Reactivation of mammalian regeneration by turning on an evolutionarily disabled genetic switch

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RESEARCH ARTICLE | ORGAN REGENERATION

Reactivation of mammalian regeneration by turning on an evolutionarily disabled genetic switch

WEIFENG LIN, XIAOHUI JIA, XIAOFENG SHI, QIUYA HE, PANYU ZHANG, XIANGLEI ZHANG, LIPING ZHANG, MINGQI WU, TENGFEI REN, YUFEI LIU, HAOHAO DENG, YANYAO LI, SHIQI LIU, SHAOYONG HUANG, JINGMIN KANG, JUN LUO, ZIQING DENG, AND WEI WANG fewer Authors Info & Affiliations

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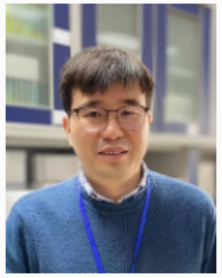

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Wang, W., Hu, C.-K., Zeng, A., Alegre, D., Hu, D., Gotting, K., Ortega Granillo, A., Wang, Y., Robb, S., Schnittker, R., Zhang, S., Alegre, D., Li, H., Ross, E., Zhang, N., Brunet, A., Sánchez Alvarado, A., 2020. Changes in regeneration-responsive enhancers shape regenerative capacities in vertebrates. ***Science*** 369, (10.1126/science.aaz3090).

Research Highlights in ***Nature***: Why some animals have the power of regeneration.
https://www.nature.com/articles/d41586-020-02529-5

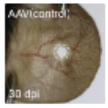
Research Highlights in ***Nature Reviews Genetics***: Enhancing regeneration.
https://www.nature.com/articles/s41576-020-00290-z

为啥兔子耳朵能再生？老鼠却不行？| 专访《Science》通讯作者王伟研究员

然后我们测试了一些其他的动物，像羊耳朵也是可以再生的，非洲刺鼠（african spiny mouse）也是有很强的再生能力，猫的耳朵也有一定的再生能力，还有一部分蝙蝠的耳朵...

尹哥聊基因 19天前 阅读 1万+

科学家打开基因"开关"实现小鼠耳廓再生



而在激活该基因后，小鼠耳廓可实现再生。这为深入理解高等哺乳动物再生能力丢失机制提供了新思路，并为再生医学和人类受损器官的重建与再生提供了重要靶标。

新华视点 23天前

Science | 唤醒沉睡的"再生"开关：研究人员让小鼠断耳再生，我们离"金刚狼"还有多远？

小伤口，大不同：一对耳朵引发的再生之谜 故事的起点，源于一个简单而又经典的观察：不同哺乳动物的再生能力，其实存在着天壤之别。研究人员将目光锁定在了一个完美的...

游离的DNA 21天前

Science：我国学者破解哺乳动物再生能力丢失之谜，激活这个基因实现耳廓再生

也就是说，小鼠耳朵上的伤口不再只是简单的结疤，而是实现了再生。此外，研究团队还将兔子的增强子 AE1 导入小鼠的基因组，结果发现，受伤后的小鼠耳廓 Aldh1a2 基因...

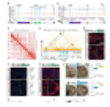
生物世界 23天前

《Science》揭维生素A分子开关可重启耳朵再生能力！？

在原本不具备组织再生能力的哺乳动物中，若能调控维生素A代谢产物视黄酸（RA）生成的关键「分子开关」——活化醛脱氢酶家族1A2成员（Aldh1a2），或直接外部补充RA...

医健大观 19天前

Science—中国在再生医学领域的重要突破和进展

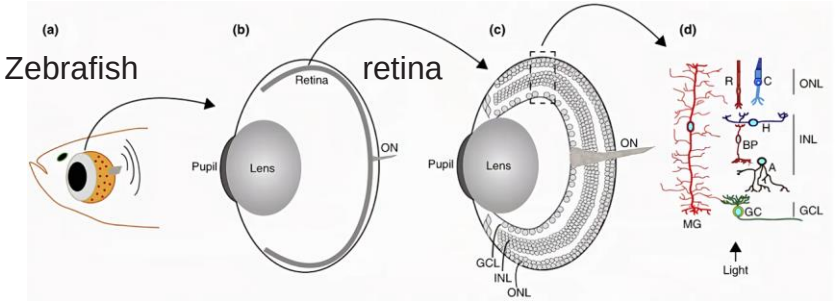


今天看到华大基因CEO尹烨采访北京生命科学研究所王伟教授的一段视频，讲诉了王伟教授在Science期刊上的一项关于再生医学的研究成果，展现了中国在再生医学领域的进...

骨研新知 21天前

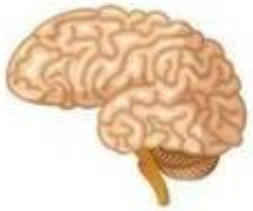
Background

Huge phylogenetic distance between highly regenerative organisms (usually lower vertebrates) and mammals



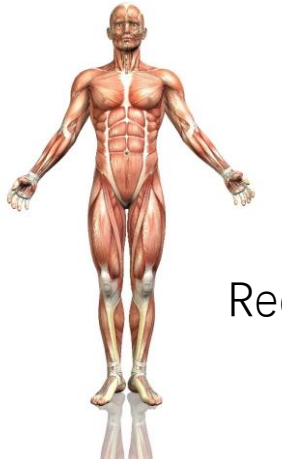
Spinal cord (脊髓)

Brain

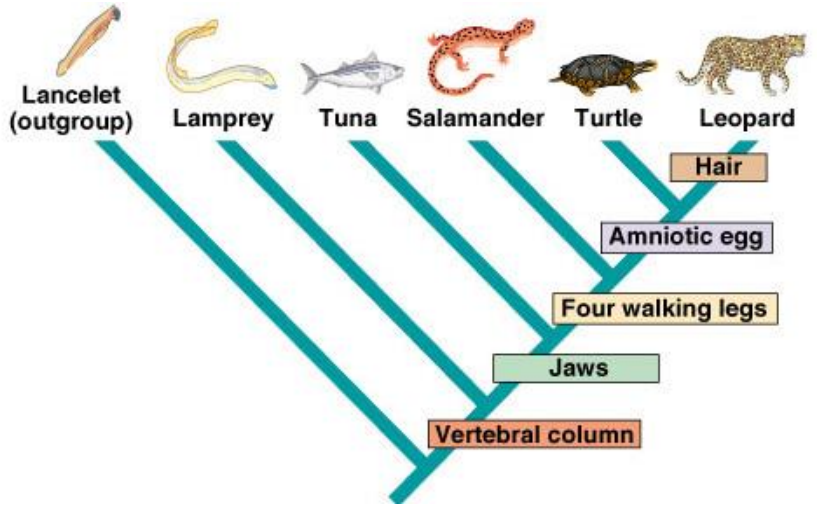


Heart

Limbs



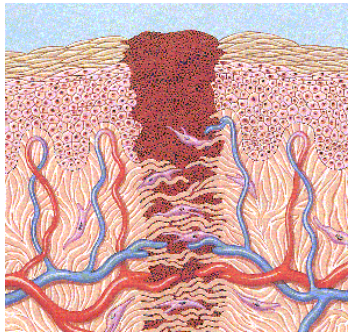
Regeneration?



Background

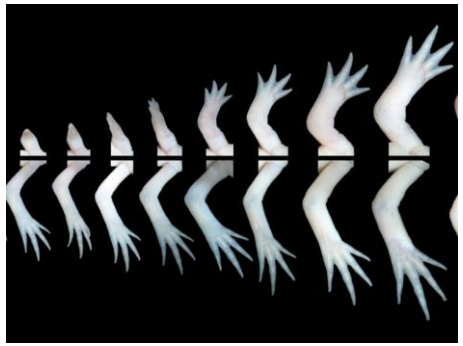
- What drive the evolution of regeneration in vetebrates?

Scar formation



vs

Regeneration



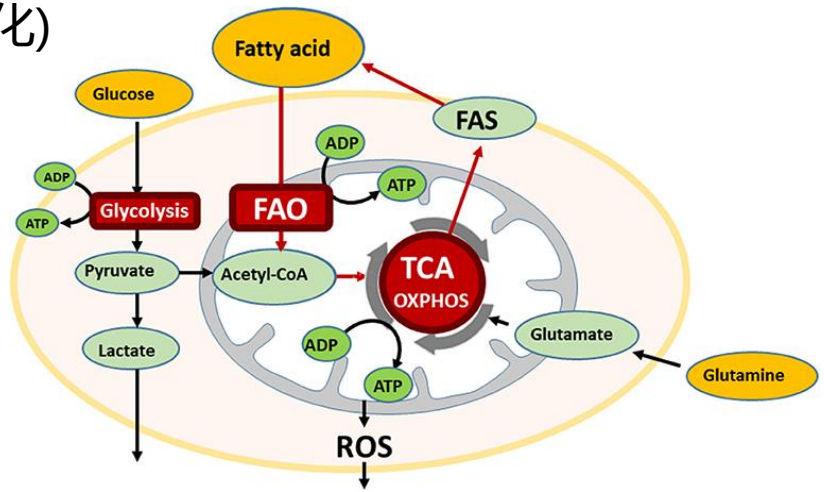
Trade-off between **regenerative potential** and **efficient healing mechanisms**

- replacement of tissue with non-functional cells that do not contribute to regeneration
- prevents infection and minimizes blood loss

- Regenerate a new organ
- activation of complex signaling pathways slower process and is energetically more demanding

The metabolic shift from glycolysis(糖酵解) to fatty acid oxidation(脂肪酸氧化)

- Benefits: enhances energy efficiency, endurance, thermoregulation
- Disadvantages: contributed to cardiomyocyte cell-cycle arrest(心肌细胞周期阻滞) in adult mammals incapable of heart regeneration



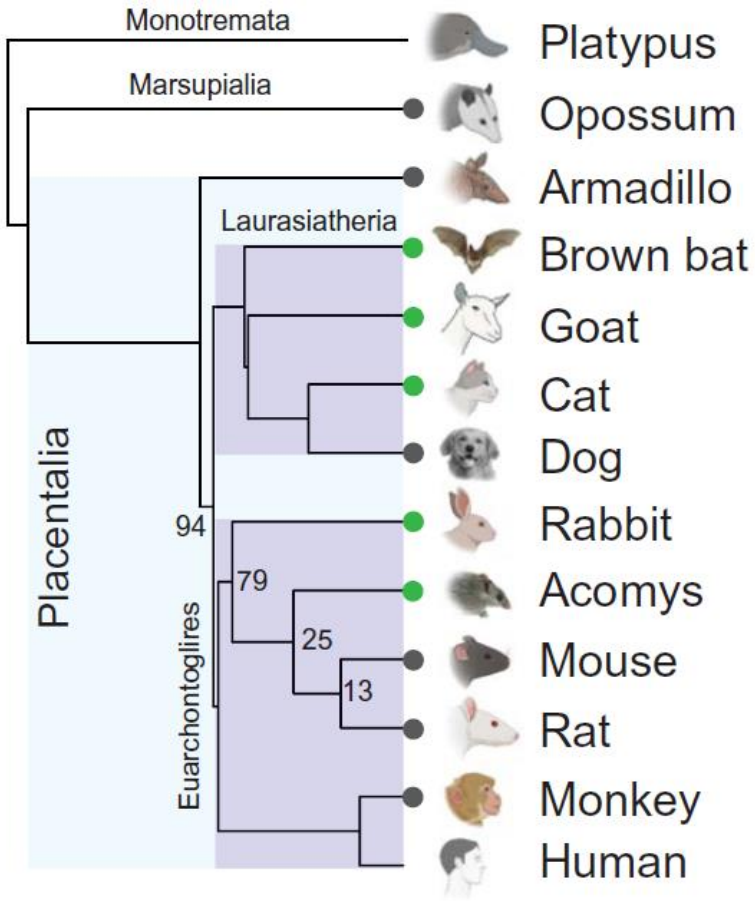
Ear pinnae!

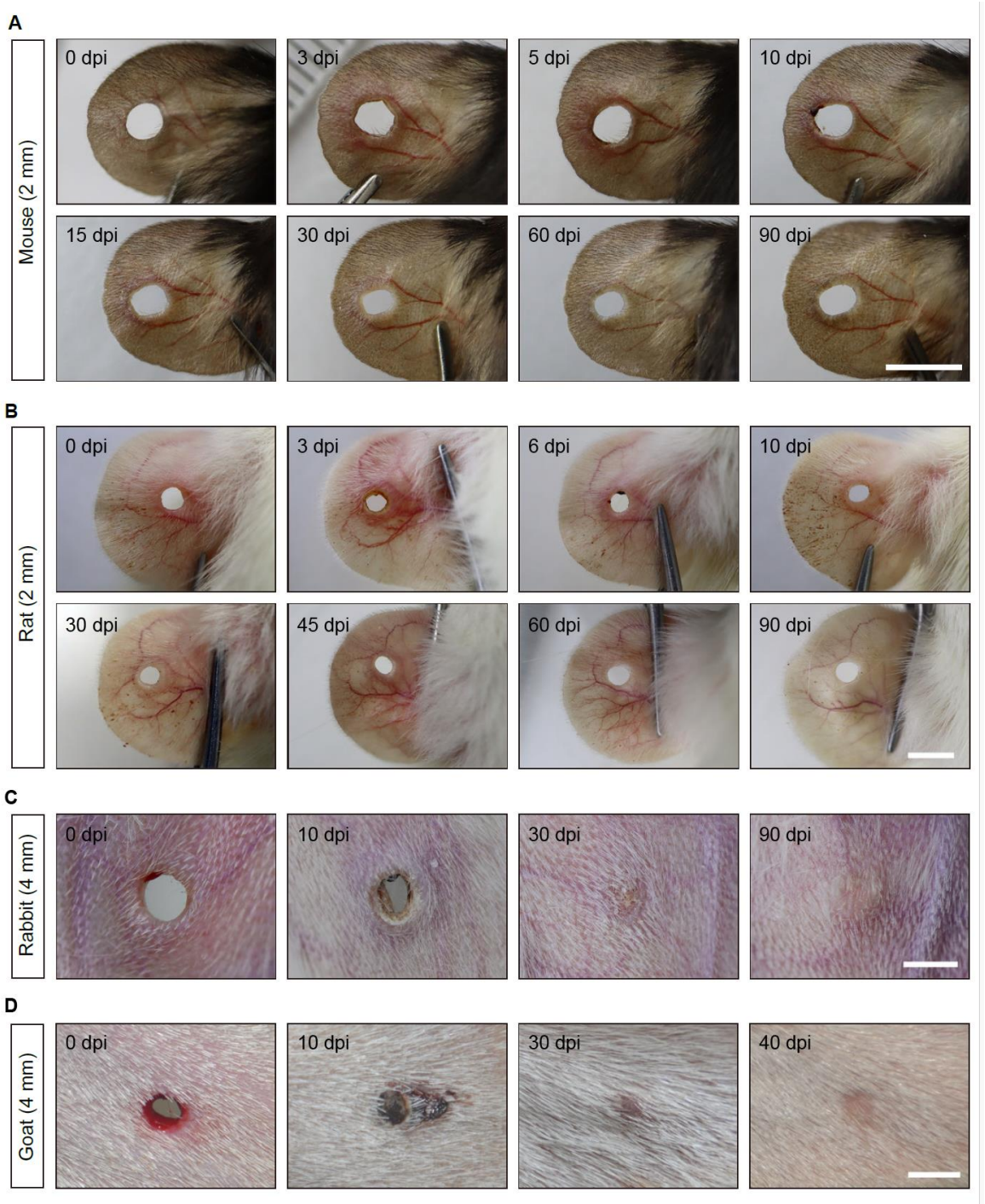
RESEARCH ARTICLE SUMMARY

ORGAN REGENERATION

Reactivation of mammalian regeneration by turning on an evolutionarily disabled genetic switch

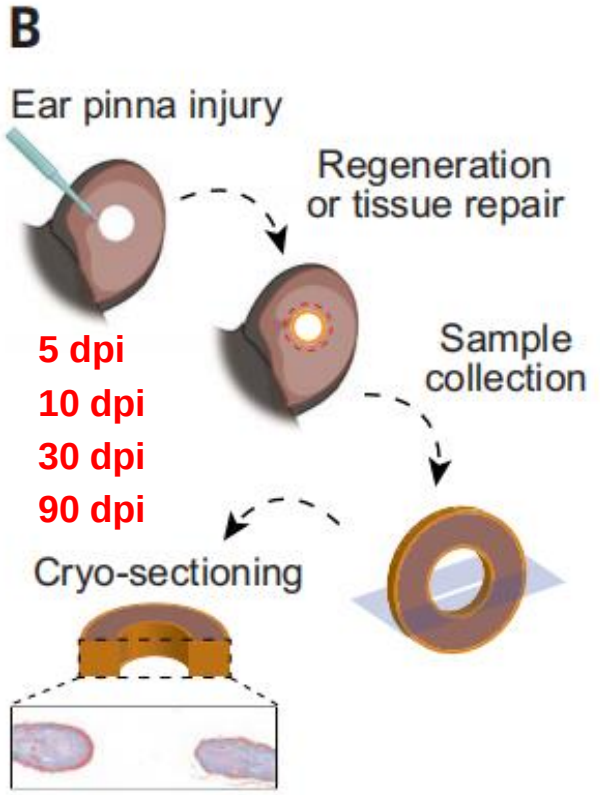
Weifeng Lin†, Xiaohui Jia†, Xiaofeng Shi†, Qiuya He†, Panyu Zhang†, Xianglei Zhang, Liping Zhang, Mingqi Wu, Tengfei Ren, Yufei Liu, Haohao Deng, Yanyao Li, Shiqi Liu, Shaoyong Huang, Jingmin Kang, Jun Luo*, Ziqing Deng*, Wei Wang*

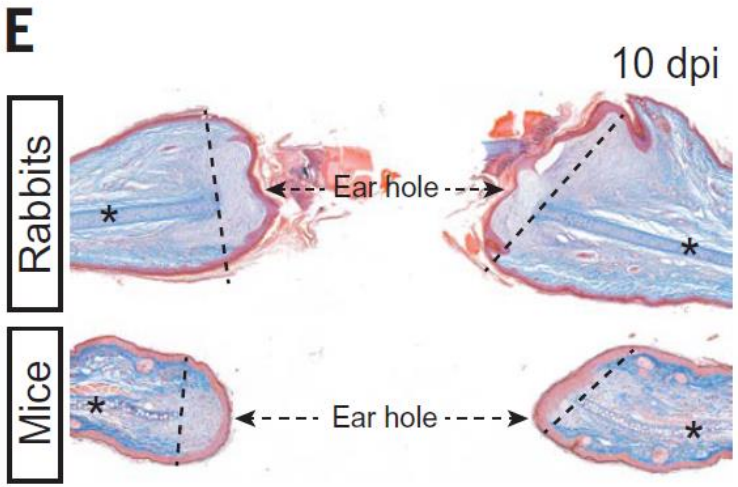


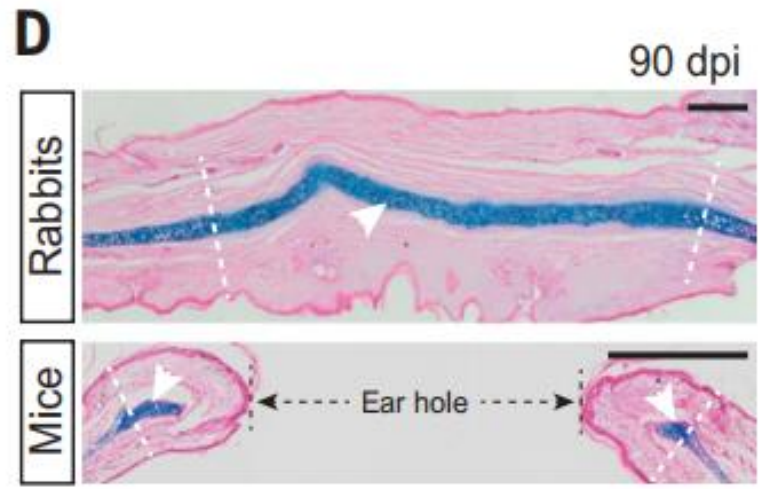


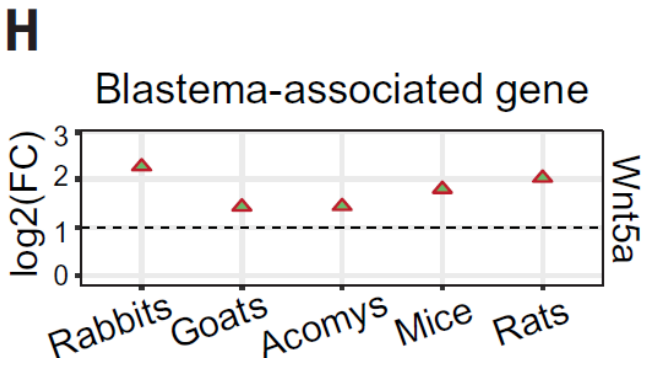
- **Focus on Blastema (芽基)**

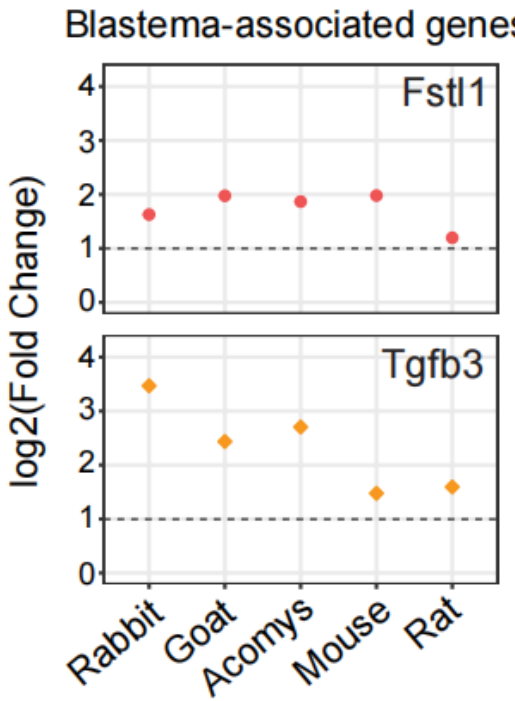
A blastema is a mass of undifferentiated cells that forms at the site of an injury in certain animals, and has the potential to regenerate lost or damaged body parts

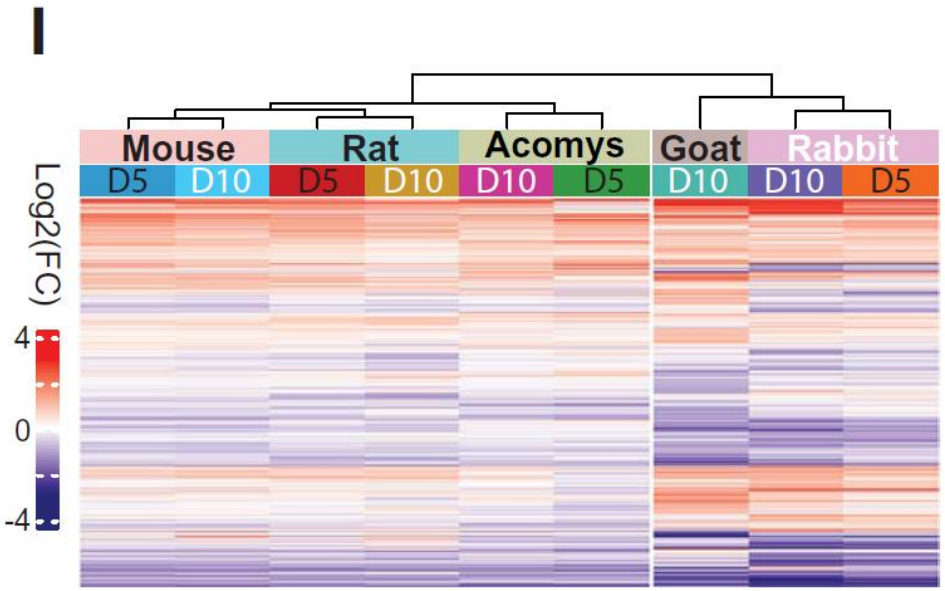






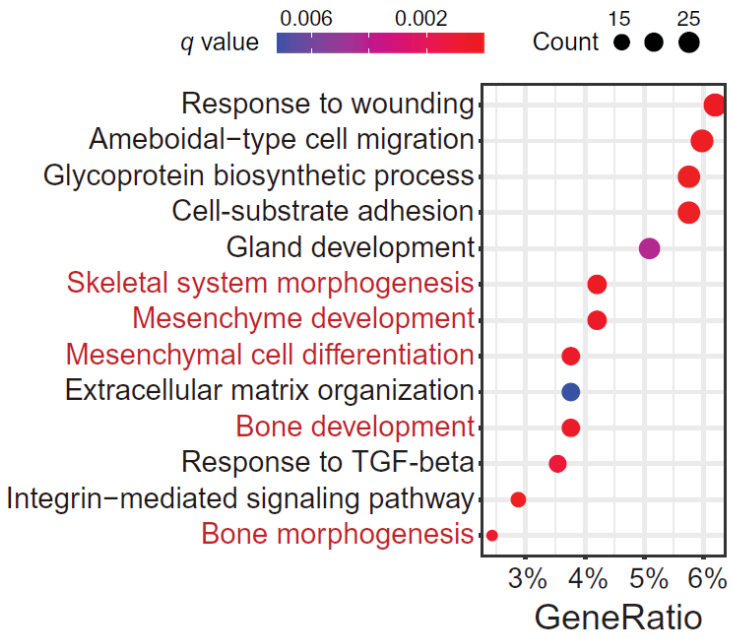






- **DEGs of Blastema among one-to-one species**

J



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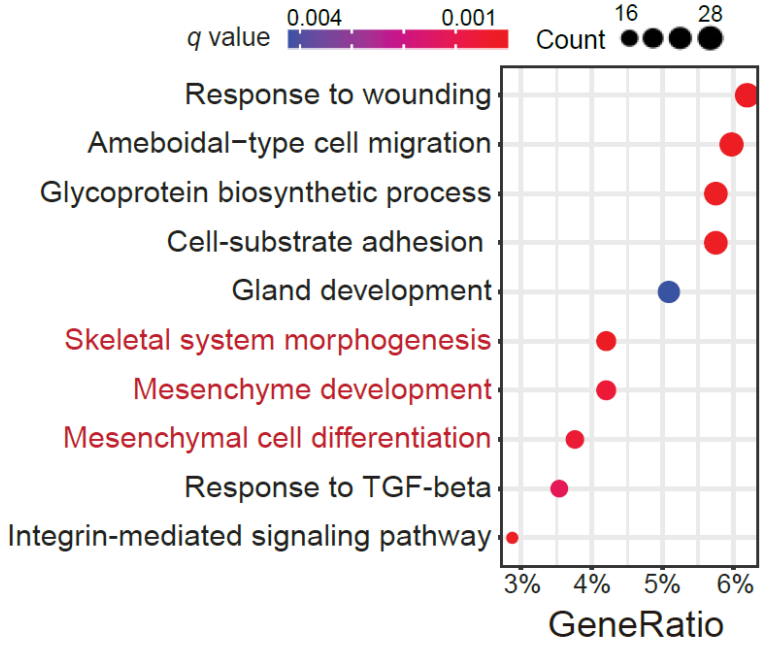
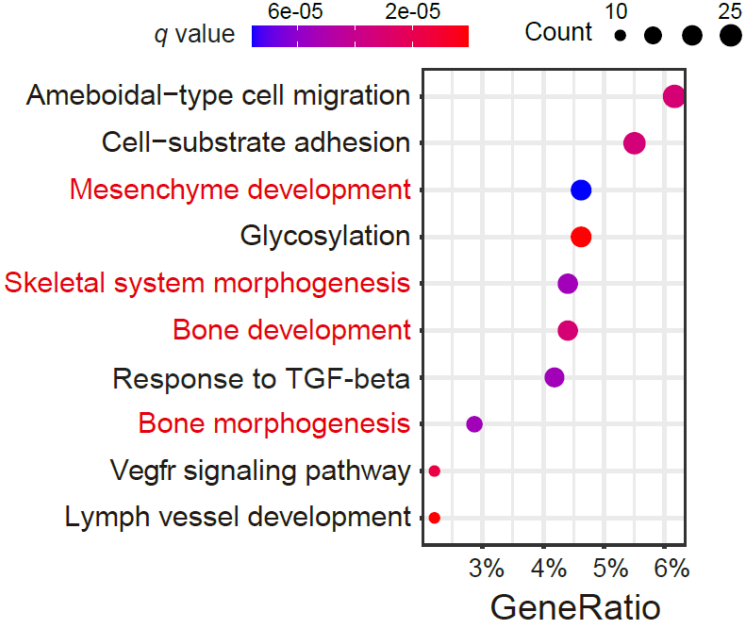


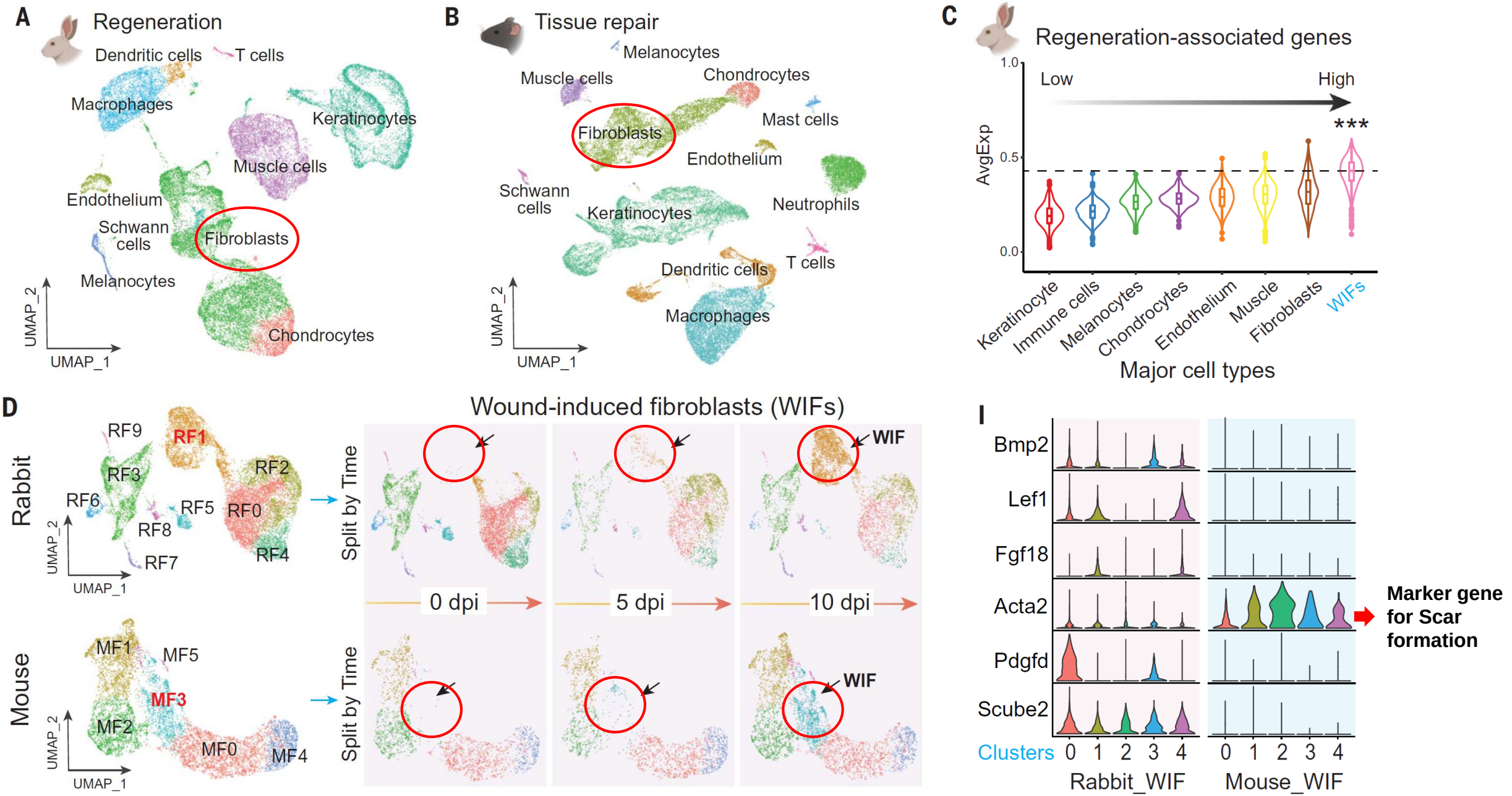
E



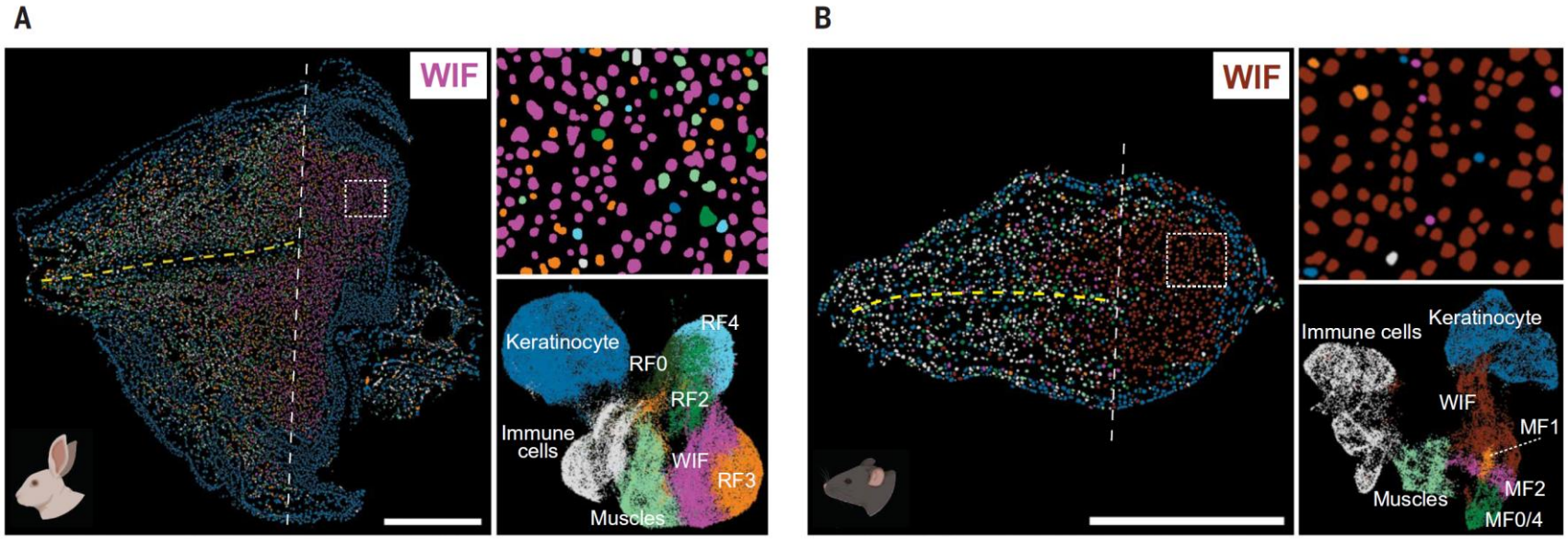
RAGs (Regeneration-associated genes): that the representative GO terms enriched for the RAGs were “skeletal system morphogenesis” and “mesenchyme development”

- **Which is the main cell type in blastema that highly expressed RAGs?**

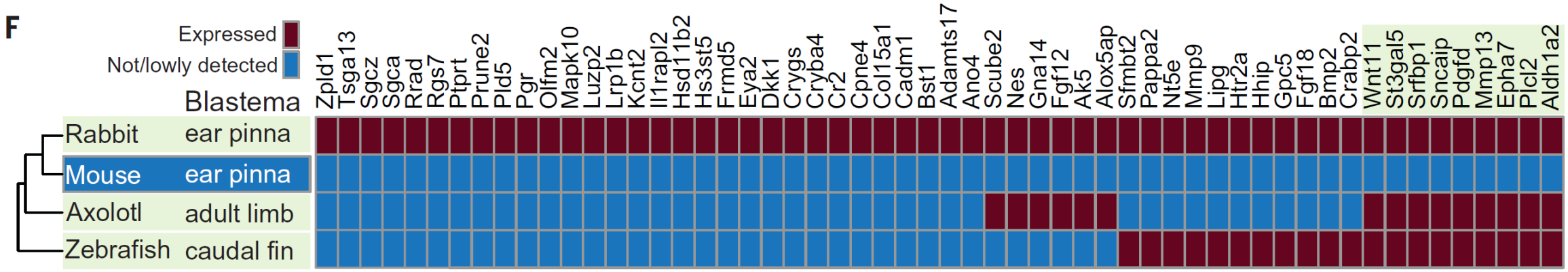
Wound-induced fibroblasts are the primary cell source for the expression of RAGs



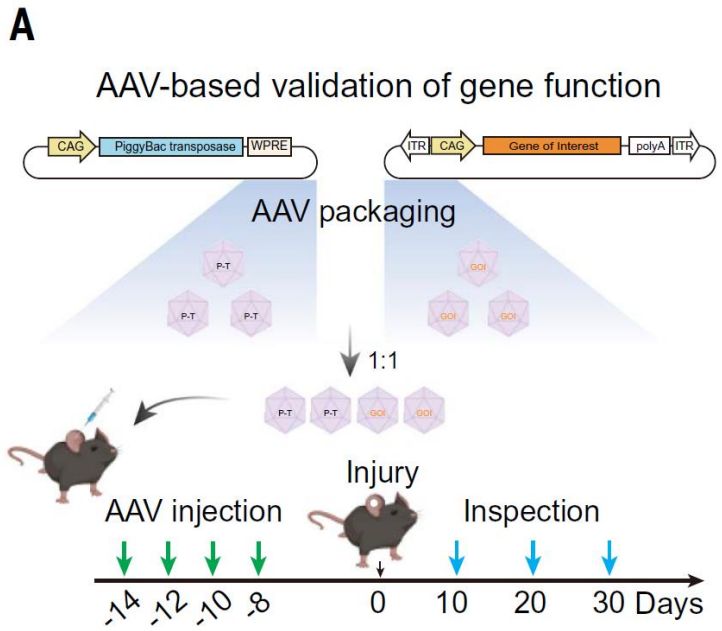
- **Identification of commonly activated genes in the blastema of animals with high regenerative potential**

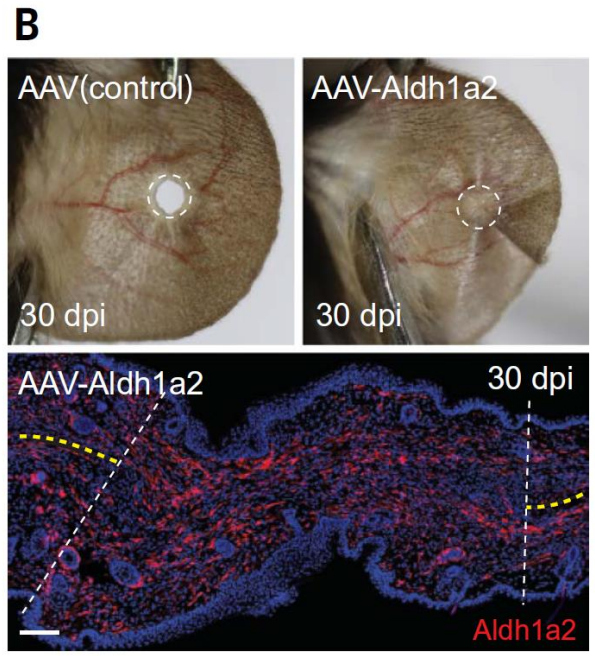


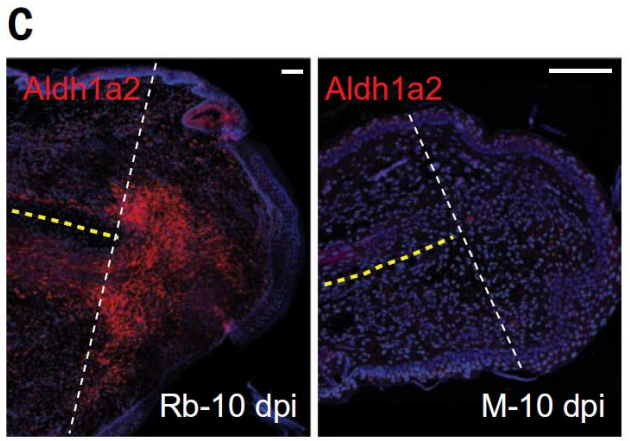
- **Spatial transcriptomics data combined with scRNA-seq data of rabbit, mouse, axolotl and zebrafish**

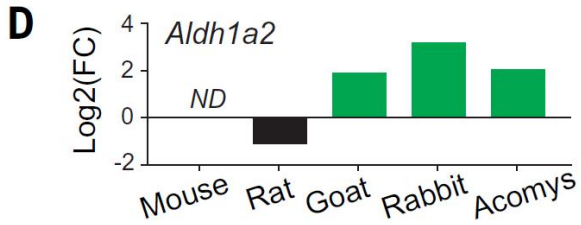


- **Insufficient production of retinoic acid (RA) is a causative mechanism for the failure of ear pinna regeneration**

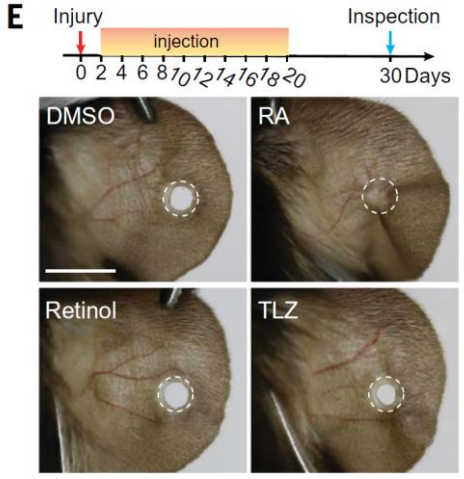


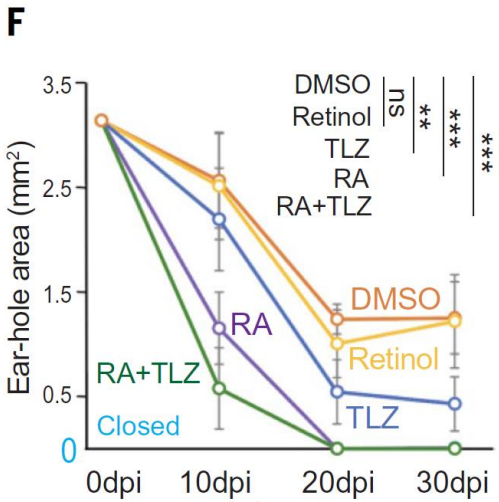


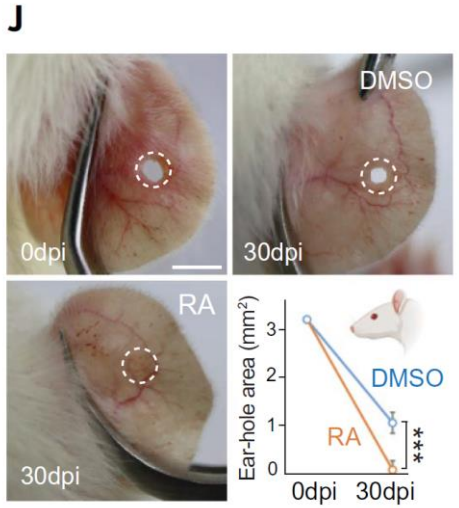


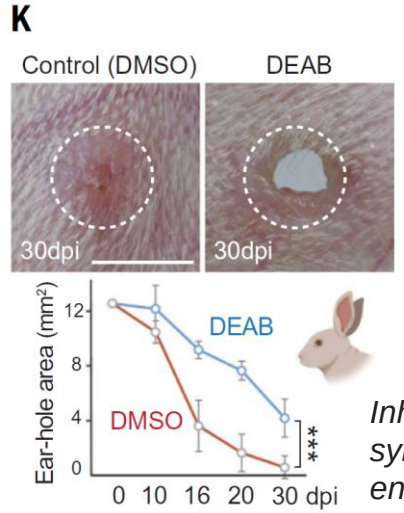


Aldehyde Dehydrogenase 1 Family Member A2 (Aldh1a2) encoding a rate-limiting enzyme in the synthesis of retinoic acid (RA)









Inhibition of RA synthesizing enzymes with DEAB

Retinol (the synthetic precursor of RA);
Talarozole (TLZ, a Cyp26 (degenerate RA) inhibitor)

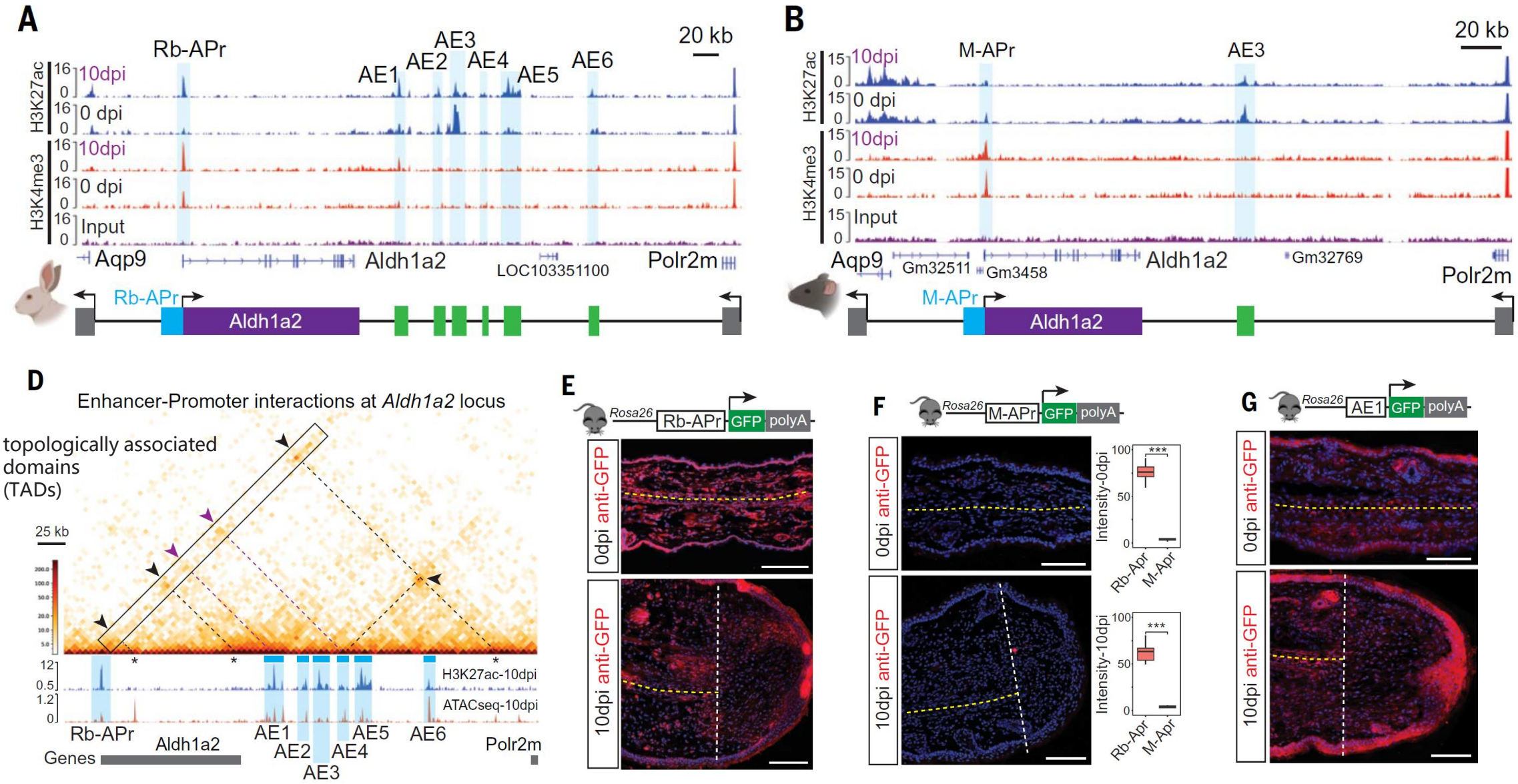
Mouse

Rat

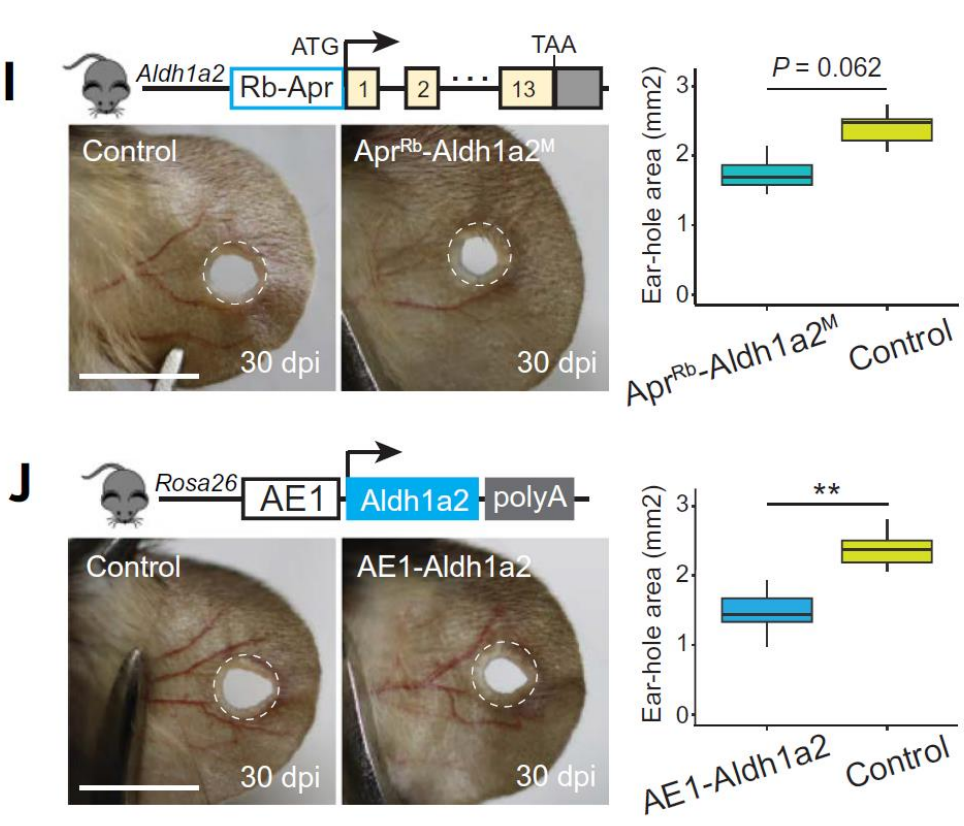
Rabbit

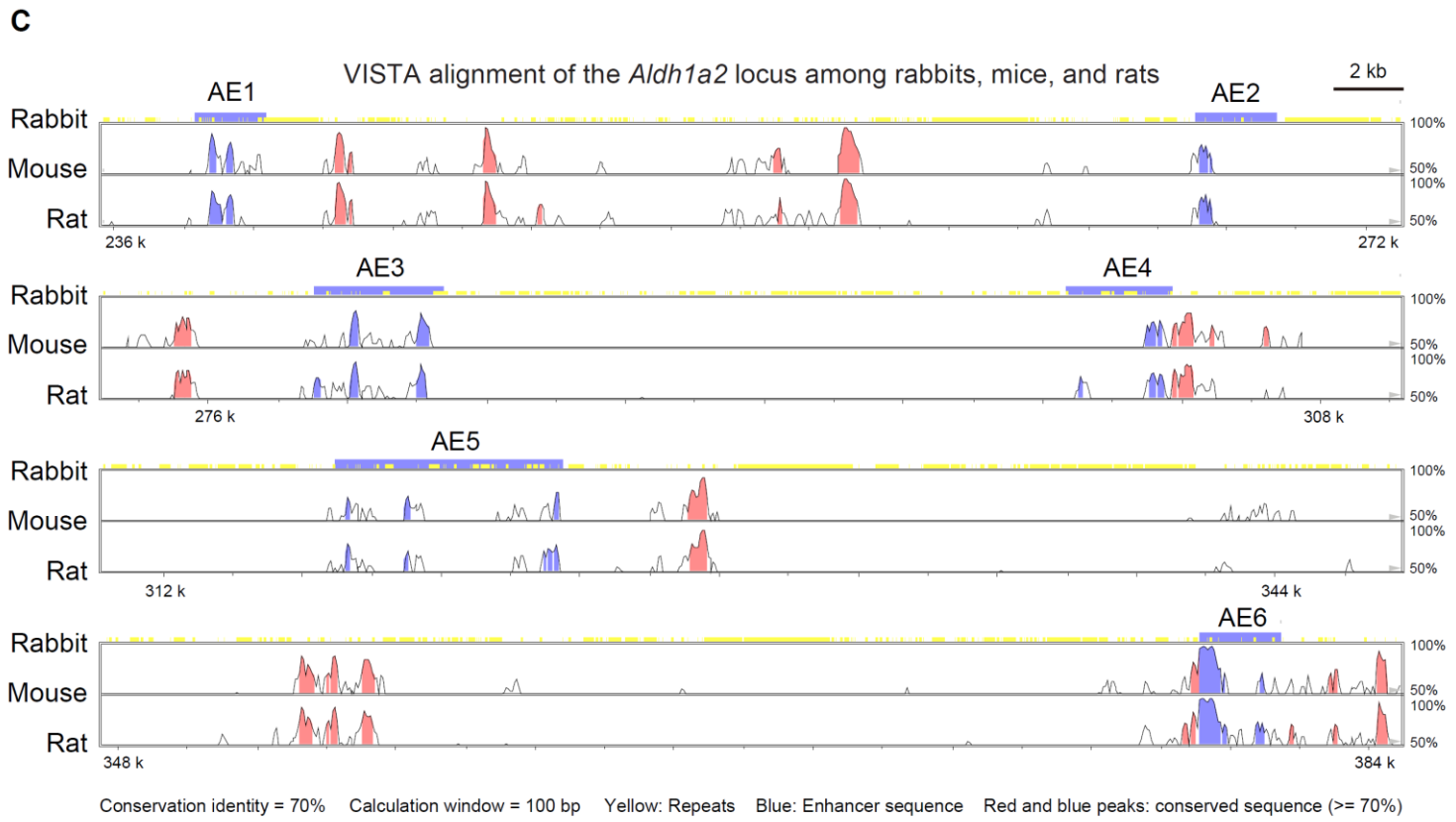
- **Why the expression level of RA exhibit difference among species?**

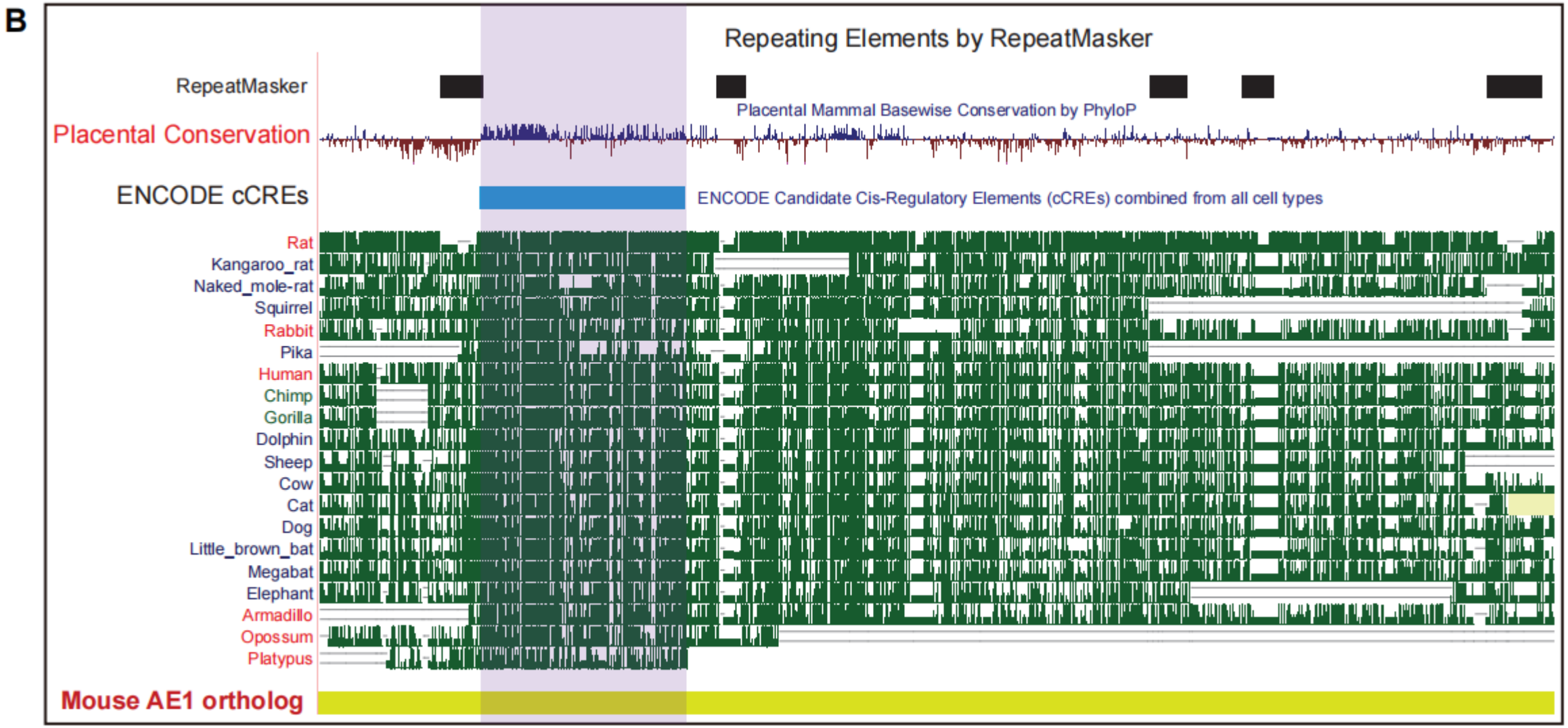
They assayed H3K4me3 and H3K27ac enrichment at 0 and 10 dpi in mouse and rabbit genomes to identify active promoters and enhancers, respectively



- **A single rabbit enhancer is sufficient to promote ear pinna regeneration in transgenic mice**

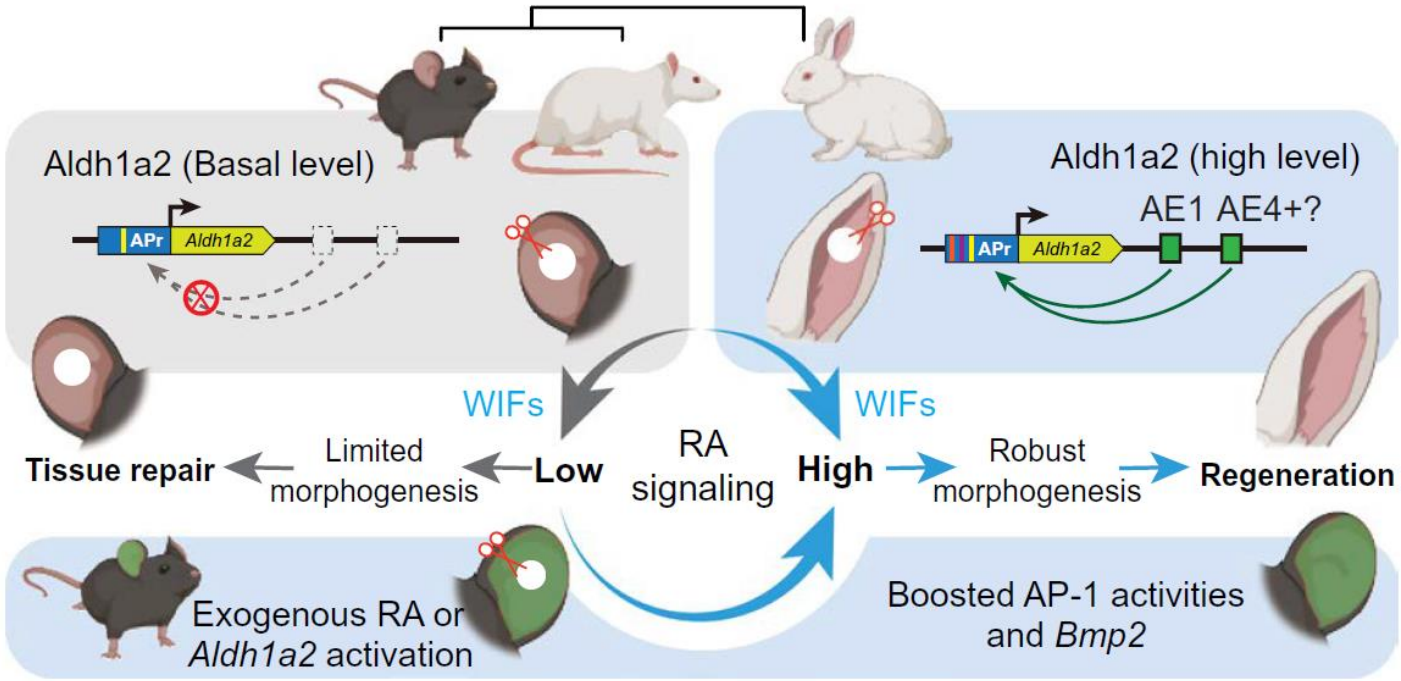






Sequences of Aldh1a2 and AE1 alignments showed that AE1 contains an ancient regulatory module with sequence conservation across different mammals including the platypus. So why the regulation of promoter and enhancer exhibits differences among species to control regeneration is still need to be explored…

Take home messages



Find Ear pinnae as model

↓

Identified RAGs

↓

scRNA identified WIFs expressed RAGs

↓

Combined with Spatial transcriptomics

↓ Add Axolotl and Zebrafish

Identified nine with the highest confidence

↓

Overexpressed experimental verification

↓

Identified regulatory elements for Aldh1a2

↓

Further experimental verification

Thanks for your attention!
Q & A

B

High sequence conservation of Aldh1a2 protein