Maternal gut microbiota influence stem cell function in offspring

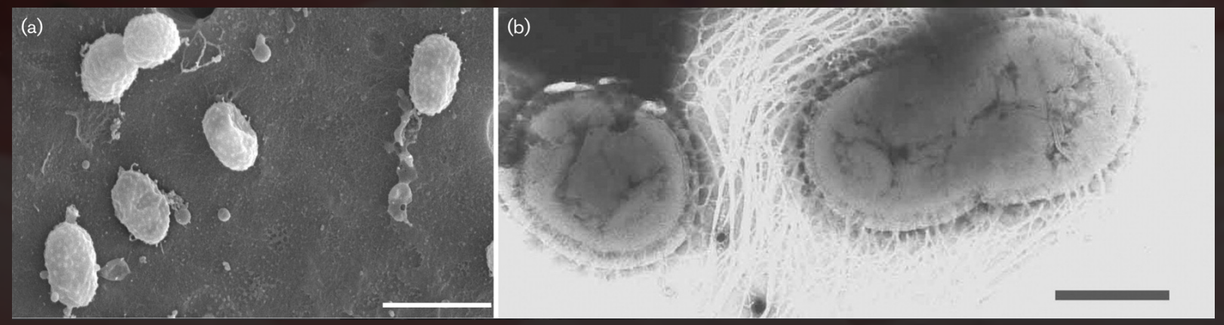
Dan Yu

2025.9.26

Why do we study maternal gut microbiota?

metabolism + immunity + brain/intestine function

Akkermansia muciniphila 嗜粘蛋白-阿克曼氏菌
--A star bacterium



- Gram-negative bacterium
- Non-motile
- obligate anaerobes
- ~3–5% of the human microbiota

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***Akkermansia muciniphila* gen. nov., sp. nov., a human intestinal mucin-degrading bacterium**

——Fisrt **identification**

News | Published: 13 May 2013

Gut microbe may fight obesity and diabetes

——Can improve **metabolic syndrome** in mice

↑ cardiovascular pathologies 心血管疾病
type 2 diabetes mellitus 2型糖尿病

Letter | Published: 01 July 2019

Supplementation with *Akkermansia muciniphila* in overweight and obese human volunteers: a proof-of-concept exploratory study

——Inactivated bacteria can improve obesity in **human**

Article | Open access | Published: 27 July 2022

***Akkermansia muciniphila* phospholipid induces homeostatic immune responses**

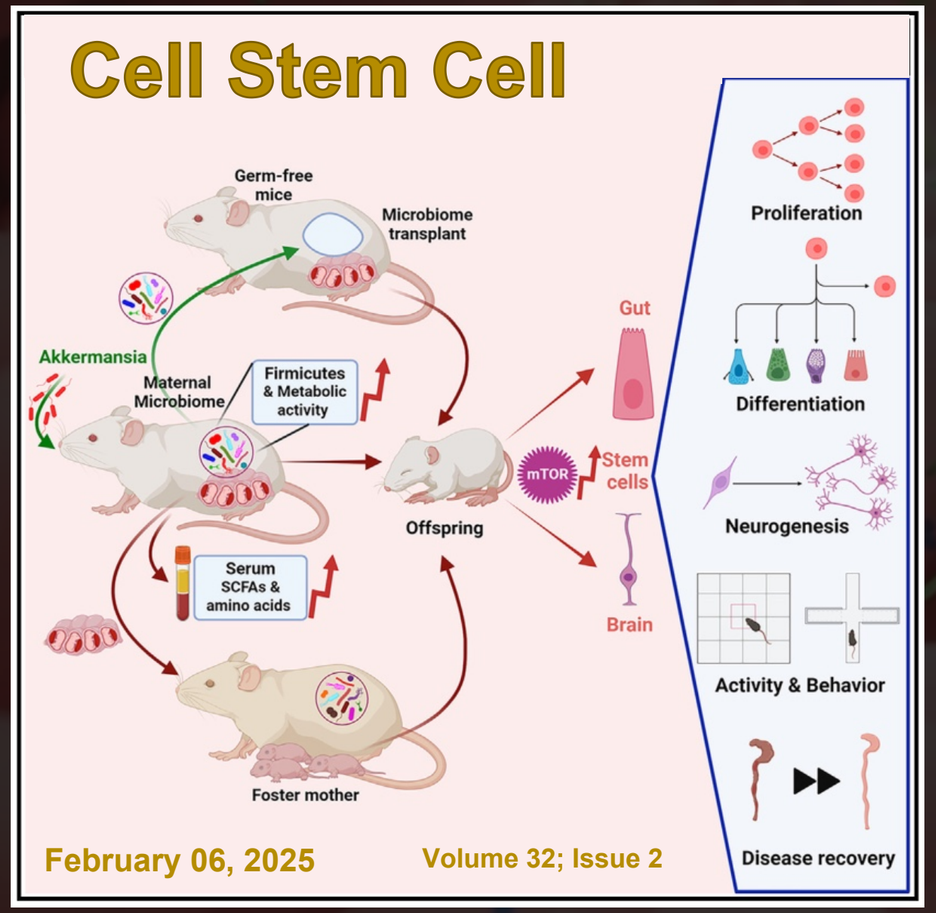
Munhyung Bae, Chelsi D. Cassilly, Xiaoxi Liu, Sung-Moo Park, Betsabeh Khoramian Tusi, Xiangjun Chen, Jaeyoung Kwon, Pavel Filipčík, Andrew S. Bolze, Zehua Liu, Hera Vlamakis, Daniel B. Graham, Sara J. Buhrlage, Ramnik J. Xavier & Jon Clardy

Nature **608**, 168–173 (2022) | Cite this article

57k Accesses | **297** Citations | **225** Altmetric | Metrics

——Lipids derived from Am enhance **immune responses**

Article Information



Maternal gut microbiota influence stem cell function in offspring

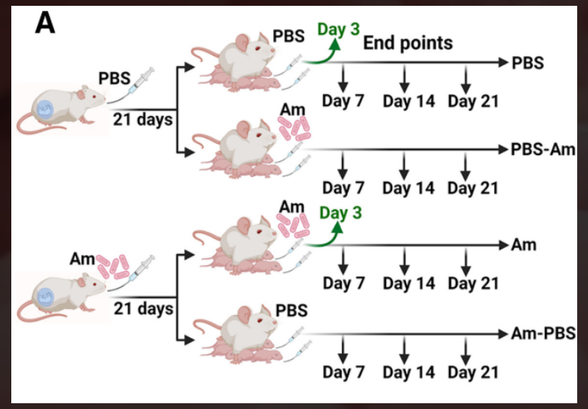
Haiyue Dang [1,2,8] · Panpan Feng [1,2,8] · Shuning Zhang [1,2,8] · Lihua Peng [1] · Shuli Xing [1] · Yuchen Li [1] · Xiang Wen [1] · Liqiang Zhou [3] · Shyamal Goswami [1] · Mingbing Xiao [4] · Nick Barker [5] · Philippe Sansonetti [6,7] · Parag Kundu [1,2,9] Show less

中国科学院上海免疫与感染研究所
SHANGHAI INSTITUTE OF IMMUNITY AND INFECTION
CHINESE ACADEMY OF SCIENCES

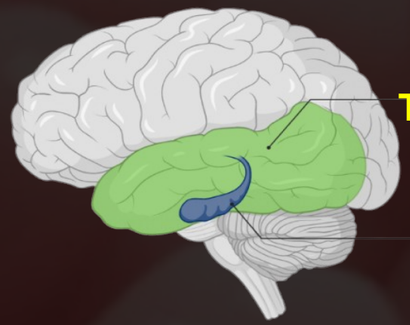
Parag Kundu

- Maternal microbiome shaping offspring stem-cell programming and long-term physiology
- Microbiota–host interactions in development and immunity

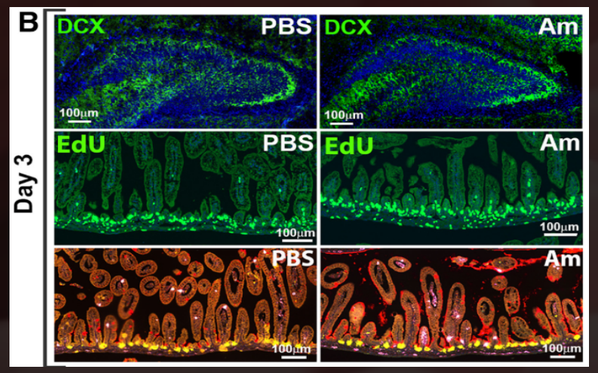
Maternal microbiome shapes offspring stem cell traits

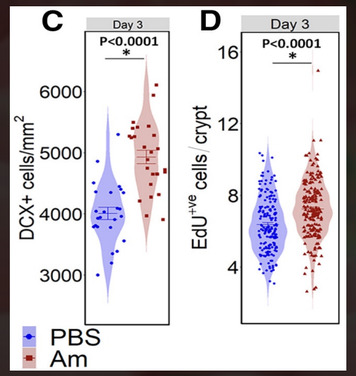


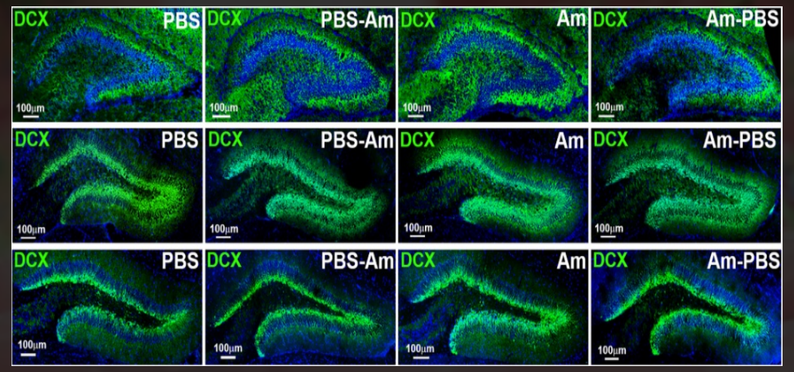
Biological Meaning of Postnatal Time Points

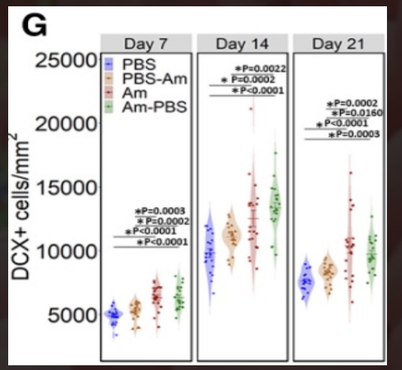
	Day 3	Day 7	Day 14	Day 21
 Temporal Lobe 颞叶 Hippocampus 海马体	Immature; original	Early migration /differentiation	Accelerated morphological differentiation	Mature neurons
 Small intestine	Initiation of crypt and villus	Migration to the villus and differentiation	Epithelial renewal is complete	Fully mature intestinal villus epithelial cells

Maternal microbiome shapes offspring stem cell traits

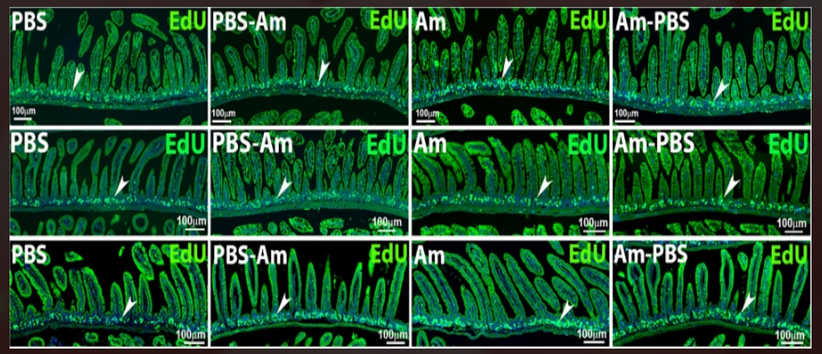


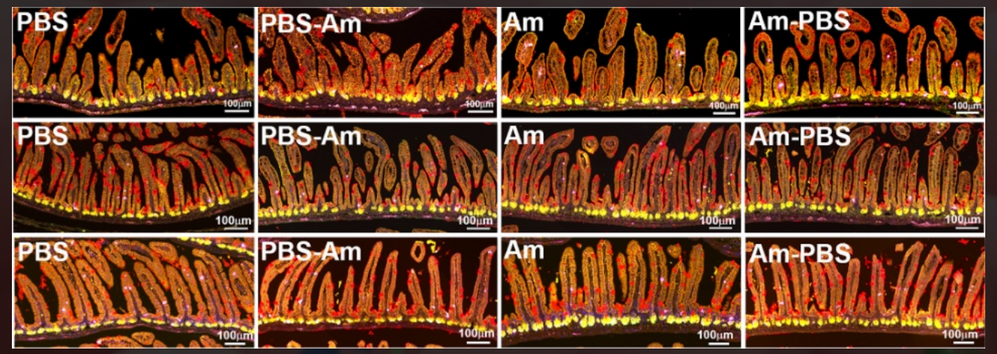






DCX--hippocampal neurogenesis
海马神经元

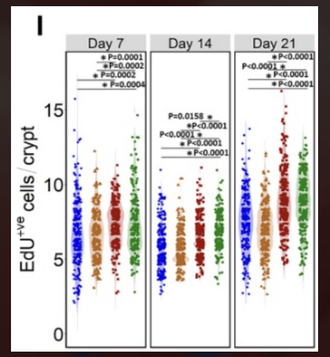




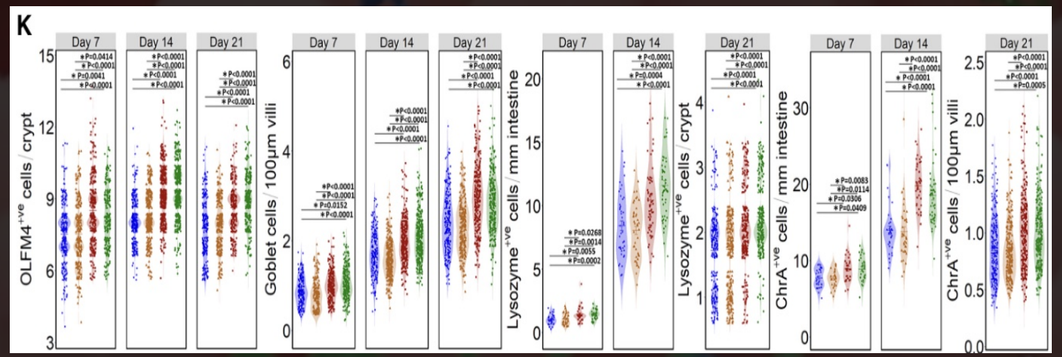
Intestinal Swiss rolls
stem cells, Paneth cells, goblet cells, enteroendocrine cells

↑

Differentiated stem cells

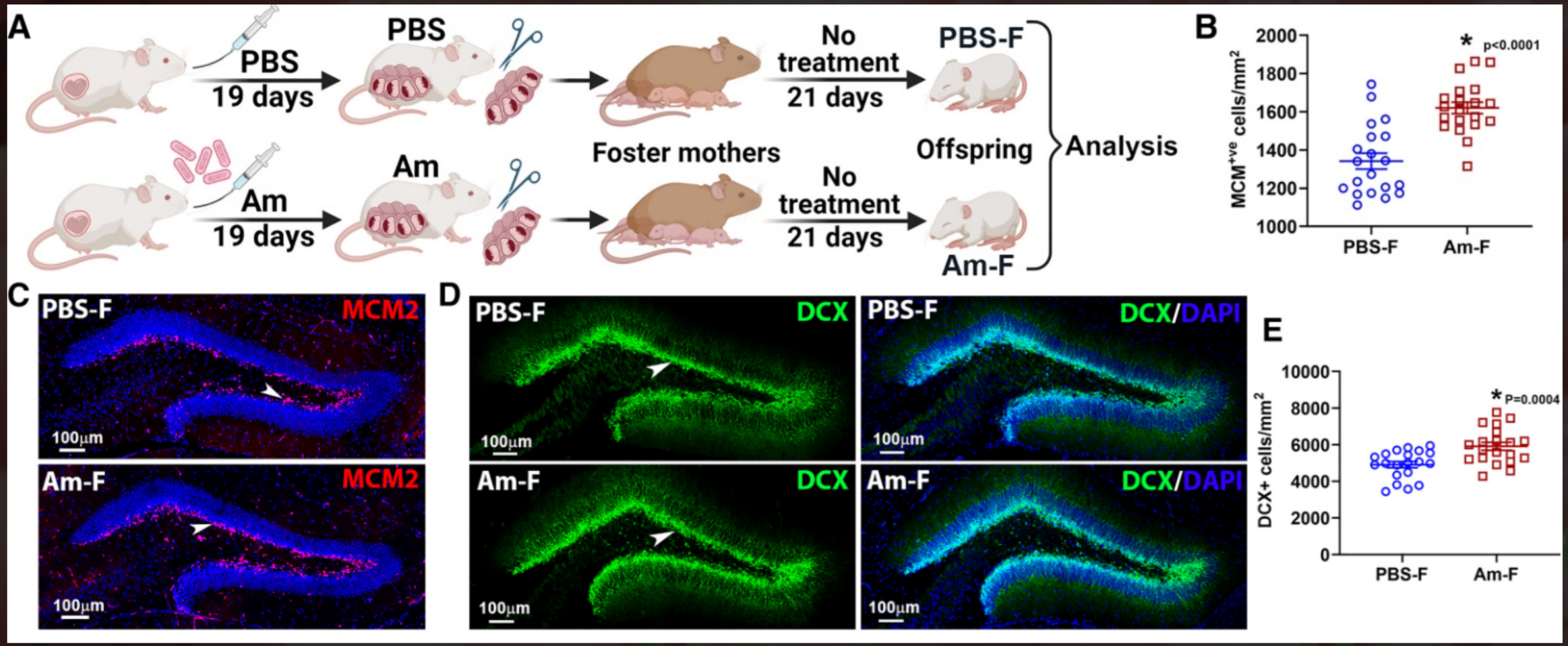


EdU--intestinal proliferating cells
小肠增殖细胞



So which matters more — the prenatal period or the breastfeeding ?

Offspring retain distinct stem cell characteristics when raised by foster mothers “换奶妈”

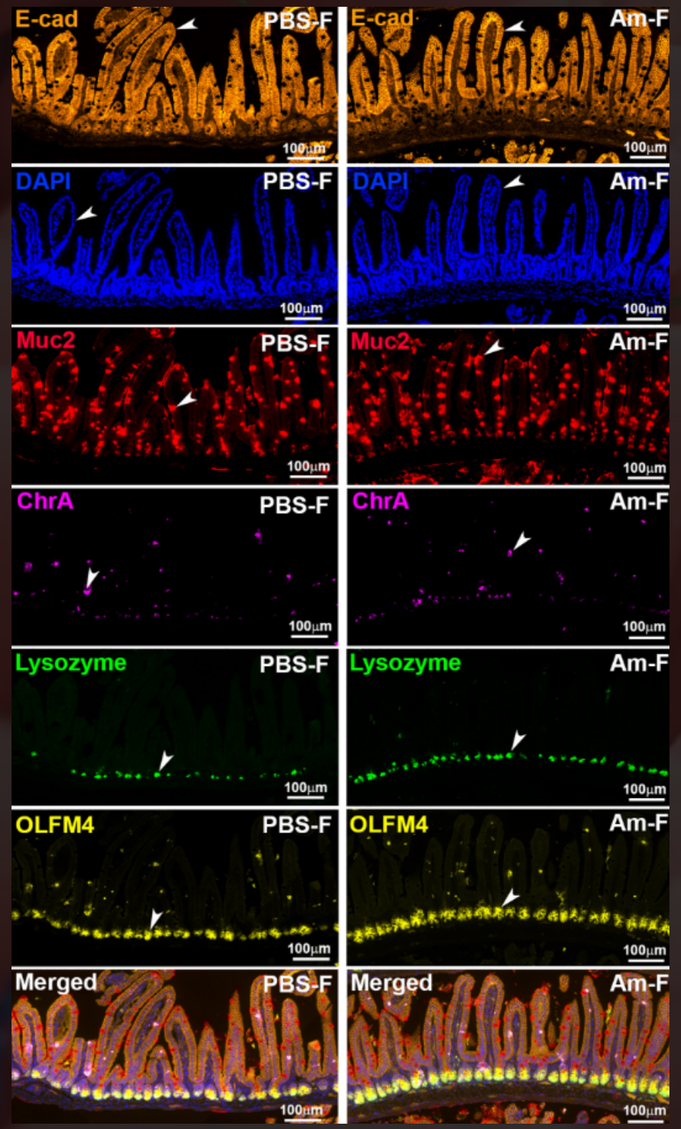


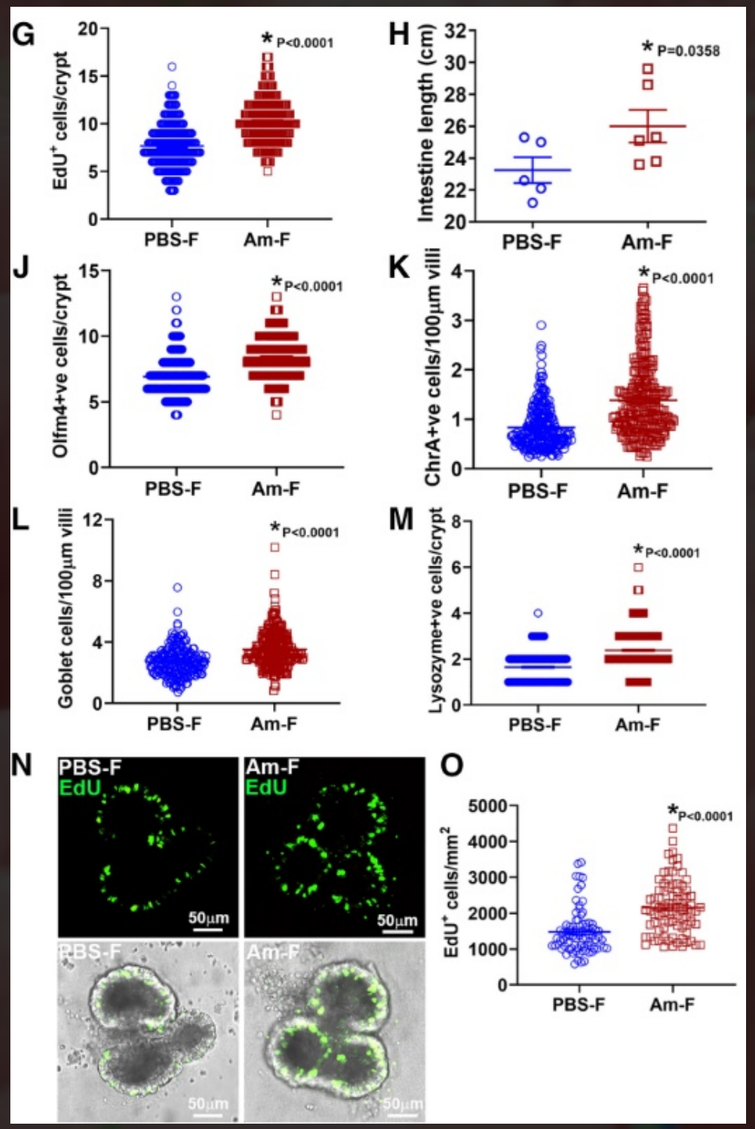
MCM2--DNA replication helicase, indicates proliferative potential

DCX--hippocampal neurogenesis

Prenatal microbiota exposure affects stem-cell formation in mouse offspring

Offspring retain distinct stem cell characteristics when raised by foster mothers “换奶妈”





Offspring stem-cell traits are mainly shaped by the maternal prenatal microbiota; breastmilk changes have little effect.

DAPI: cell nuclear stain (DNA dye)

E-cadherin: epithelial cell adhesion molecule

Muc2: mucin (mucus protein) 黏液

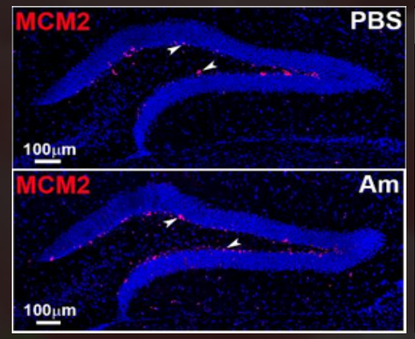
Chromogranin A: marker of enteroendocrine (hormone-secreting) cells

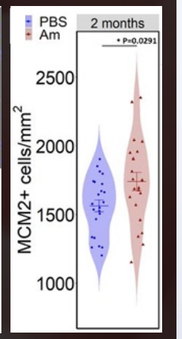
Lysozyme: antimicrobial enzyme 杀菌

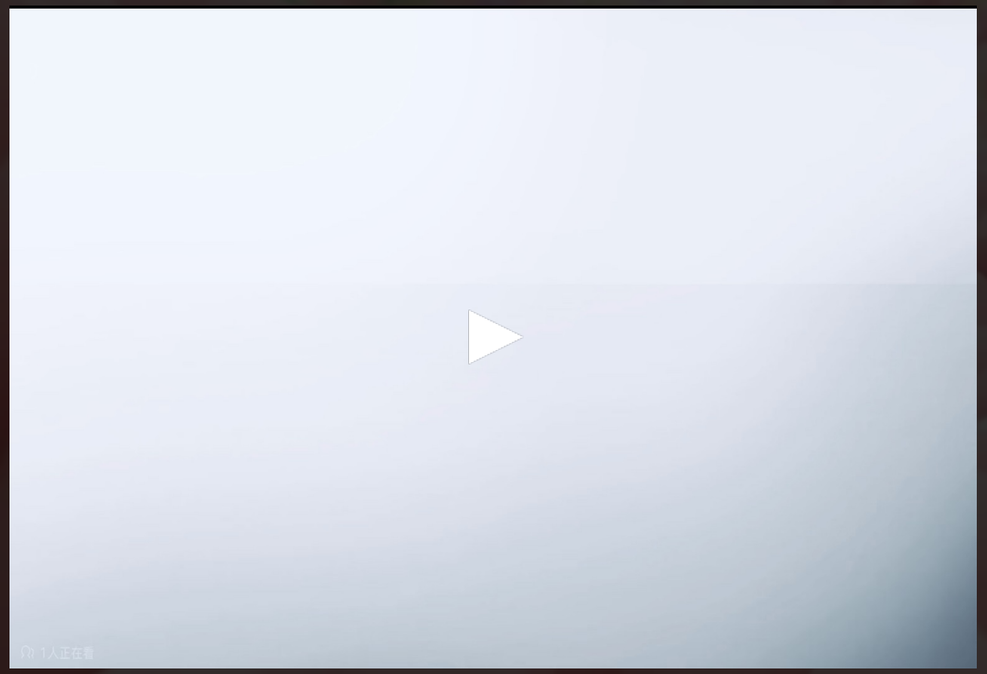
OLFM4: intestinal stem-cell marker

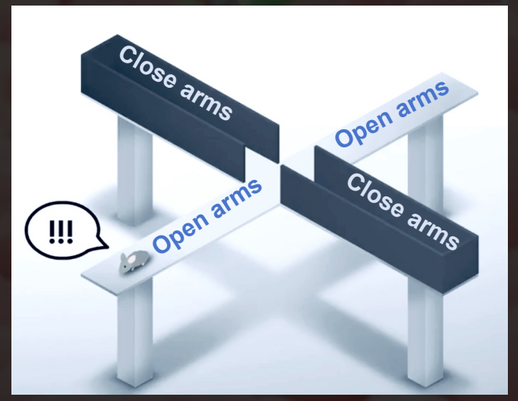
Maternal microbiota has a long-term impact

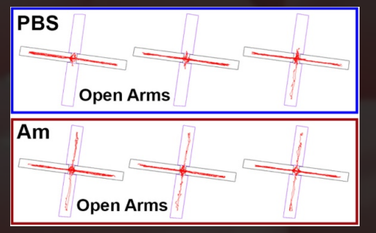
Elevated plus maze 悬臂十字迷宫

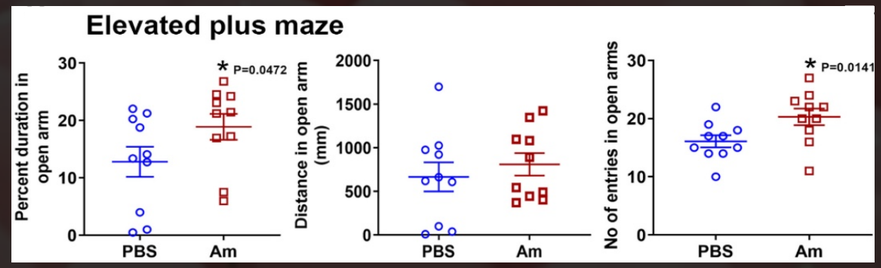








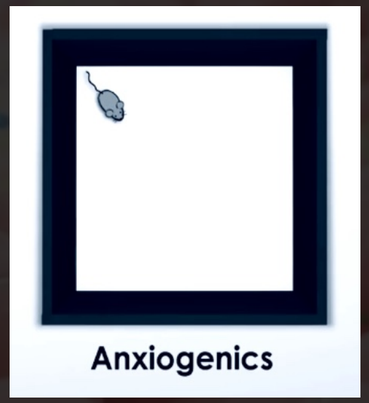




- Stays in the closed arms → higher anxiety (seek a safer, enclosed space)
- Enters the open arms → lower anxiety (willing to venture out and explore)

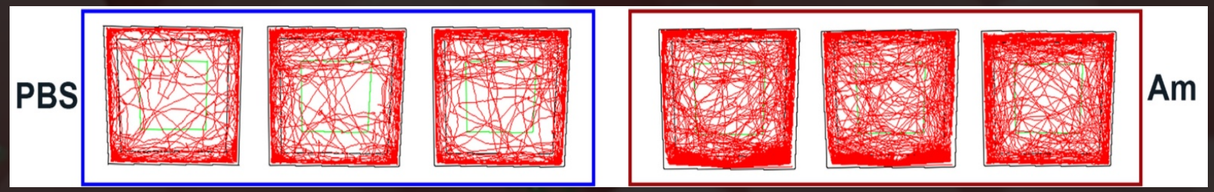
Maternal microbiome has a long-term impact

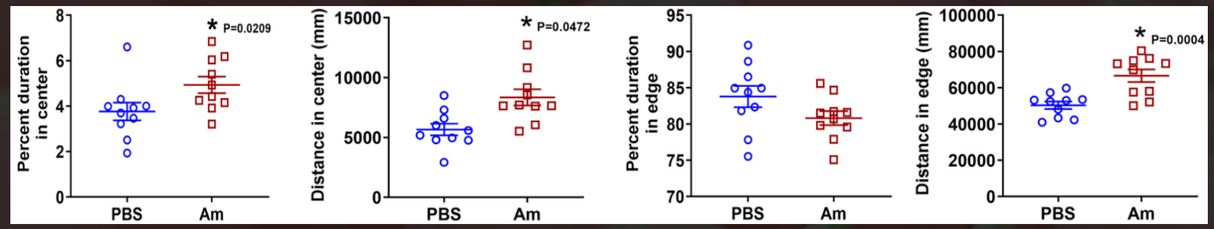
Open field 开放场实验



焦虑的
Avoid open spaces, hugging the walls

不焦虑的
Ventures into the center, showing exploration





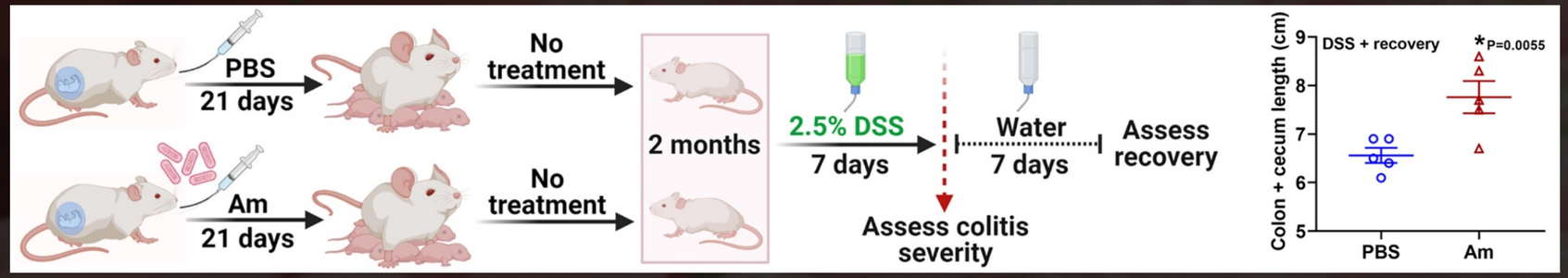
Behavioral assays indicate reduced anxiety-like behavior and increased exploratory activity in Am offspring

Maternal microbes reprogram offspring stem cells and shift exploration/anxiety behaviors.

What is the practical significance of these stem-cell changes in adulthood?

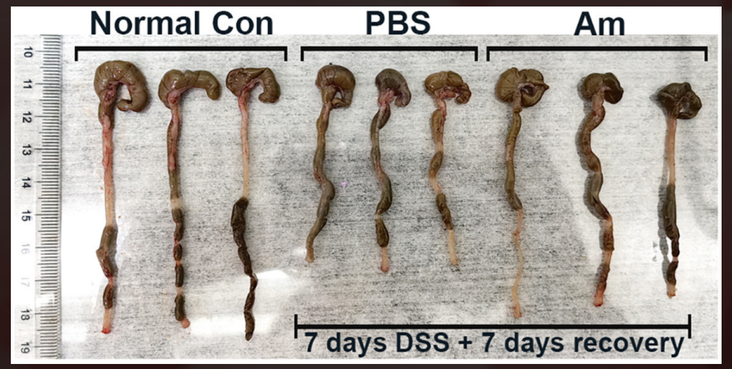
Maternal microbiome has a long-term impact

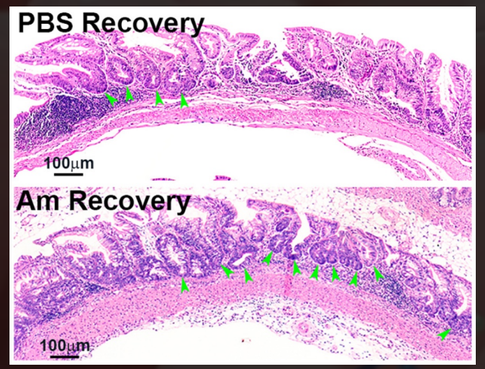
急性肠道“风暴”--结肠炎

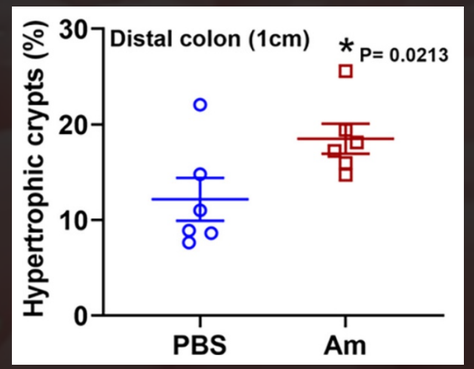


+2.5% DSS
2.5%硫酸葡聚糖

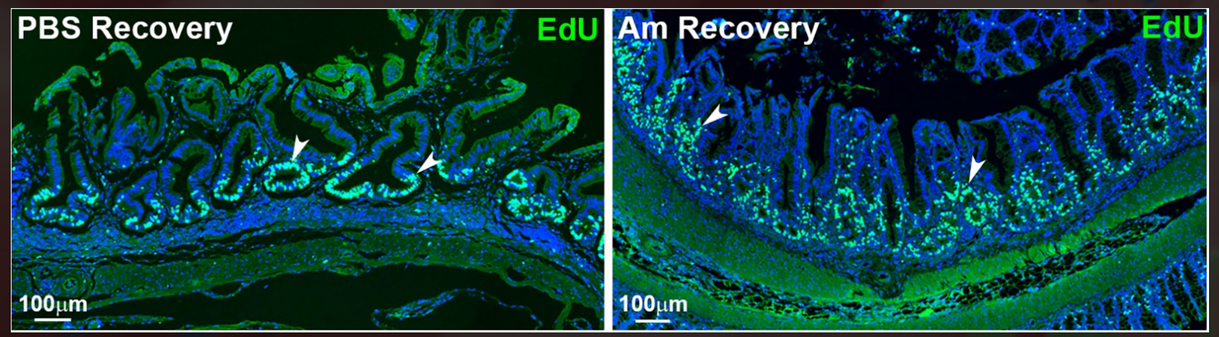
Colitis
结肠炎

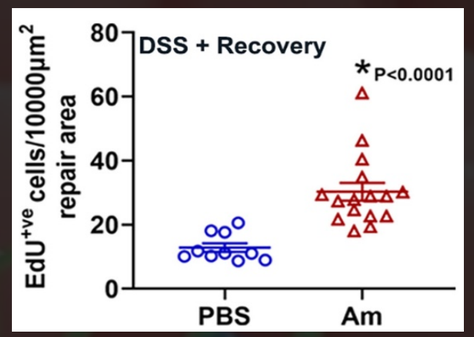






	PBS-exposed group	Am-exposed group
colon length	shorter	longer
hypertrophic crypts	less	more
intestinal proliferating cells	less	more



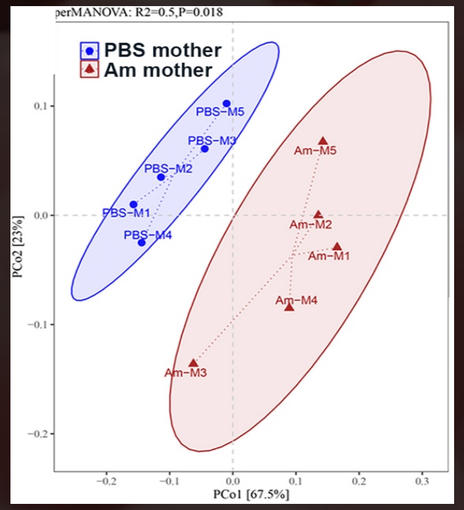


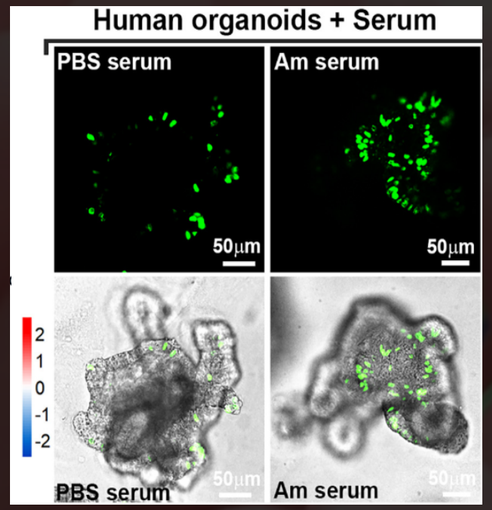
- **Suggesting that changes in maternal microbiomes during pregnancy may influence offspring’s disease susceptibility**

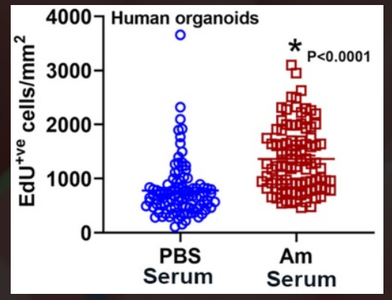
What is the mechanism of this phenotype?

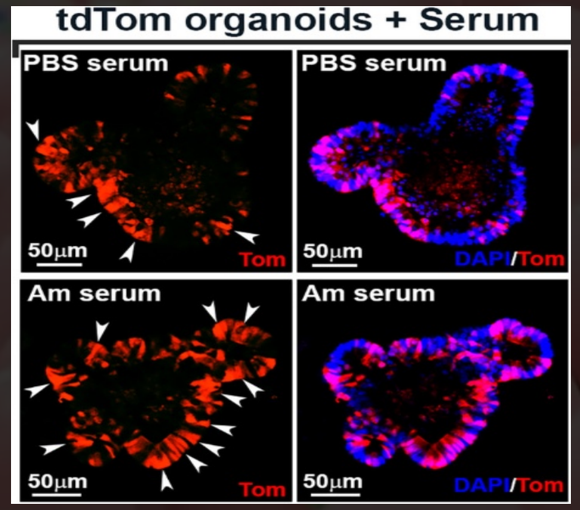
Metagenomic and metabolomic signatures

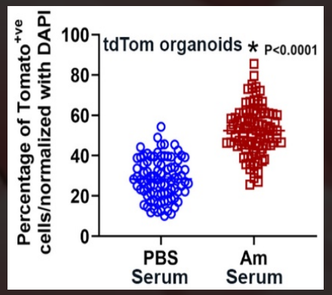
血清处理





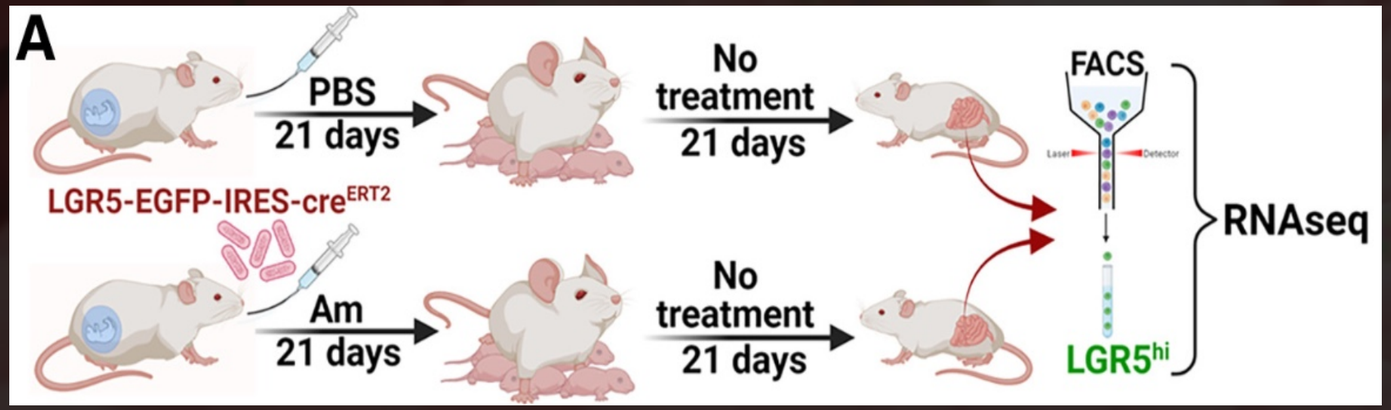


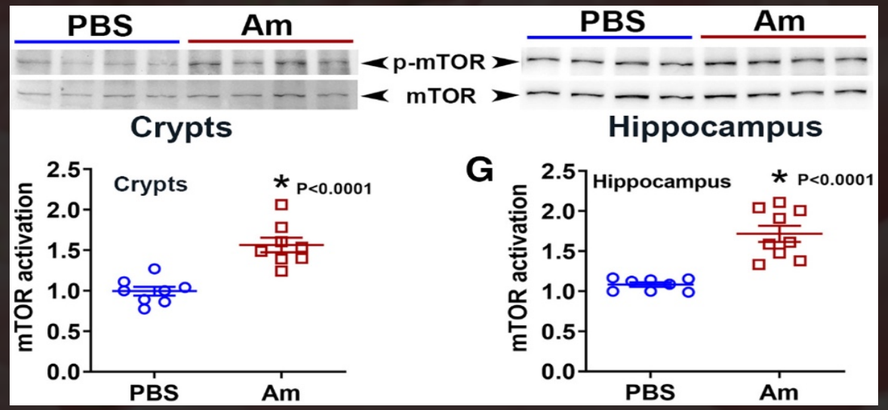


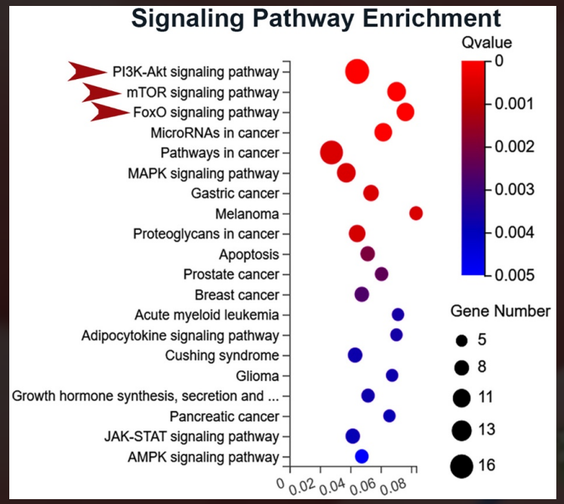


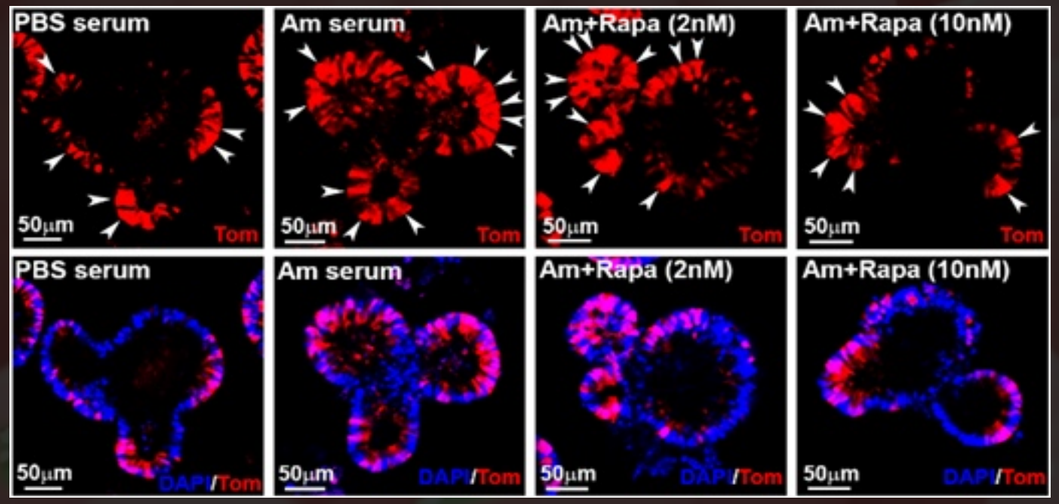
Maternal Akkermansia exposure alters gut microbes and metabolites during pregnancy

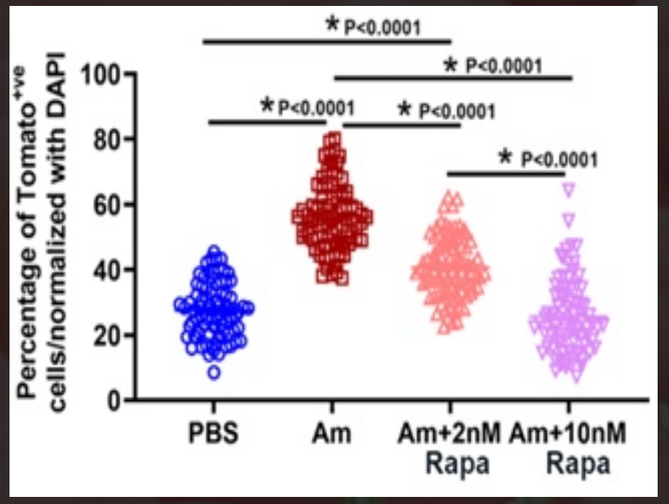
Identify the core pathway











Maternal serum from Am-treated mice boosted human intestinal organoid stem-cell activity

Key Findings

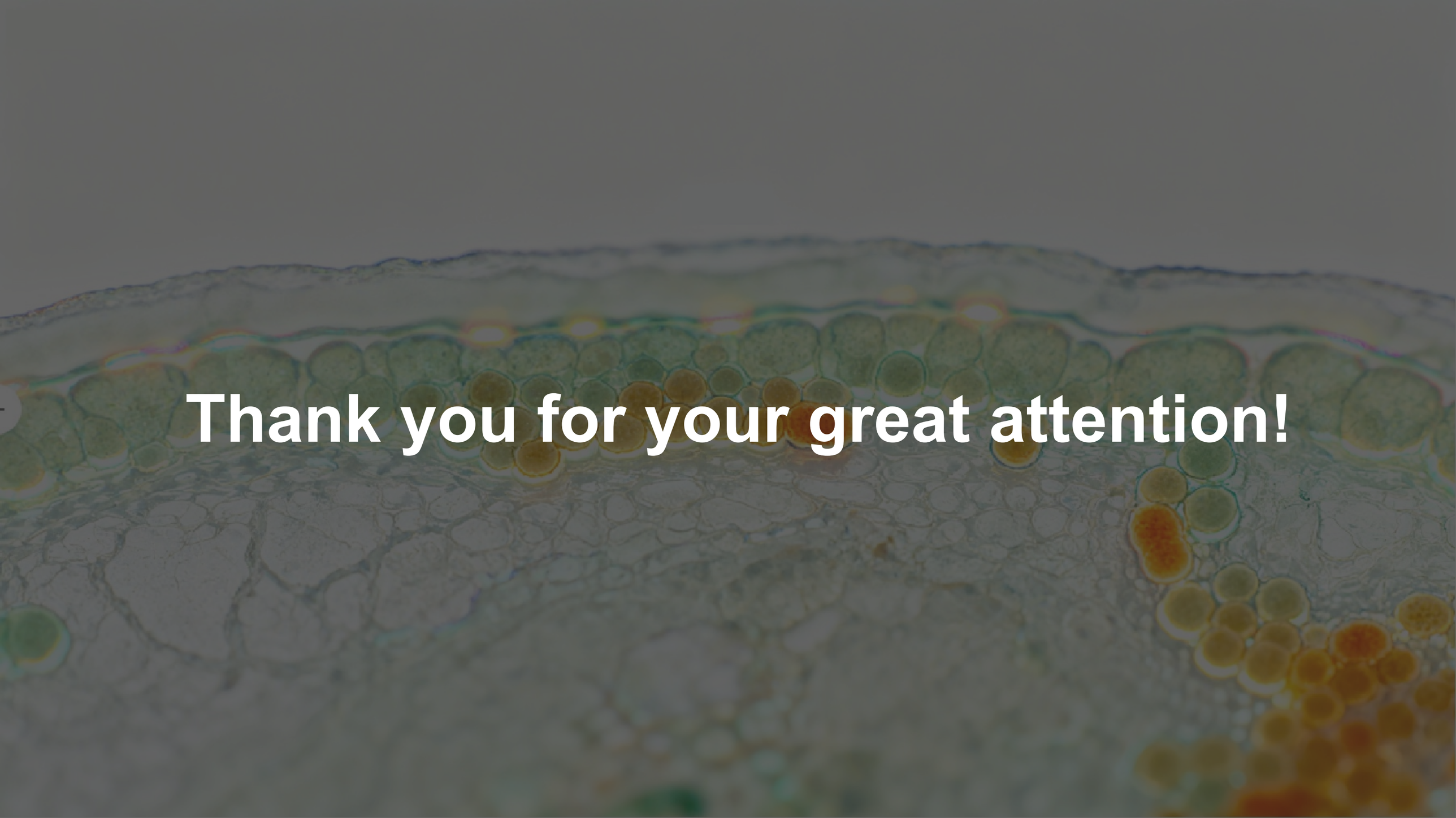
- Maternal microbiota, especially Akkermansia, reprogram offspring stem cells (neural & intestinal).
- These stem-cell changes shape behavior.
- They also alter disease susceptibility in adulthood.
- gut microbes -- metabolites -- mTOR signaling

Limitations of the Study

- **Species limitation**
  - Human relevance remains uncertain; only limited in vitro validation with organoids.

- **Mechanism incompleteness**
  - Identified metabolomic differences, but did not pinpoint the specific metabolites responsible for mTOR activation.

- **Microbiota complexity**
  - Oversimplifies the role of the broader maternal microbiota ecosystem.


Thank you for your great attention!