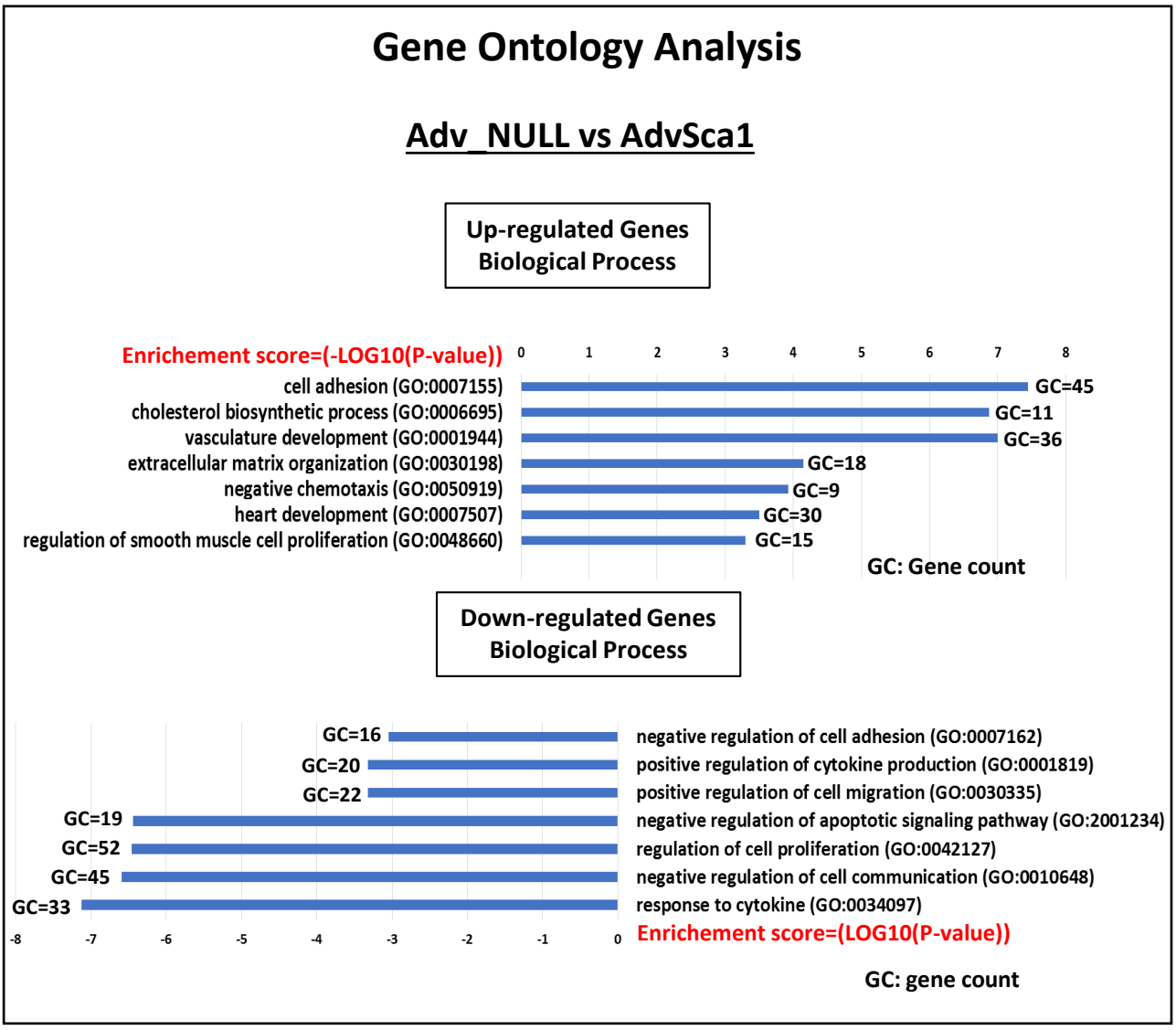

Figure III: Gene ontology analysis of the differentially regulated genes between Adv_NULL and Adv_Sca1. Gene ontology analysis was performed on the upregulated and downregulated genes of Adv_NULL compared to Adv_Sca1. Enrichment in gene ontology of biological processes are revealed. Significance of enrichment was evaluated by p-value.

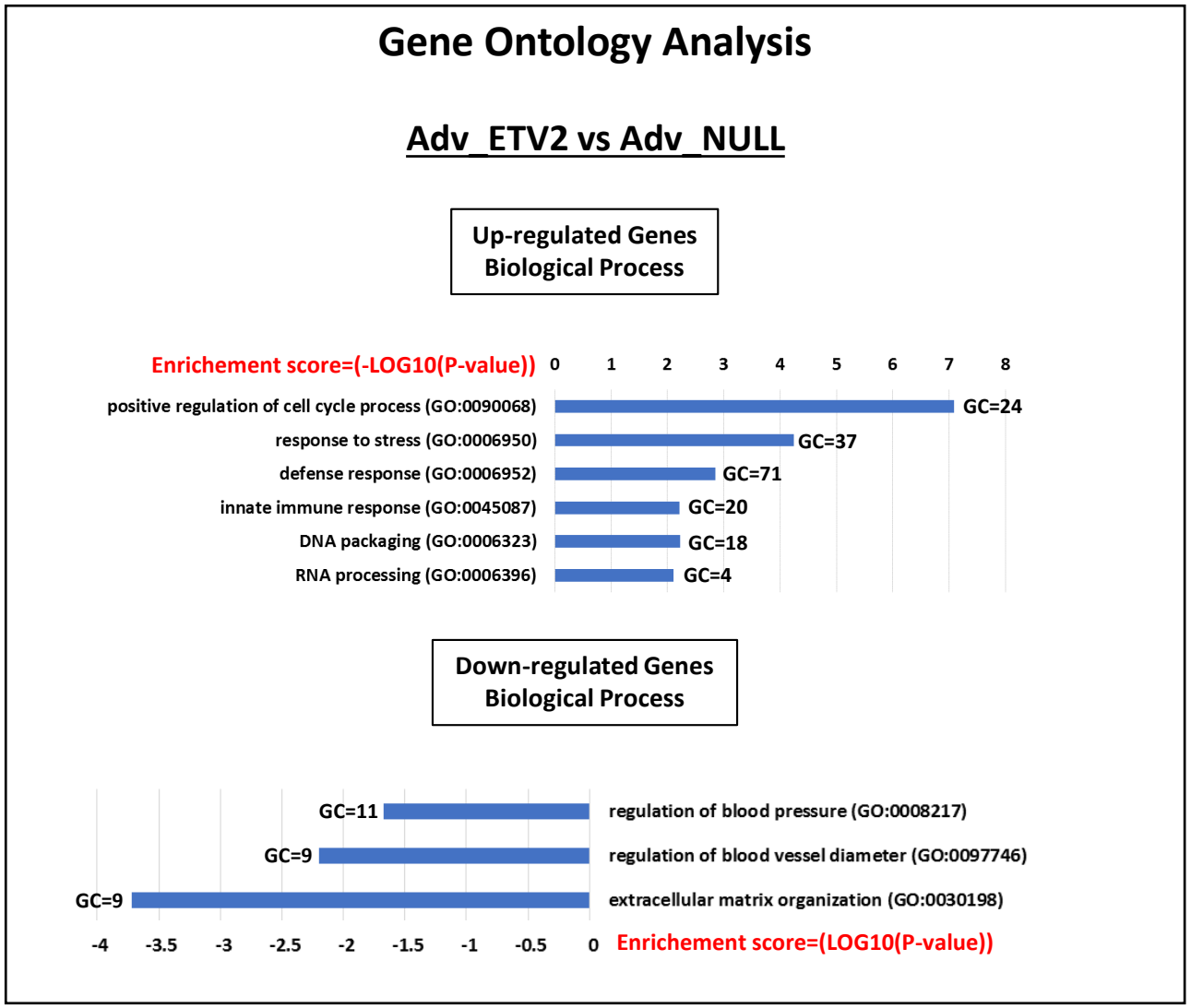

Figure IV. Gene ontology analysis of the differentially regulated genes between Adv_ETV2 and Adv_NULL. Gene ontology analysis was performed on the upregulated and downregulated genes of Adv_ETV2 compared to Adv_NULL. Enrichment in gene ontology of biological processes are revealed. Significance of enrichment was evaluated by p-value.

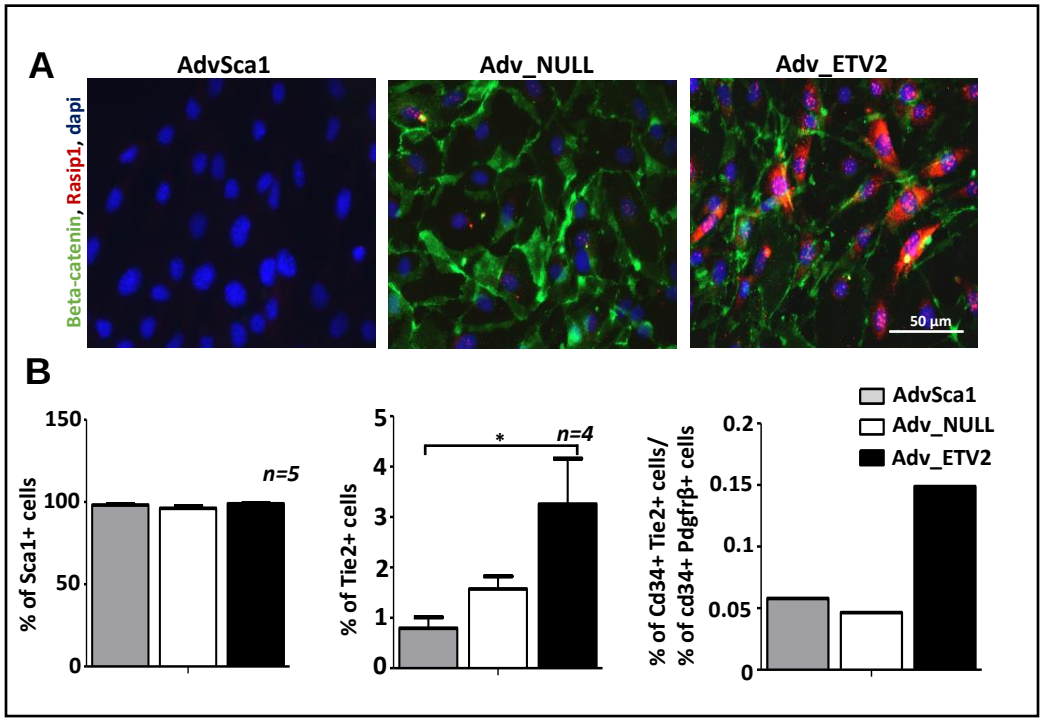

Figure V. Phenotypic characterization of AdvSca1, Adv_NULL and Adv_ETV2 cells. **A,** Immunofluorescence staining of AdvSca1, Adv_NULL and Adv_ETV2 cells for Rasip1 (red) and beta-catenin (green). **B,** Quantification of the percentage of Sca1+ cells, Tie2+ cells and measurement of the cd34+Tie2+/cd34+Pdgfrβ+ ratio in AdvSca1, Adv_NULL and Adv_ETV2 cells (*p<0.05, n=4-5 independent experiments).

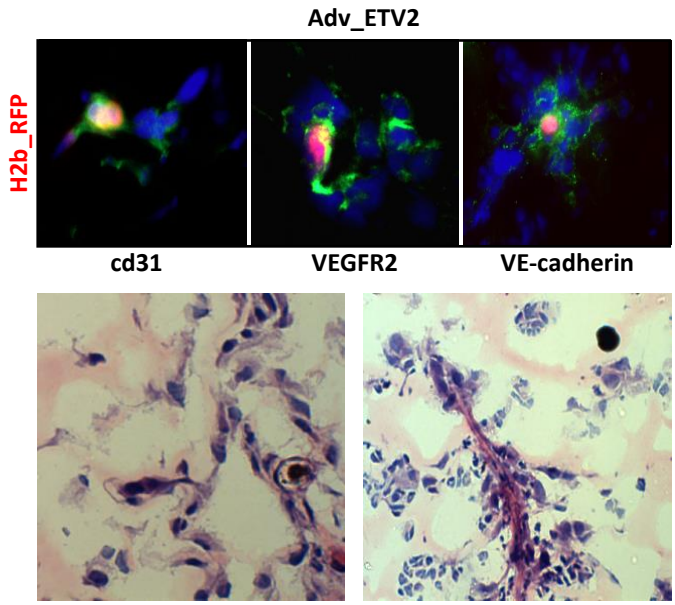

Figure VI. Adv_ETV2 cells express EC markers *in vivo* and form functional vascular networks in a subcutaneous matrigel plug assay. **(Top)** Immunofluorescence staining for cd31, VEGFR2, and VE-cadherin, of matrigel plugs sections where Adv_ETV2 cells stably expressing nuclear RFP were seeded. **(Bottom)** Sections of matrigel plugs seeded with Adv_ETV2 cells and stained for Hematoxylin and eosin staining showed the presence of blood cells in the newly formed vessels.

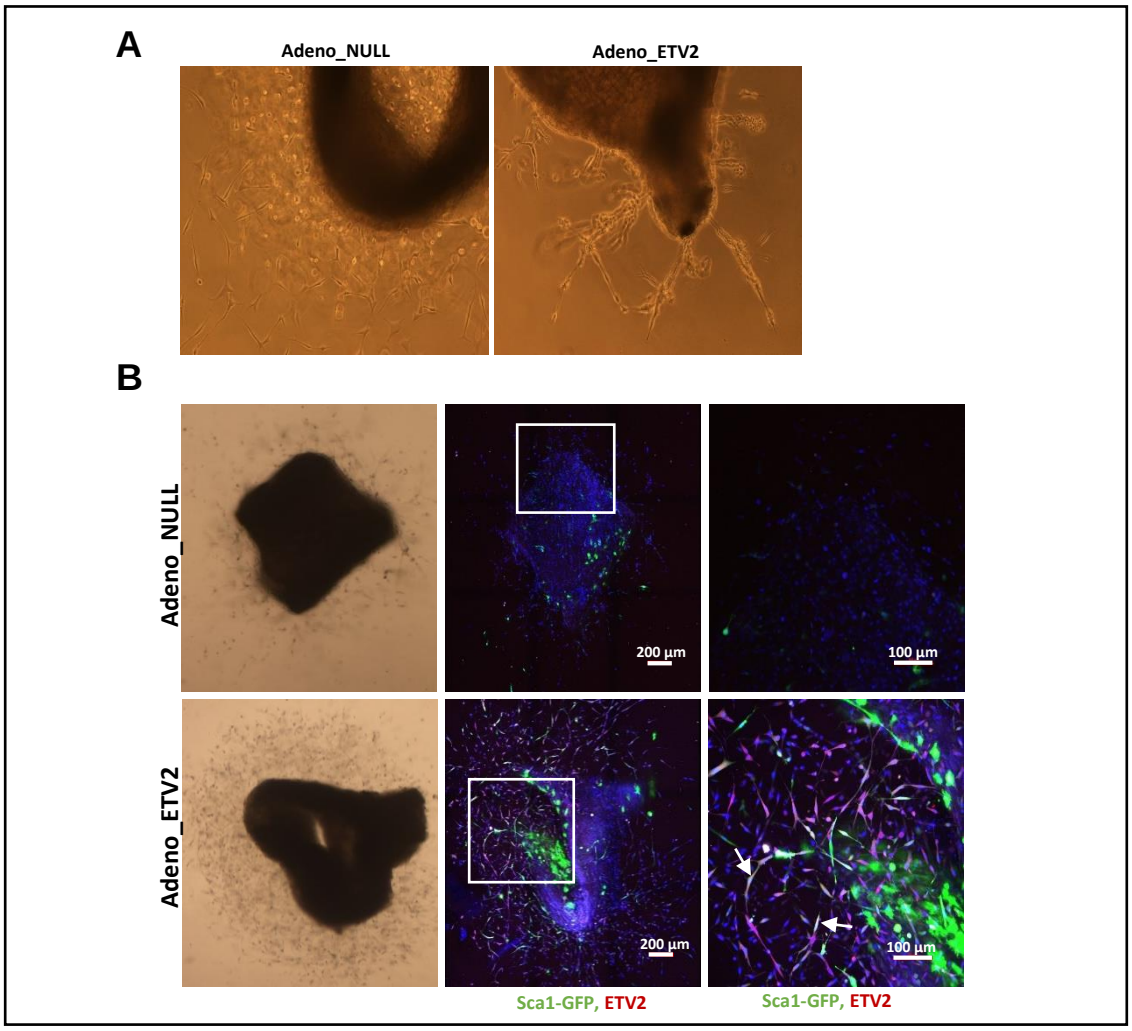

Figure VII. *Ex vivo* adenoviral delivery of ETV2 in Sca1+ cells of aortic ring explants increases vascular sprouting. Aortic rings from Sca1-GFP mice were cultured for 7 days in presence of control NULL or ETV2 overexpressing adenovirus. **A.** Higher magnification pictures of the aortic rings explants allows the visualization of the vascular sprouts. **B,** Both groups of rings were stained by immunofluorescence for ETV2 (red). GFP+ cells (Sca1+) (white arrows) can be seen expressing ETV2 in the rings treated with ETV2 adenovirus and included in the vascular sprouts.

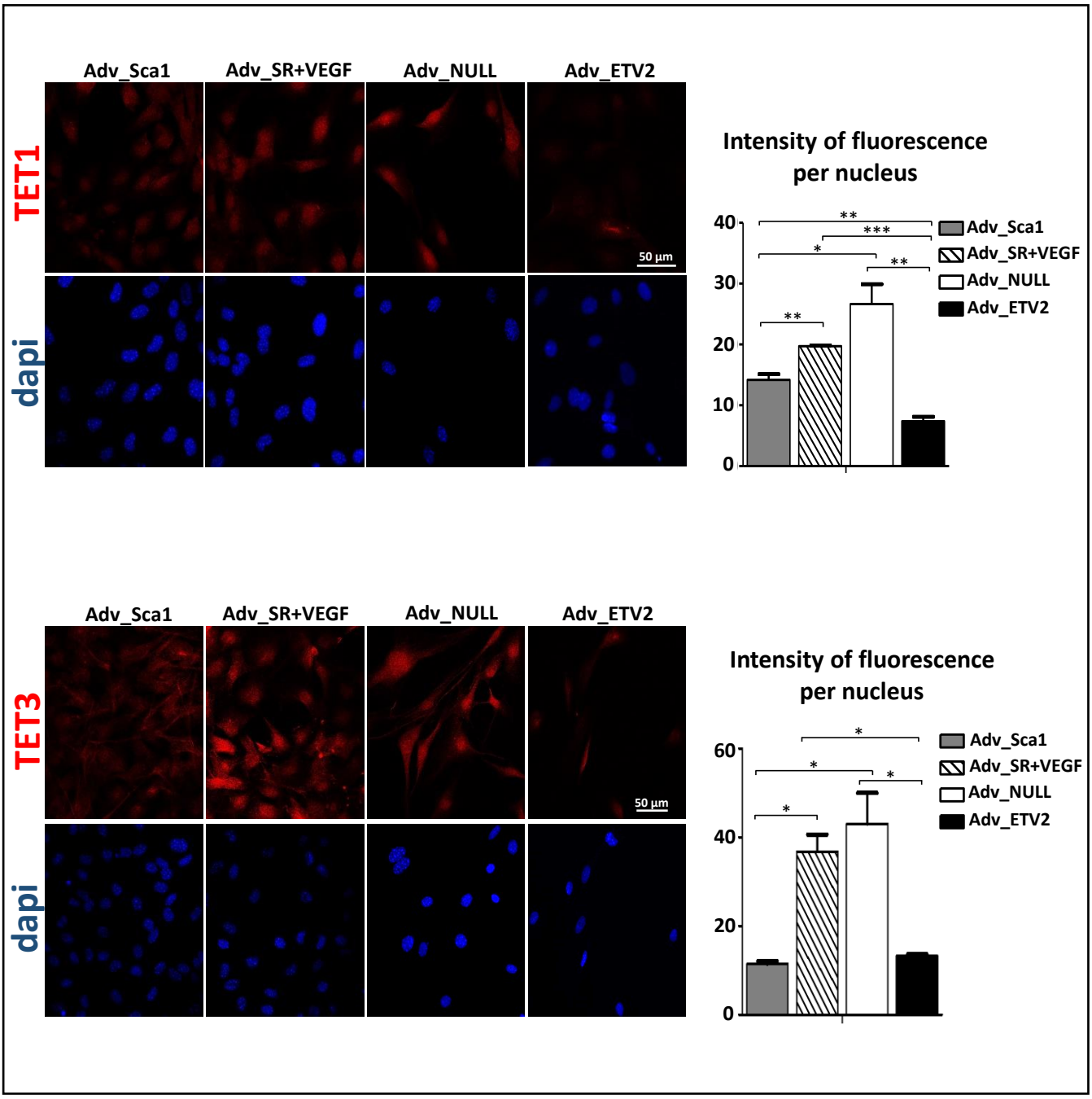

Figure VIII. Tet methylcytosine dioxygenases are differentially expressed in AdvSca1 cultured in FBS+LIF (AdvSca1) or SR+VEGF (Adv_SR+VEGF), Adv_NULL and Adv_ETV2 cells. Immunofluorescence staining for TET1 and TET3 (red). DAPI stains nuclei blue and quantification of intensity of fluorescence per nucleus and per x40 magnification field, n=3 magnification fields (*p < 0.05, **p < 0.01, ***p < 0.001)

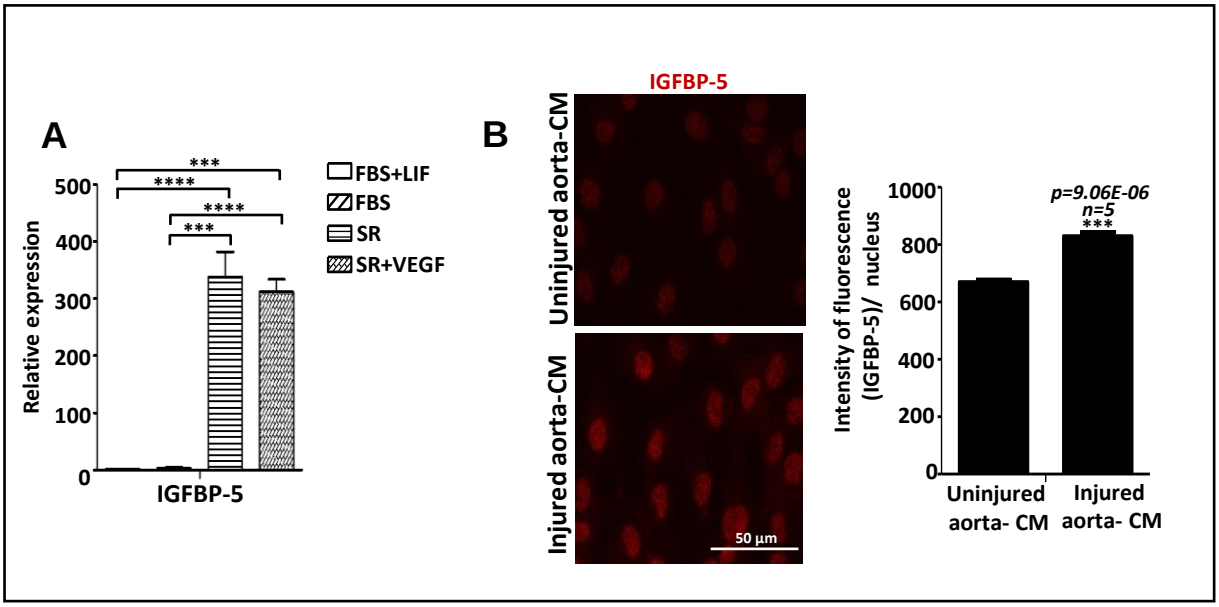

Figure IX. IGFBP-5 is involved in SMC differentiation of AdvSca1 cells. **A,** Quantitative RT PCR analysis of IGFBP-5 expression in AdvSca1 cells after culture in different conditions (Experiment performed in triplicate, ***p<0.001, ****p<0.0001, data representative of 2 independent experiments)**.** **B,** Immunofluorescence staining for IGFBP-5 (red), of AdvSca1 cells cultured for 5 days in CM from uninjured or injured rat artery. Intensity of fluorescence per nucleus and per x40 magnification field, n=5 magnification fields, ***p < 0.001 versus uninjured aorta-CM**.** The histogram is representative of results obtained from 3 different arteries.

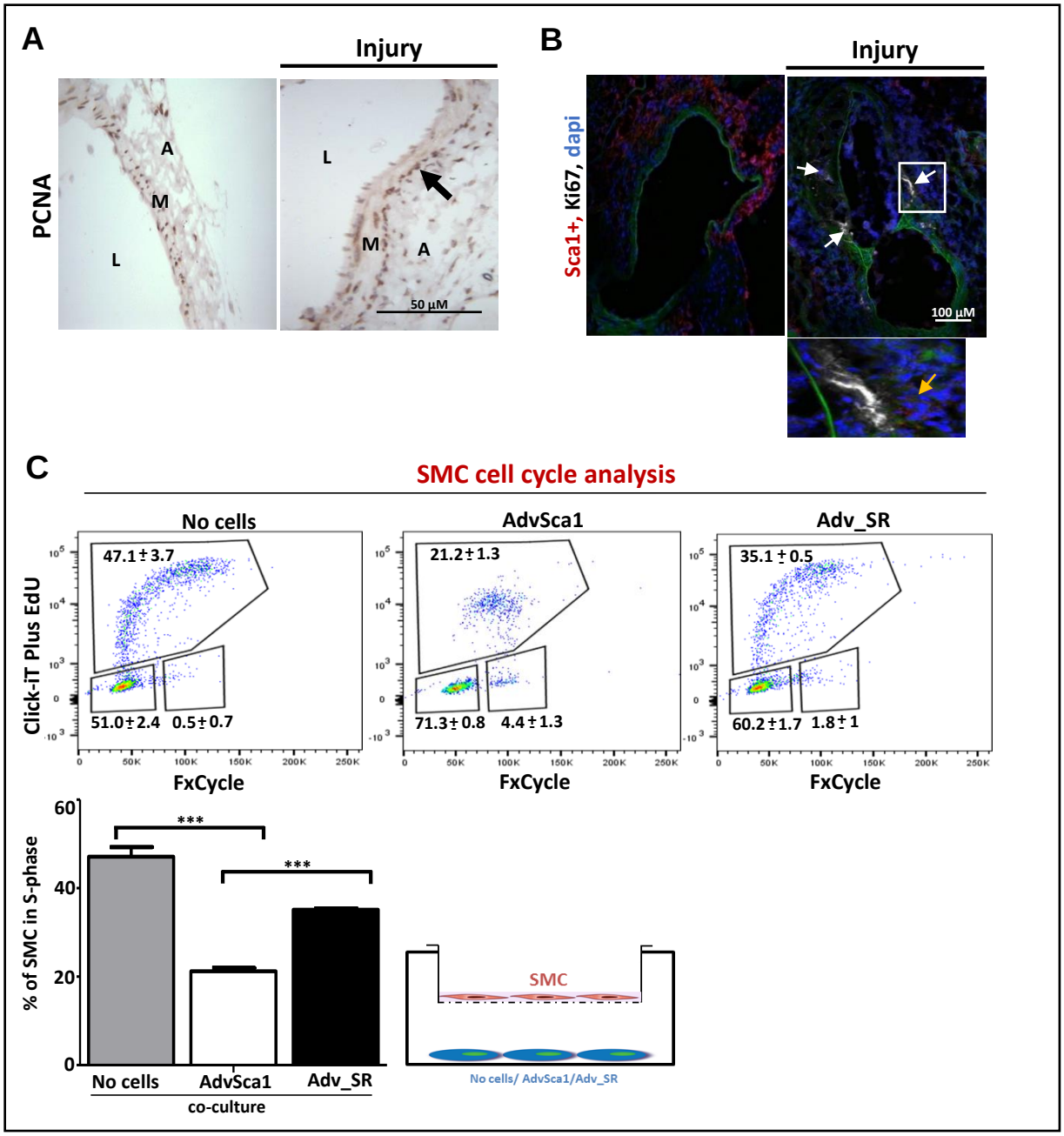

Figure X. AdvSca1 cells modulate SMC proliferation. **A,** Immunohistochemistry using PCNA antibody on sections from uninjured and 2 weeks post injury femoral arteries. **B,** Immunofluorescence staining using Sca1 (in red) and ki67 (in white) antibodies on sections from uninjured and 1 week post-injury femoral arteries. White arrows indicate ki67+ cells in the media and at the border media/ adventitia. The yellow arrow in the inset indicates Sca1+ cells. The internal elastic lamina can be seen by autofluorescence (green channel). **C,** SMC were cultured for 48 hours alone or in co-culture with undifferentiated AdvSca1 or cells differentiated in SR for 3 days (Adv_SR). SMC were analyzed for Edu and cell cycle distribution by flow cytometry (***p<0.001, n=3, data representative of 2 independent experiments).

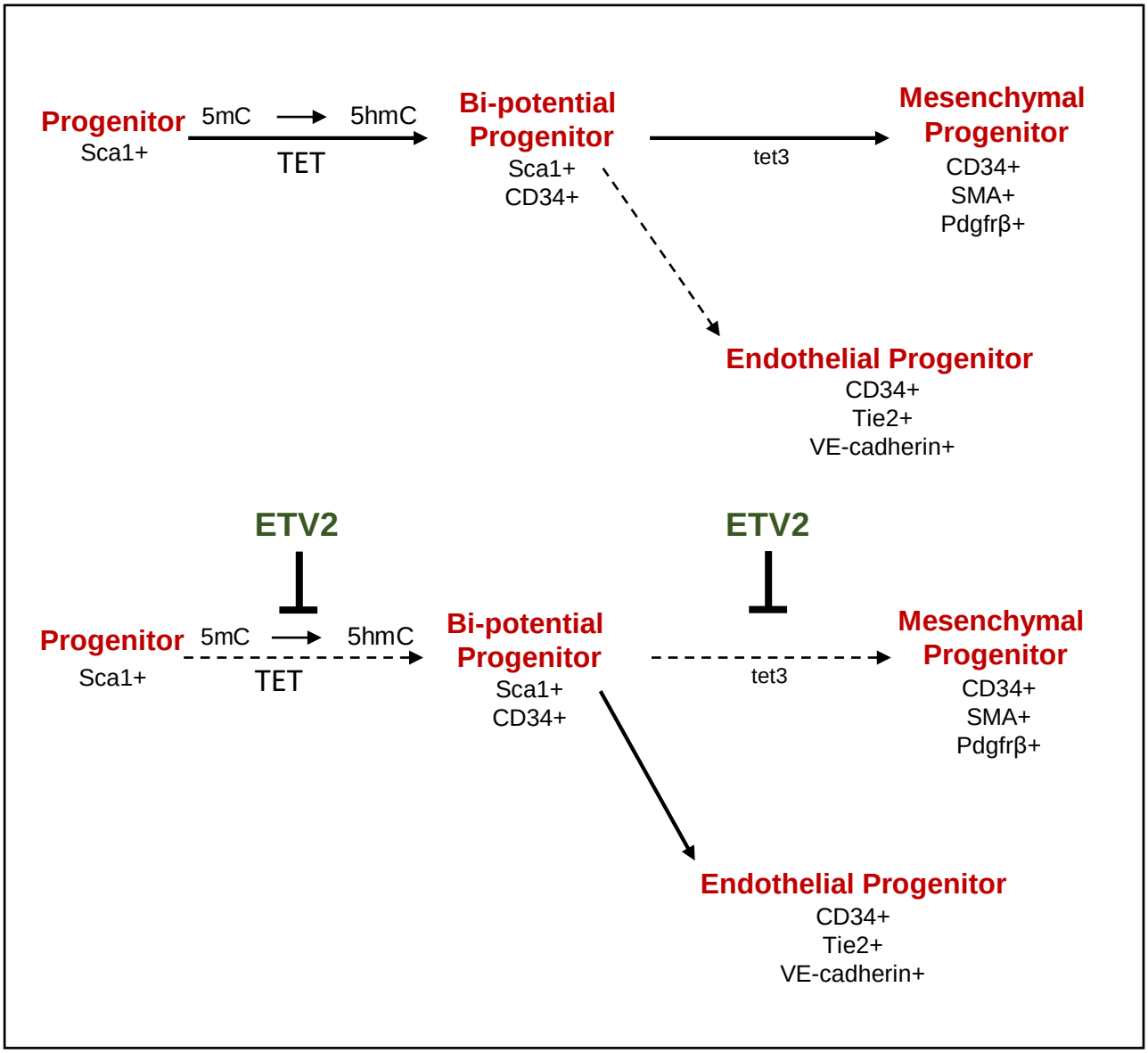

Figure XI. Schematic of AdvSca1 cells differentiation and ETV2 reprogramming model. When placed in differentiation conditions, AdvSca1 cells escape a multipotent progenitor state for a Sca1+ cd34+ bipotent progenitor state through DNA hydroxymethylation. ETV2 overexpression decreases the expression of tet3, preventing further DNA hydroxymethylation of SMC/mesenchymal genes and reducing their expression, therefore forcing the differentiation AdvSca1 cells towards the endothelial fate.