Lactobacillus rhamnosus GG triggers intestinal epithelium injury in zebrafish revealing host dependent beneficial effects

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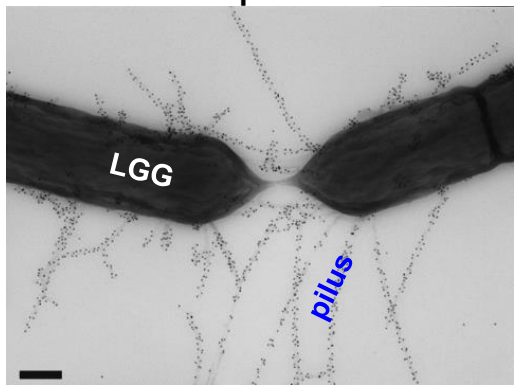
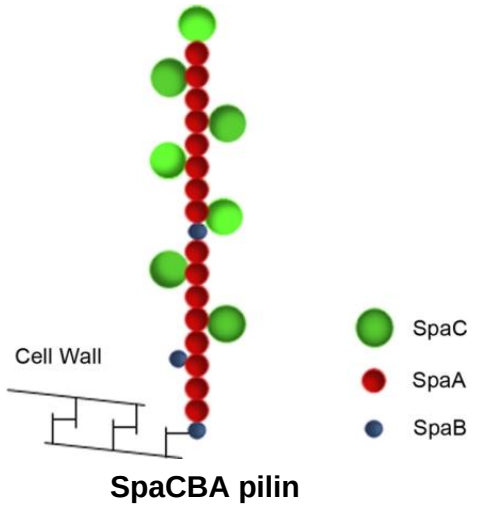
Introduction

Lactobacillus rhamnosus GG (LGG), a human-derived probiotic strain

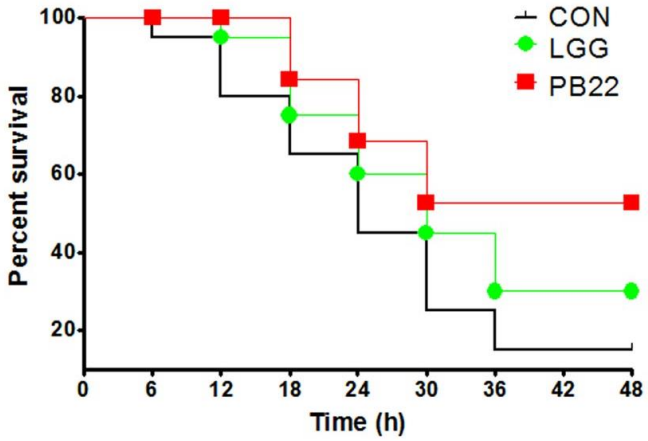


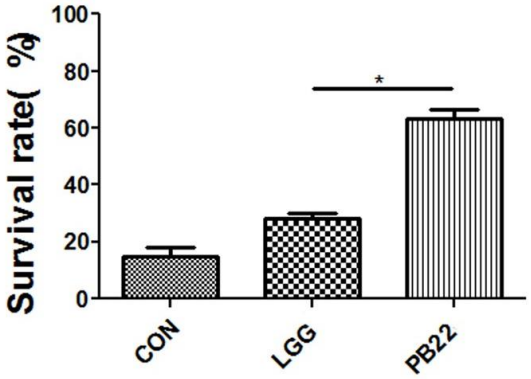


SpaCBA pilin

(*Reunanen J et al., 2012; Cynthia-E et al., 2015*)

PB22: the mutant strain of LGG lacking pilin SpaCBA



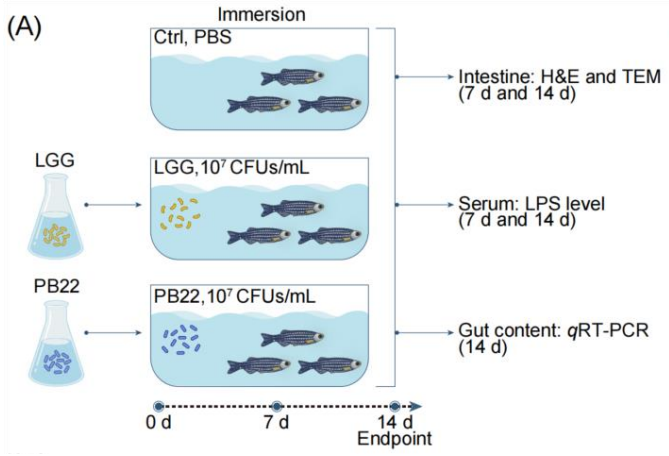


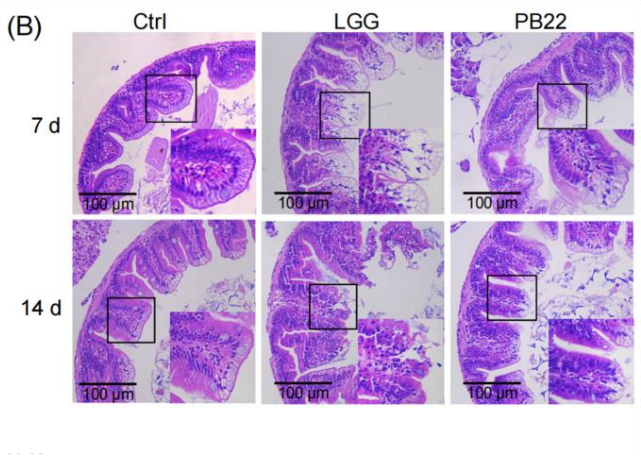
Compared with PB22, LGG did not enhance the resistance to pathogen of zebrafish

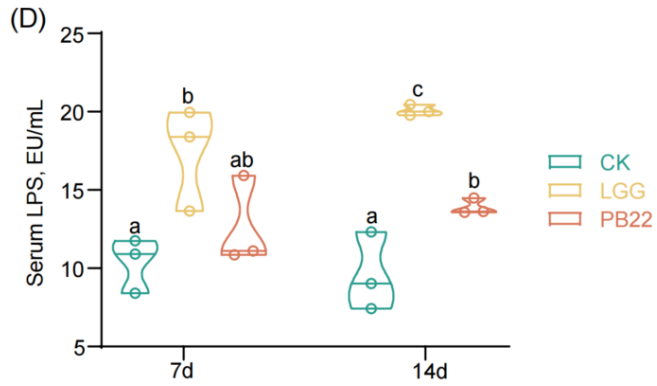
(*He SX et al., 2017*)

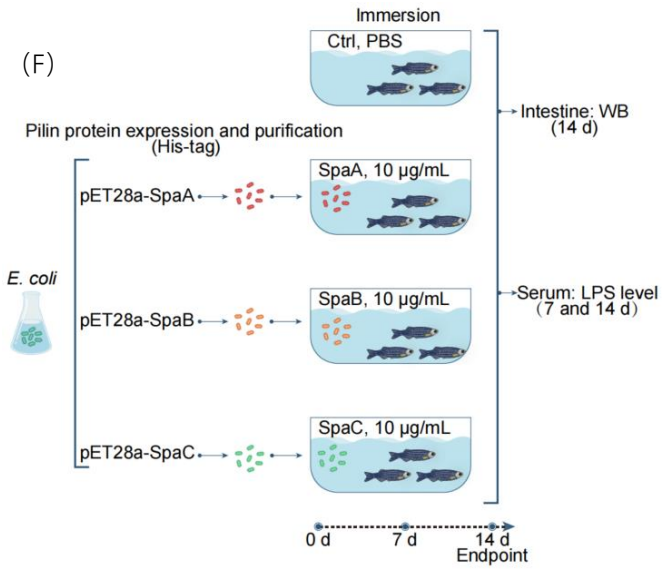
Results

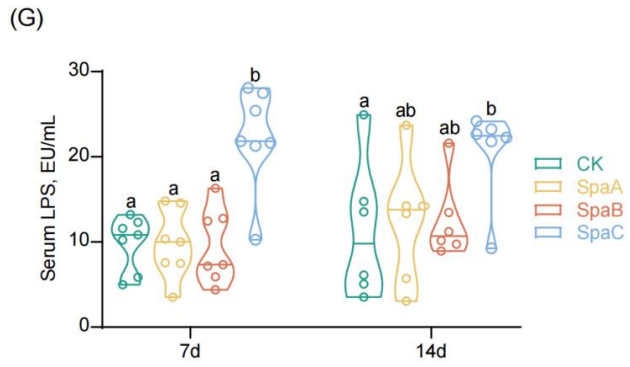
1. SpaC pilin subunit is responsible for the zebrafish intestinal mucosa damage

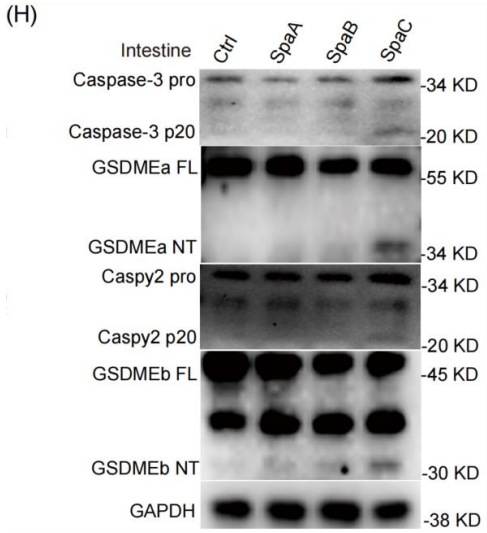








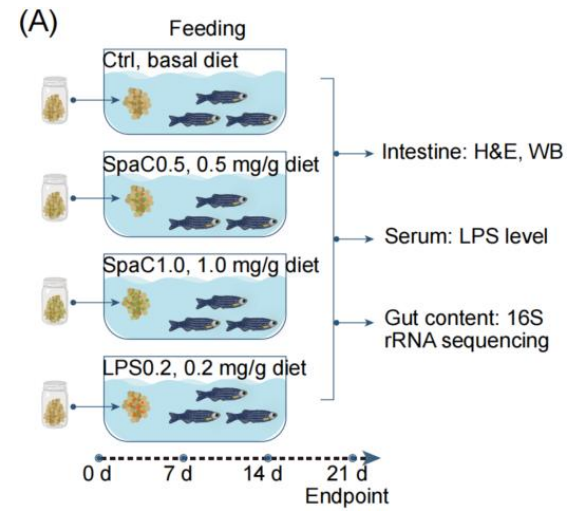


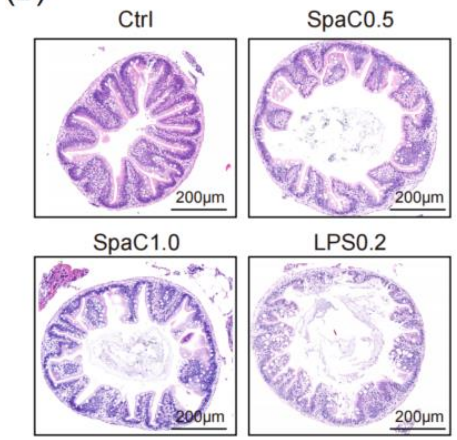


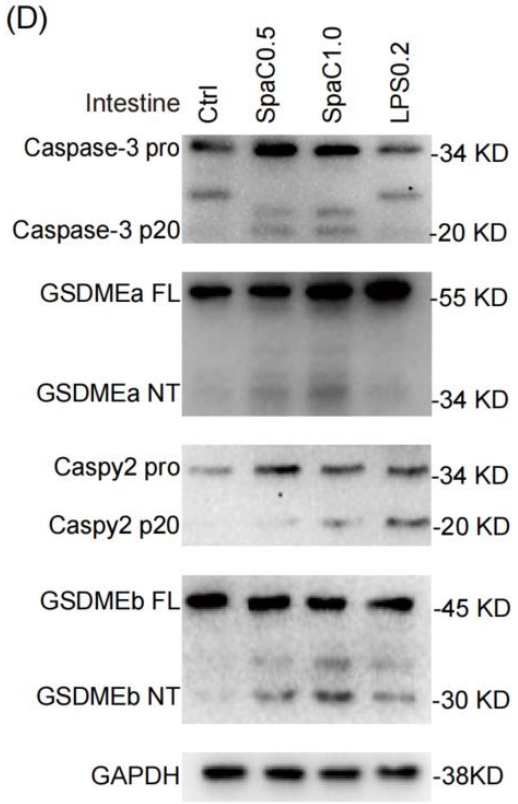
- SpaC pilin subunit is responsible for the intestinal mucosa-damaging of LGG in zebrafish.
- Pyroptosis participates in the intestinal mucosa-damaging effect of SpaC pilin subunit in zebrafish.

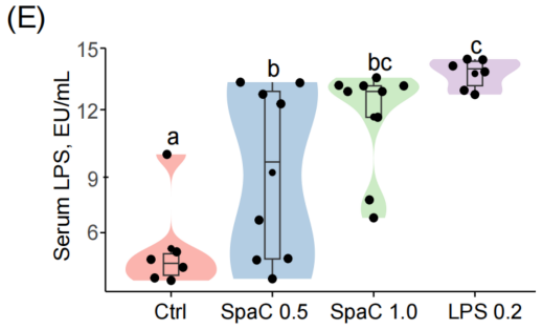
Results

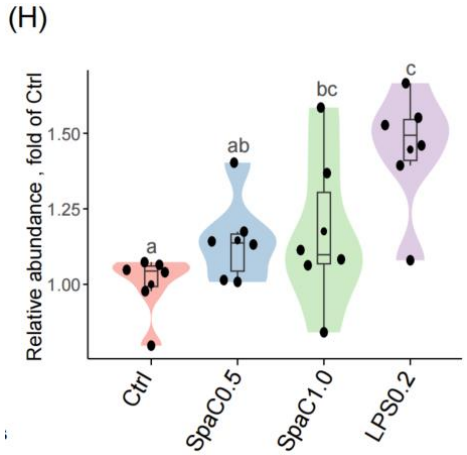
2. Dietary SpaC induces intestinal pyroptosis and gut microbial dysbiosis in zebrafish







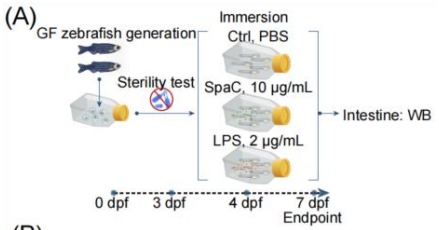


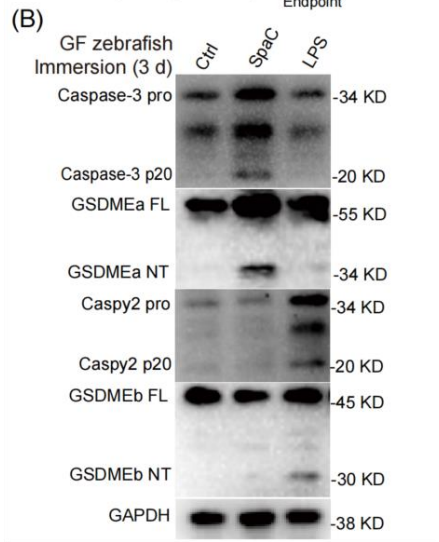


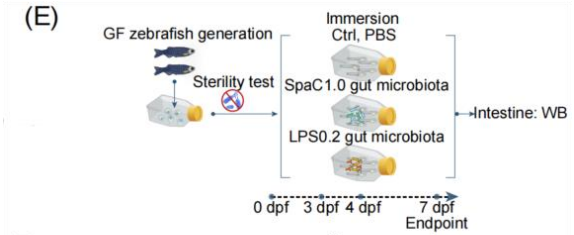
- SpaC can activate Caspase-3−GSDMEa and Caspy2−GSDMEb pyroptosis pathways, while lipopolysaccharide (LPS) can only activate Caspy2-GSDMEb pyroptosis pathway in the intestinal mucosa of zebrafish.
- Both diets containing SpaC and LPS can lead to gut microbiota dysbiosis and elevation of serum LPS.

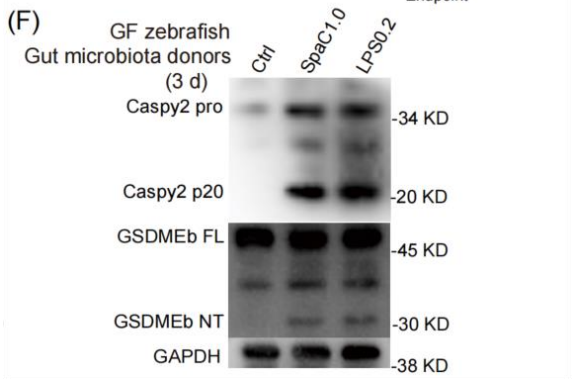
Results

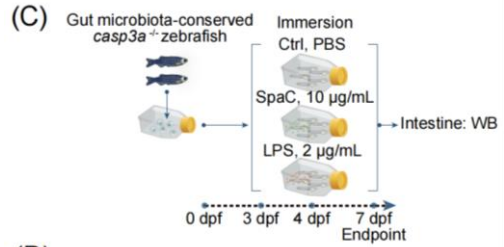
3. Gut microbiota partly accounts for the intestinal pyroptosis induced by the SpaC-containing diet

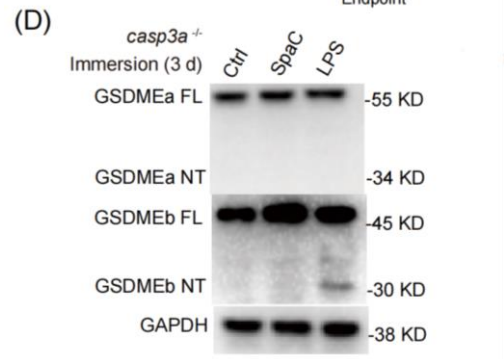


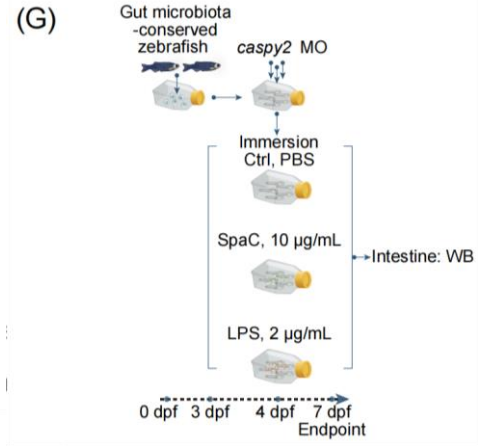


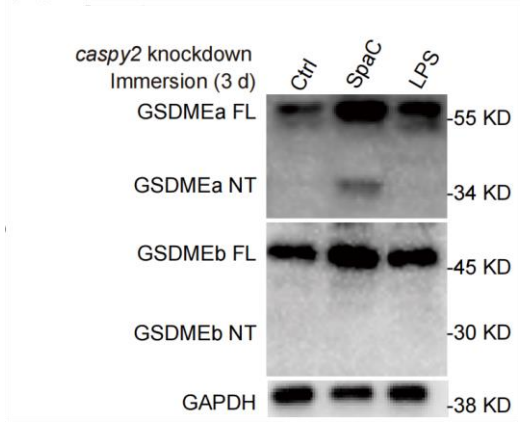










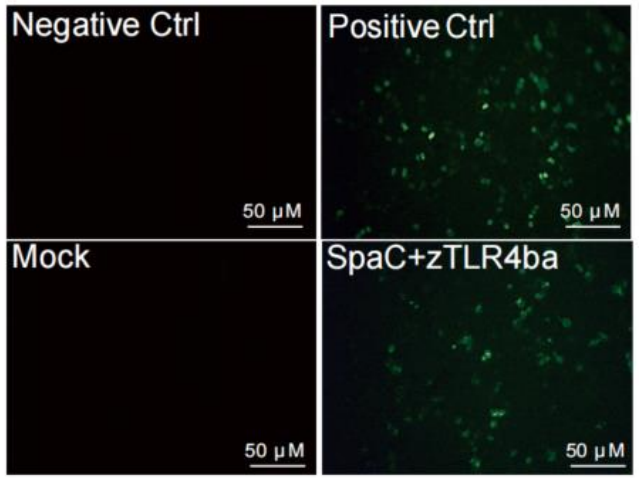


- With no involvement of gut microbiota, SpaC only activated Caspase-3−GSDMEa pathway.
- Gut microbiota induced by the SpaC-containing diet can activate intestinal pyroptosis at least through the pathway of Caspy2−GSDMEb.
- The activation of the Caspy2−GSDMEb pathway is a secondary result of the SpaC-induced Caspase-3−GSDMEa pathway.

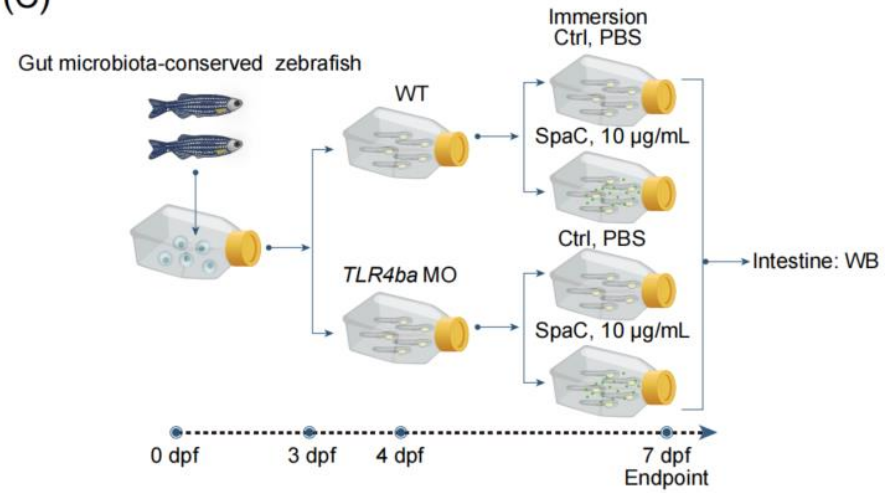
Results

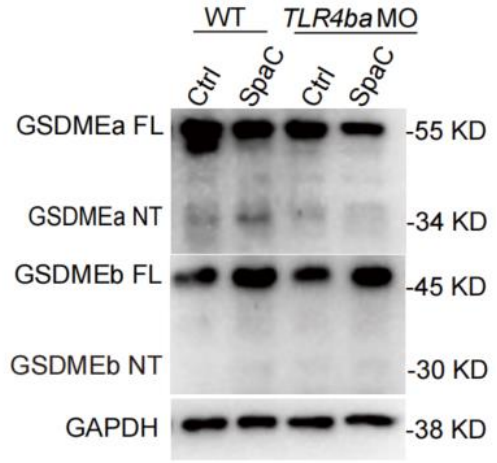
4. The interaction between SpaC and zebrafish toll-like receptor 4ba (TLR4ba) initiates intestinal pyroptosis

(B)



(C)

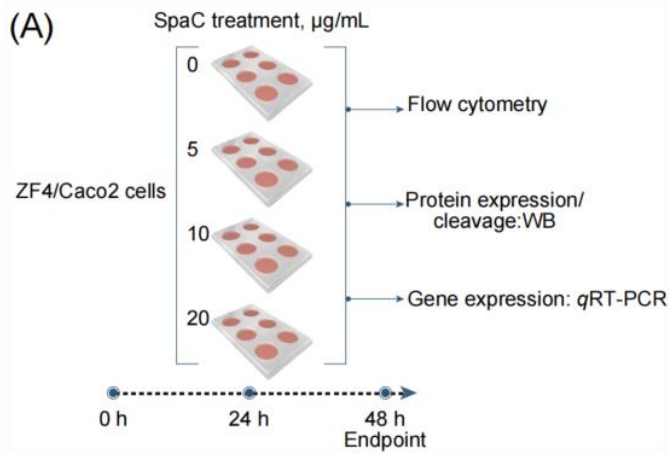


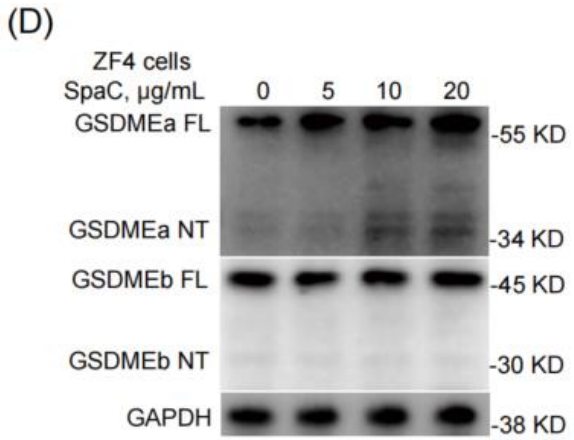


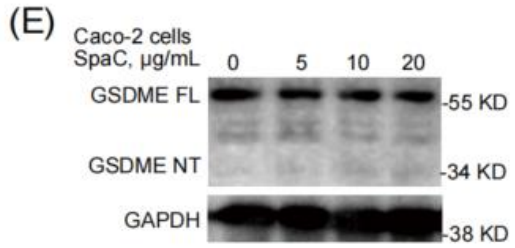
- TLR4ba is essential for SpaC-induced pyroptosis.

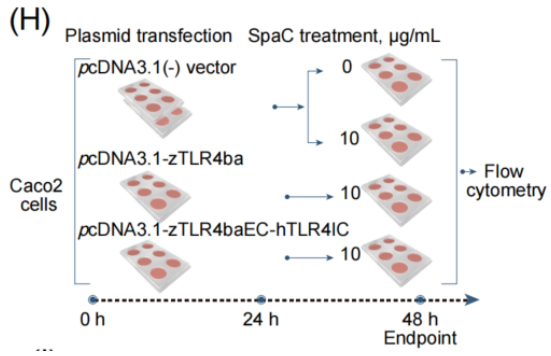
Results

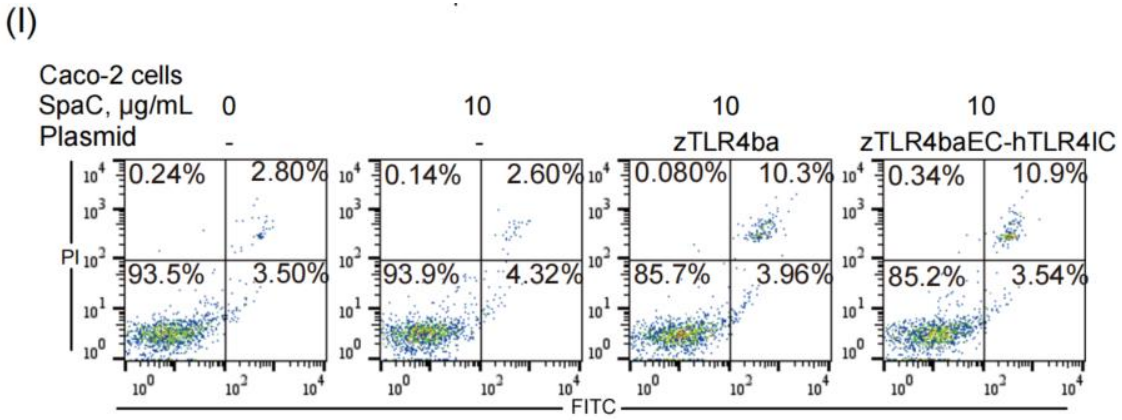
5. The comparative TLR signaling to SpaC in zebrafish and human

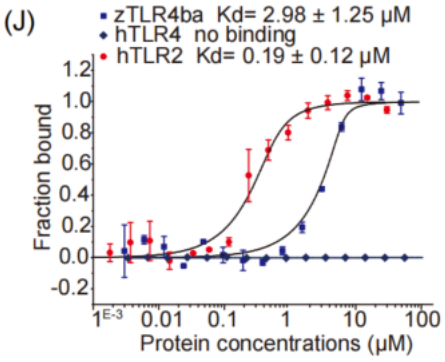








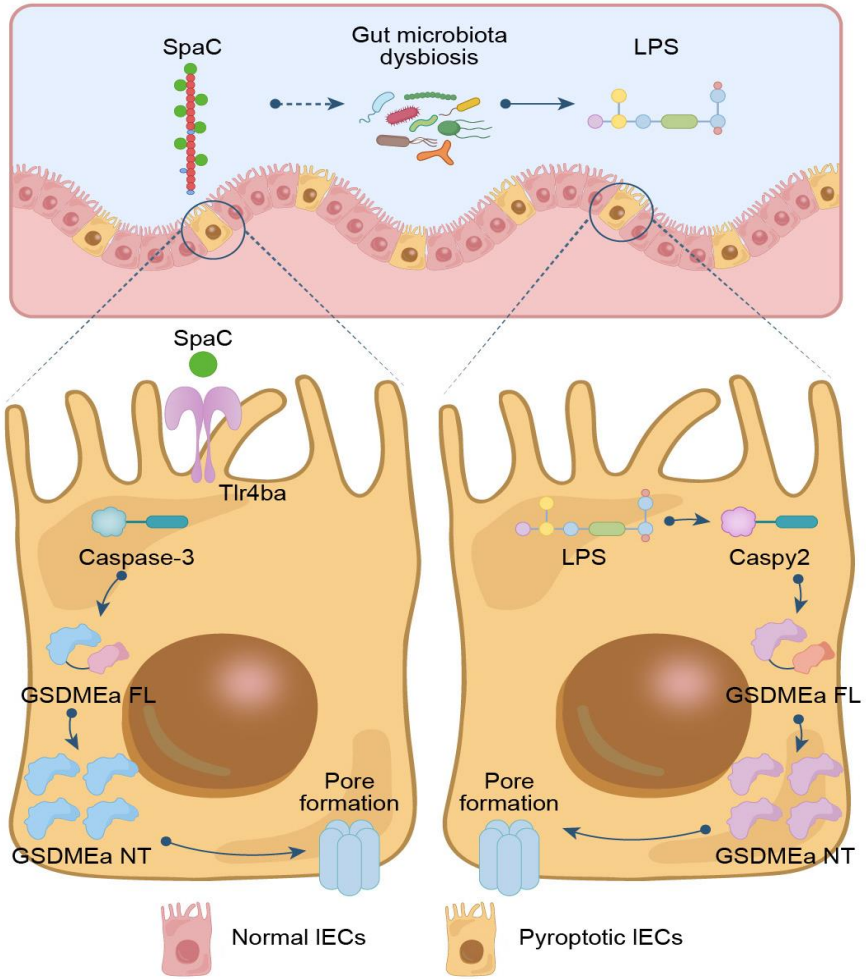




- SpaC induce cell pyroptosis in zebrafish but not in humans.
- The extracellular domain of zTLR4ba contributes to the species-specific recognition to SpaC.
- SpaC can interact with zTLR4ba and hTLR2 but not hTLR4.

Summary

The mechanisms underlying the activation of SpaC to intestinal pyroptosis



- SpaC pilin acts a causative factor of LGG-induced intestinal mucosa damage in zebrafish.
- Dietary SpaC directly induces intestinal pyroptosis by activating GSDMEa in zebrafish.
- Dietary SpaC induces gut microbial dysbiosis characterized by higher abundance of LPS-producing gut microbes in zebrafish.
- LPS-producing gut microbes subsequently activate Gaspy2−GSDMEb pyroptosis pathway in zebrafish.

This study presents the risk of non-host-assosiated classic probiotics on fish!

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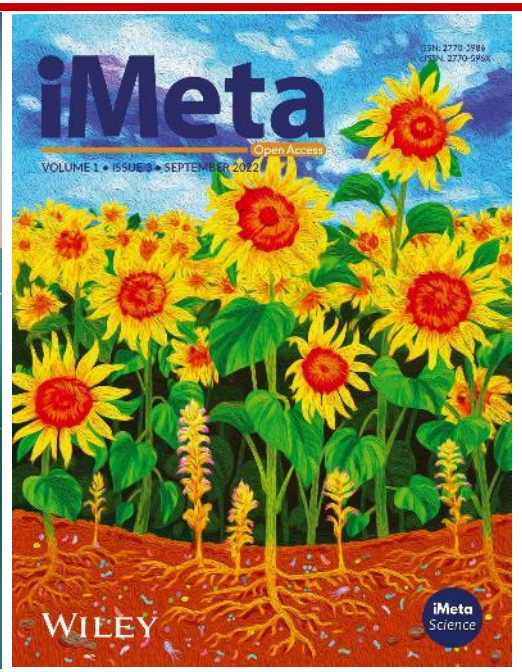

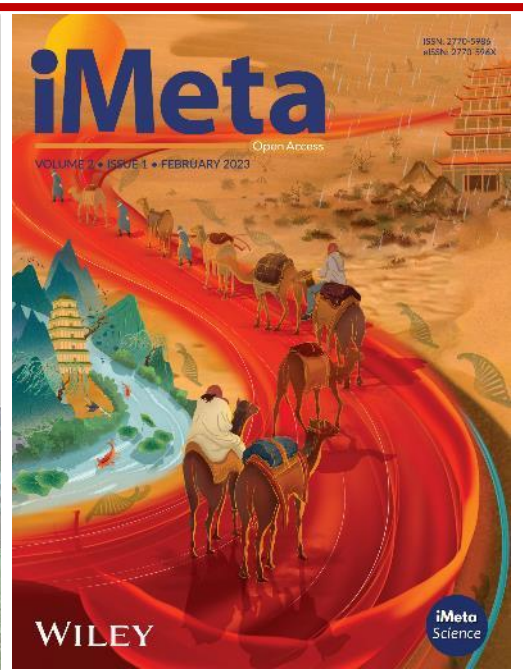

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