



# Gut microbiota-derived butyric acid regulates calcific aortic valve disease pathogenesis by modulating GAPDH lactylation and butyrylation

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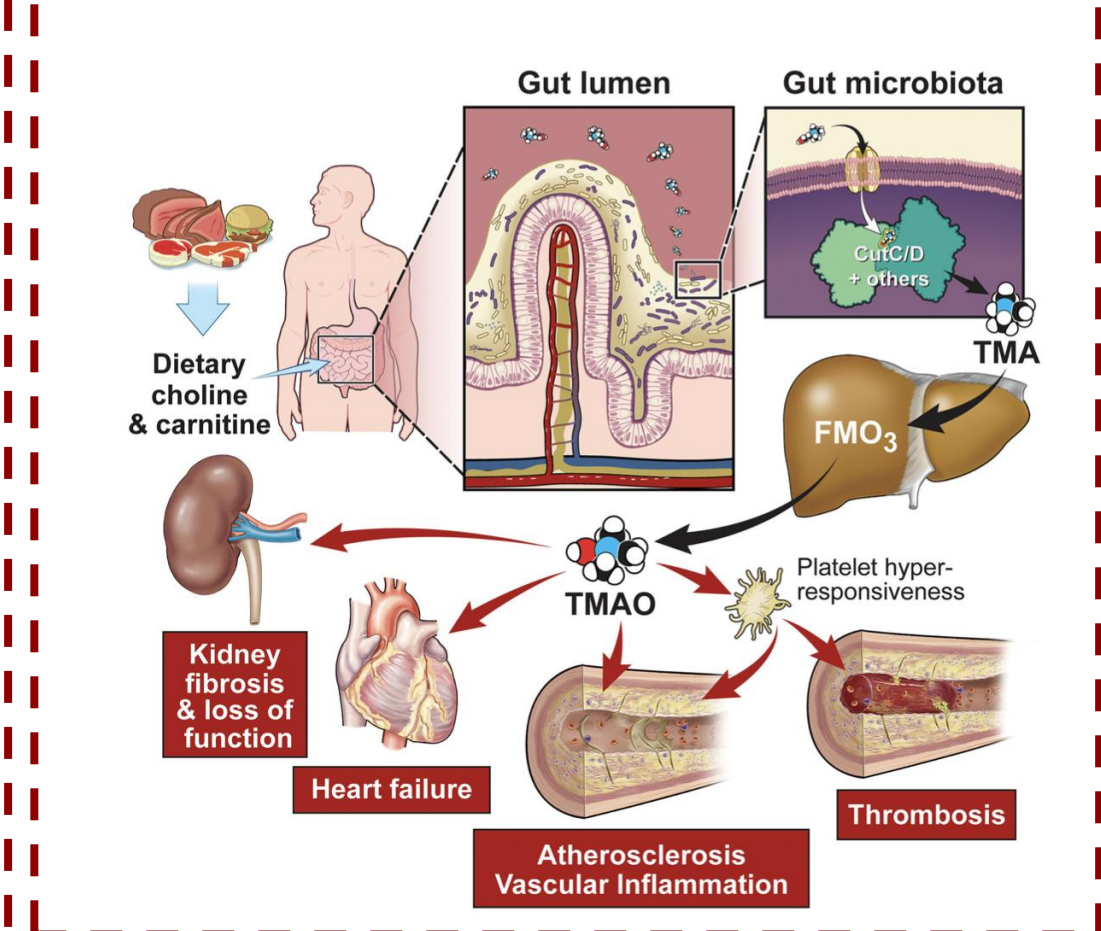
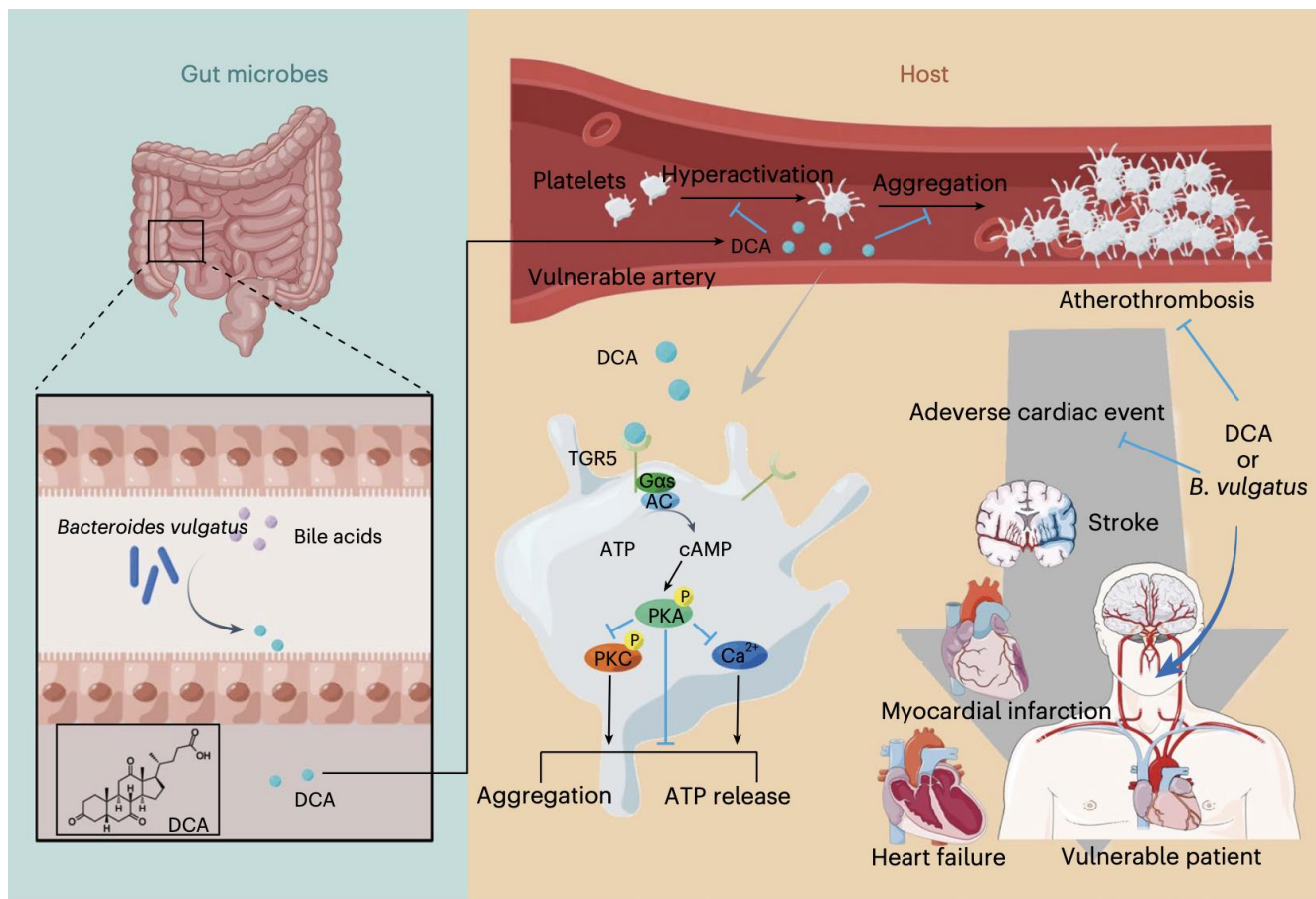
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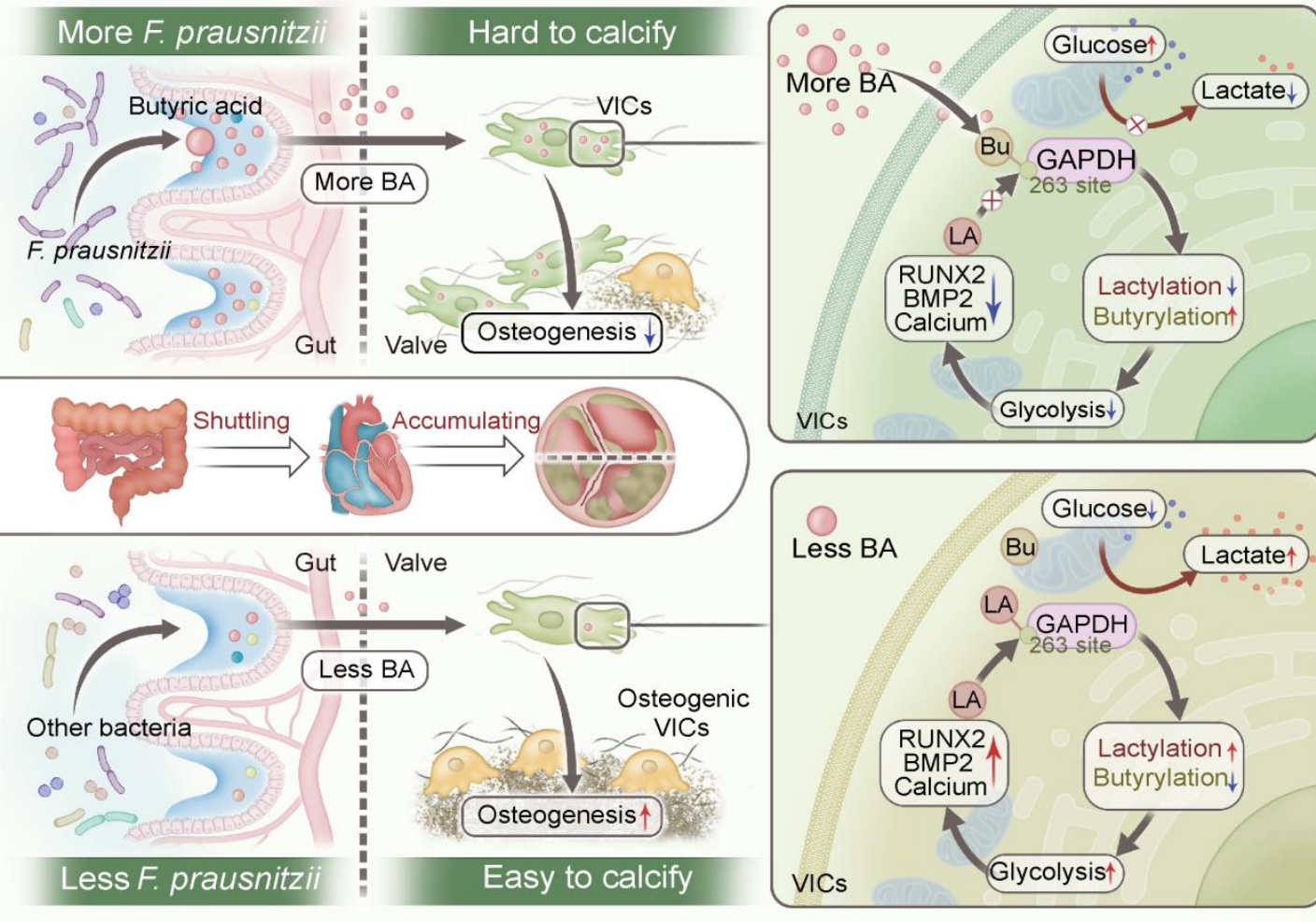
# Introduction



**Gut microbiota** play a key role in the development and progression of cardiovascular diseases.

Gut microbiota-derived **metabolites** regulate vascular diseases.

# Highlights



- ❑ The inseparable relationship between the gut microbiota and calcific aortic valve disease development.
- ❑ *Faecalibacterium prausnitzii* (*F. prausnitzii*)-derived butyric acid (BA) played an important role in anti-calcification functions.
- ❑ BA-derived butyrylation (Kbu) blocked lactylation (Kla) at the same site by occupying the GAPDH 263 lysine.
- ❑ The gut microbial-metabolite-epigenetic modification pathway represents a promising therapeutic target for calcific aortic valve disease (CAVD).

# Aortic valve calcification is modulated by fecal microbiota and cage environment

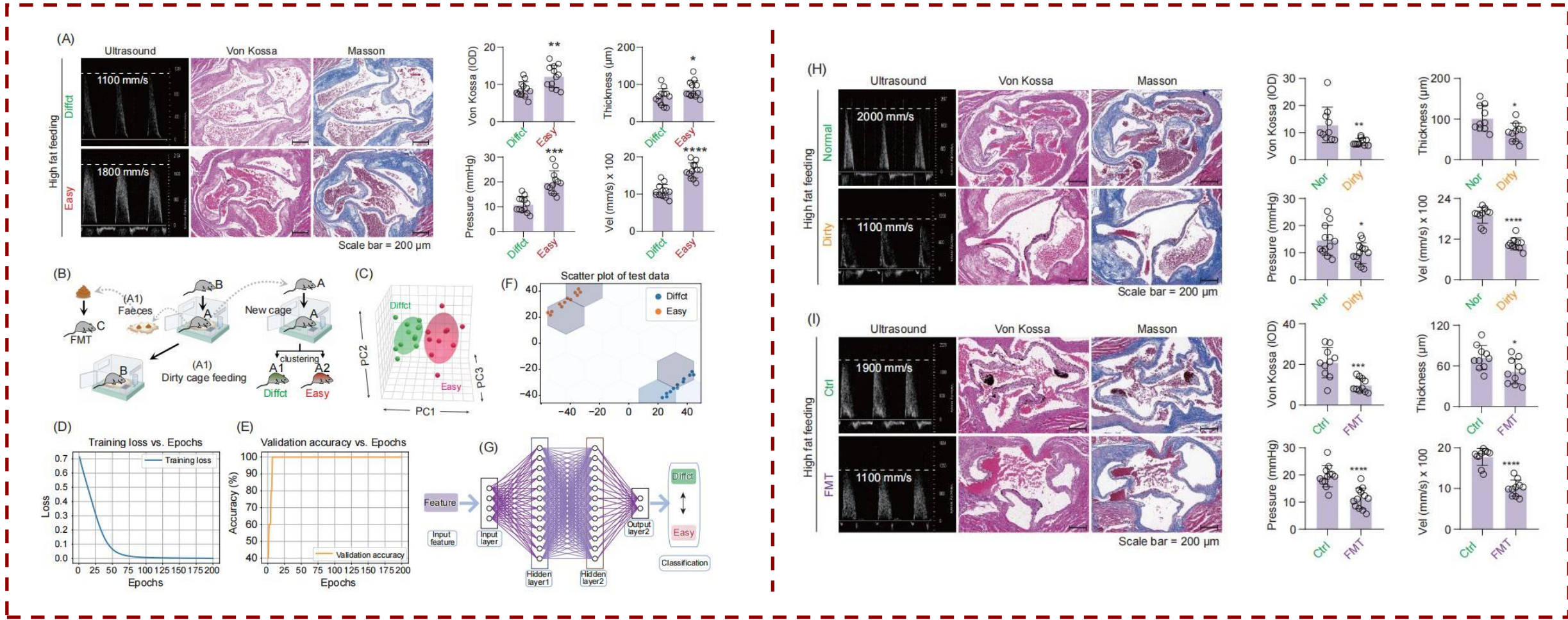


Figure 1. Aortic valve calcification is closely related to the gut microbiota.

# *F. prausnitzii* is the key strain inhibiting valve calcification in the faeces of ApoE<sup>-/-</sup> mice

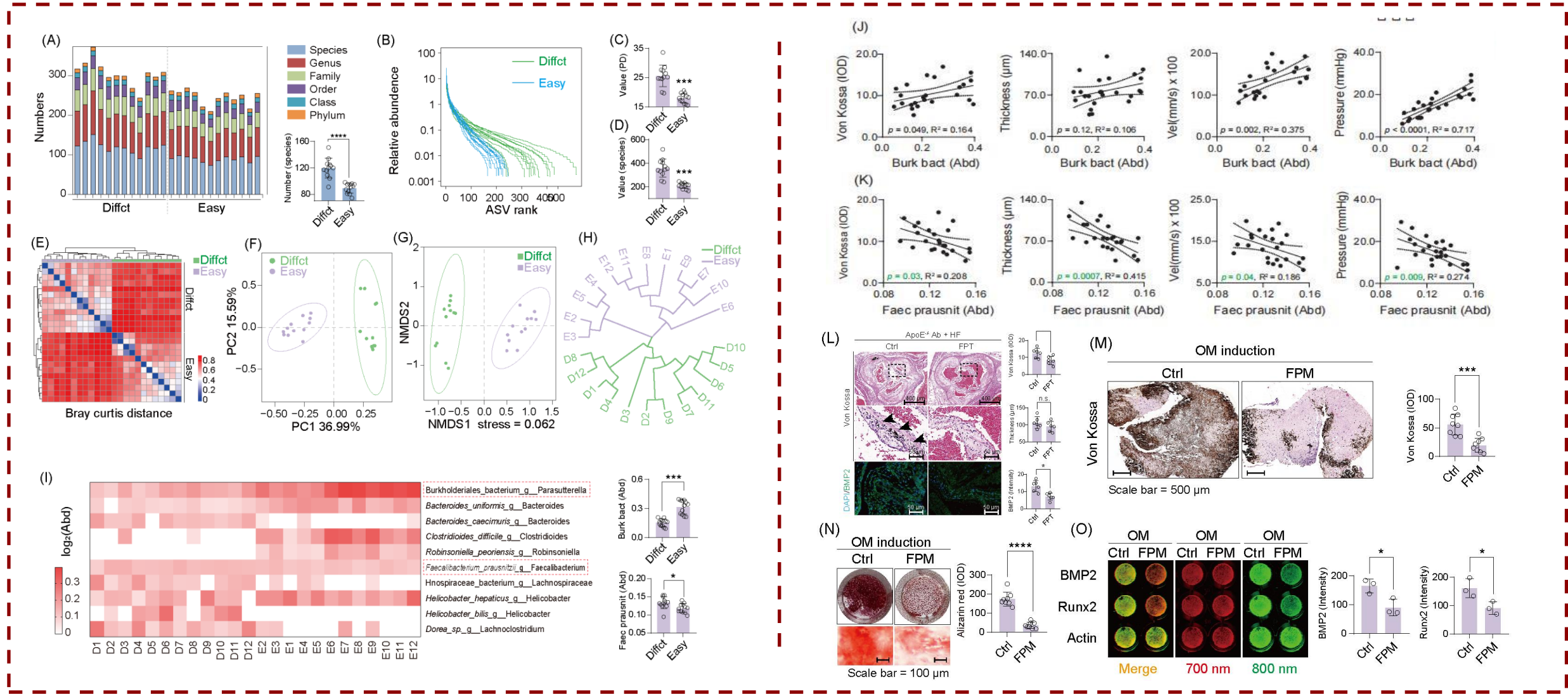


Figure 2. Gut microbial sequencing identified *F. prausnitzii* as the key species in faeces that inhibits valve calcification.

# Butyric acid plays a key role in CAVD associated with *F. prausnitzii*

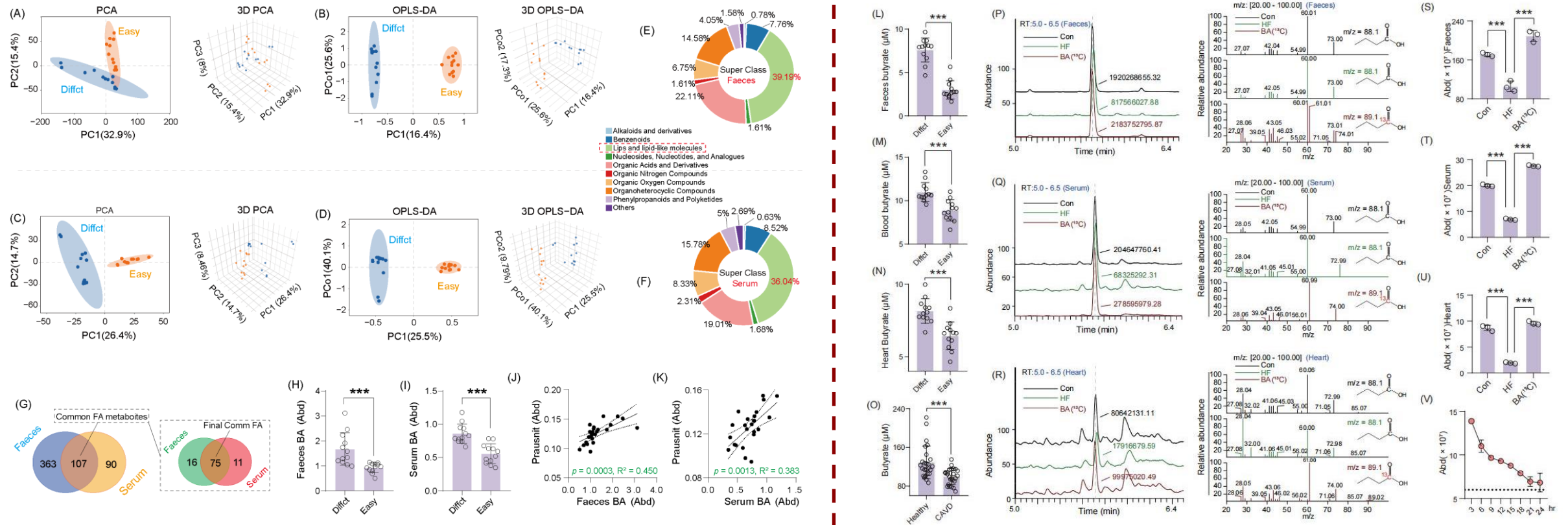


Figure 3. Metabolomic analysis of faeces and serum identified butyric acid as a key mediator of anticalcification in *F. prausnitzii*.



# Butyric acid ameliorates aortic valve calcification *ex vivo* and *in vivo*

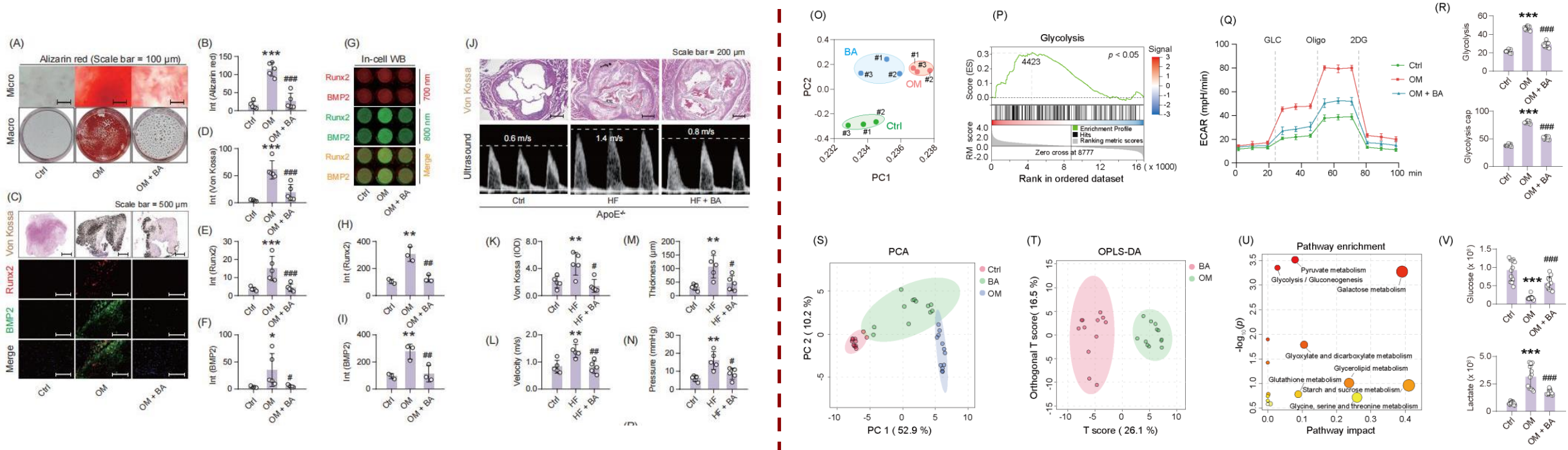


Figure 4. Butyric acid inhibited heart valve calcification through regulating glycolytic metabolism in hVICs.

# Butyric acid inhibits aortic valve calcification by competitively blocking GAPDH lactylation

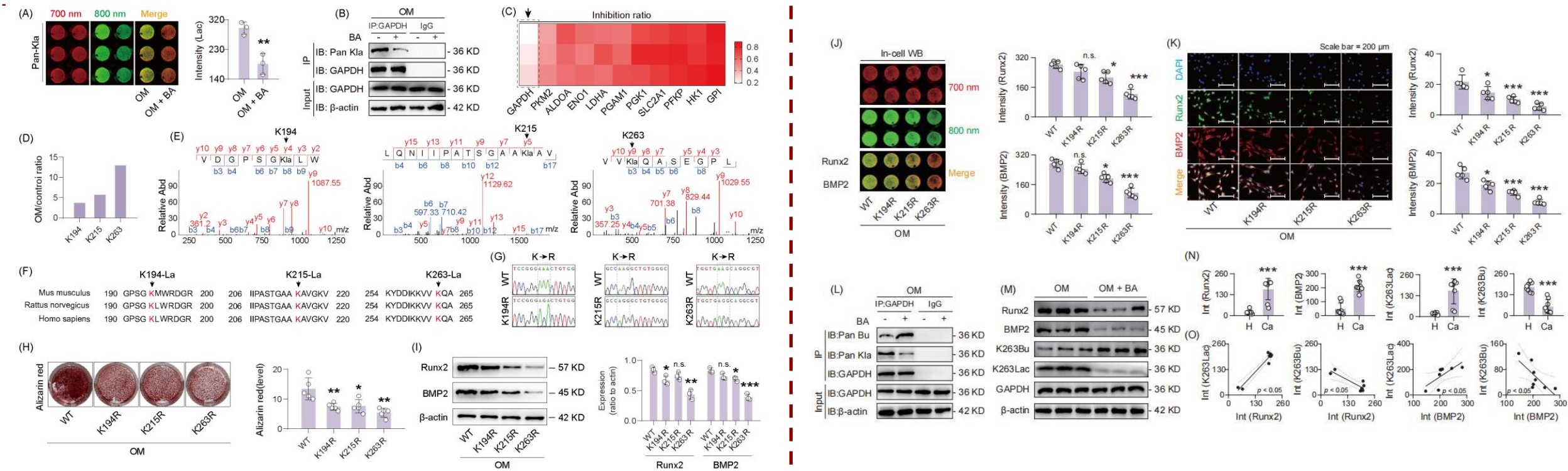


Figure 5. Butyric acid exerts antivalvular calcification effects by competitively inhibiting GAPDH lactylation.



# Summary

- ❑ We identified *F. prausnitzii*, a key gut microbiota, as being negatively associated with CAVD risk.
- ❑ *F. prausnitzii* slows the osteogenic differentiation of hVICs and decelerates the progression of CAVD through the previously undescribed metabolite butyric acid/epigenetic reshaping/glycolysis pathway.
- ❑ The present study demonstrated that *F. prausnitzii* and butyric acid are promising candidates for CAVD prevention and treatment.



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