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The succinate receptor GPR91 is involved in the pressure overload-induced ventricular hypertrophy



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Right ventricular hypertrophy (RVH)

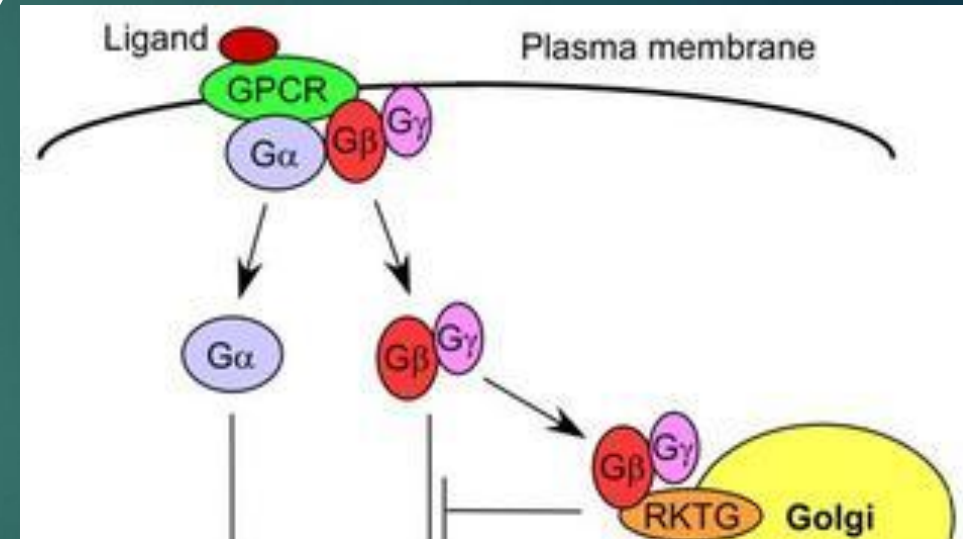
- ▶ the right ventricular (RV) after-load gradually increases and results in right ventricular hypertrophy (RVH) which is closely related to survival of patients with PAH.
- ▶ These properties greatly influence the RV contraction and diastole function and eventually lead to right heart failure (HF), which is a leading cause of PAH mortality worldwide.





GPR91

- ▶ Recently, it was demonstrated that succinate, via a specific receptor G-Protein-Receptor 91 (GPR91), could act as signaling molecules relevant to immunity, hyperglycemia, hypertension and ischemic liver injury.
- ▶ It was also demonstrated that succinate could act the apoptosis of cardiomyocytes which closely tied to RVH, while the role of succinate in the RVH remains unclear.
- ▶ Here, we reported a novel role for succinate and its receptor GPR91 in the pressure overload-induced RVH.





METHOD

- ▶ Group I served as a sham group.
- ▶ Group II received a single intraperitoneal injection of succinate (50 mg/kg).
- ▶ Group III received a single subcutaneous injection of PAB (60 mg/kg).
- ▶ Groups IV, V and VI received PAB as in group III followed by daily intraperitoneal injection of succinate (50 mg/kg) or wortmannin (5 μ g/kg) or both, respectively.



Pulmonary arterial bending (PAB) model establishment

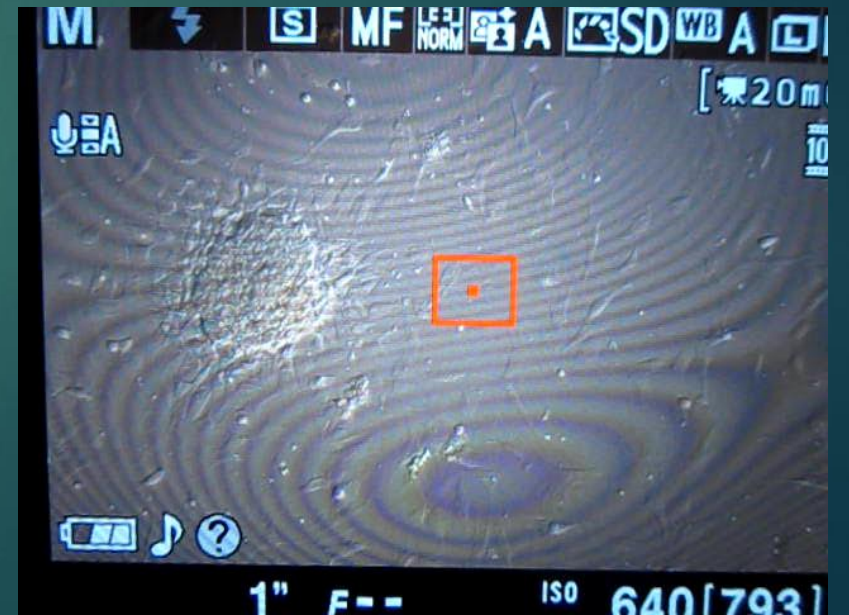
- ▶ PAB was induced by surgical placement of a 1.3mm pulmonary arterial (PA) band.
- ▶ A median sternotomy was performed and the PA was dissected free from the aorta and left atrium. A silk suture was placed around the PA and a loose knot formed.
- ▶ A 16-gauge needle was inserted through the knot, parallel to the PA. The suture was tied tightly and the needle was withdrawn, creating a stenosis equal to the needle's diameter (1.6 mm)





Cultured neonatal rat cardiomyocytes

- ▶ Cells from the hearts of 1-day-old SD rats were seeded at a density of 1×10^6 /well onto 6-well culture plates.
- ▶ The cells were kept quiescent for 48 hours, and then the medium was changed to either 10% FBS (Invitrogen, USA)/DMEM (Invitrogen, USA) / BrdU (Bi Yun-tian, China) alone or with the addition of succinate or of succinate plus wortmannin.

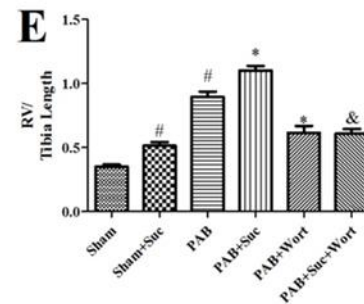
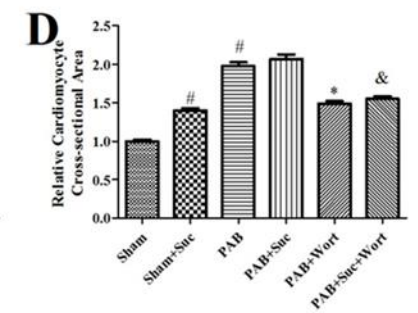
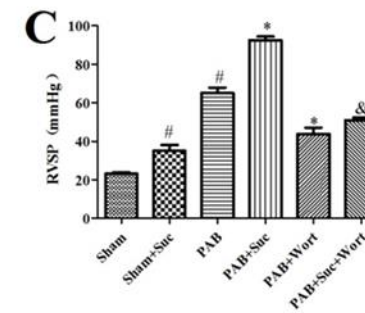
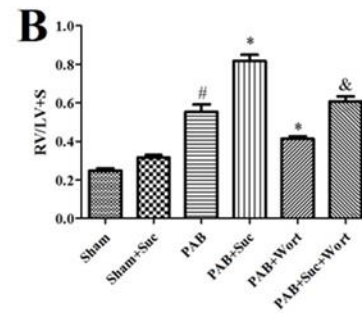
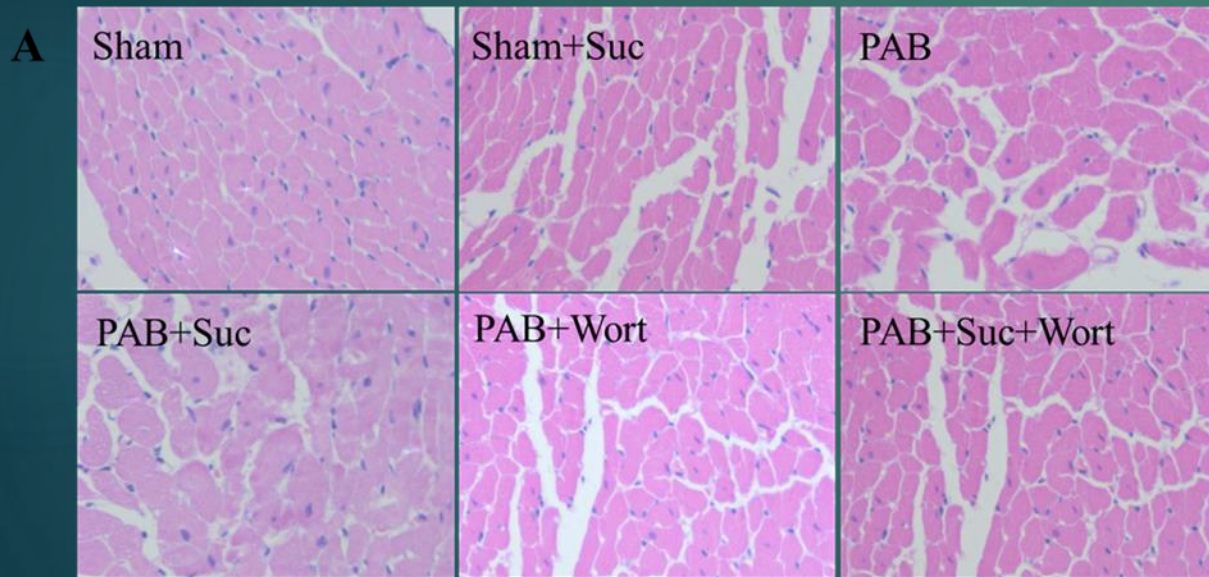




Statistical analysis

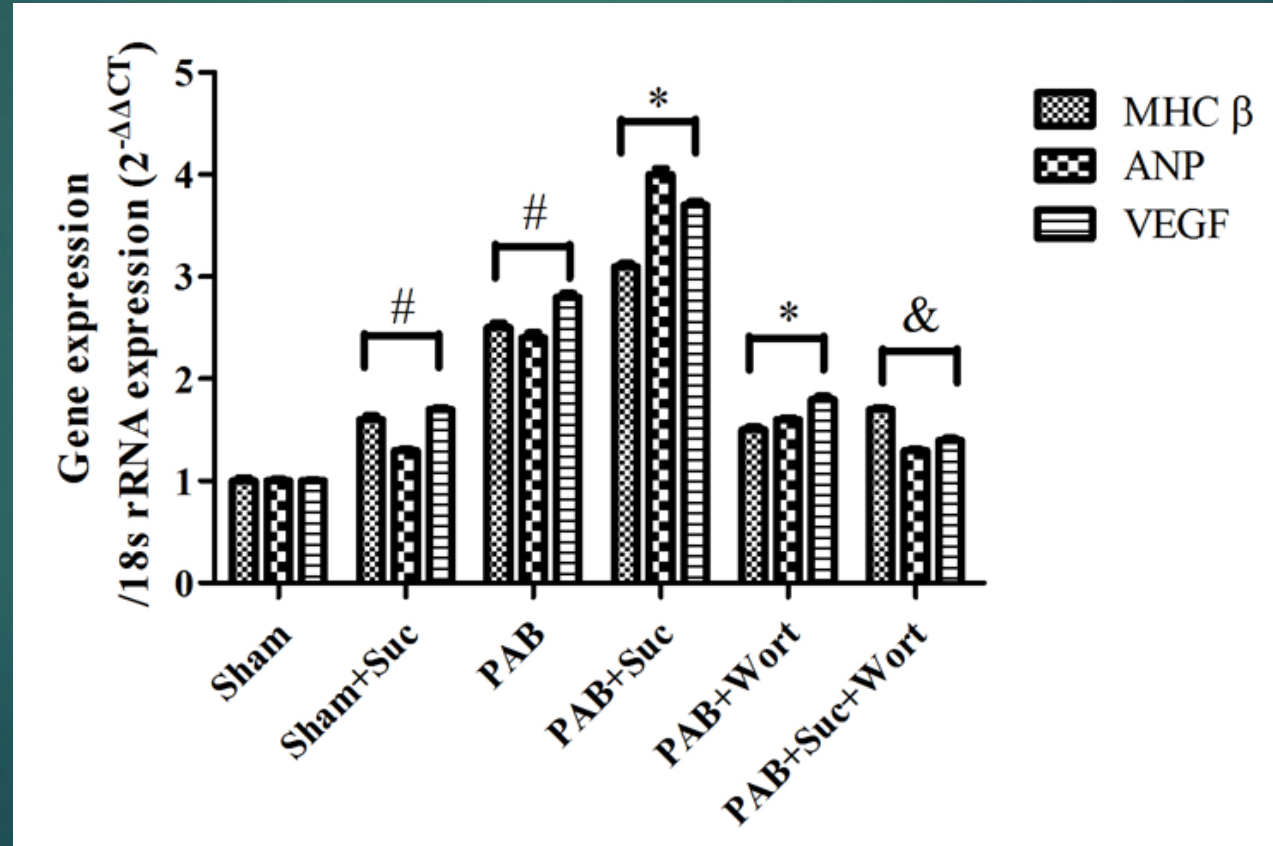
- ▶ The data are presented as the mean \pm SEM. Statistical analyses were performed using the IBM SPSS Statistics 19 statistical software program.
- ▶ The means among groups were compared using one-way ANOVA, followed by Student-Newman-Keuls's post hoc test.
- ▶ Statistical significance was set at $P < 0.05$.

The representative images of HE-stained RV sections and RVH data



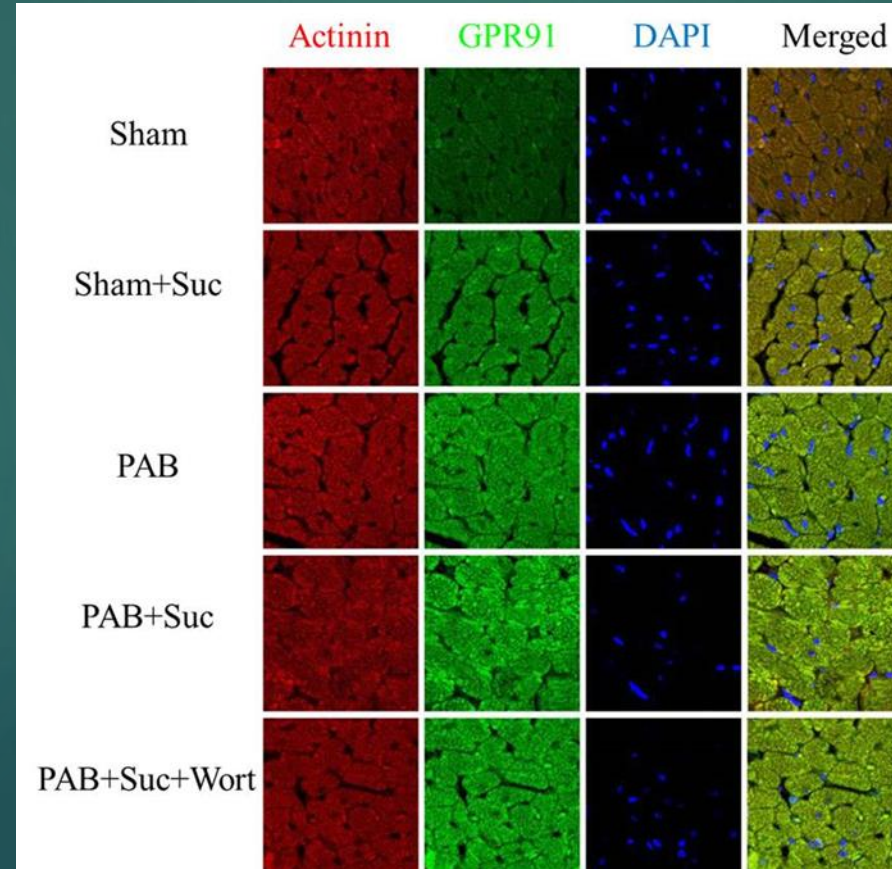


The expression levels of genes associated with RVH

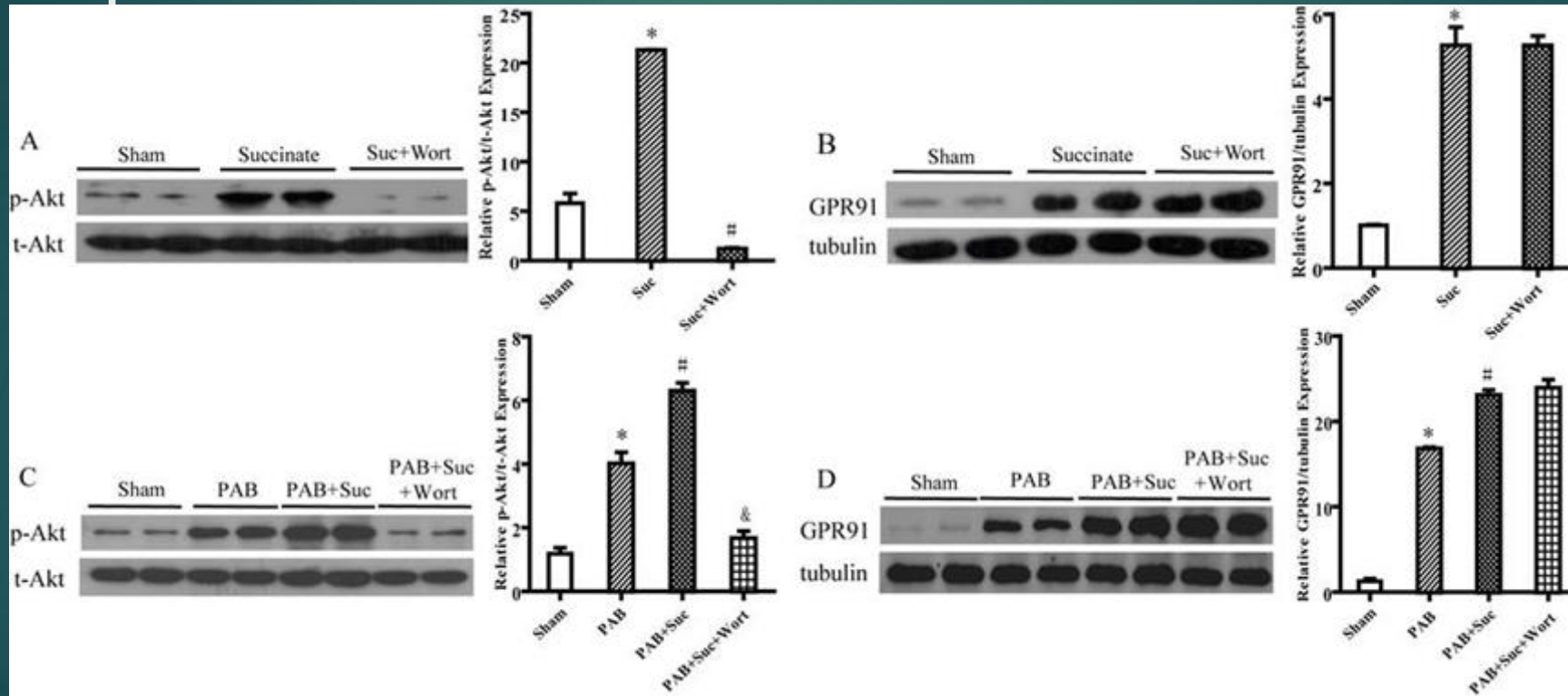




Expression and distribution of GPR91 in each group

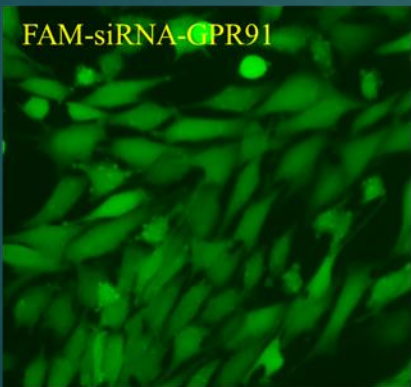


The PI3K/Akt signaling in each group

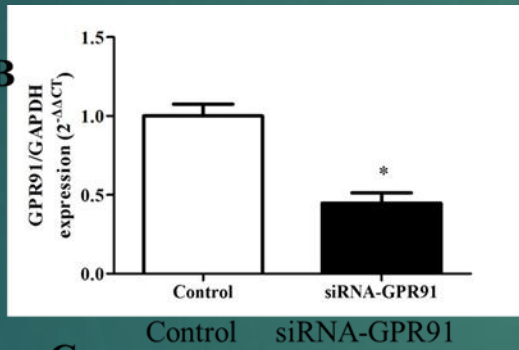


The ANP gene and PI3K/Akt signaling in the cardiac cell

A



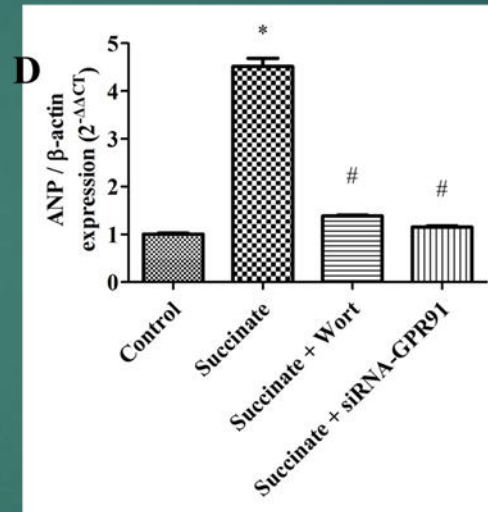
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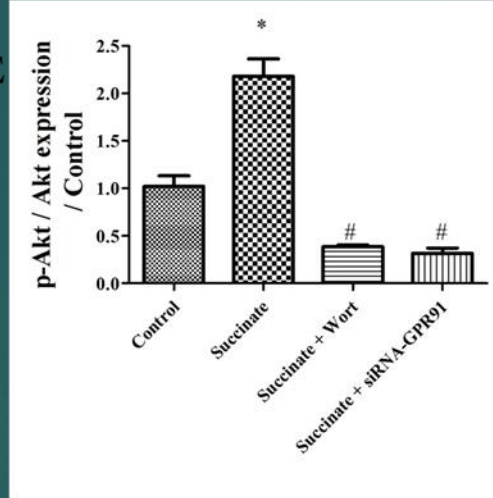
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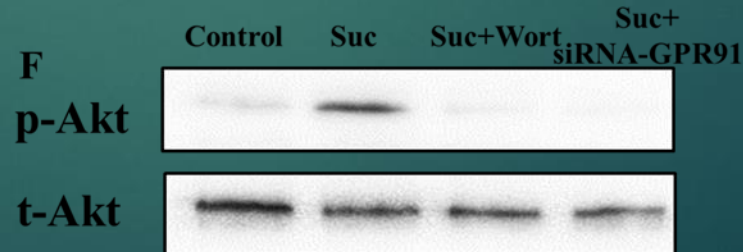
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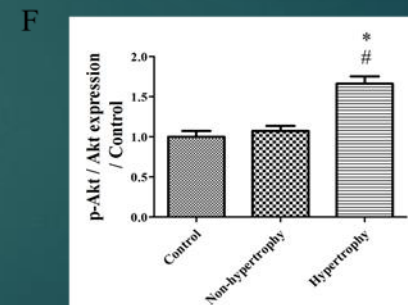
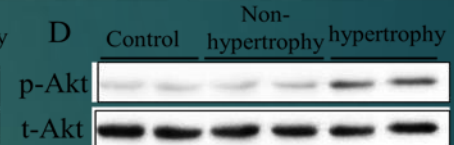
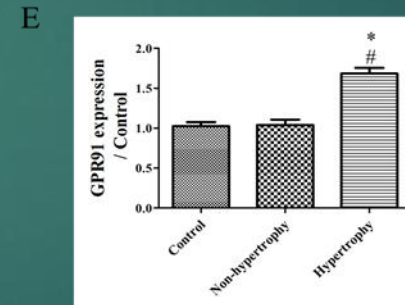
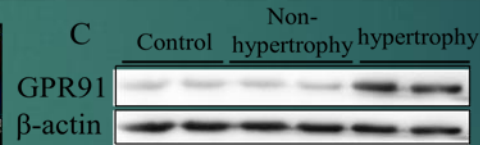
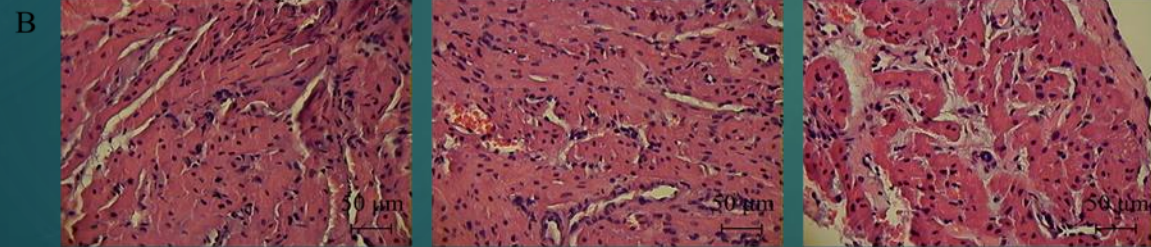
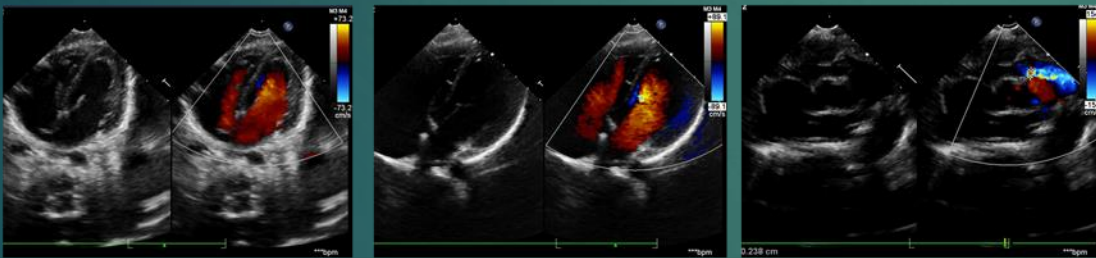


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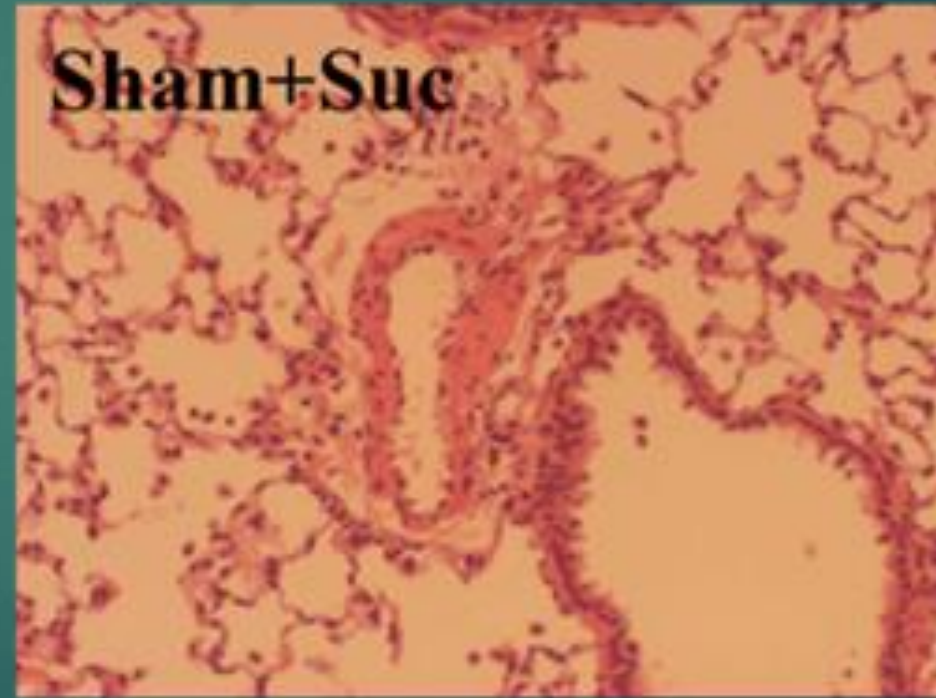
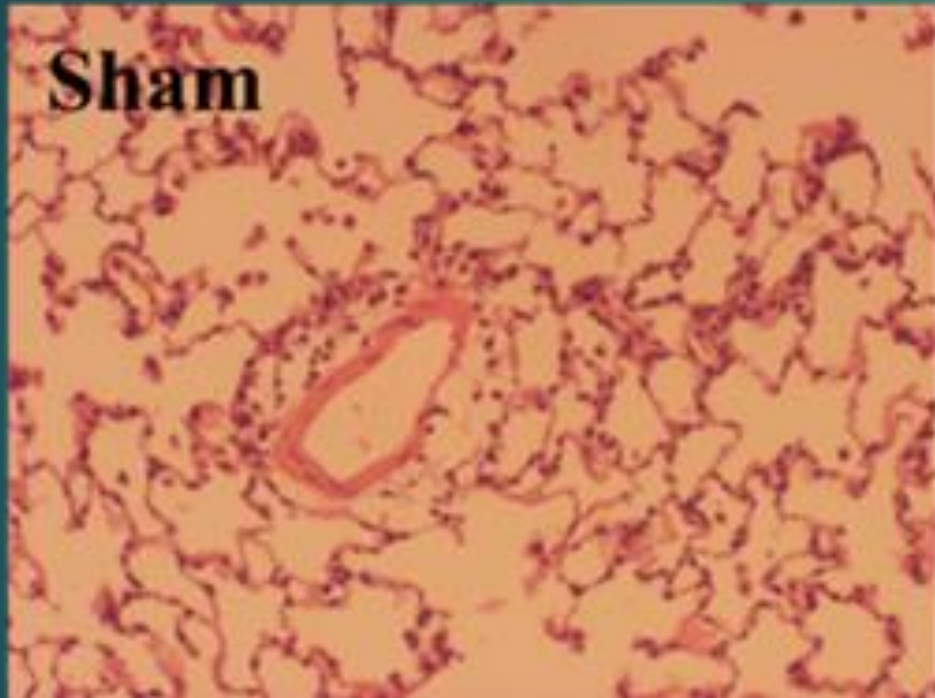
GPR91-PI3K/Akt signaling also existed in the human heart

A Control Non-hypertrophy Hypertrophy





pulmonary sections from Sham and Sham + Suc





Discussion

- ▶ Although succinate was intensively studied for more than 60 years in the context of energy production, the recent demonstration that it could induce cellular signaling transduction through GPR91 raised the possibility of physiological properties beyond its traditional role as a Krebs cycle metabolite.
- ▶ In the present study, we noted that the succinate-GPR91-PI3K/Akt axis existed in RVH.



RV in the PAH

- ▶ Initially, RVH can be compensatory to preserve RV function, particularly its ability to increase contractility to preserve efficient dealing with the lesion pulmonary vascular;
- ▶ however, RVH is still ongoing, characterized by an increase of cardiomyocyte size and fibrosis, and leads to the enlargement of the heart, depression of contractile function and eventually right heart fail.
- ▶ Therefore, failing adaption of the RV to the increased after-load is the main cause of death in PAH patient



Succinate in the RVH

- ▶ the succinate circulating concentrations up to the millimolar range were detected due to the imbalance between energy demand and oxygen supply in the RVH.
- ▶ Therefore, succinate appears to be particularly important in the setting of pathological conditions in the pressure-overloaded heart;
- ▶ As the Krebs cycle and the respiratory chain are ancestral processes that are intimately involved with energy production in cardiomyocytes, it is not surprising that cardiomyocytes exploit at least one metabolite, succinate, as a crucial regulator of RVH induced by pressure overload.



mitochondrial pathway in the RVH

- ▶ In the recent article in nature, it is found that the ischemic accumulation of succinate controls reperfusion injury through mitochondrial ROS which also play an important role in the RVH that when the mitochondrial ROS increased, it always induces cardiomyocyte hypertrophy.
- ▶ Furthermore, these findings may reveal a new mitochondrial pathway of GPR91 the RVH.



GPR91 in the lung vessel muscularization

- ▶ Our results also showed that succinate administration developed significant muscularization in of the pulmonary atrial. The RVSP elevation often caused by the muscularization of the pulmonary vessel wall contributing to increase the afterload of RV.
- ▶ Hence, this could be the reason for the succinate leading to the RVSP elevation in RVH and suggest a role of succinate alone in the development of lung vessel muscularization.



In conclusion

- ▶ succinate-GPR91 may be involved in pressure overload-induced RVH.
- ▶ It also indicated that the PI3K/Akt signaling pathway was involved in the effects of succinate-GPR91-mediated RVH.



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Thank you!