浙江大学生命演化研究中心

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Targeting symbionts by apolipoprotein L proteins modulates gut immunity

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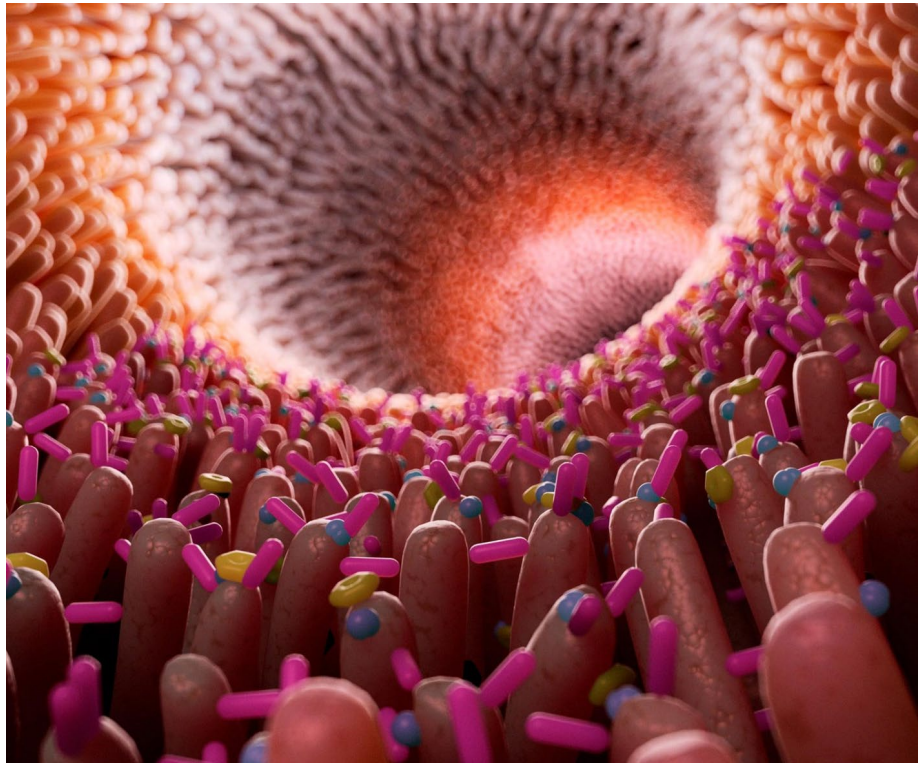
载脂蛋白 L 共生体靶向调节肠道免疫

Research Background

- The mammalian gut is home to trillions of bacteria that play roles in host health.

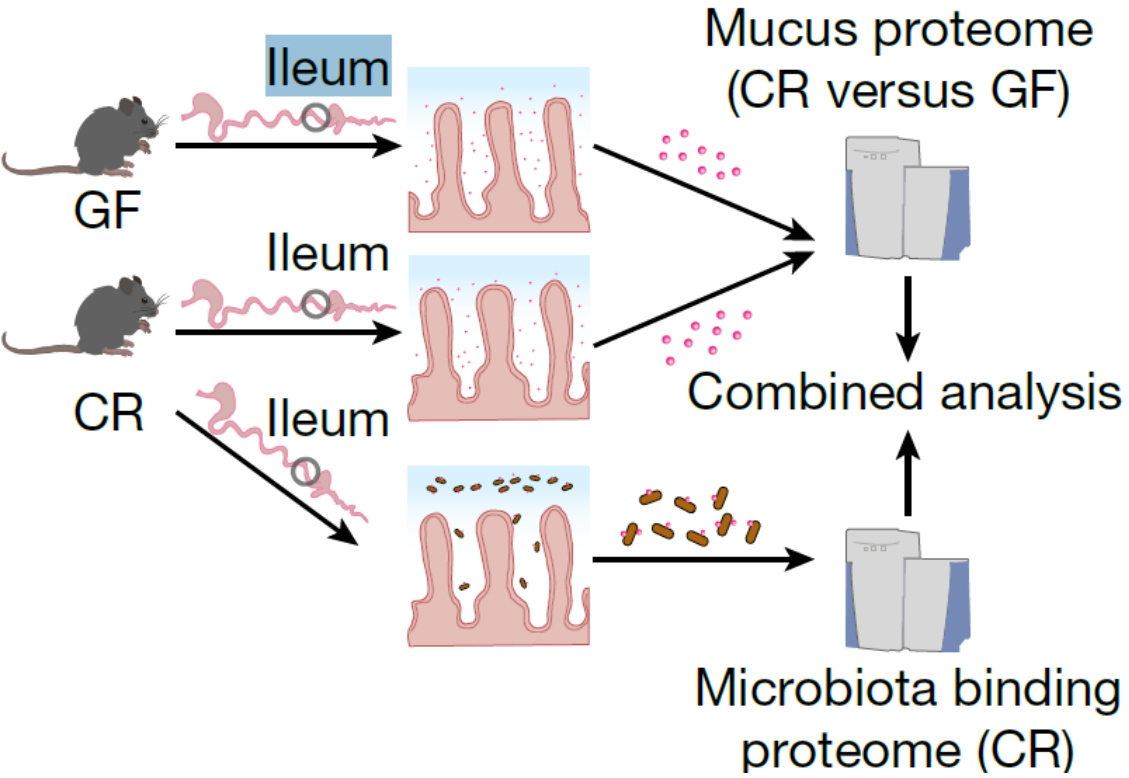
- While the gut has known defense mechanisms (e.g., antimicrobial proteins, antibodies and so on), their targeting specificity is broad and does not show a strong phylogenetic preference.

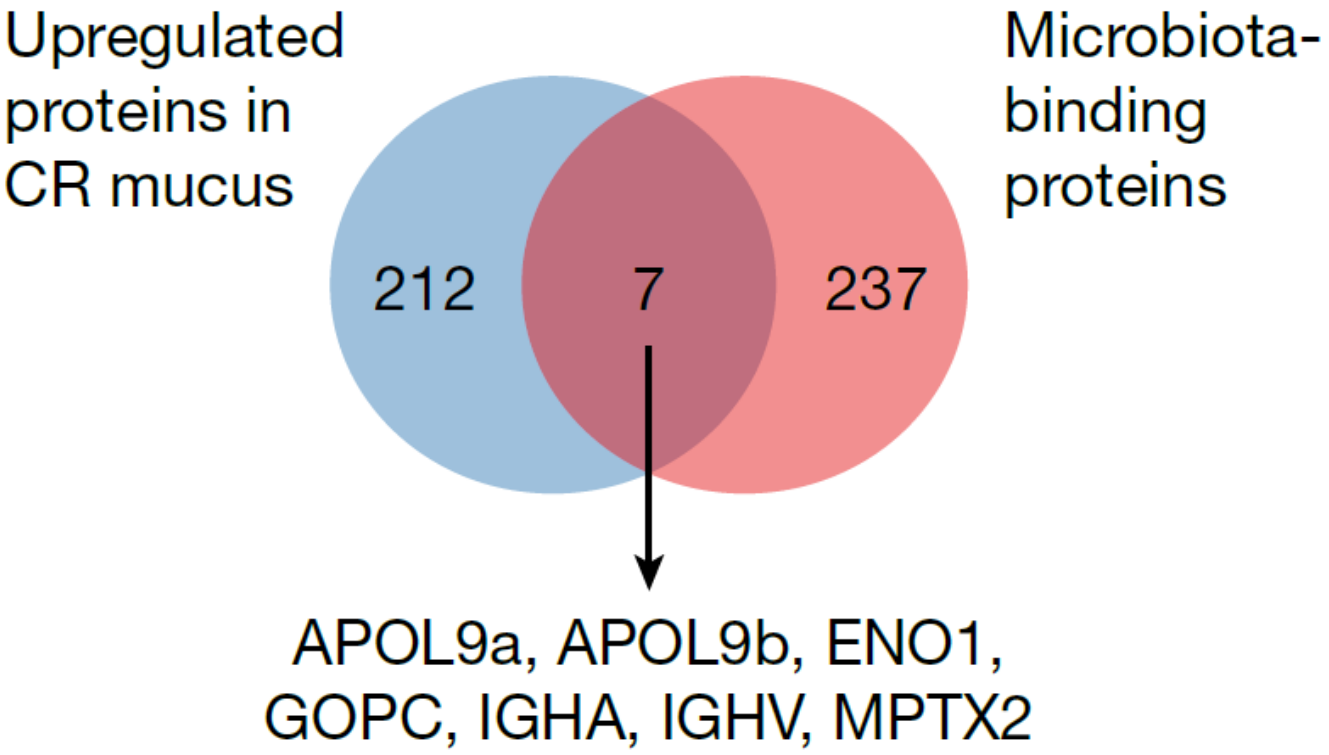
- How hosts **precisely** manage bacteria to maintain benefits?



Gut enterocytes produce apolipoprotein L9a/b

Previous studies found that bacteria induces transcriptional changes in the IECs

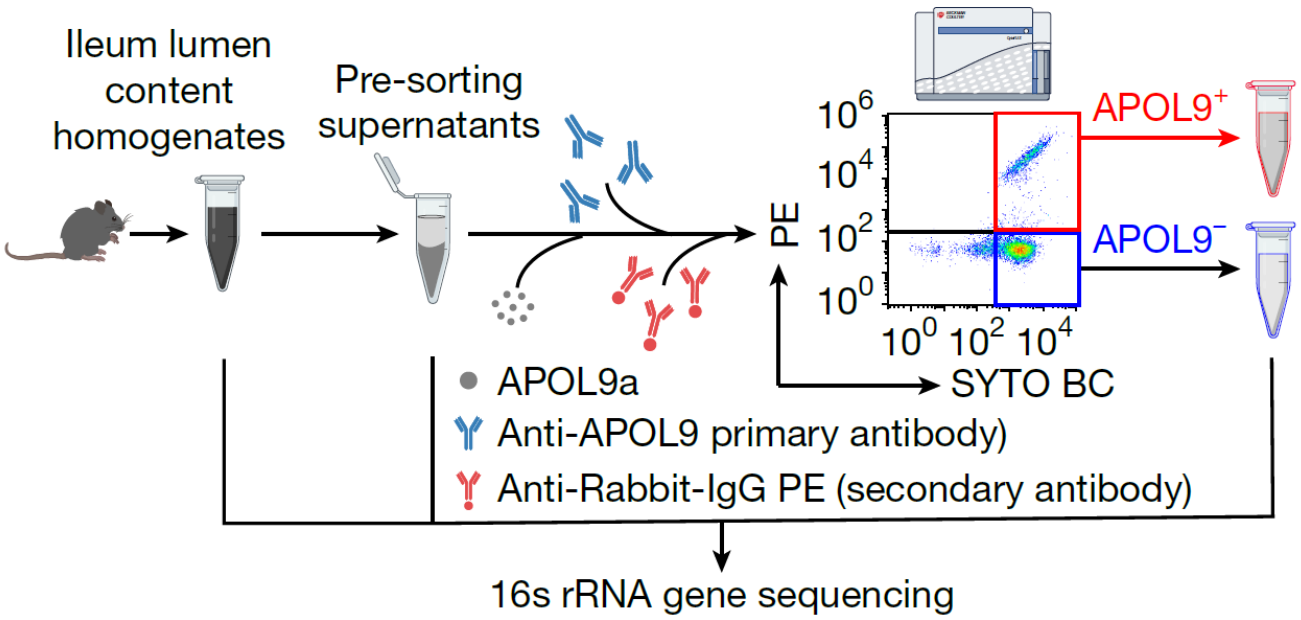


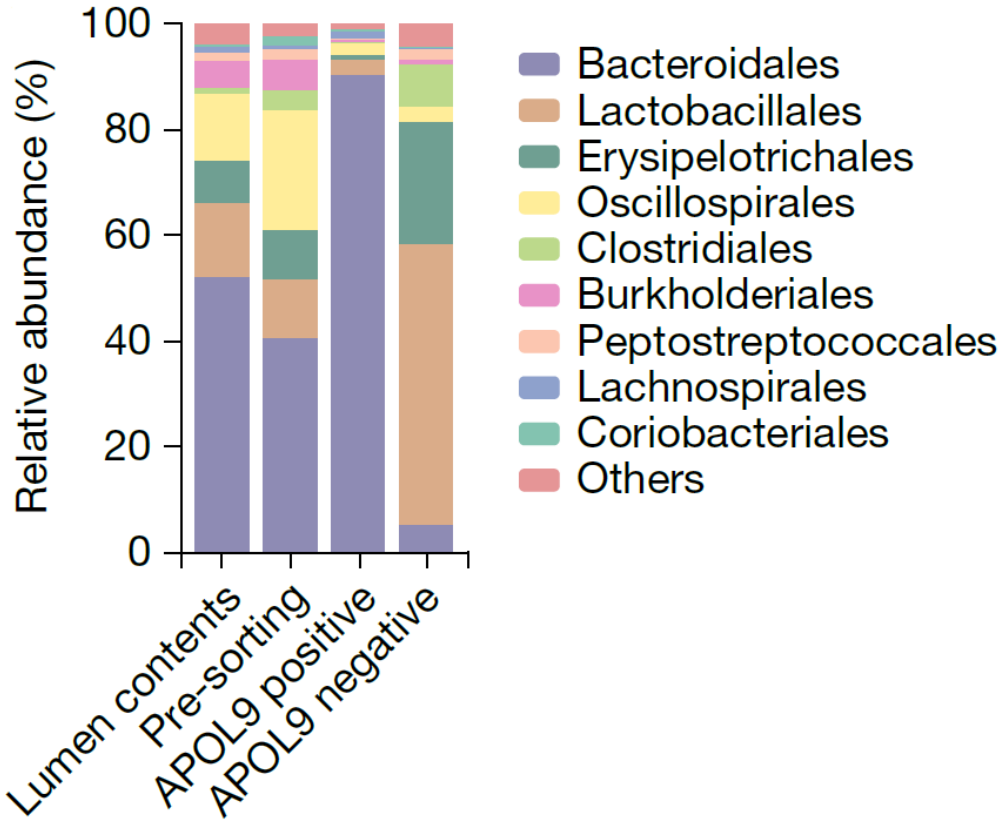


Ileal (回肠)
IECs(回肠上皮细胞)
CR: conventionally raised (常规饲养)
GF: germ-free (无菌饲养)

Besides immune molecules, they noticed that APOL9a/b

Gut APOL9a/b target Bacteroidales



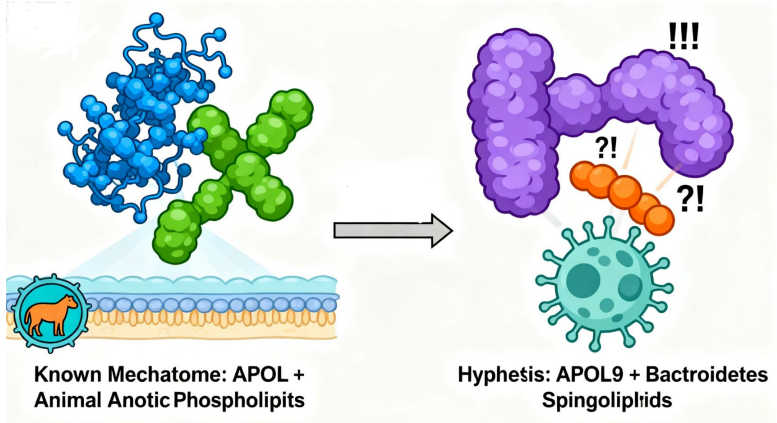


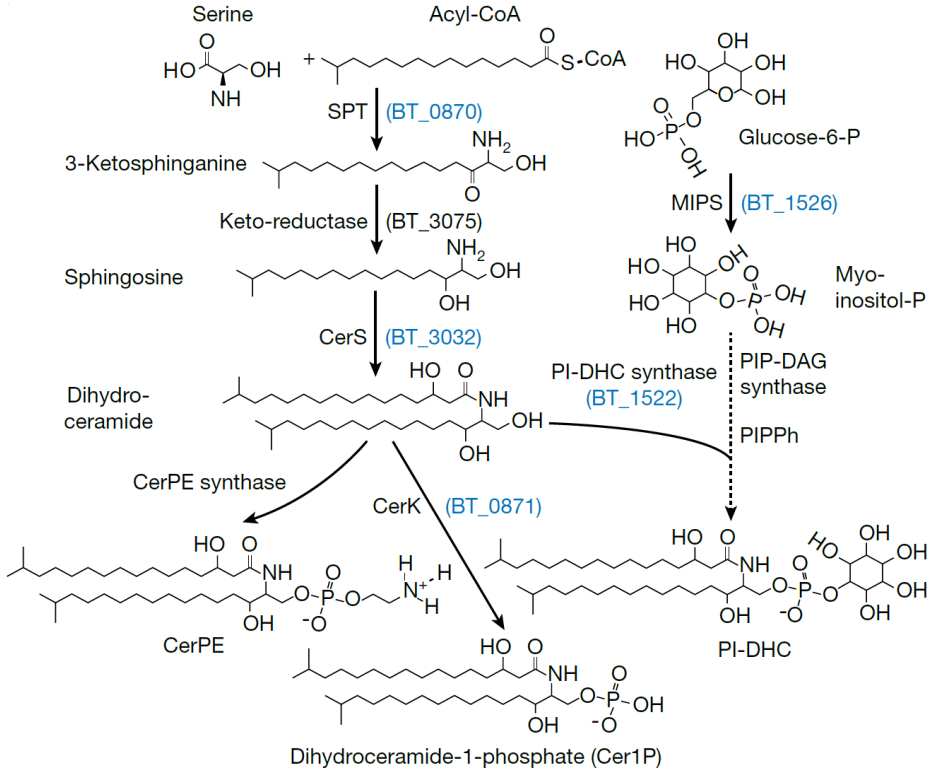
APOL molecules have a preference for Bacteroidales

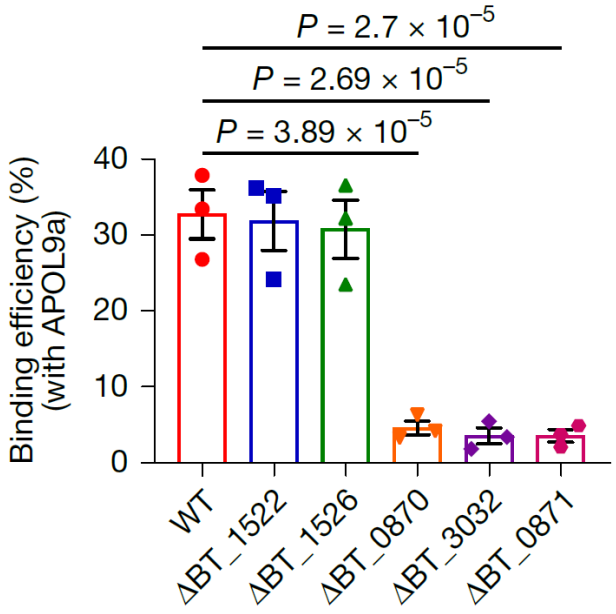
Bacterial Cer1Ps mediate the binding

Hypothesis:
They known that APOL proteins can bind to anionic phospholipids in animal cells.
Bacteroidetes produce sphingolipids similar to those in animals.

Sphingolipids could be responsible for APOL9 binding.



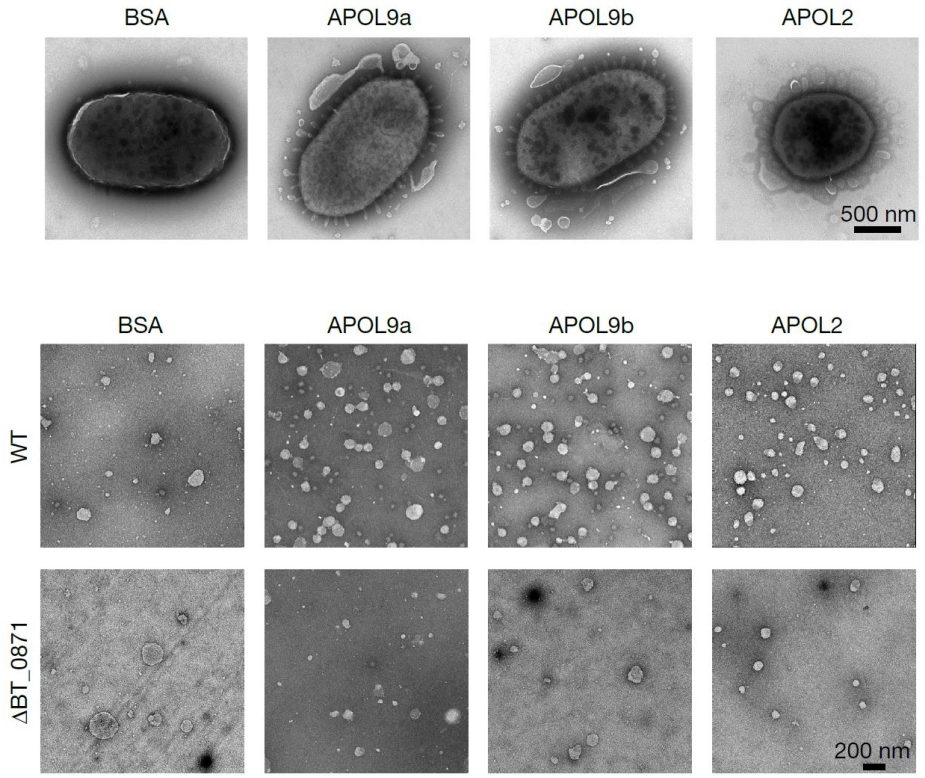


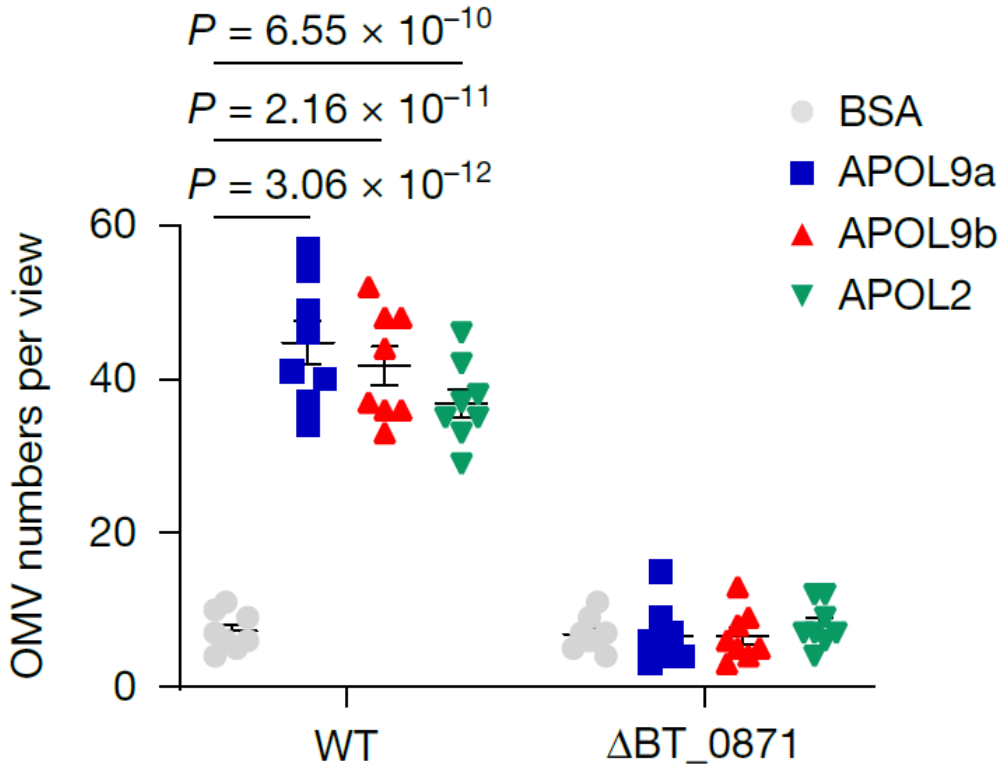


Approach: They generated a series of knock-out mutants in *B. thetaiotaomicron* across the sphingolipid synthesis pathway.

Key Finding: When they deleted the gene for Cer1P, APOL9 could no longer bind to the bacteria. Cer1Ps are what mediate the binding between APOL9 and Bacteroidales.

APOL9a/b induce OMV releasing



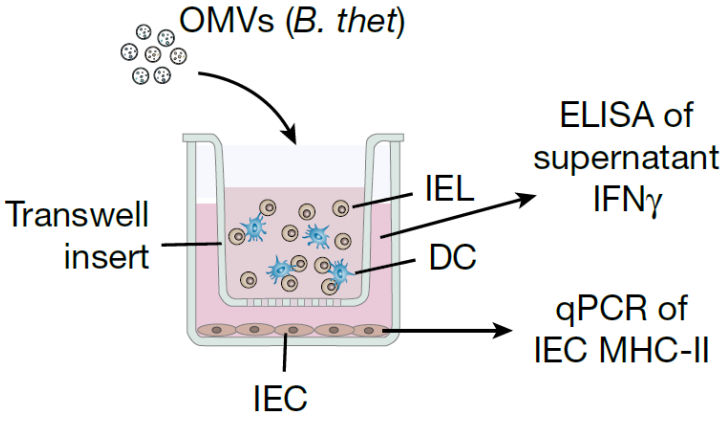


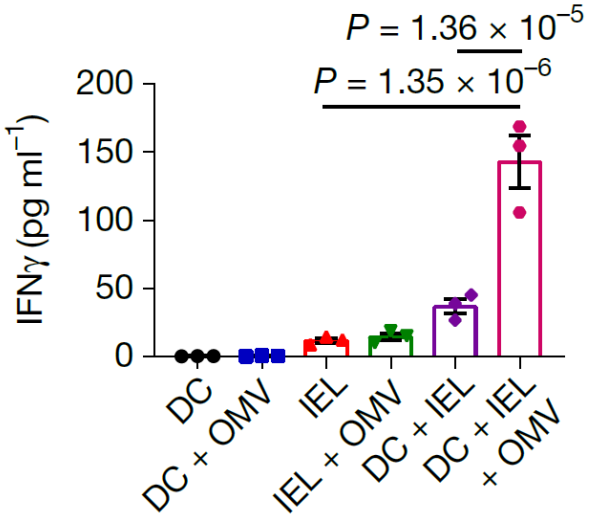
Transmission Electron Microscopy (TEM) shows APOL9a/b trigger **outer membrane vesicle (OMV)** release from Bacteroidales.

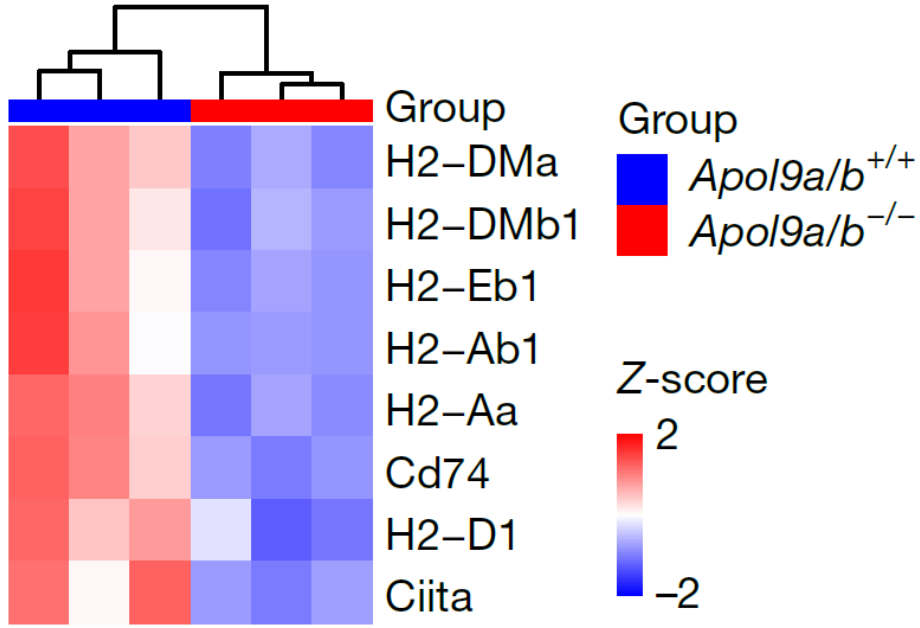
OMV: small bubbles from the bacteria, contain proteins, lipids, and sometimes genetic material.

OMV production is Cer1P-dependent: ΔBT_0871 does not release extra OMVs upon APOL treatment.

OMVs promote IEC MHC-II expression







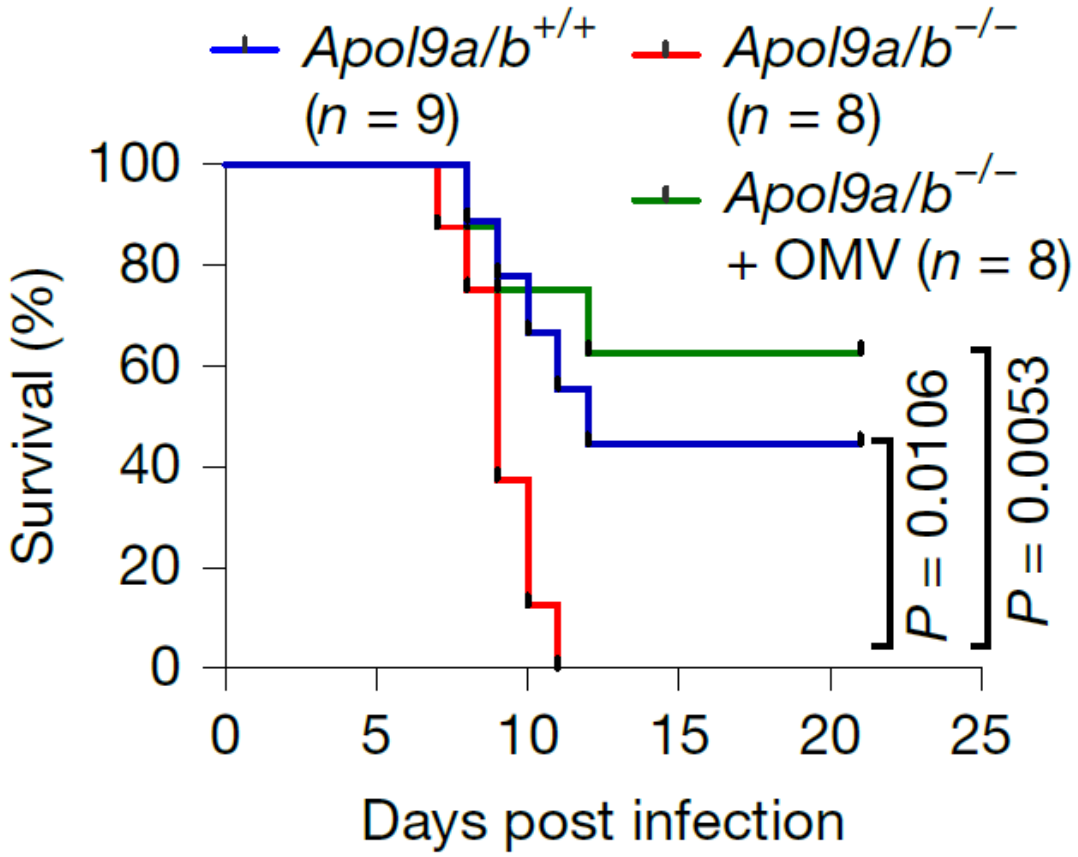
Using a **DC-IEL-IEC Transwell co-culture system**, they mapped the pathway:

Bacteroidales-OMVs are sensed by **Dendritic Cells (DCs)**.

Activated DCs promote **Intraepithelial Lymphocytes (IELs)** to produce **Interferon-gamma (IFNγ)**.

IFNγ acts on **IECs to upregulate MHC-II** expression.

APOL9a/b modulate gut IELs and infection



Test: They challenged mice with gut pathogen *Salmonella*.（沙门氏菌）

Result: The survival rate of Apol9a/b$^{-/-}$ mice decreased dramatically compared to wild-type controls.
Oral OMV administration protected *Apol9a/b*$^{-/-}$ mice.

Conclusion: The APOL9-OMV pathway is **critical for maintaining a strong immue barrier** against pathogens.

Summary

- **Novel Mechanism:** host uses a special protein (**APOL9**) to **precisely target** beneficial **Bacteroidales** via a specific lipid (**Cer1P**).
- **Functional Shift:** This interaction **induces OMV release**, converting a bacterial membrane component into an **immunoregulatory signal**.
- **Immune Pathway:** OMVs activate a multicellular circuit (**DC → IEL → IFNγ → IEC**) to boost **MHC-II** expression and maintain immune homeostasis.
- **Overall Impact:** This pathway is essential for gut immunity and protecting against fatal infection, revealing a new way of **symbionts coexistence**.