



国家神经系统疾病临床医学研究中心
China National Clinical Research Center for Neurological Diseases

WIP1磷酸酶调控小鼠胚胎造血干 细胞发育的功能和机制

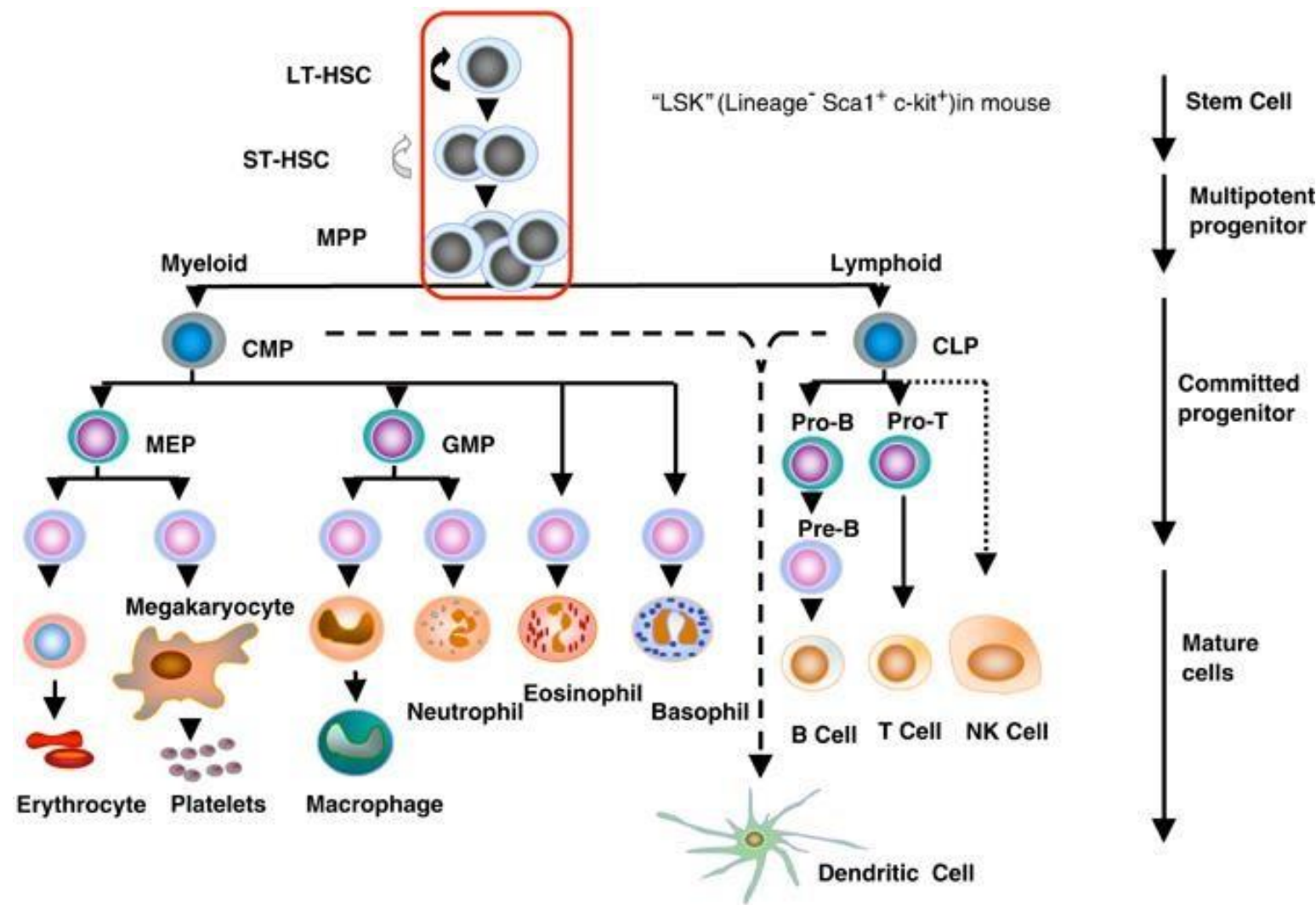
贺文艳

基础与转化医学中心

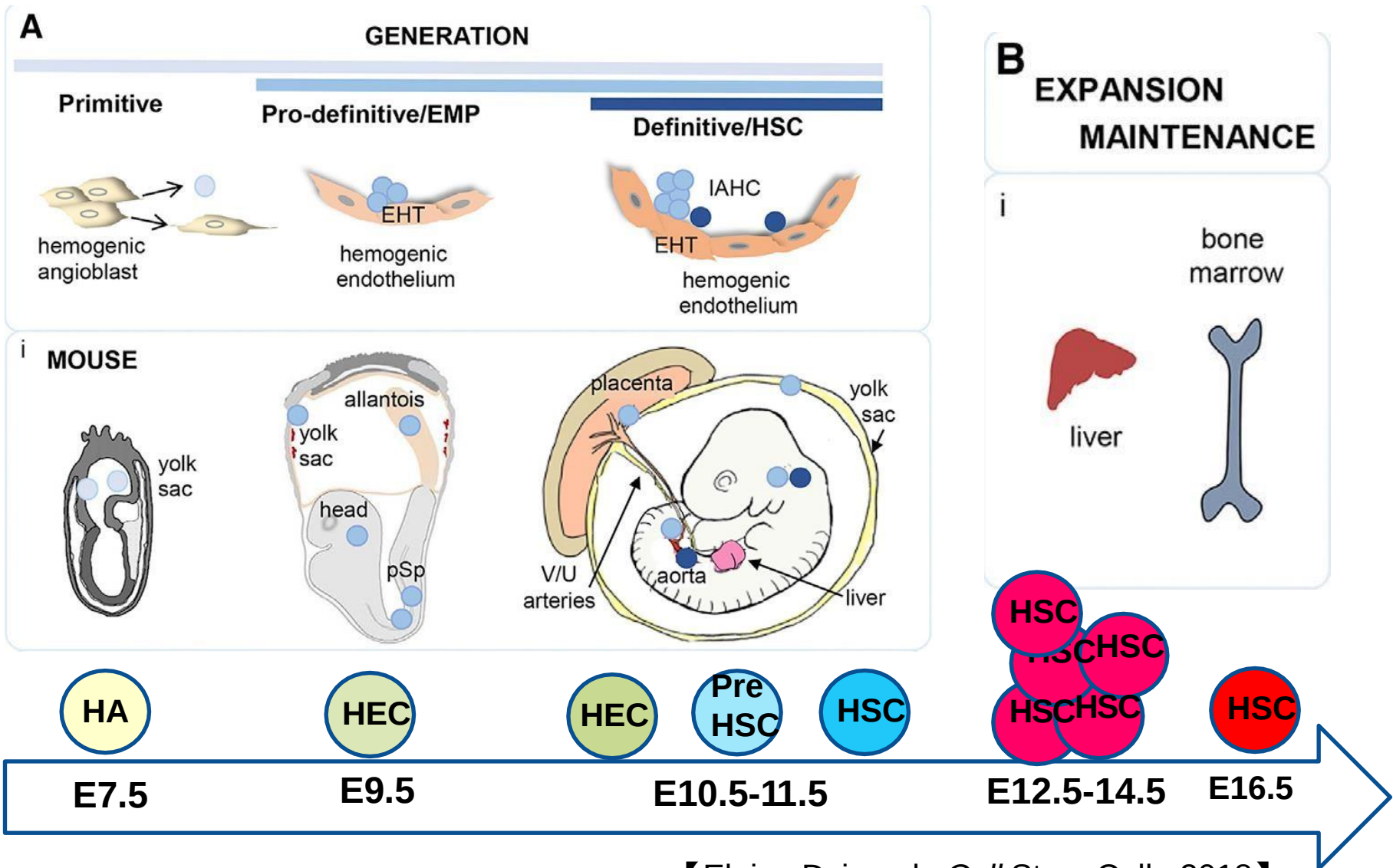
2020-04-08

造血干细胞 (hematopoietic stem cell, HSC)

自我更新和多系分化

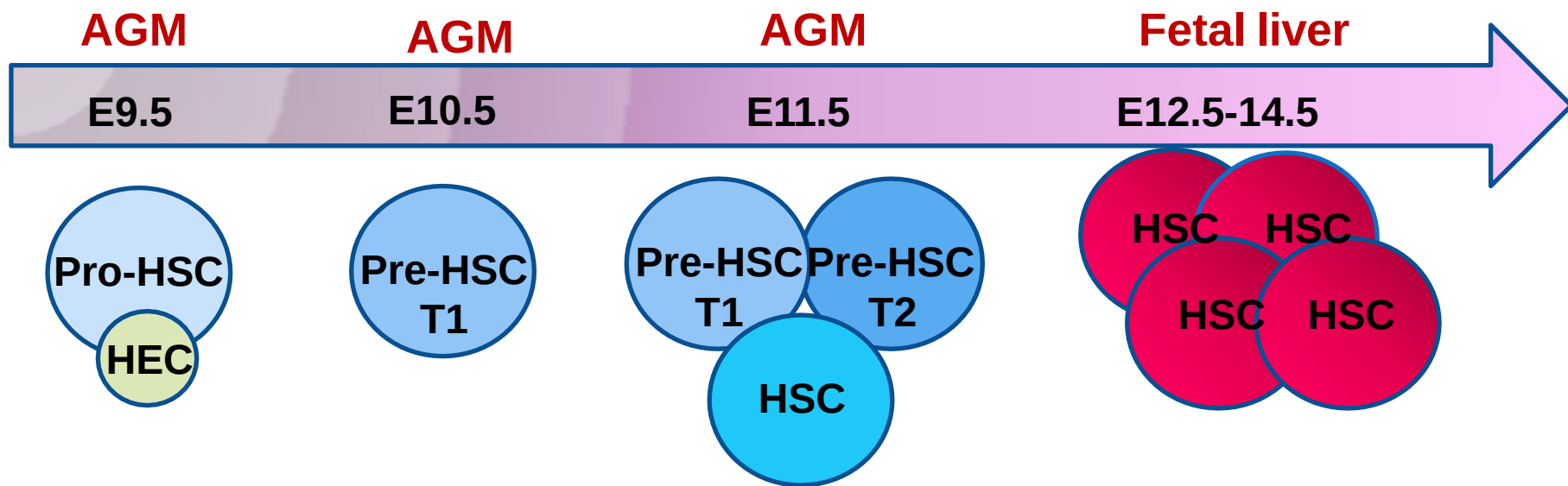


小鼠胚胎造血干、祖细胞产生概况



【Elaine Dzierzak, Cell Stem Cell, 2018】

小鼠胚胎造血干细胞前体的免疫表型



1. **HEC** (CD31⁺VE-Cadherin⁺CD41⁻CD43⁻CD45⁻Ter119⁻ in E9.5 AGM region)
2. **Pre-HSC I** (CD31⁺CD45⁻CD41^{low}c-Kit⁺CD201^{high} in E10.5 AGM region)
3. **Pre-HSC II and Pre-HSC** (CD31⁺CD45⁺c-Kit⁺CD201^{high} in E11.5 AGM region)
4. **E12.5 HSC** (Lin⁻Sca1⁺Mac1^{low}CD201⁺ in E12.5 fetal liver)
5. **E14.5 HSC** (CD45⁺CD150⁺CD48⁻CD201⁺ in E14.5 fetal liver)

WIP1磷酸酶功能概况

- ◆ WIP1(the wild-type p53 induced phosphatase1): 一种 PP2C家族的丝氨酸 / 苏氨酸蛋白磷酸酶。
- ◆ *Wip1*是致癌基因，在乳腺癌，神经细胞瘤和卵巢透明细胞癌等癌症中高表达。
- ◆ *Wip1*是p38MAPK/p53通路的负反馈调节因子，即DNA损伤反应过程中内环境稳定的调节剂，随着损伤修复的完成让细胞返回正常状态。

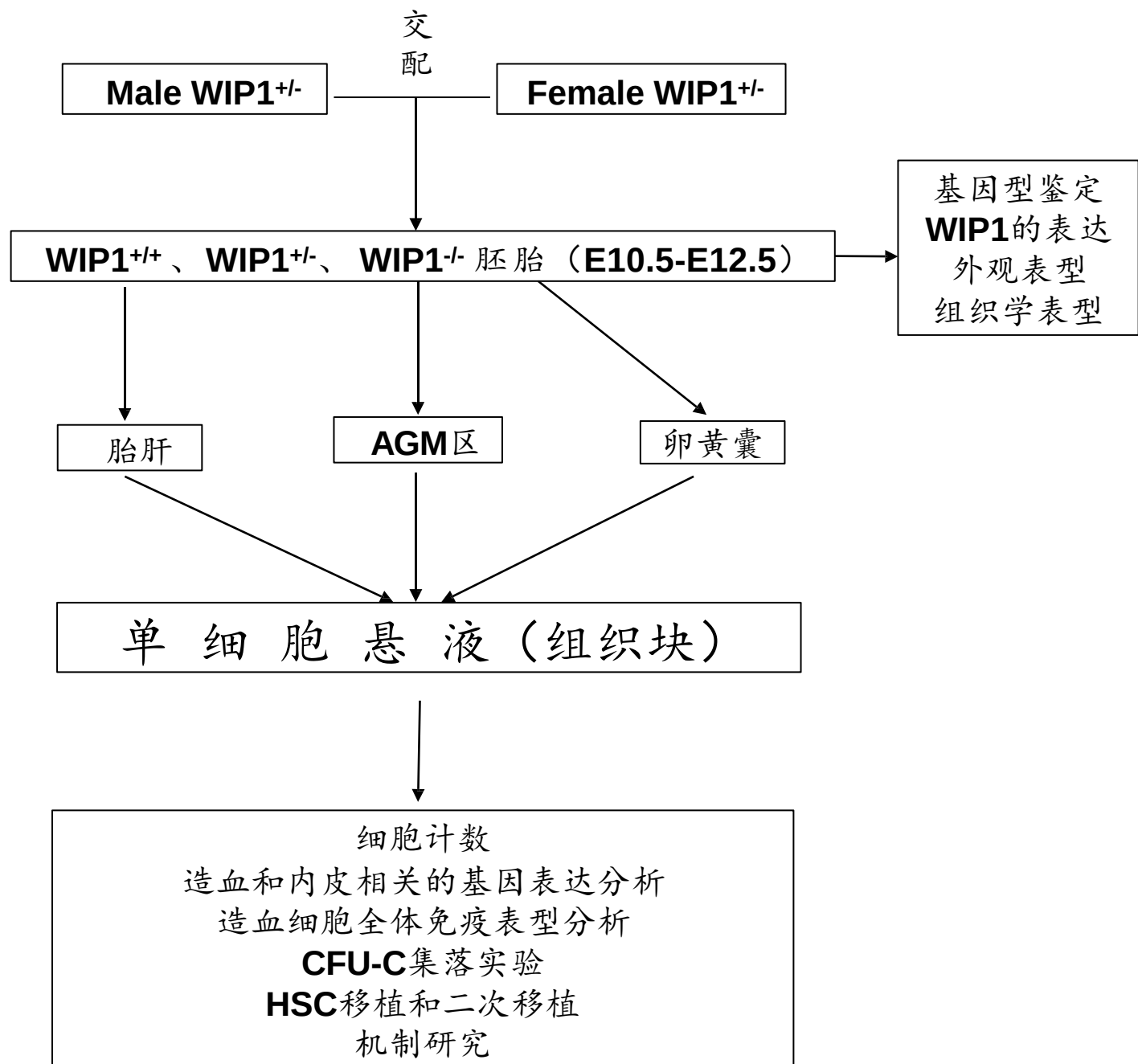
Wip1基因与小鼠造血细胞发育

成体： **Wip1**基因缺失：

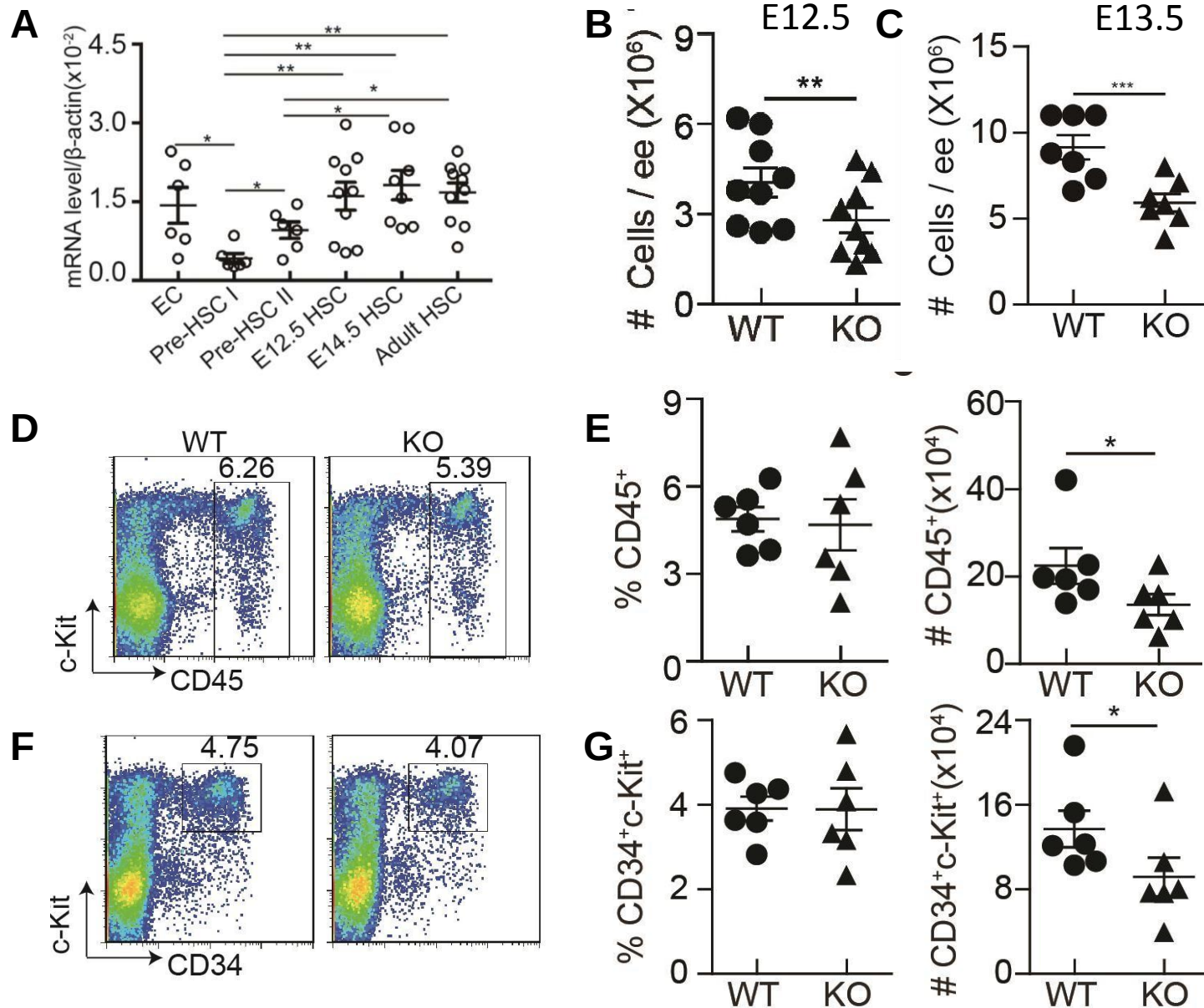
- ✓ 胸腺**T**淋巴细胞发育障碍
- ✓ 骨髓**B**淋巴细胞发育障碍
- ✓ 骨髓中性粒细胞发育异常，稳态破坏
- ✓ 骨髓造血干细胞数目增加，功能障碍

胚胎： **Wip1**基因缺失：

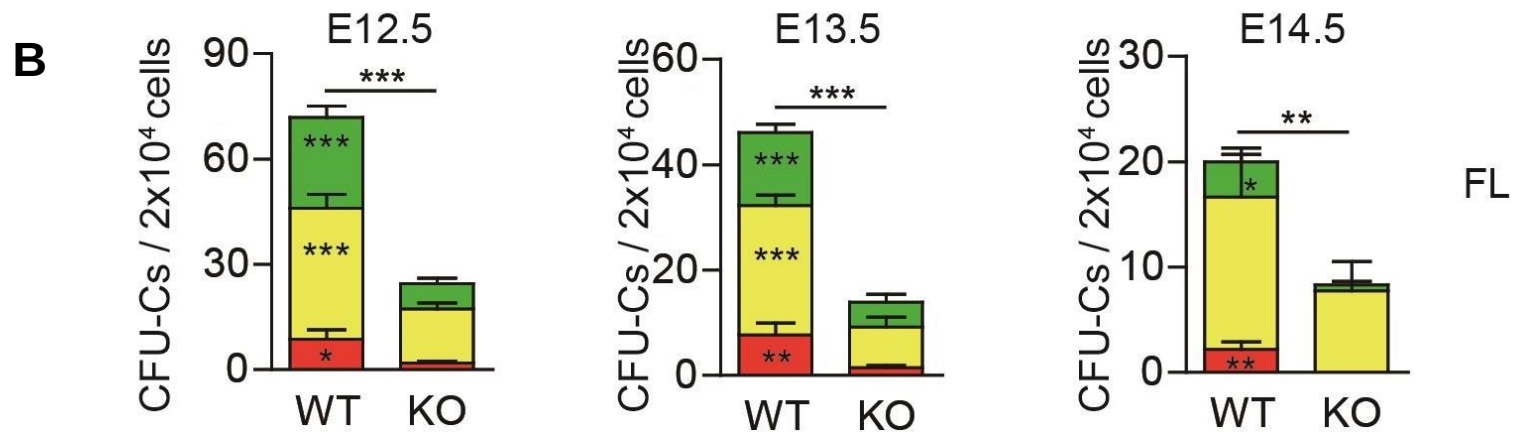
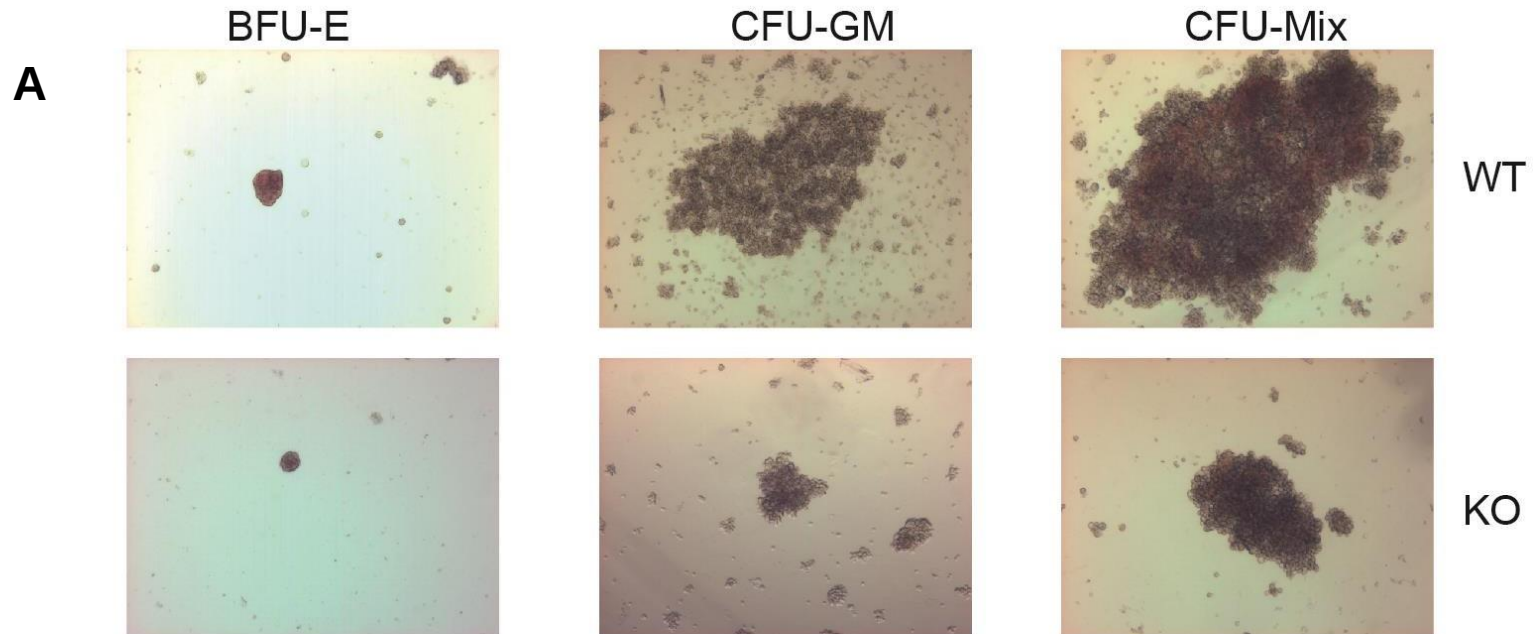
造血干细胞发育是否异常及机制？



Wip1 缺失胎肝及造血祖细胞显著减少



Wip1缺失胎肝造血祖细胞显著减少



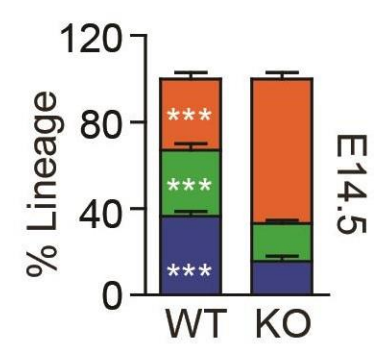
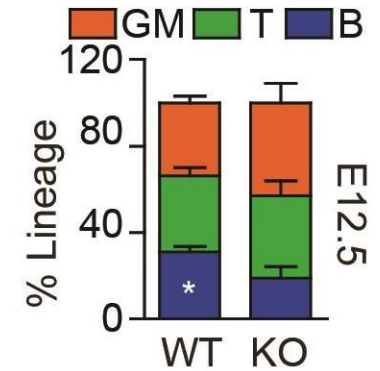
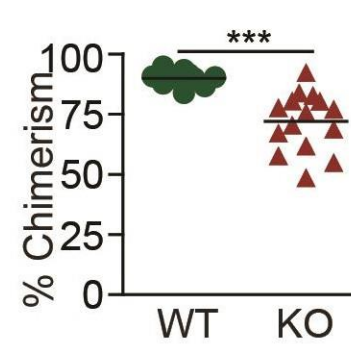
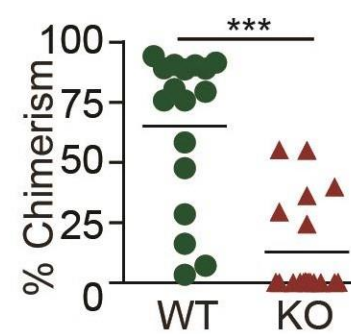
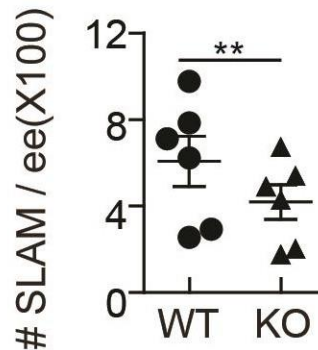
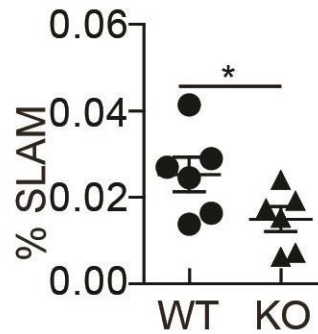
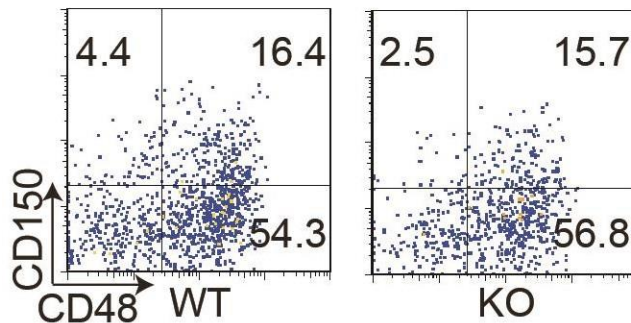
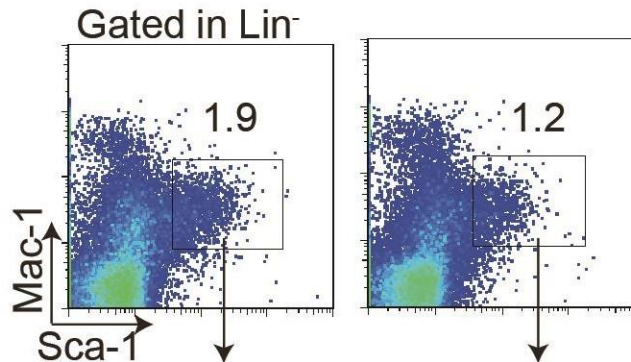
*Wip1*缺失胎肝造血干细胞显著减少，功能障碍

HSC免疫表型

Lin⁻Sca1⁺Mac1^{low}CD150⁺CD48⁻

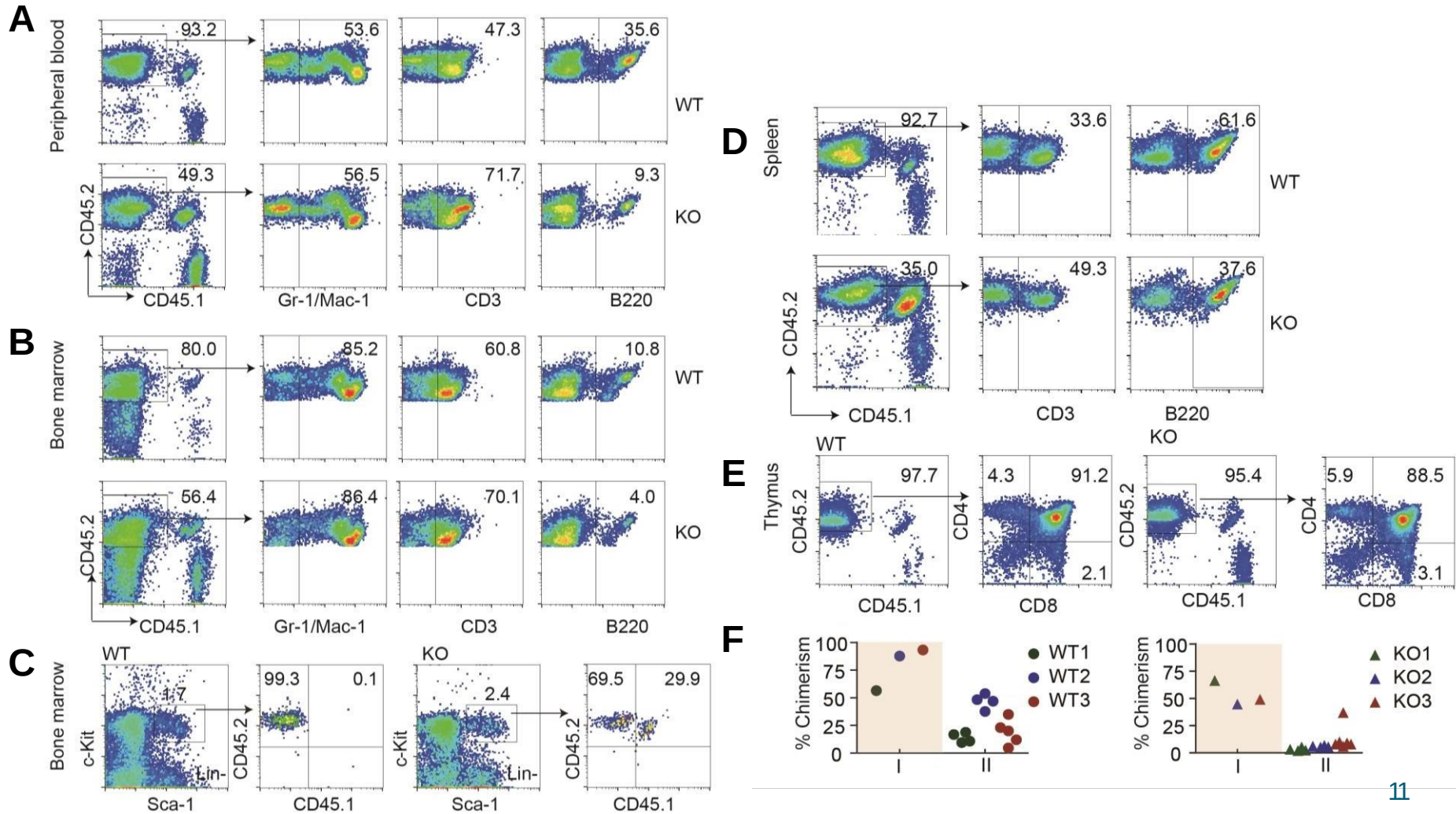
HSC直接移植

受体重建比例和分化

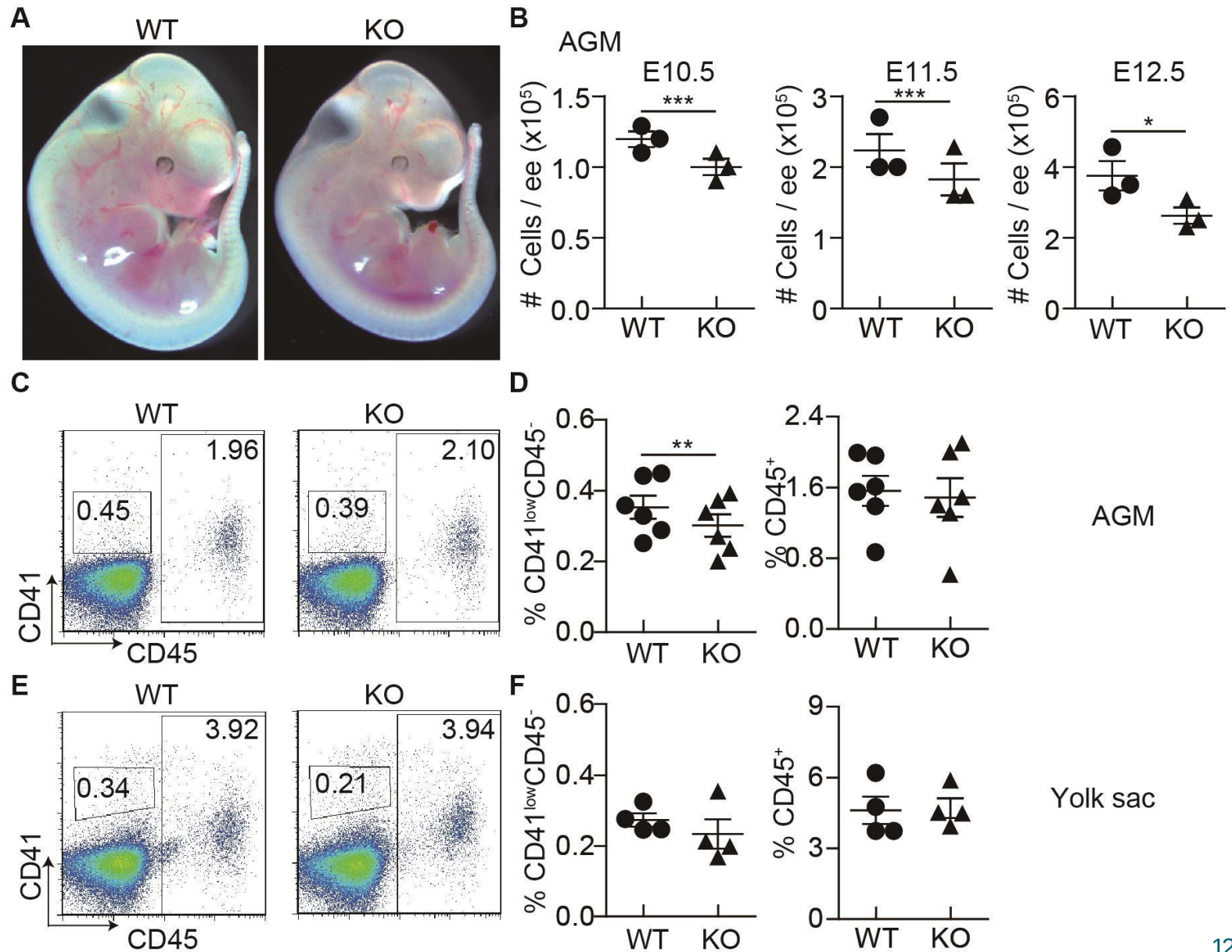


Wip1 缺失胎肝造血干细各系分化和自我更新功能障碍

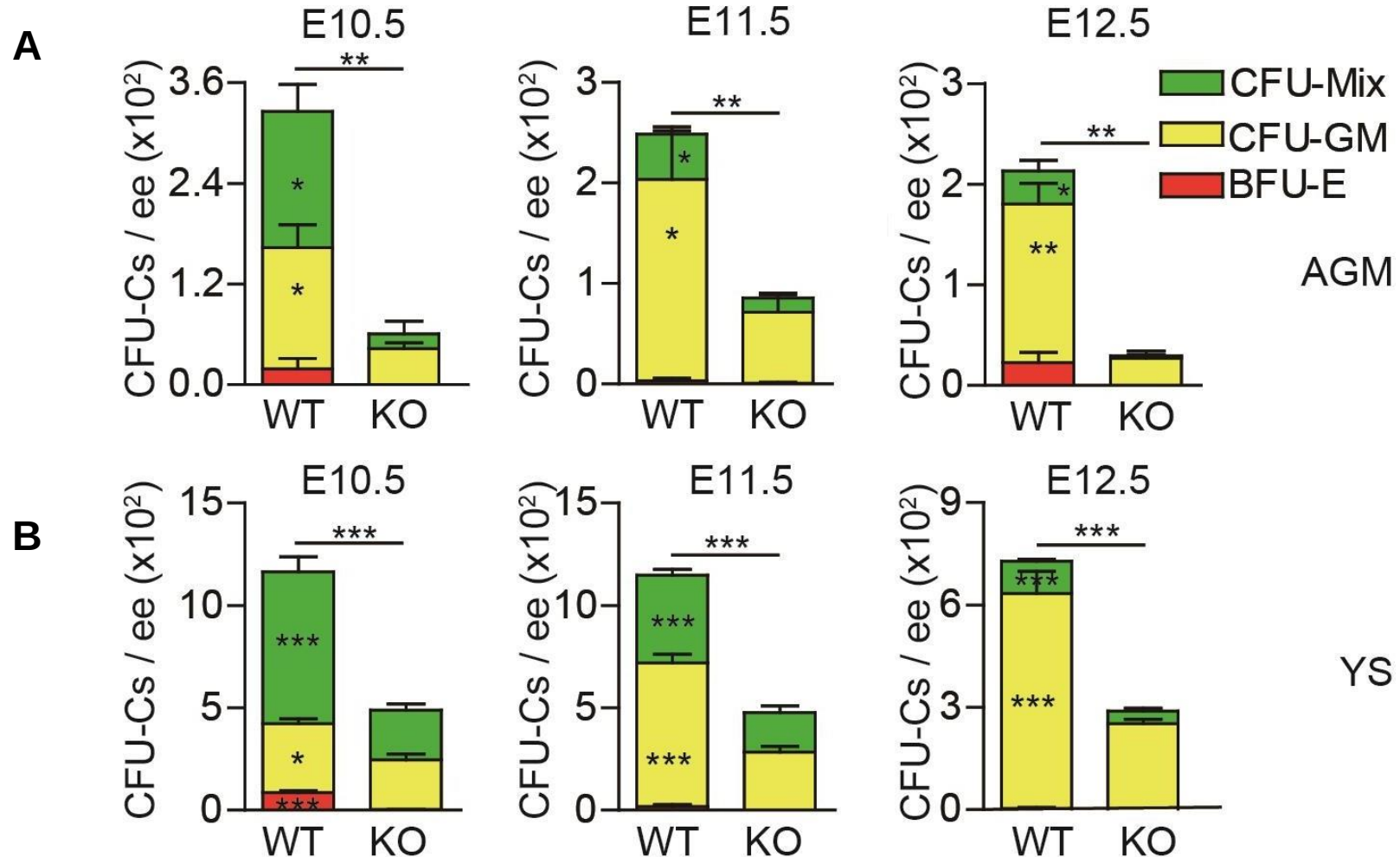
Peripheral blood , bone marrow , spleen , thymus



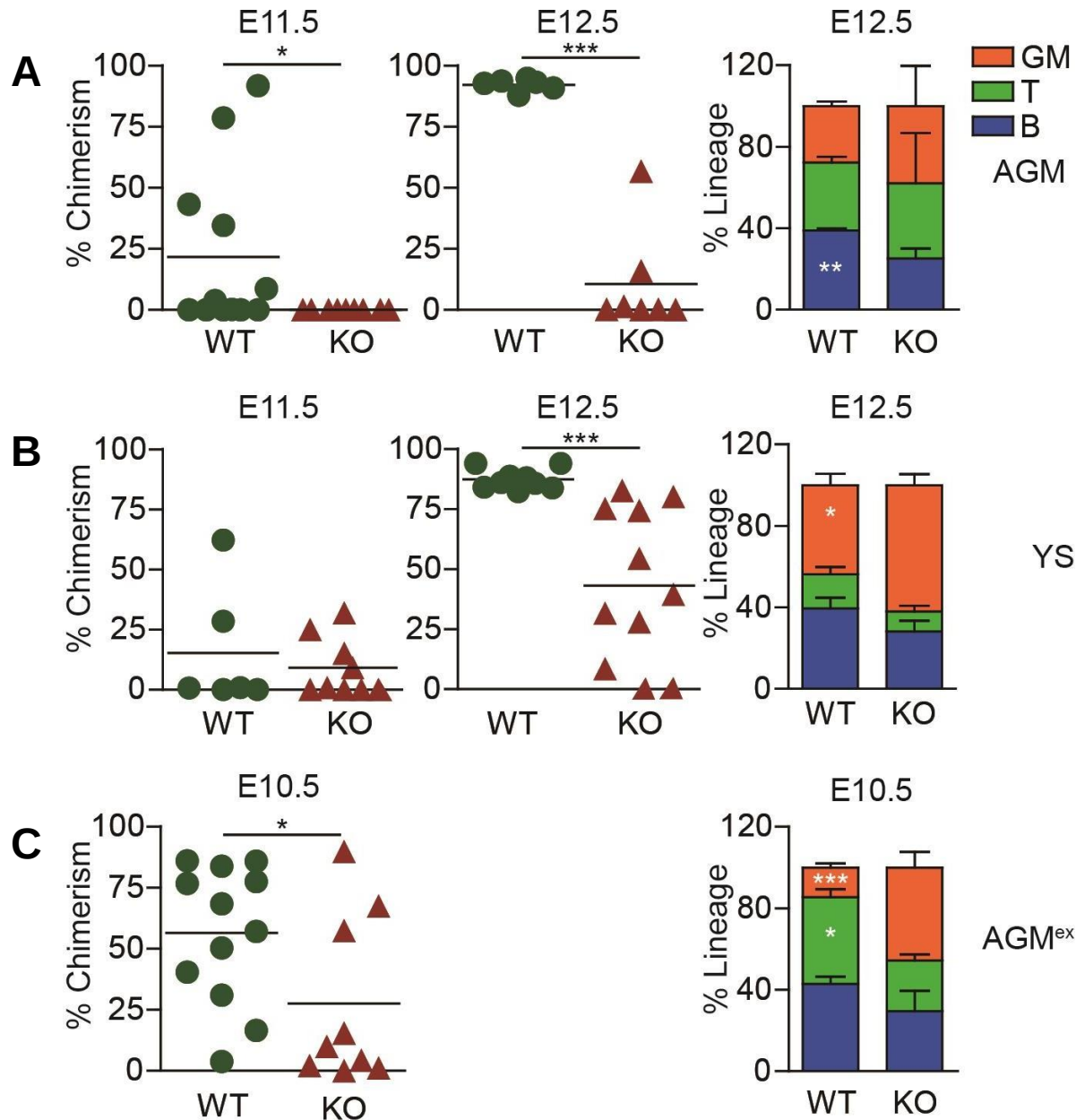
Wip1 缺失胚胎 AGM 区造血祖细胞显著减少



*Wip1*缺失胚胎AGM区造血祖细胞显著减少

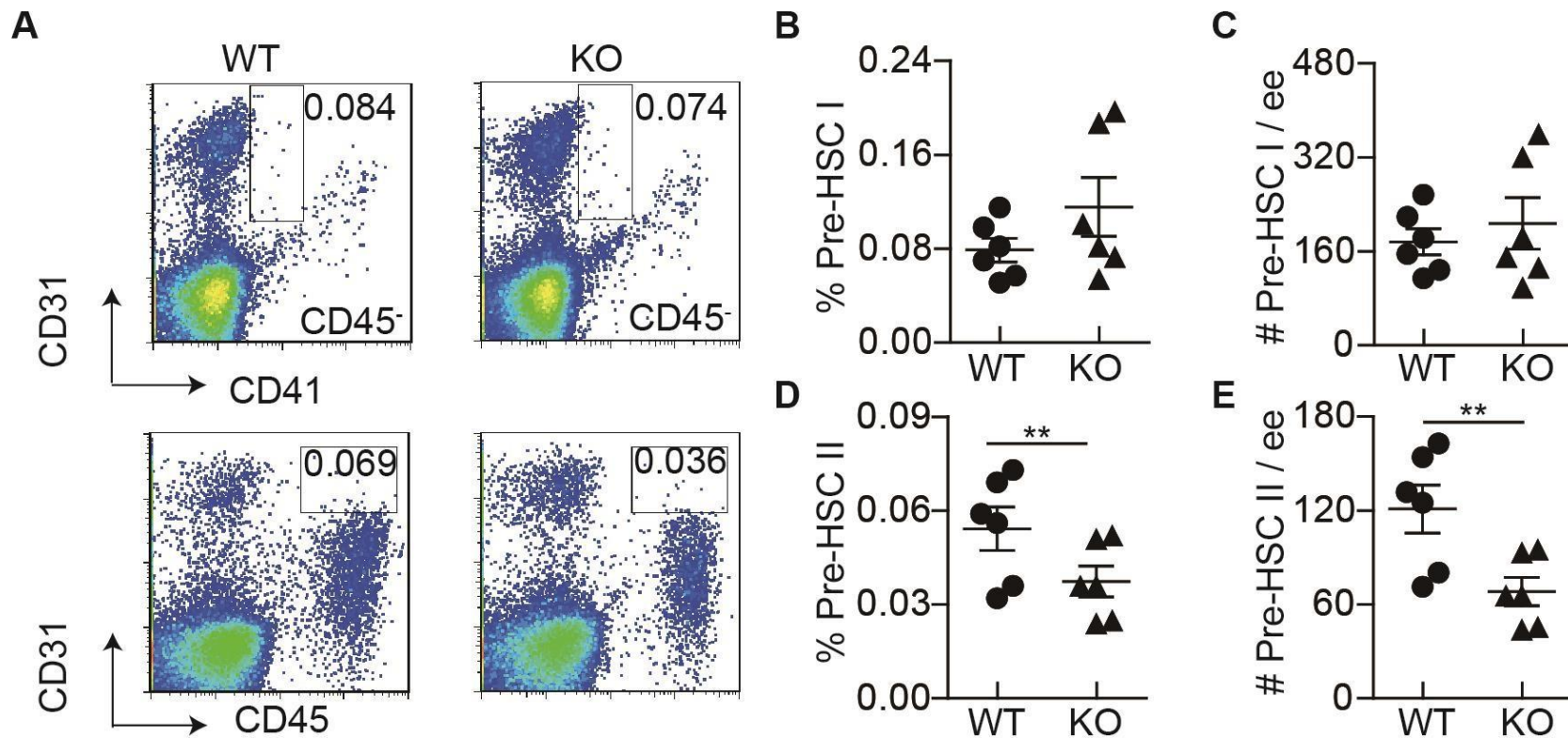


Wip1 缺失胚胎 AGM 区 HSC 显著减少，功能障碍

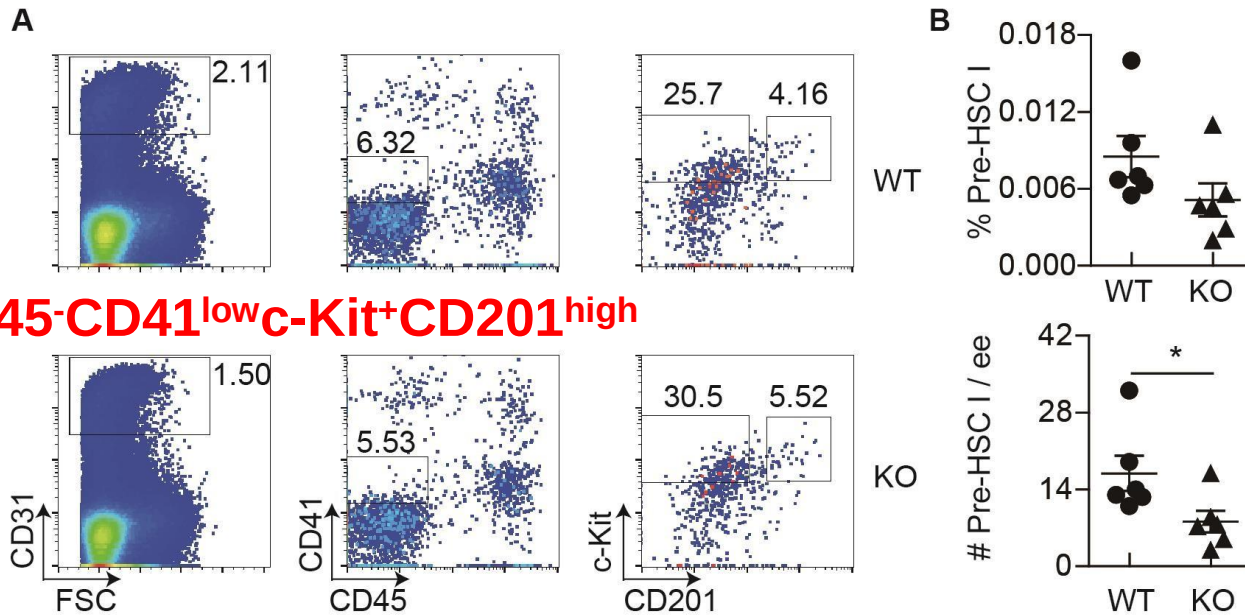


***Wip1* 缺失胚胎 AGM 区 Pre-HSC I 基本正常 而 Pre-HSC II 显著减少**

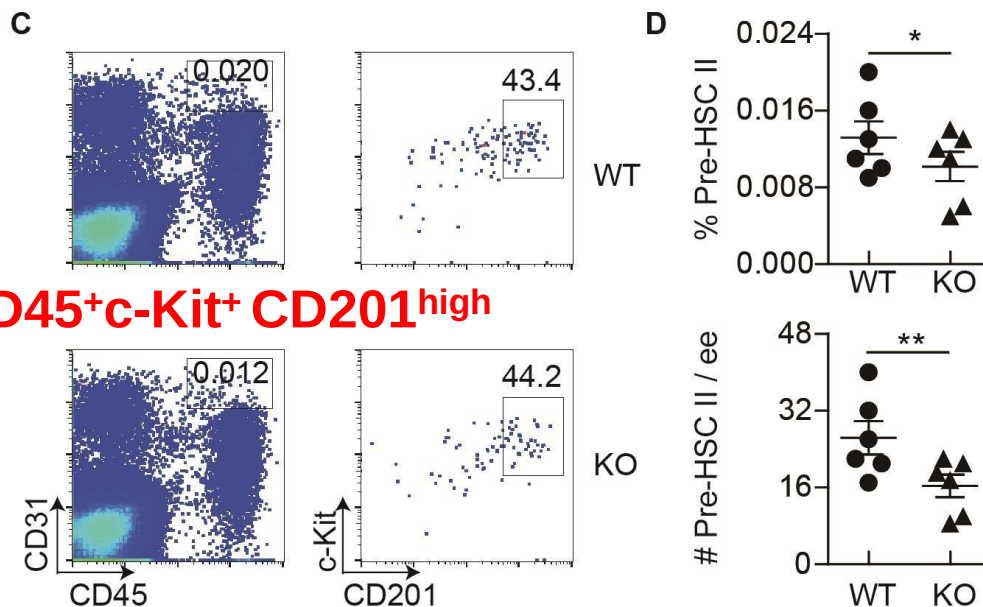
Pre-HSC I: CD31+CD41+CD45-
Pre-HSC II: CD31+CD45+



*Wip1*缺失胚胎AGM 区Pre-HSC T1/T2均显著减少



T1 $CD31^{+}CD45^{-}CD41^{low}c\text{-Kit}^{+}CD201^{high}$

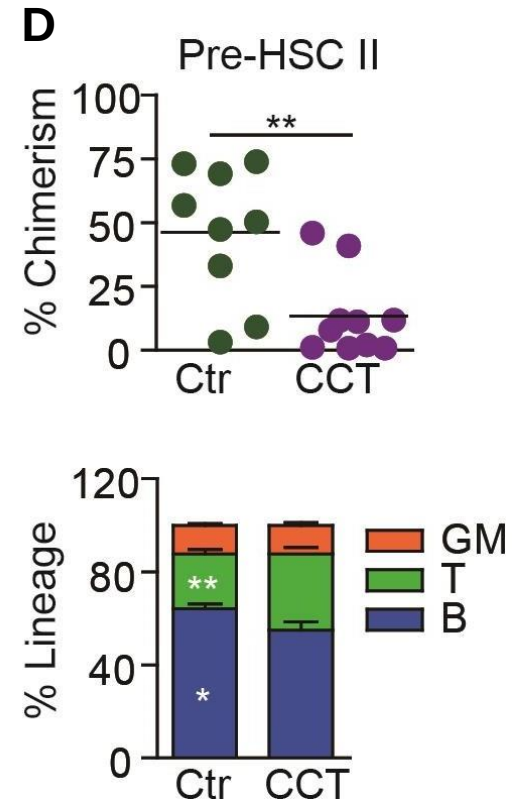
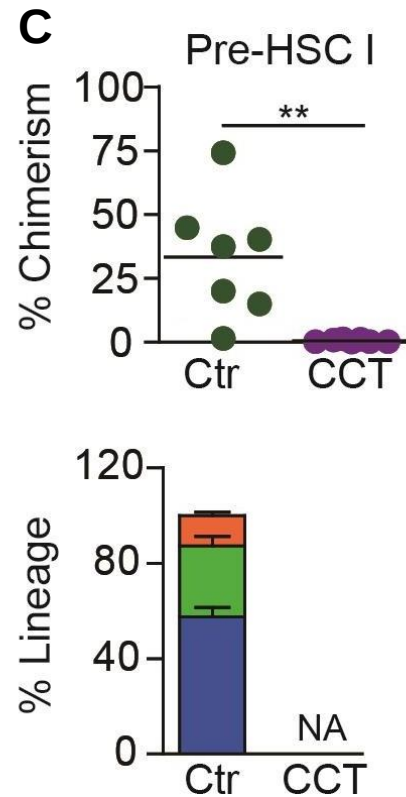
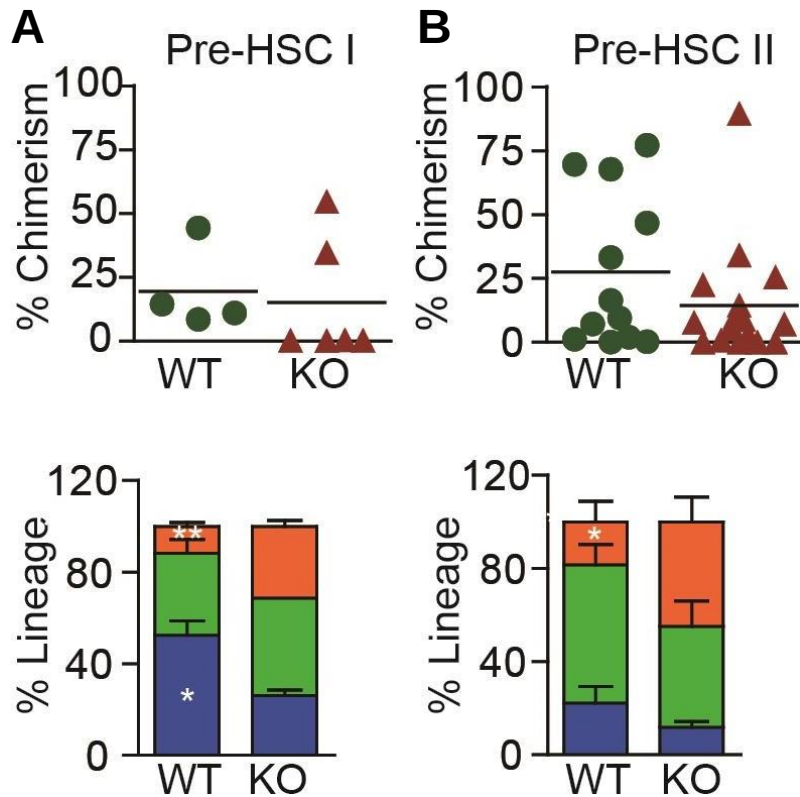


T2 $CD31^{+}CD45^{+}c\text{-Kit}^{+}CD201^{high}$

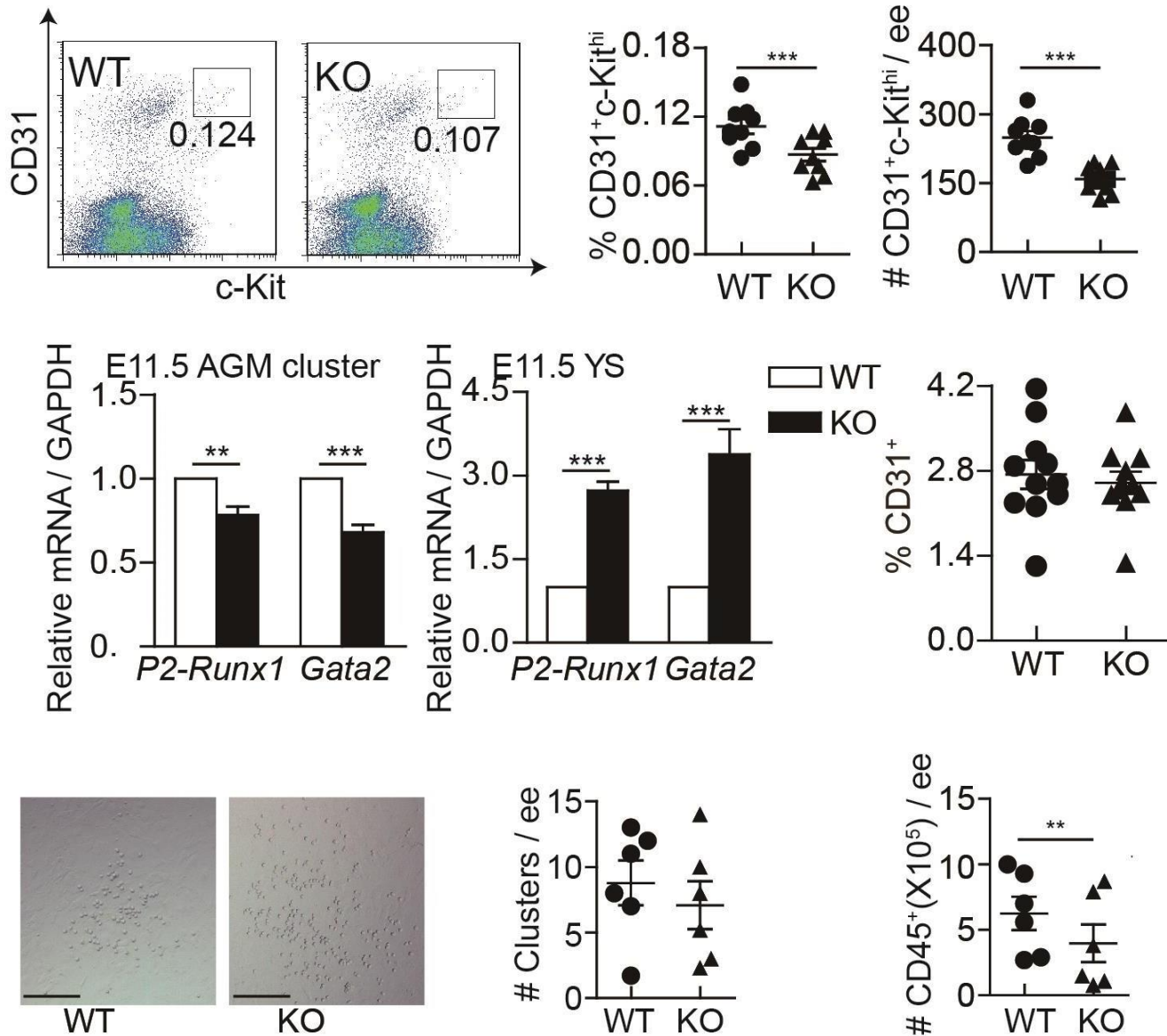
Wip1 缺失胚胎 AGM 区 Pre-HSC 成熟障碍

Pre-HSC 孵育后移植

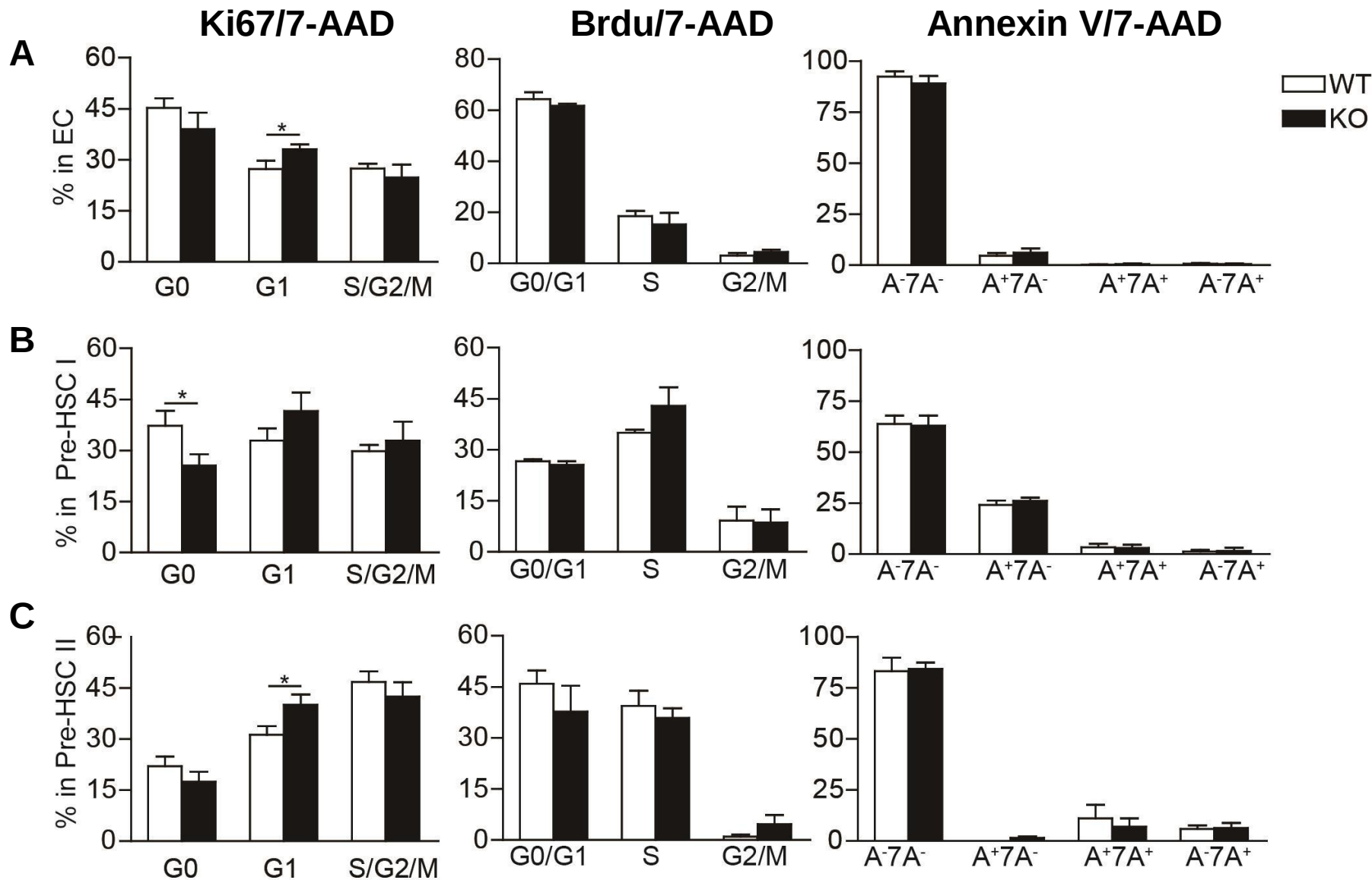
Pre-HSC 孵育后移植 ± WIP1 inhibitor
(CCT007093)



Wip1缺失胚胎**AGM** 区生血能力正常 但血细胞成熟障碍



*Wip1*调控Pre-HSC的细胞周期，但不影响细胞存活



Thank you