Shifts in Glycolytic Phenotype in Smooth Muscle Cells of Sporadic Aortic Aneurysms and Acute Dissections

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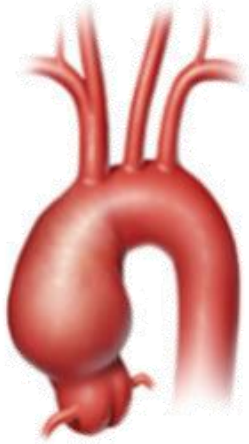
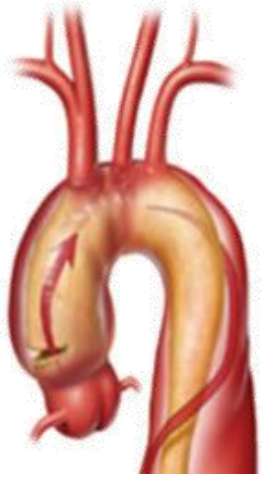
Aortic Aneurysm and Dissection





Normal Aorta **Aortic Aneurysm** **Aortic Dissection**

- Aortic aneurysm formation and dissection are driven by aortic wall degeneration.
- This is characterized by progressive smooth muscle cell (SMC) loss and extracellular matrix (ECM) degradation.

Dysregulation of glycolysis in aortic disease

- Metabolism is key to maintaining cell function.
- Dysregulation of glucose metabolism contributes to the pathogenesis of vascular diseases, cancer, metabolic syndrome, infection, and degenerative diseases.
- In prior literature, increased glycolytic activity and lactate production has been shown to promote matrix metalloproteinase activity and ECM degradation in abdominal aortic aneurysm development.

Inhibition of Development of Abdominal Aortic Aneurysm by Glycolysis Restriction

Toshihiro Tsuruda, Kinta Hatakeyama, Shigeki Nagamachi, Yoko Sekita, Sumiharu Sakamoto, George J. Endo, Masanori Nishimura, Masakazu Matsuyama, Koichi Yoshimura, Yuko Sato, Toshio Onitsuka, Takuroh Imamura, Yujiro Asada and Kazuo Kitamura
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LDHA mediated degradation of extracellular matrix is a potential target for the treatment of aortic dissection

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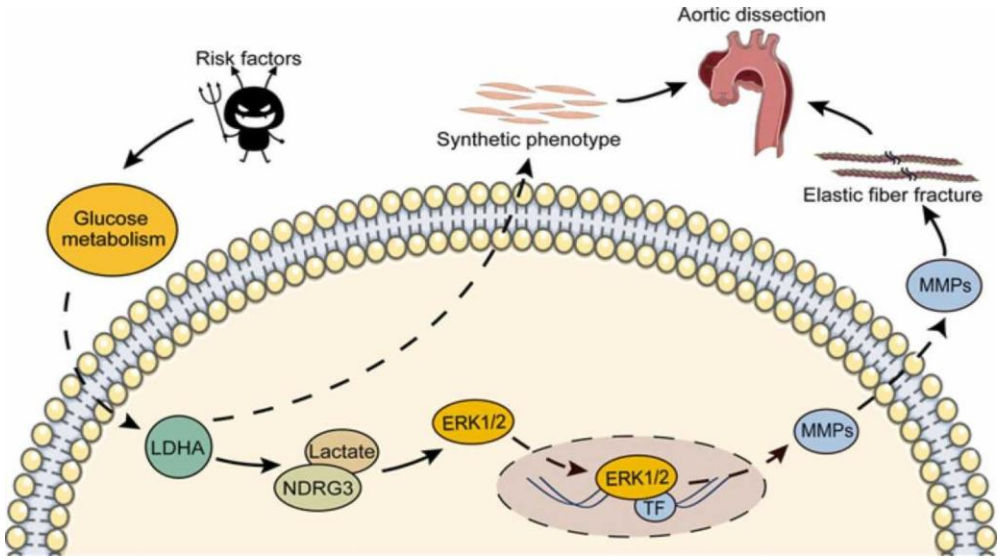
Pharmacological Research. 2022; 10.1016/j.phrs.2021.106051



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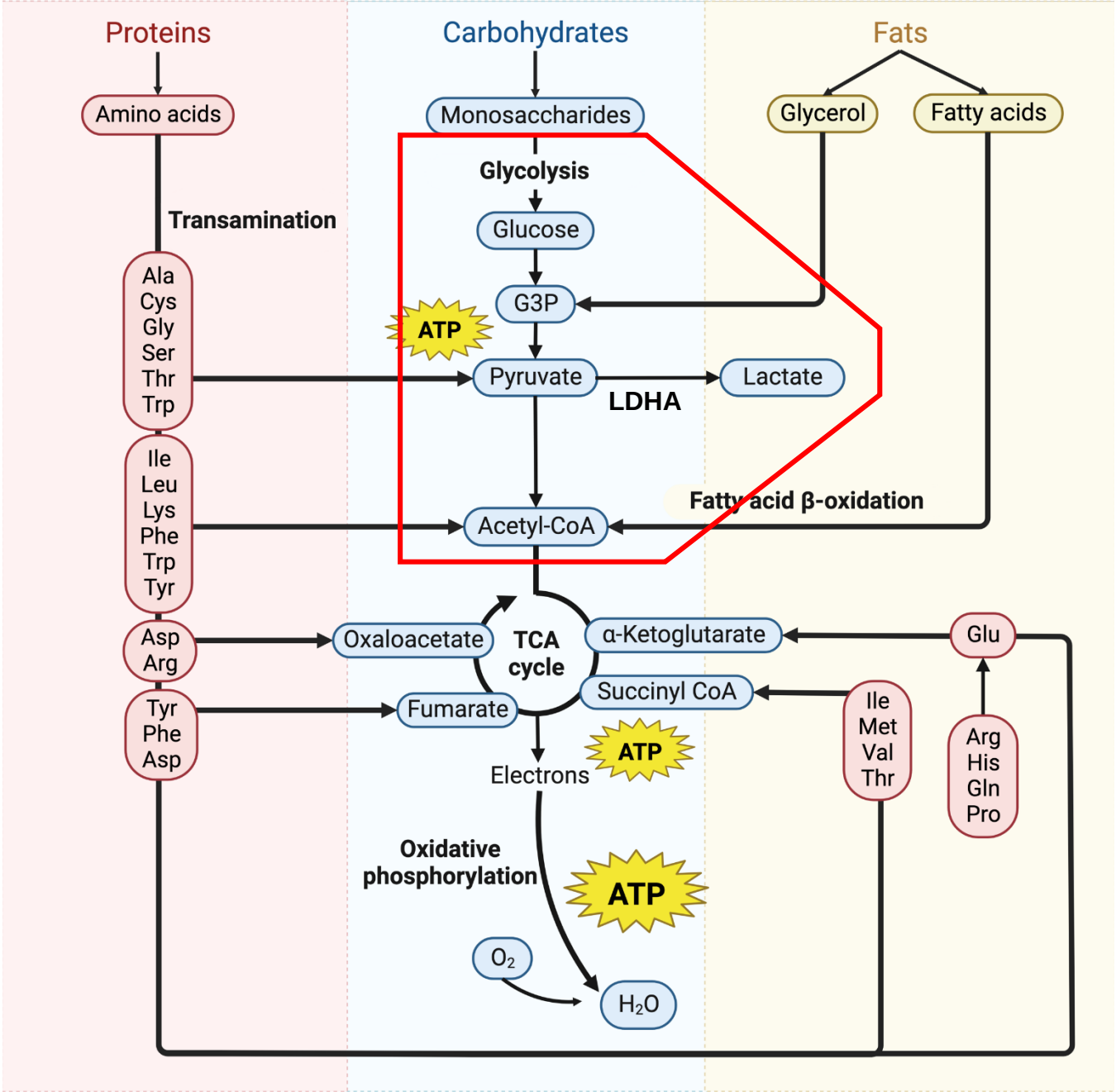
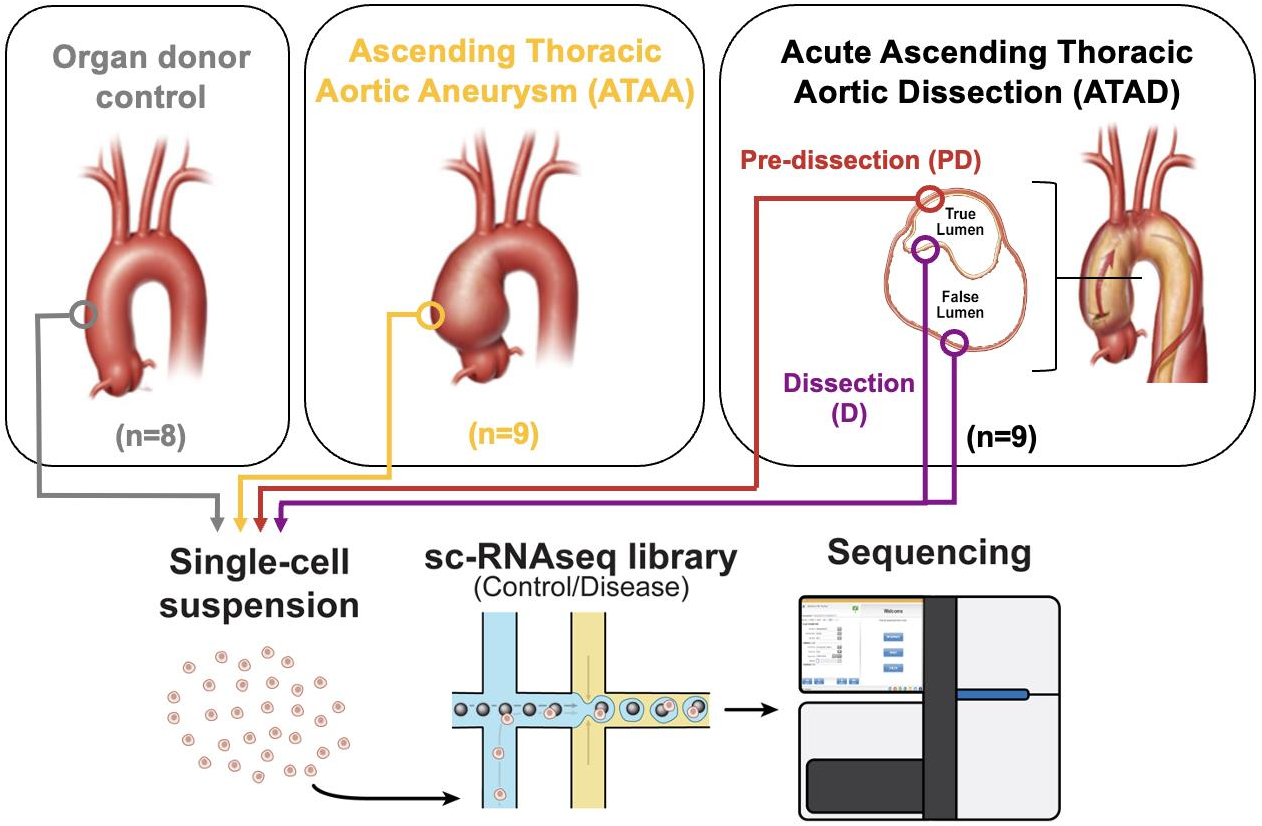
Objective

We hypothesized that expression of glycolysis genes in smooth muscle cells (SMCs) is elevated in aortic aneurysms and dissections (AAD).

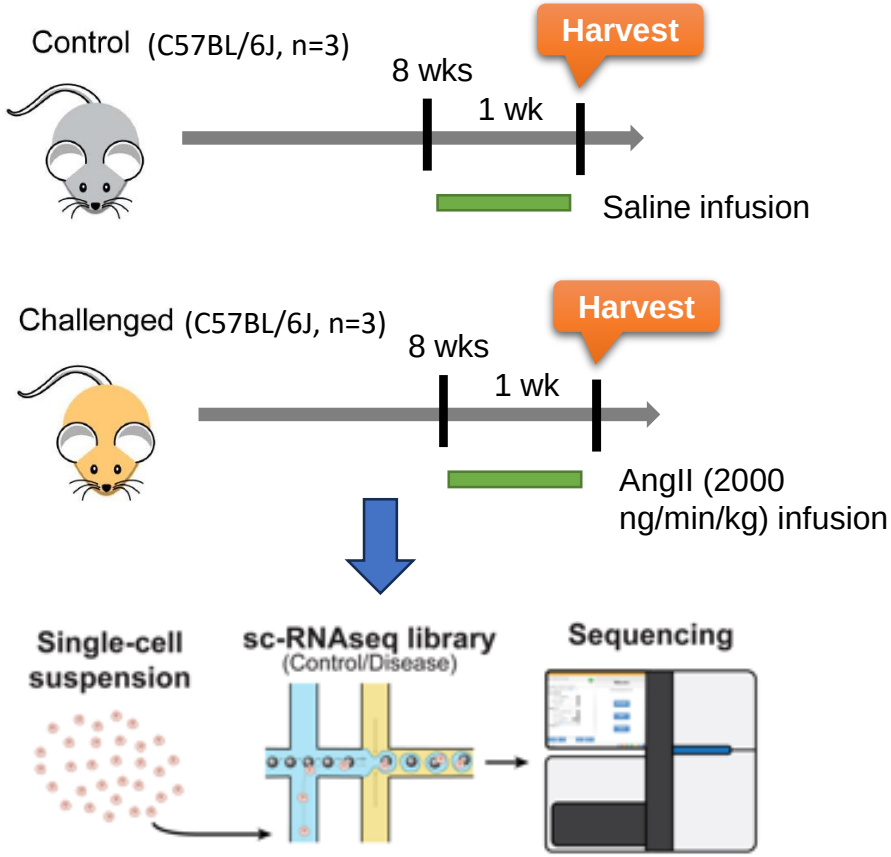


Aim 1: Examine expression of genes in glycolysis in aortic disease

Methods (human tissue)



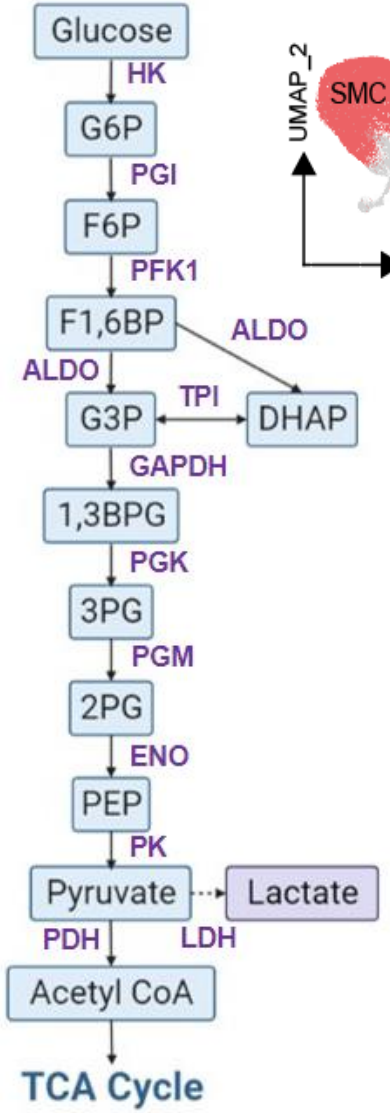
Methods (mouse model)

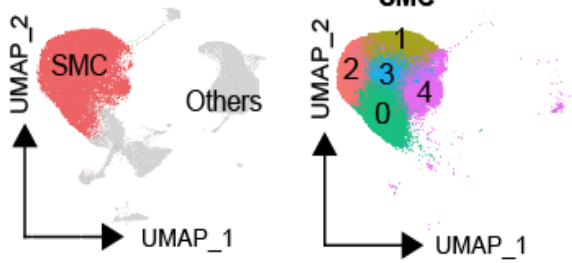


Single-cell RNA sequencing (scRNA-seq) analysis was performed on ascending aortic tissues samples of both human patients and mice infused with saline and angiotensin II.

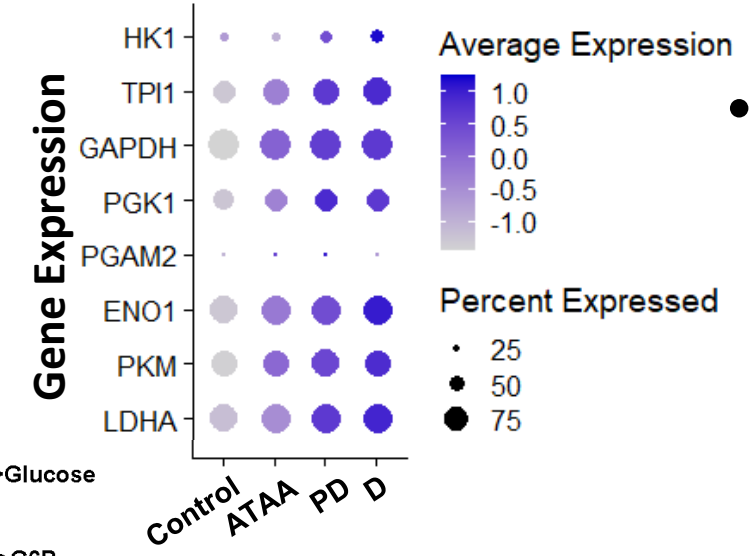
Aim 1: Examine expression of genes in glycolysis in aortic disease

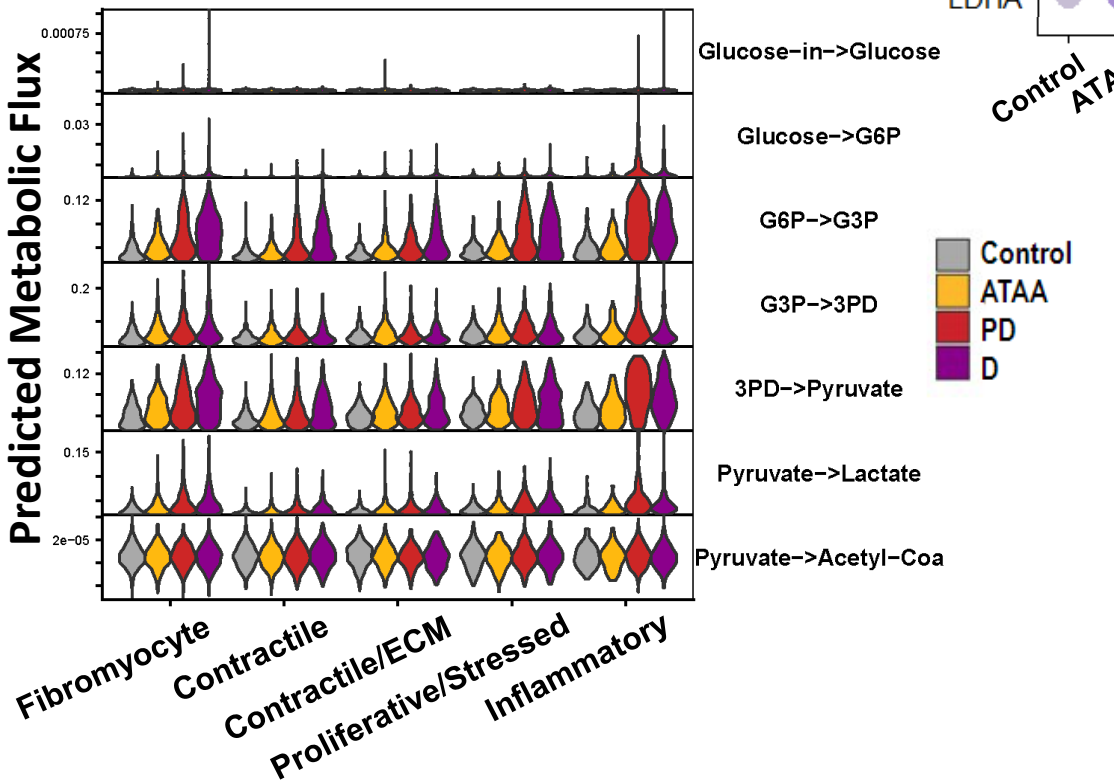
Results (human tissue)





0 – Fibromyocyte
1 – Contractile
2 – Contractile/ECM
3 – Proliferative/Stressed
4 – Inflammatory

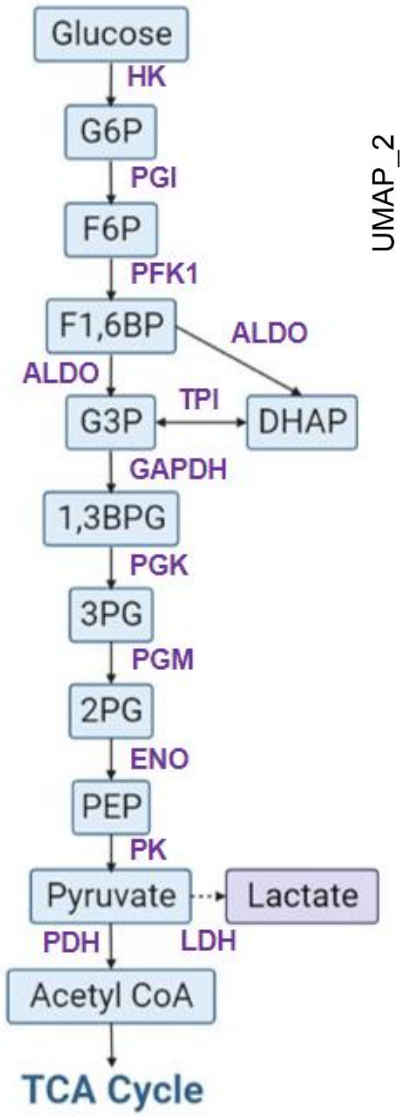


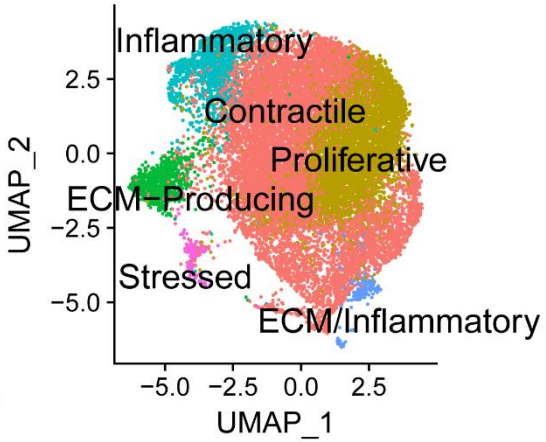


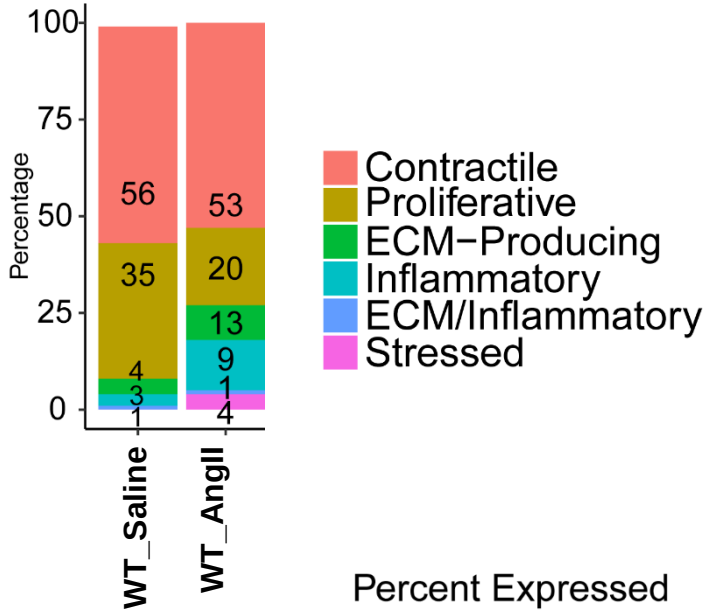
- Five SMC clusters were classified via cell-type specific markers.
- Both glycolytic gene expression and predicted glycolytic activity **progressively increased** from control to aneurysm to dissection.

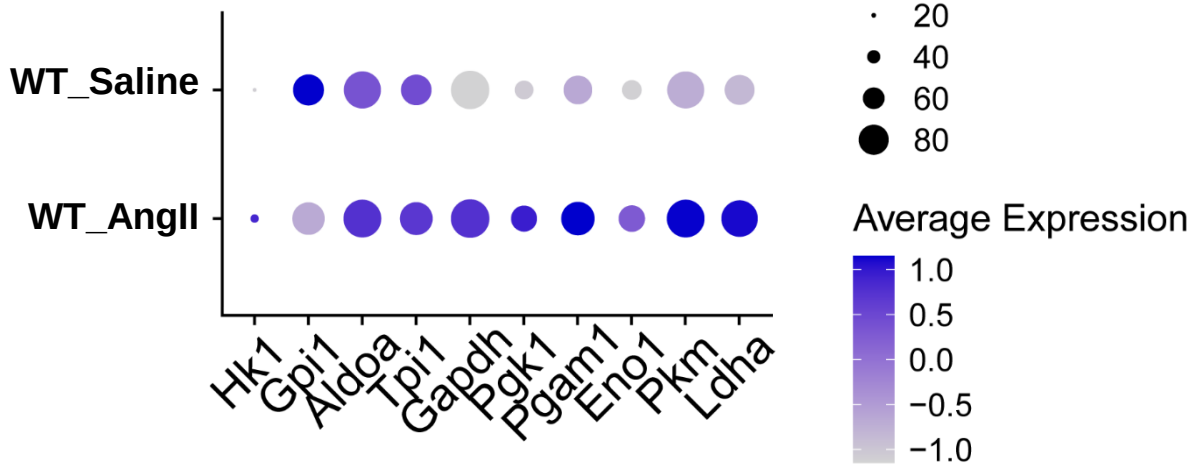
Aim 1: Examine expression of genes in glycolysis in aortic disease

Results (mouse model)





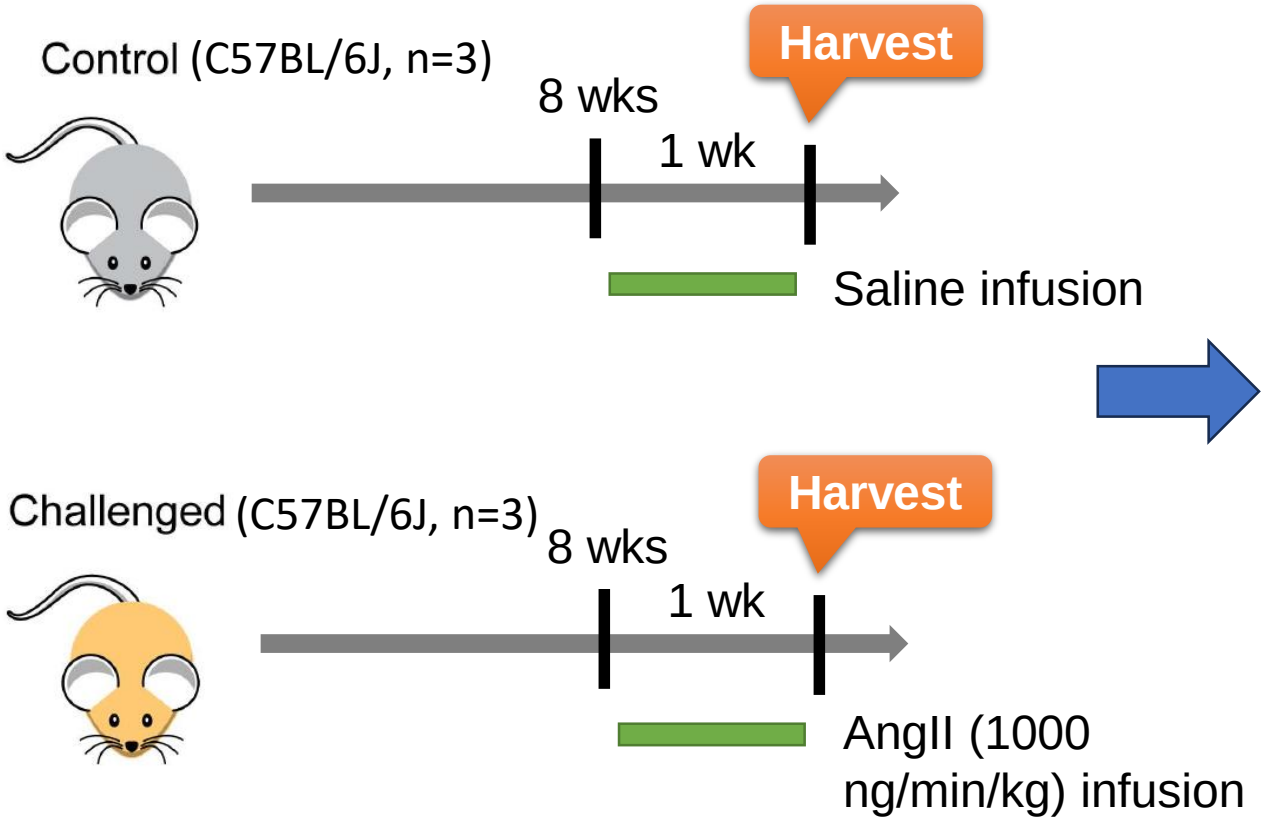


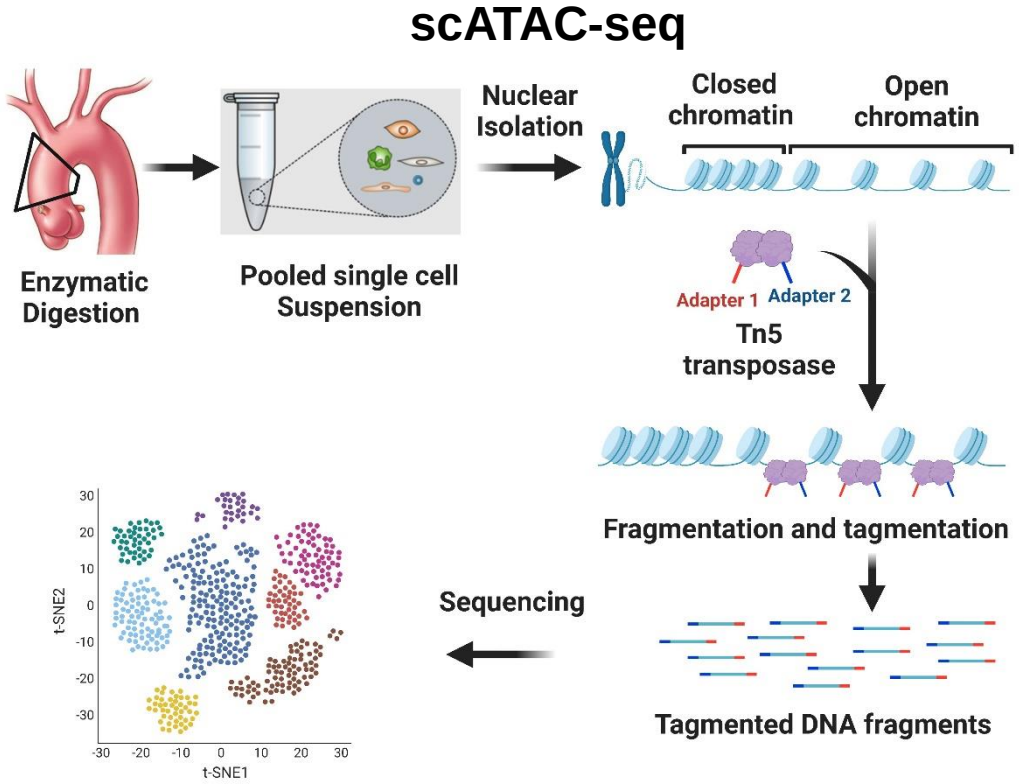


- Six SMC clusters were classified via cell-type specific markers.
- Glycolytic genes were **upregulated** in AngII-infused mice.

Aim 2: Identify transcription factors that may regulate glycolysis genes at epigenetic level in aortic disease

Methods

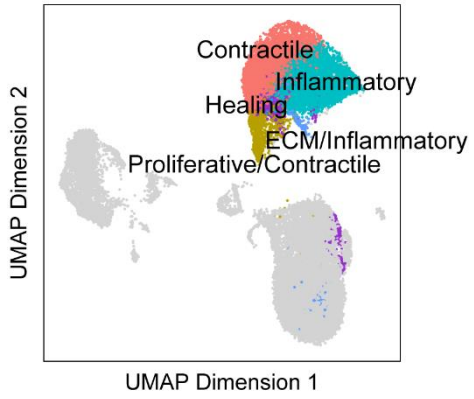


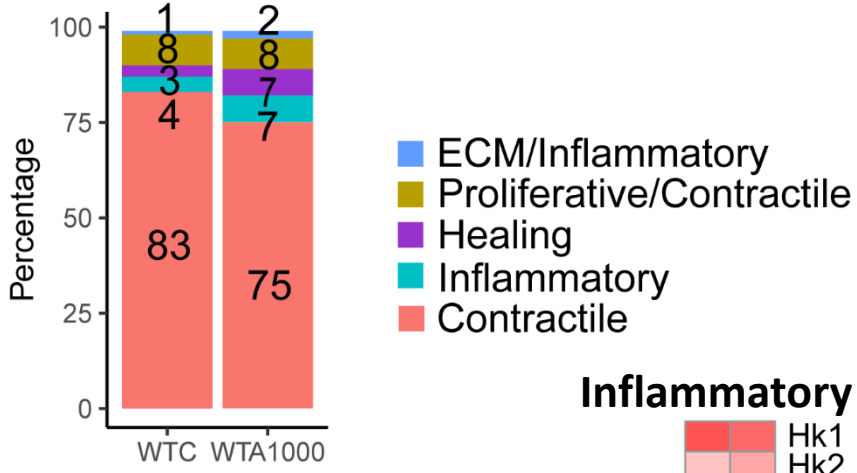


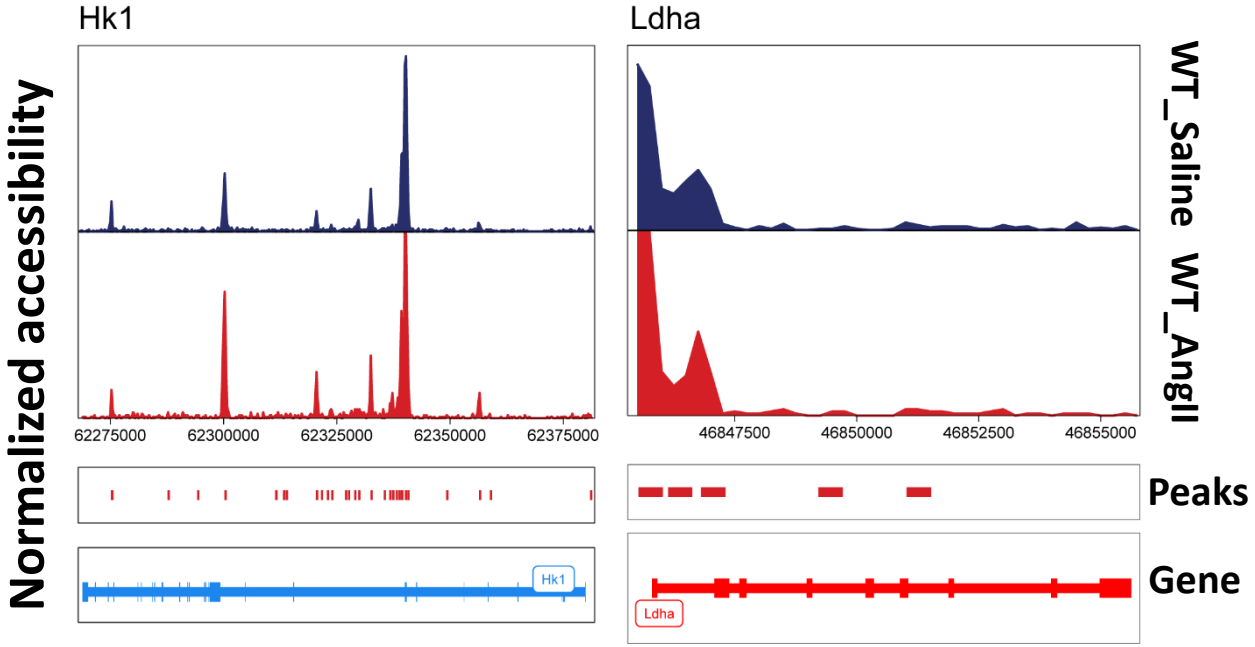
Single-cell ATAC sequencing (scATAC-seq) analysis examined genome-wide chromatin accessibility in aortic SMCs of saline-infused and AngII-infused mice.

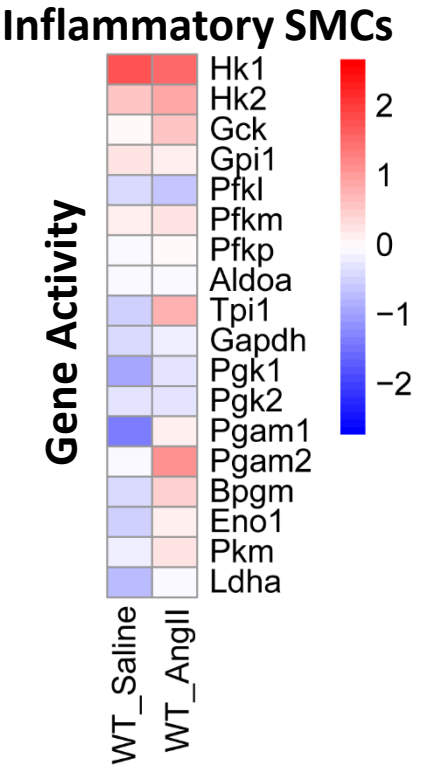
Aim 2: Identify transcription factors that may regulate glycolysis genes at epigenetic level in aortic disease

Results





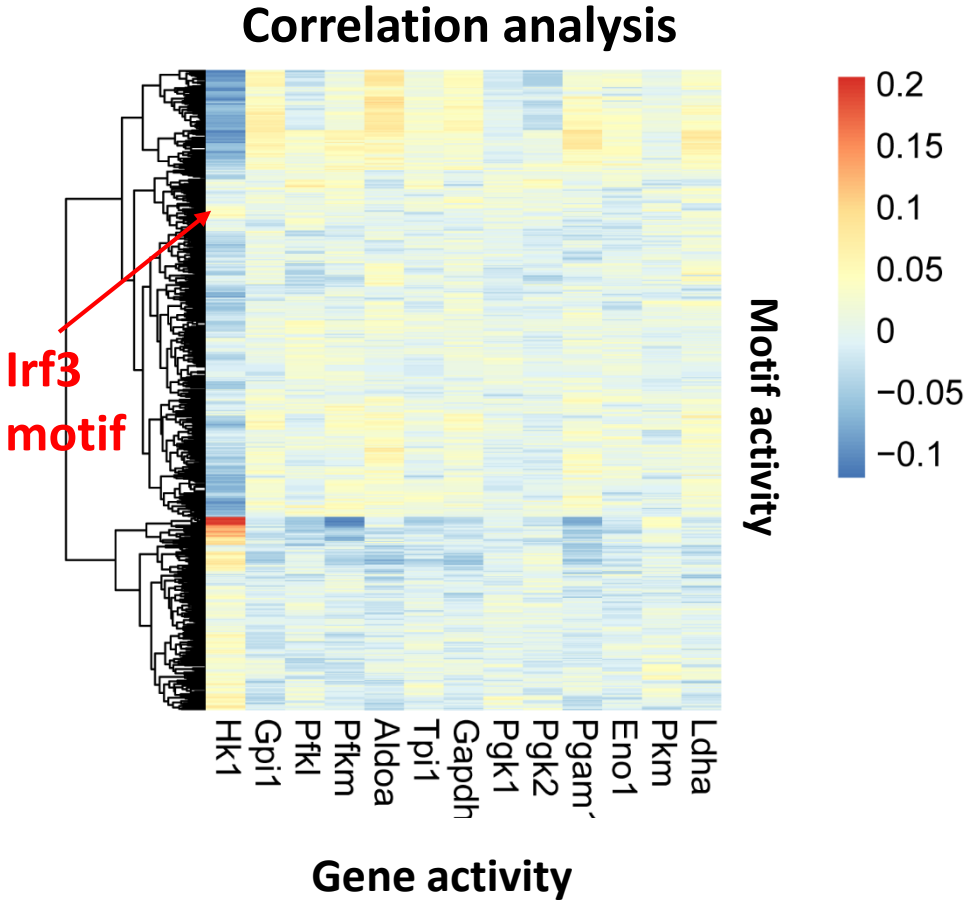


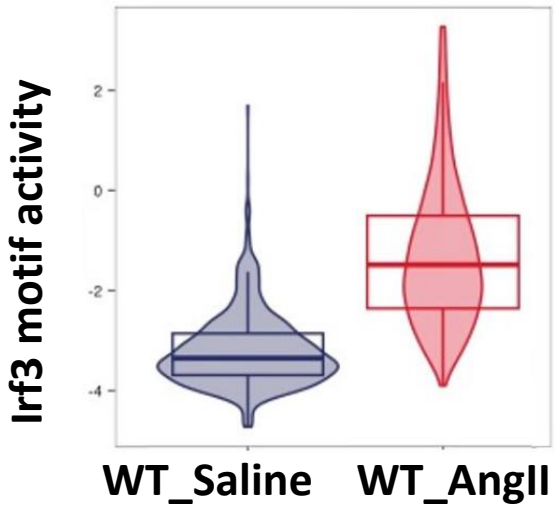


- Proportion of inflammatory SMCs were significantly higher in AngII-infused mice.
- Genes *Hk1* and *Ldha* exhibited **higher chromatin accessibility in AngII-infused mice.**
- Gene activity score of glycolysis genes in the inflammatory SMCs were slightly increased in AngII-infused mice.

Aim 2: Identify transcription factors that may regulate glycolysis genes at epigenetic level in aortic disease

Results

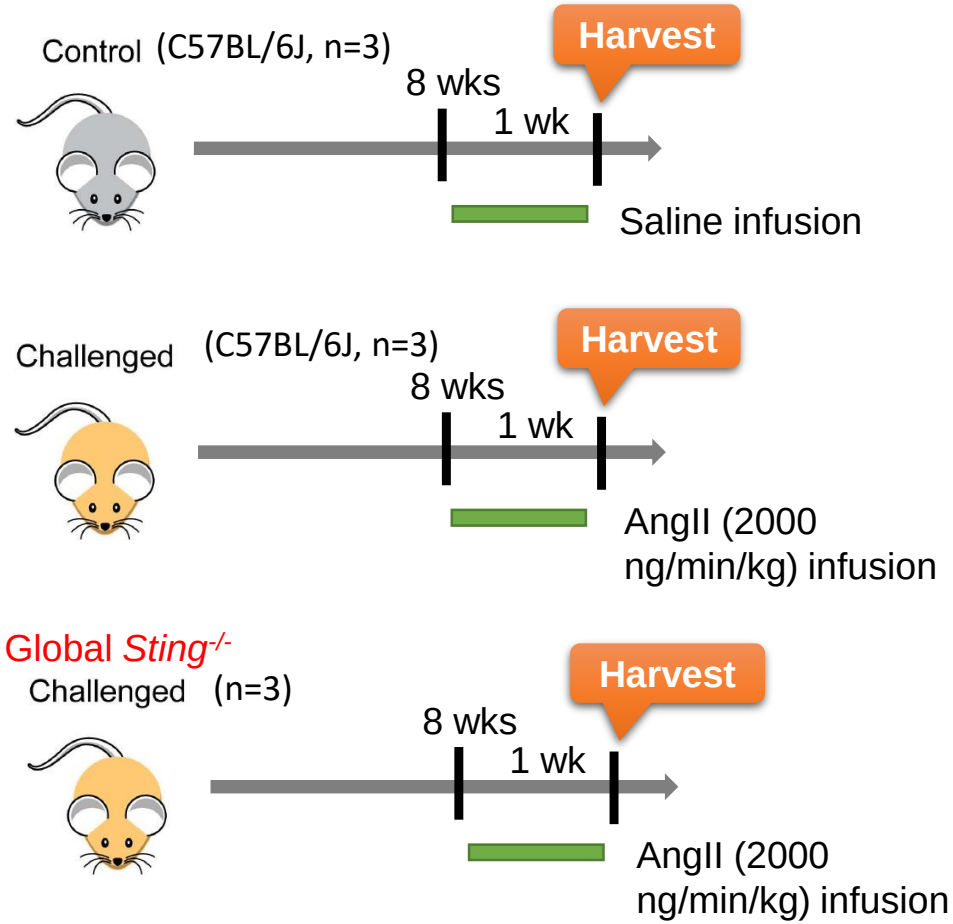


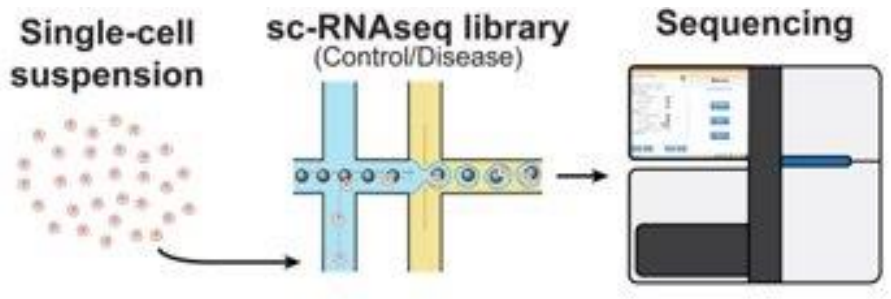


- Gene activity of glycolysis genes were **positively associated** with the motif activity of Irf3, a downstream transcription factor activated by the STING pathway.
- The motif activity of Irf3 was confirmed to be higher in AngII-infused mice.
- Irf3 may be involved in the upregulation of glycolysis genes.

Aim 3: Identify potential pathways that are involved in regulating glycolysis genes

Methods

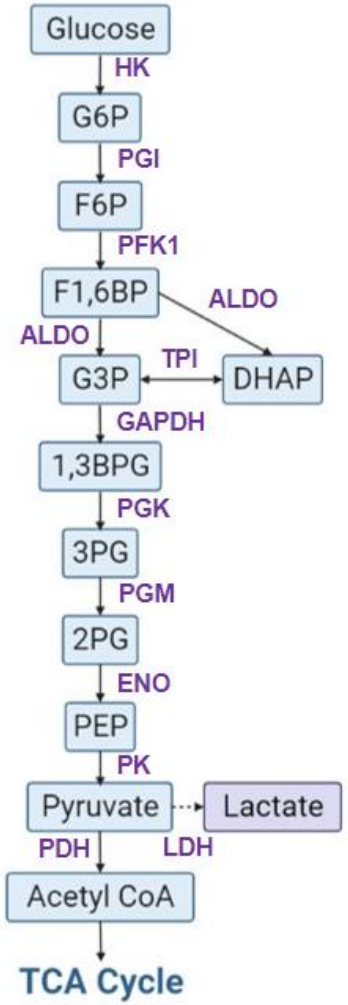


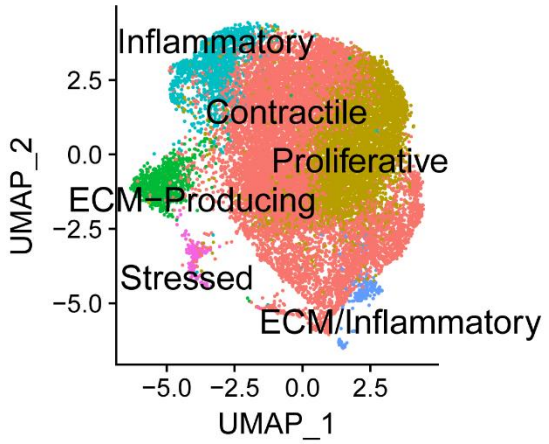


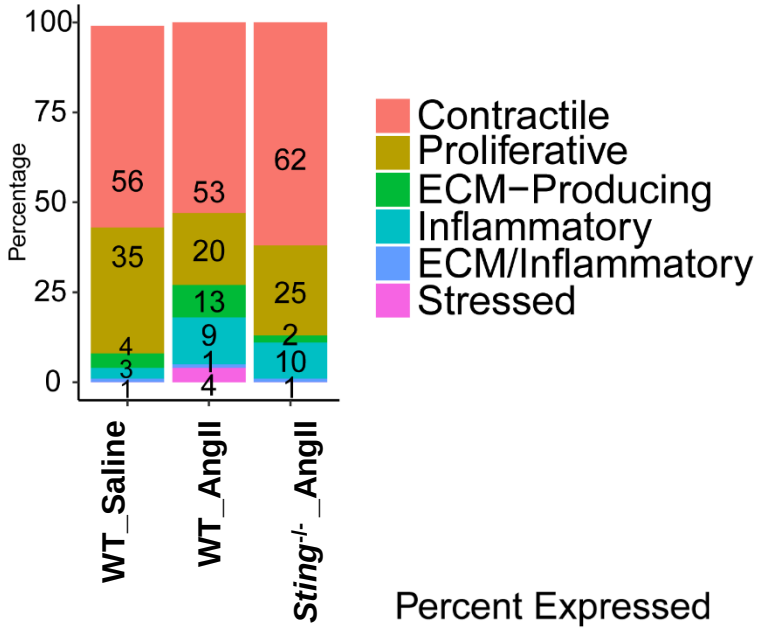
scRNA-seq analysis was performed on ascending aortic tissues samples of saline-infused and AngII-infused mice as well as AngII-infused global *Sting* knockout mice.

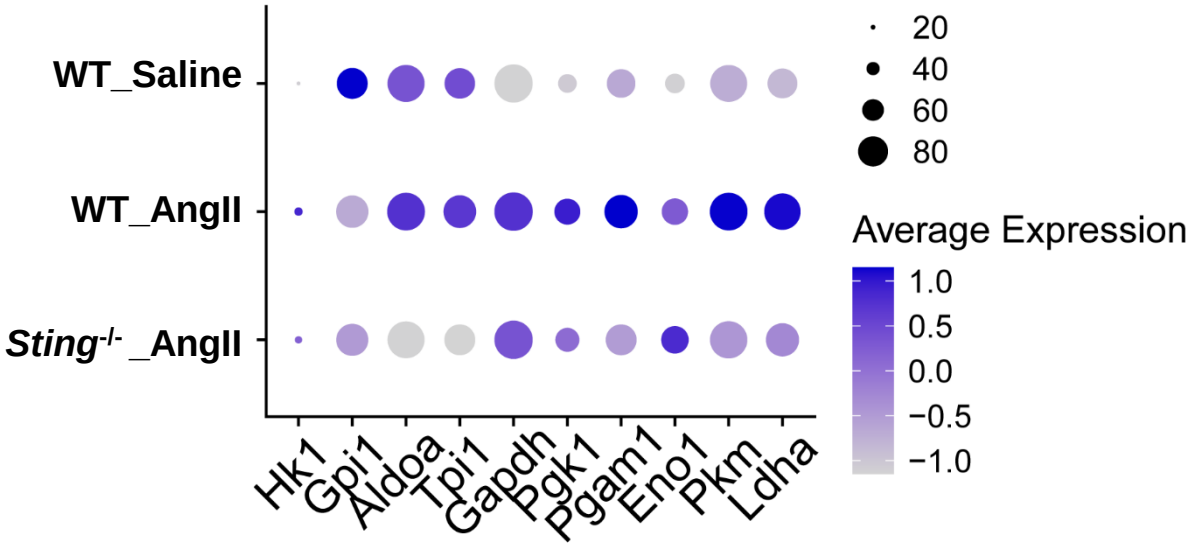
Aim 3: Identify potential pathways that are involved in regulating glycolysis genes

Results



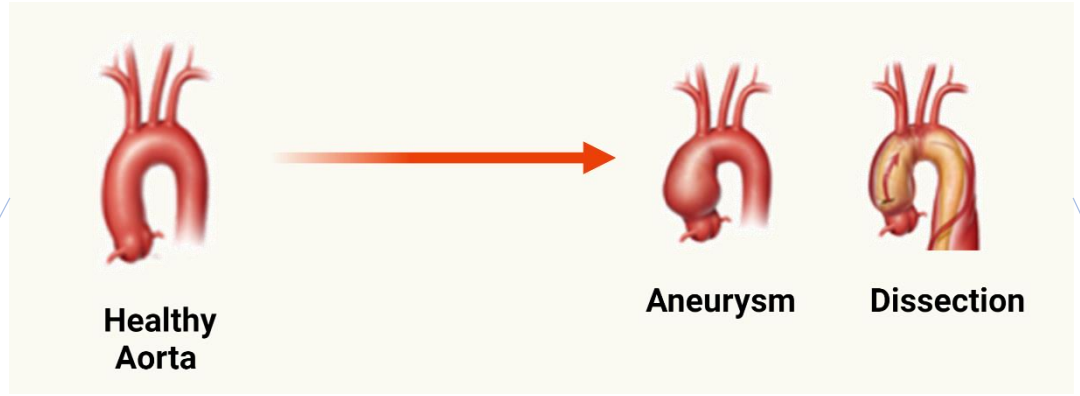


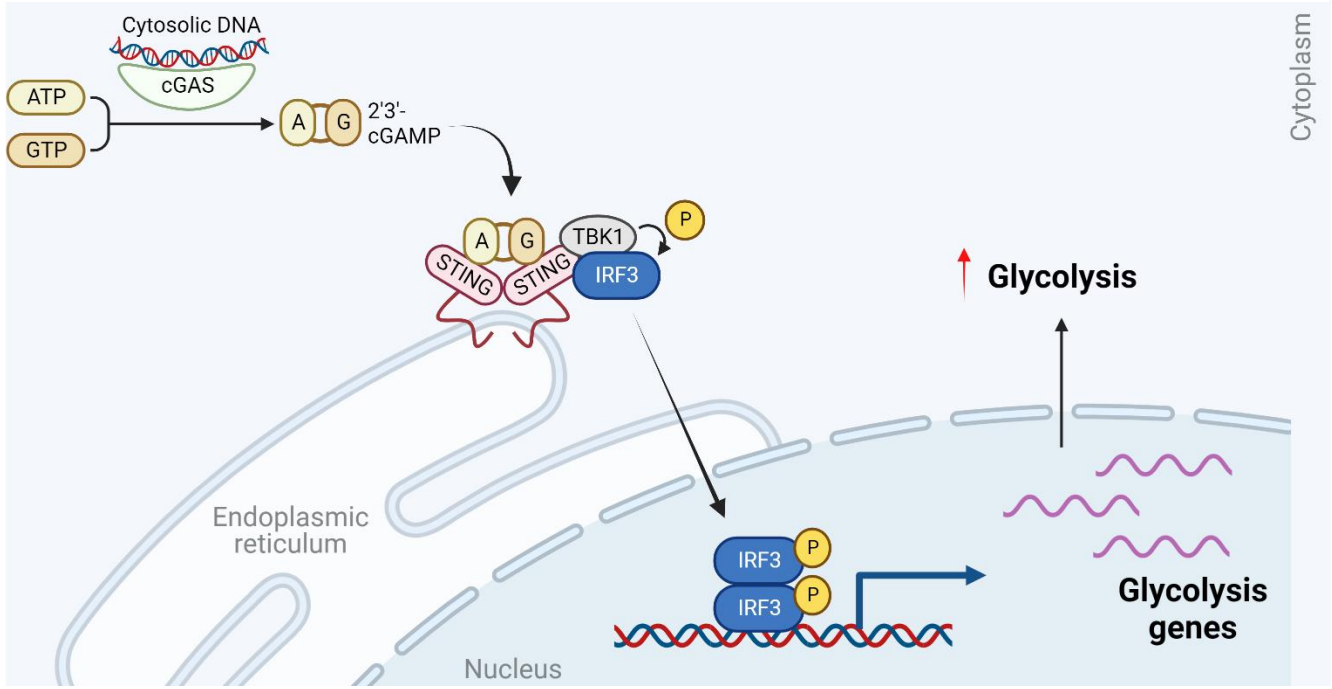




- Glycolytic genes were **upregulated** in SMCs of **AngII-infused mice** but are **decreased** in SMCs of **AngII-infused *Sting*$^{-/-}$ mice**.
- The STING pathway, and subsequent Irf3 activation, is involved in the stress-induced upregulation of glycolysis in SMCs.

Conclusions





1. Glycolytic gene expression in SMCs were progressively increased from control to aneurysm to dissection.
2. Upregulation of glycolysis genes were partially controlled by chromatin remodeling.
3. Activation of the STING-IRF3 pro-inflammatory pathway may play a critical role in epigenetic induction of glycolysis genes and contribute to the development of aortic aneurysm and dissections.

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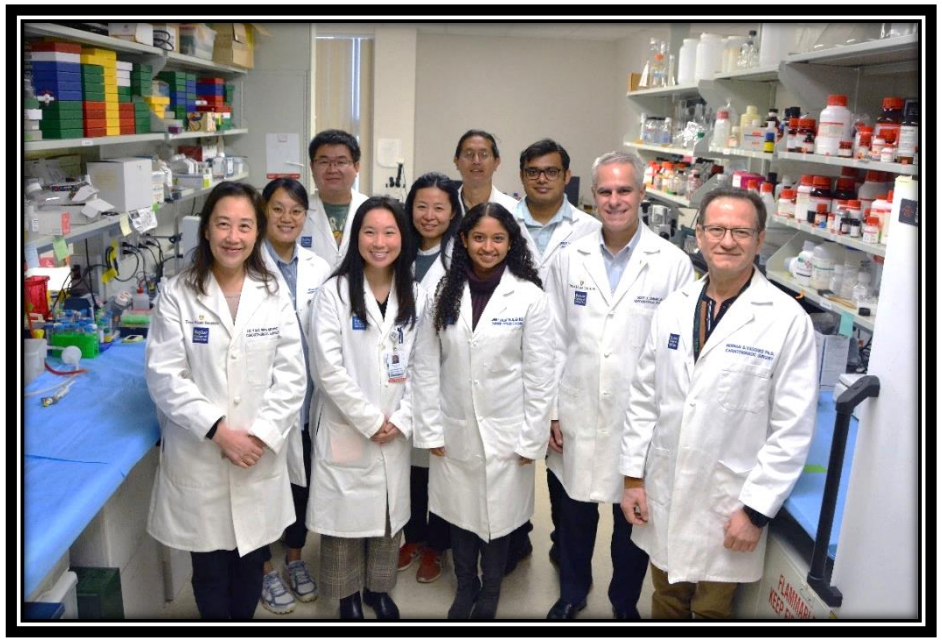

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