Limosilactobacillus reuteri enhances ovarian function and female fertility

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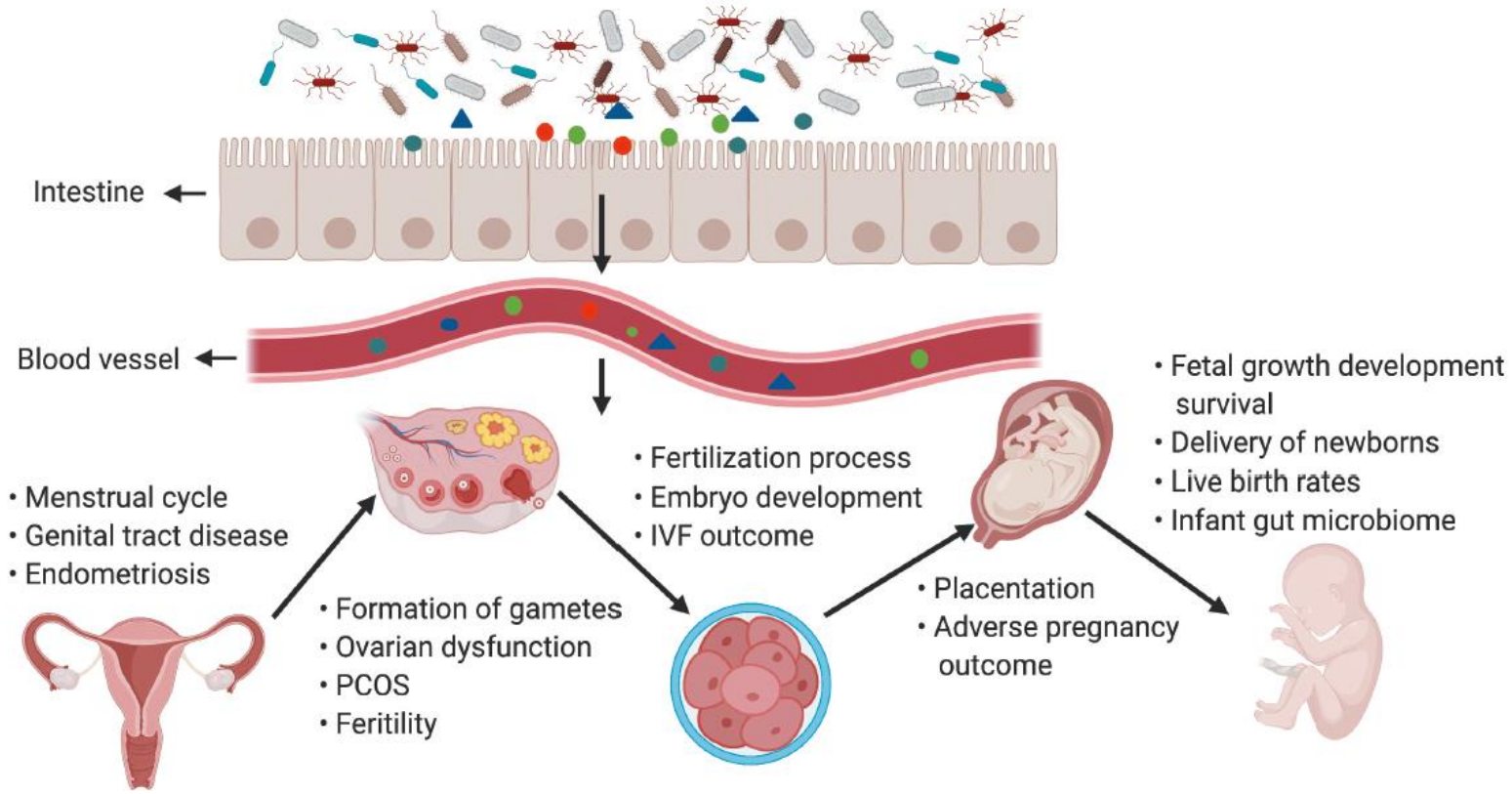
Introduction



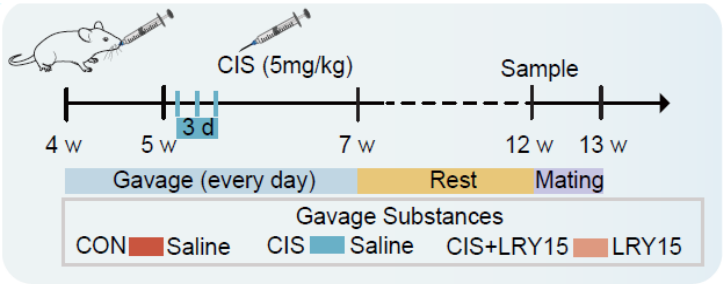
Qi X, et al., *Gut Microbes*, 2021.

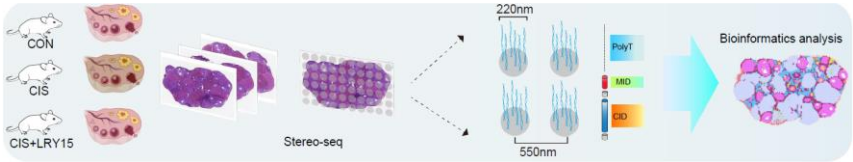
Scientific Questions:

The specific microbial molecules mediating the beneficial effects on ovarian function and other species of microbes that enhance ovarian function and female fertility remain underexplored

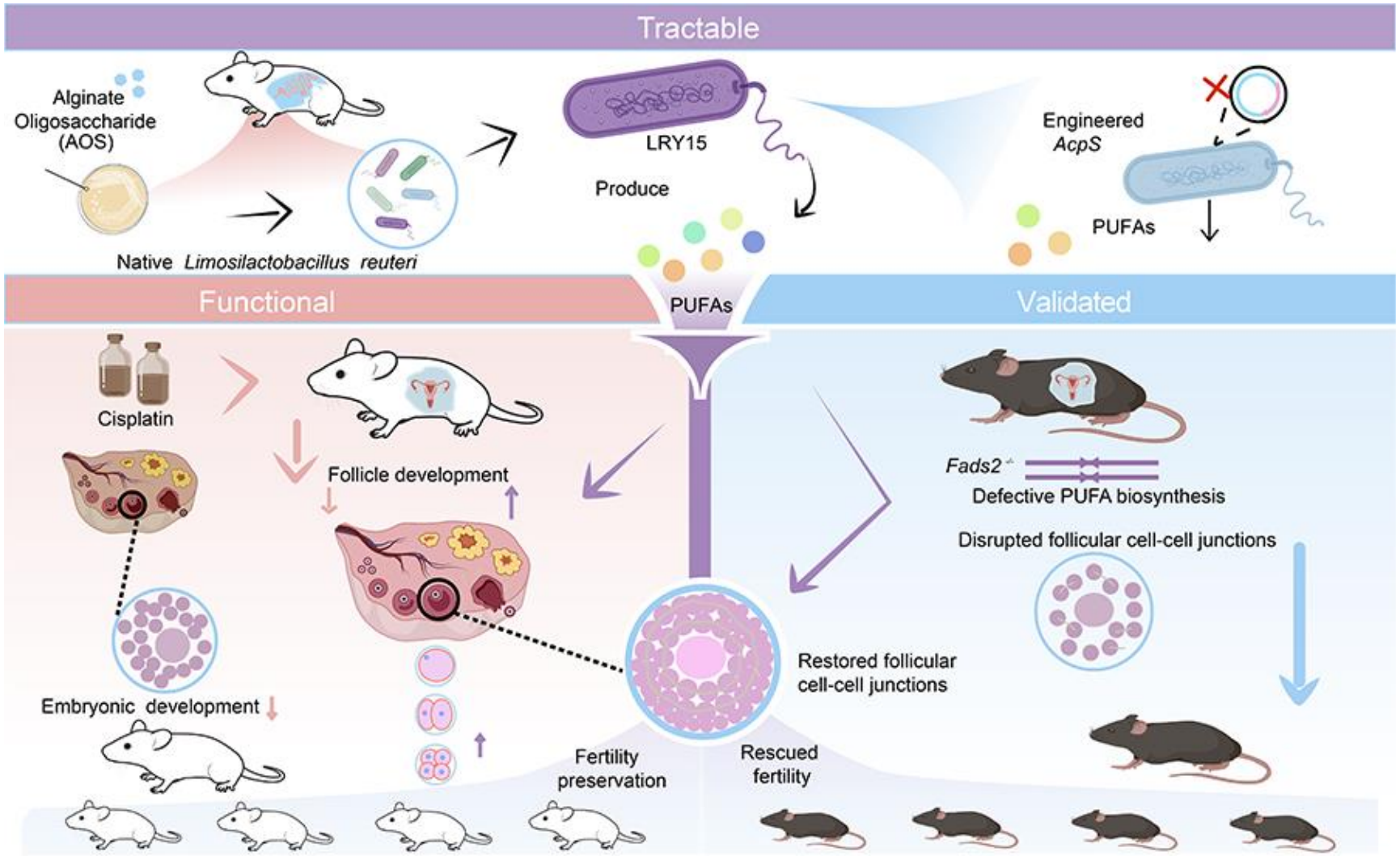
Study Design and Objective:

The current study was conducted to investigate native gut microbes from animals and microbially derived molecules that enhance ovarian function and female fertility.



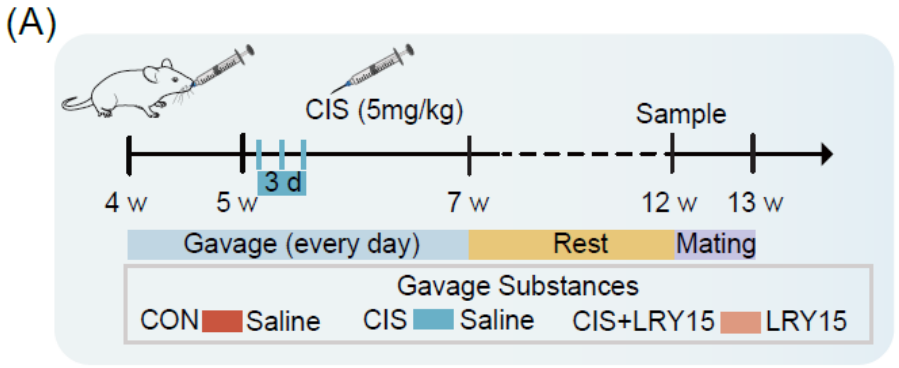


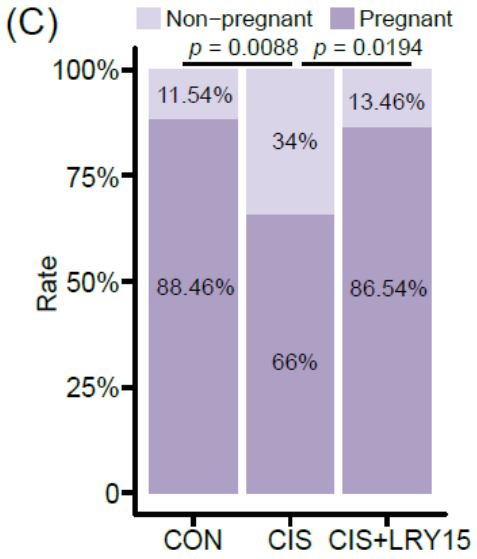
Highlights

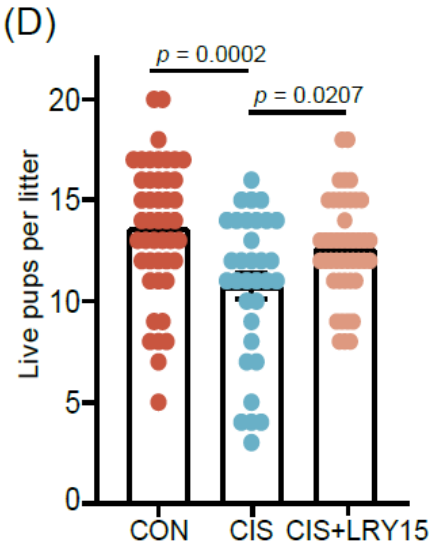


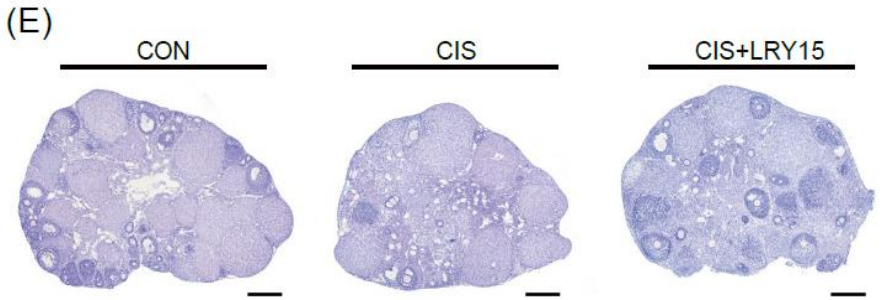
- Native *Limosilactobacillus reuteri* Y15 (LRY15) from murine gut synthesizes PUFAs.
- LRY15 can be engineered to delete synthetase *AcpS* to inhibit PUFA production.
- LRY15-derived PUFAs restore ovarian cell-cell junctions to enhance female fertility.

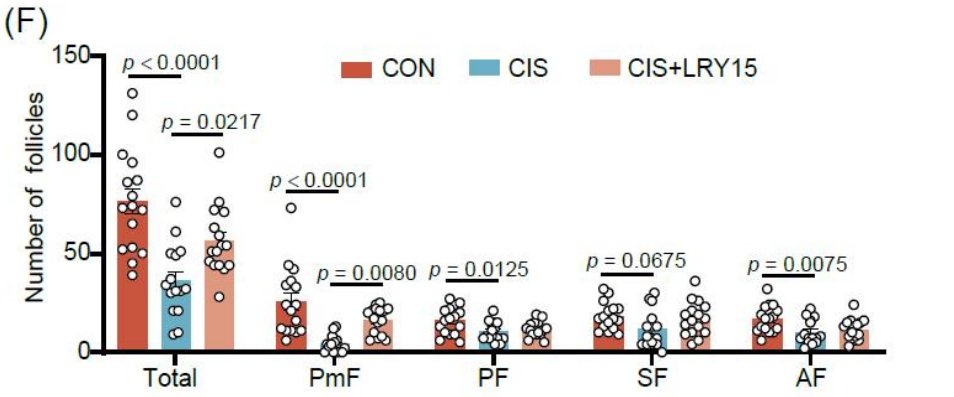
LRY15 enhanced ovarian function and female fertility in CIS-induced subfertile mice











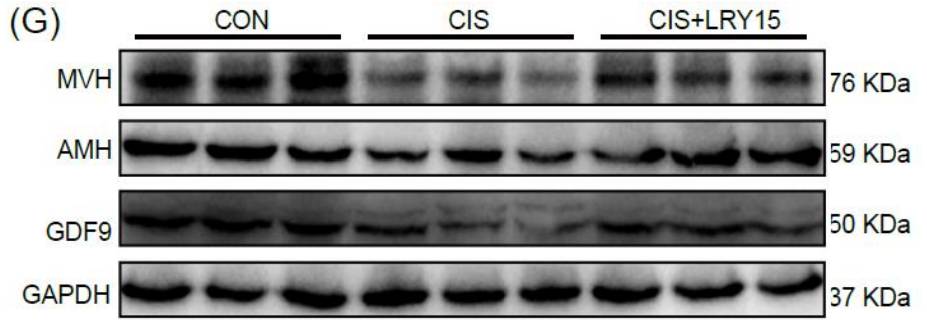


Figure 1. Polyunsaturated fatty acids (PUFAs) mediate the effects of *Limosilactobacillus reuteri* Y15 (LRY15) on enhancing ovarian and female fertility.

(A) Scheme of LRY15 transplantation in improving ovarian function and female fertility. (C) The pregnant rate. (D) The number of live pups per litter.

(E) Representative H&E staining of ovaries. (F) The number of follicles at different stages. (G) Western blot analysis of ovarian MVH, AMH, GDF9.

Loss of PUFA production activity attenuated the beneficial effects of LRY15 on Ovarian function and female fertility in CIS-induced subfertile mice

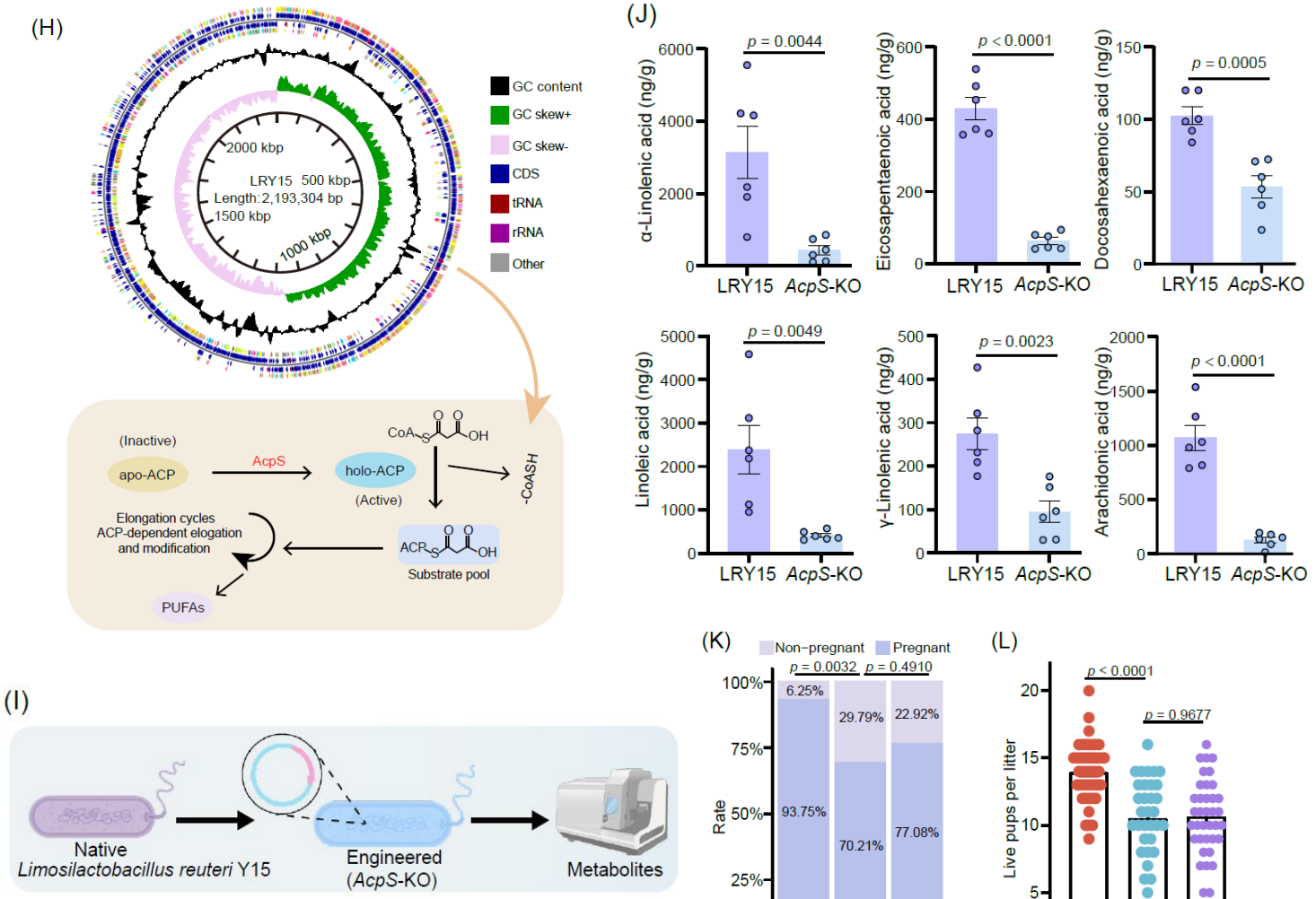


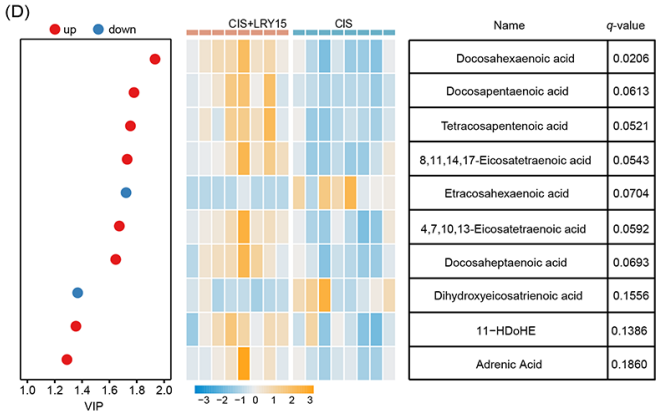
Figure 1. Polyunsaturated fatty acids (PUFAs) mediate the effects of *Limosilactobacillus reuteri* Y15 (LRY15) on enhancing ovarian and female fertility.

(H) Circular representation of the LRY15 genome. The lower panel shows the schematic overview of *holo*-acyl carrier protein synthase (*AcpS*)-dependent PUFA synthesis supported by LRY15. (I) Experimental strategy for engineering native *Limosilactobacillus reuteri* Y15 (*AcpS*-KO strain) and determination of metabolite profiling.

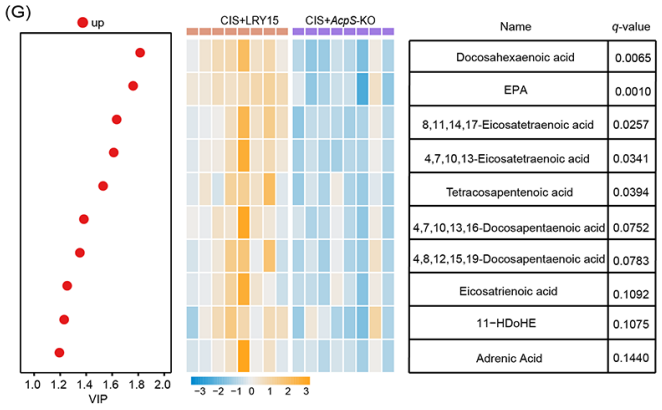
(J) Quantification of ALA, EPA, DHA LA, GLA, ARA in LRY15 and *AcpS*-KO microbial. (K) The pregnant rate. (L) The number of live pups per.

LRY15 increased plasma and ovarian PUFA levels in CIS-induced subfertile mice

Figure S3 LRY15 increases polyunsaturated fatty acids (PUFAs) levels in plasma in CIS-treated mice.

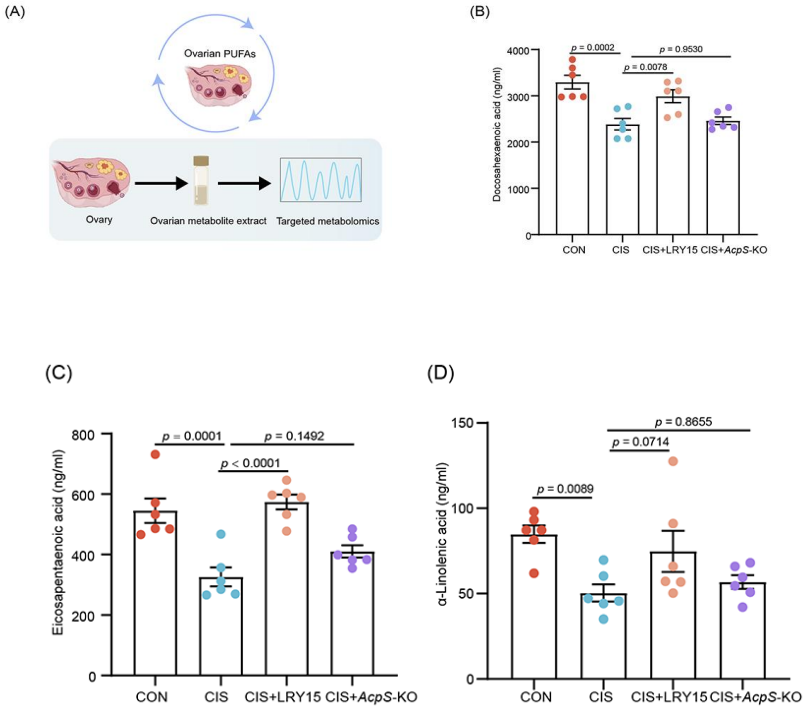


Name	q-value
Docosahexaenoic acid	0.0206
Docosapentaenoic acid	0.0613
Tetracosapentenoic acid	0.0521
8,11,14,17-Eicosatetraenoic acid	0.0543
Etracosahexaenoic acid	0.0704
4,7,10,13-Eicosatetraenoic acid	0.0592
Docosaheptaenoic acid	0.0693
Dihydroxyeicosatrienoic acid	0.1556
11−HDoHE	0.1386
Adrenic Acid	0.1860



Name	q-value
Docosahexaenoic acid	0.0065
EPA	0.0010
8,11,14,17-Eicosatetraenoic acid	0.0257
4,7,10,13-Eicosatetraenoic acid	0.0341
Tetracosapentenoic acid	0.0394
4,7,10,13,16-Docosapentaenoic acid	0.0752
4,8,12,15,19-Docosapentaenoic acid	0.0783
Eicosatrienoic acid	0.1092
11−HDoHE	0.1075
Adrenic Acid	0.1440

Figure S4 LRY15 increases PUFA levels in ovaries in CIS-treated mice.

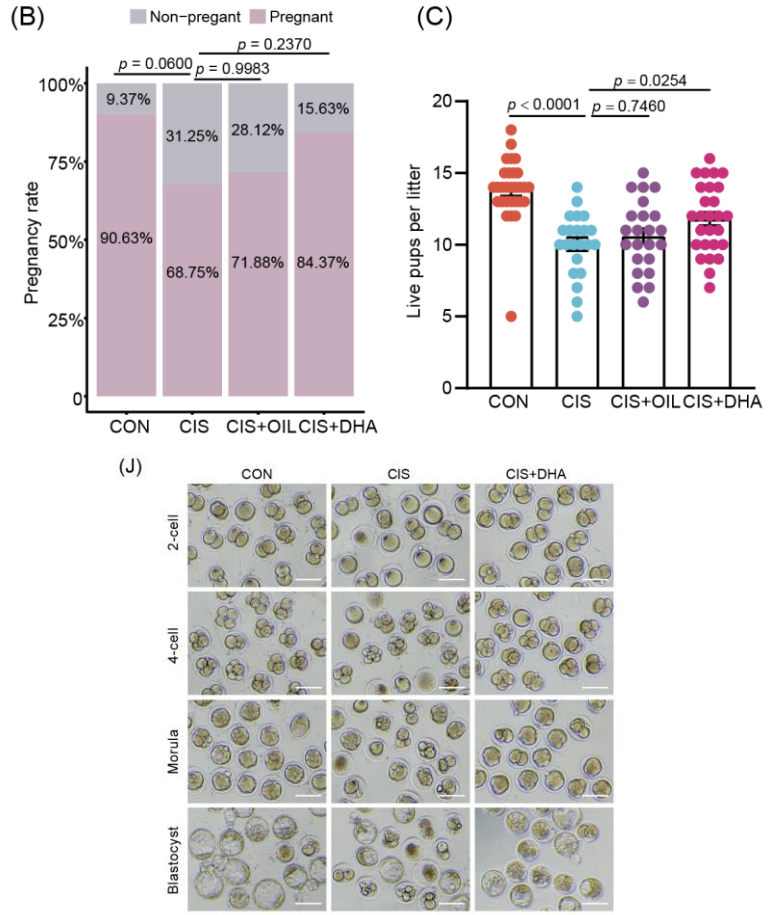


(A) Schematic overview of the targeted metabolomic analysis of PUFAs in the ovary. (B) Ovarian docosahexaenoic acid concentrations. (C) Ovarian eicosapentaenoic acid concentrations. (D) Ovarian α-linolenic acid concentrations.

(D) Variable importance in projection (VIP) analysis and differentially metabolic profile of PUFAs in plasma metabolites between CIS+LRY15 and CIS groups. (G) VIP analysis and differentially metabolic profile of PUFAs in plasma metabolites between CIS+LRY15 and CIS+*AcpS*-KO groups.

DHA supplementation recapitulated the beneficial effects of LRY15 on ovarian function and female fertility in CIS-induced subfertile mice

Figure S5 DHA improves ovarian function and fertility in CIS-treated mice.



(B) The pregnant.

(C) The number of live pups per.

(J) Representative images of early embryos. Bar = 100 μm.

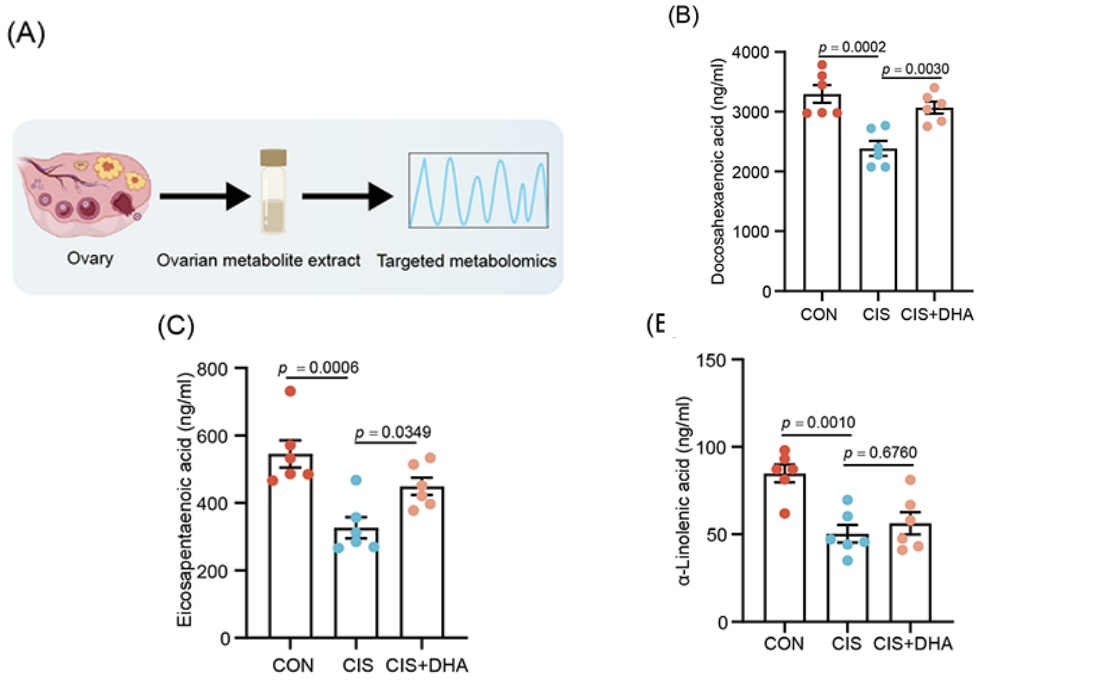


Figure S6 DHA increases PUFA levels in ovaries and embryonic development potential of oocytes in CIS-treated mice.

(A) Schematic overview of the targeted metabolomic analysis of PUFAs in the ovary.

(B) Ovarian docosahexaenoic acid concentrations.

(C) Ovarian eicosapentaenoic acid.

(E) Ovarian α-linolenic acid concentrations.

LRY15 and DHA alleviated gut microbial dysbiosis in CIS-induced subfertile mice

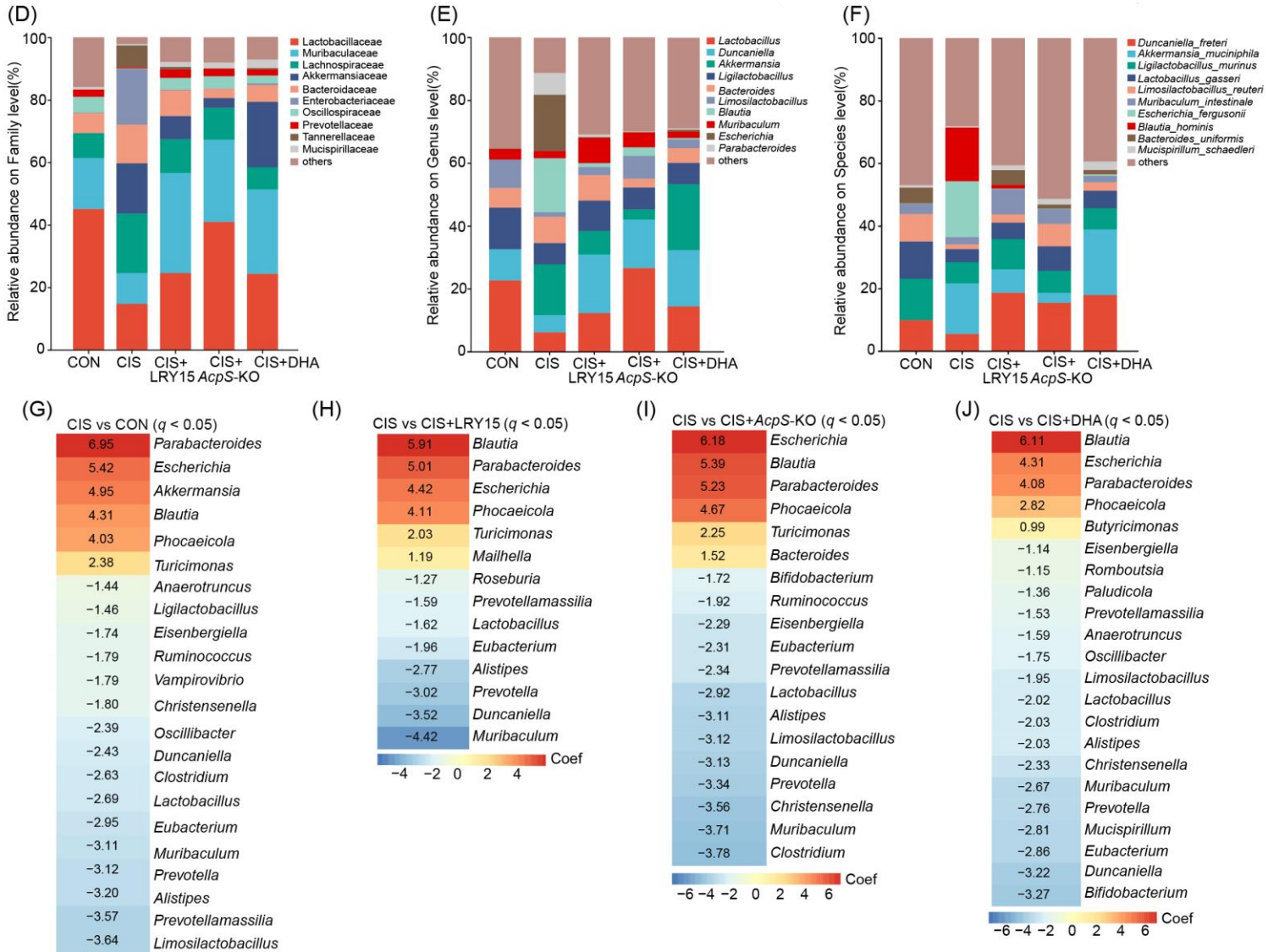


Figure S7 Effects of LRY15, *AcpS*-KO, and DHA on colonic microbiota.

(D-F) Relative abundance of colonic microbiota at family, genus, and species levels, respectively. (G-J) The differential bacterial genera in the colon in CIS vs. CON, CIS vs. CIS+LRY15, CIS vs. CIS+*AcpS*-KO, and CIS vs CIS+DHA identified by MaAsLin2 analysis ($q < 0.05$). The color scale represents the regression coefficient (Coef), with red indicating taxa enriched in the CIS and blue indicating taxa enriched in the CIS+LRY15, CIS+*AcpS*-KO, and CIS+DHA, respectively.

Stereo-seq revealed restoration of granulosa cell and oocyte function by LRY15 in CIS-induced subfertile mice

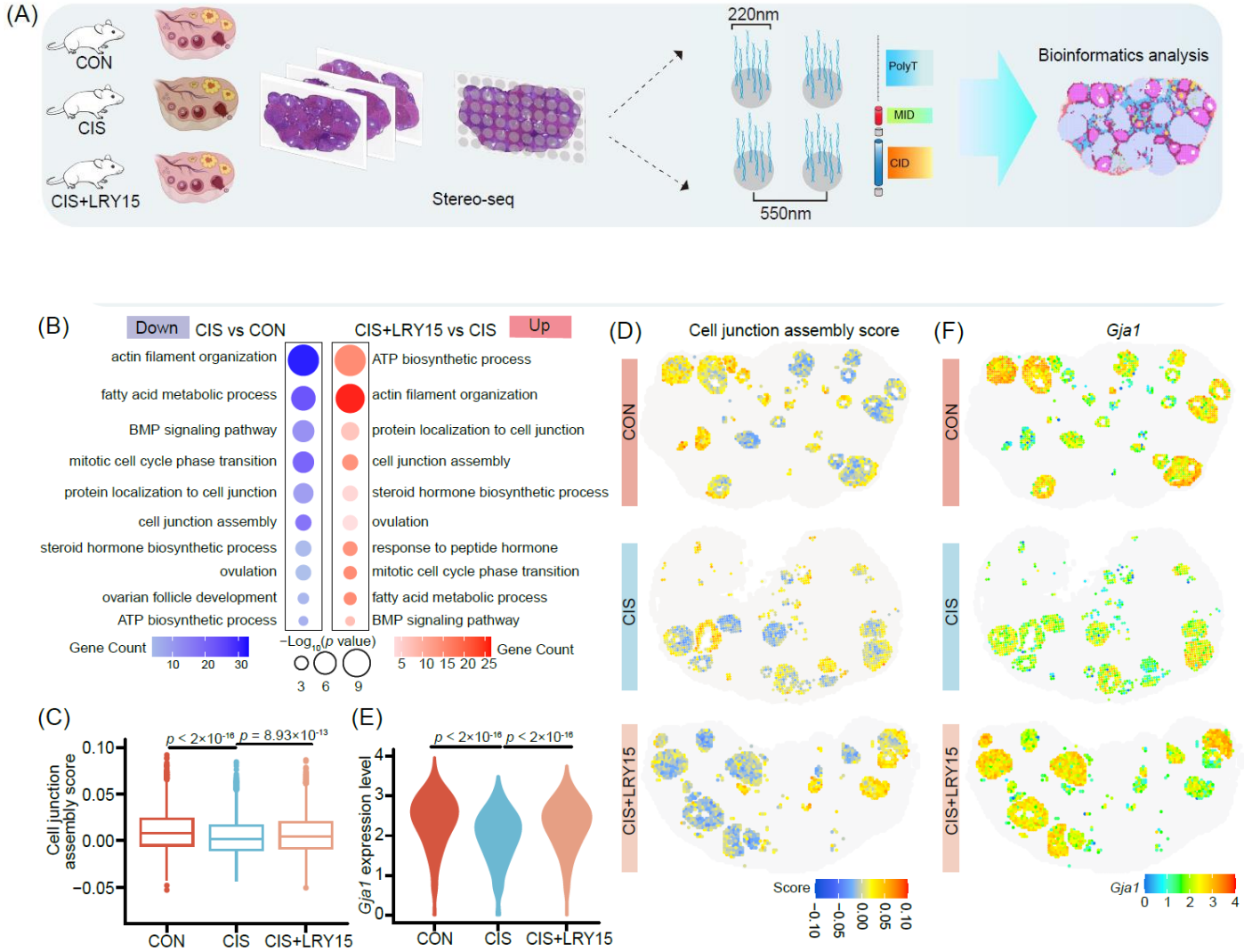


Figure 2 LRY15 recovers ovarian cell-cell junctions via PUFA pathways to enhance ovarian function and female fertility.

(A) Overview of the workflow for establishing an ovarian spatial transcriptomic atlas using stereo-seq. (B) Representative gene ontology (GO) terms enriched for differentially expressed genes (DEGs) in granulosa cells downregulated in CIS vs. CON but upregulated in CIS+LRY15 vs. CIS. (C) Gene set scoring of cell junction assembly in granulosa cells. Box-and-whisker plots show the minimum, 25th percentile, median, 75th percentile and maximum. (D) The spatial distribution of cell junction assembly score was shown in representative ovarian samples. (E) Violin plot illustrating the expression of *Gja1* in granulosa cells. (F) The spatial distribution of *Gja1* expression in representative ovarian samples.

LRY15 restored ovarian cell-cell junctions to enhance female fertility in CIS-induced subfertile mice

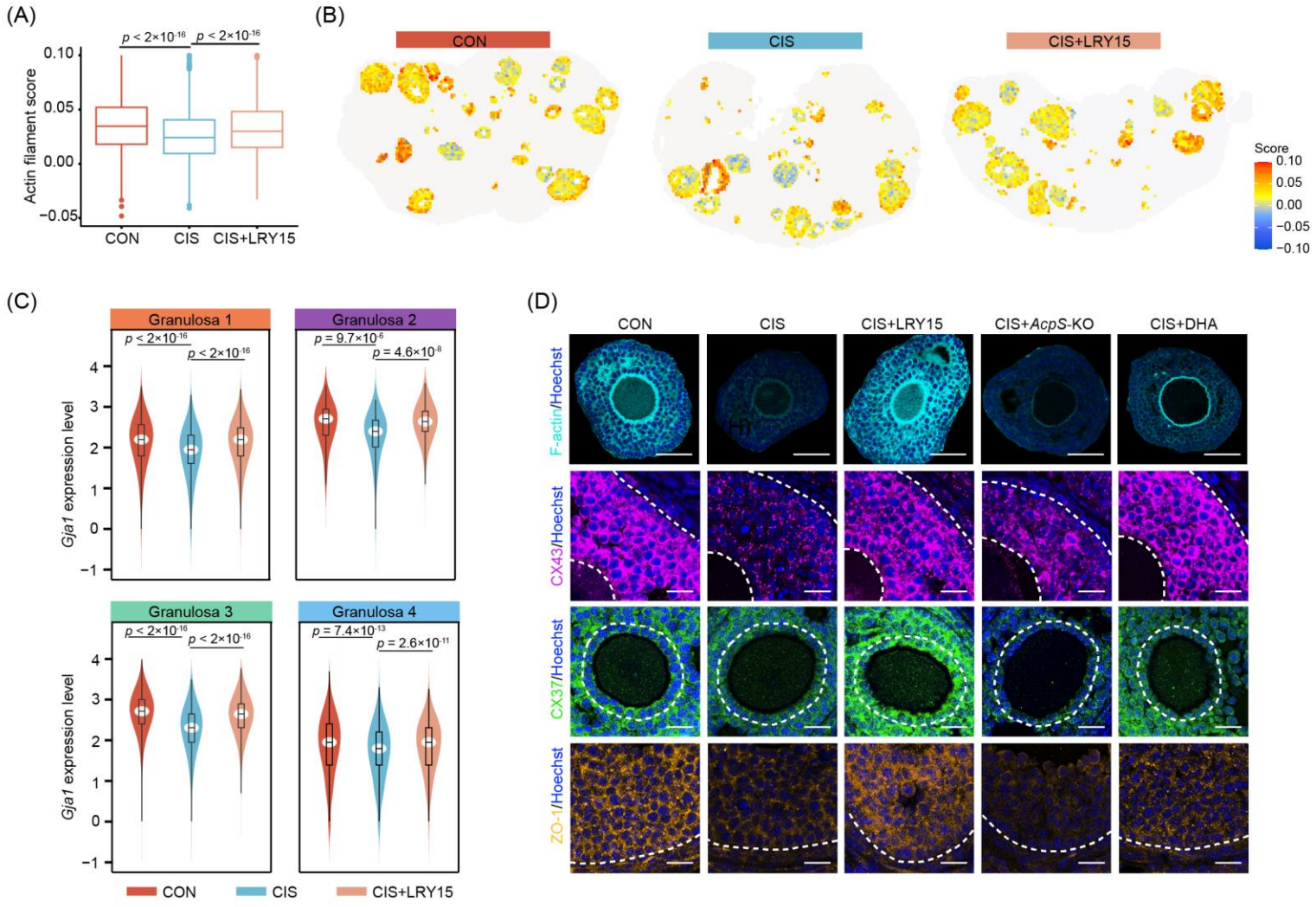


Figure S13 LRY15 and DHA recovers ovarian cell-cell junction in CIS-treated mice.

(A) Gene set scoring of actin filament in granulosa cells. Box-and-whisker plots show the minimum, 25th percentile, median, 75th percentile and maximum. (B) The spatial distribution of actin filament score was shown in representative ovarian samples. (C) Violin plot illustrating the expression of *Gja1* in four subtypes of granulosa cells. (D) Representative images of immunofluorescence staining for F-actin, CX43, CX37 and ZO-1 in ovarian sections.

PUFAs derived from LRY15 restored ovarian cell-cell junctions and improved female fertility in *Fads2*$^{-/-}$ subfertile mice

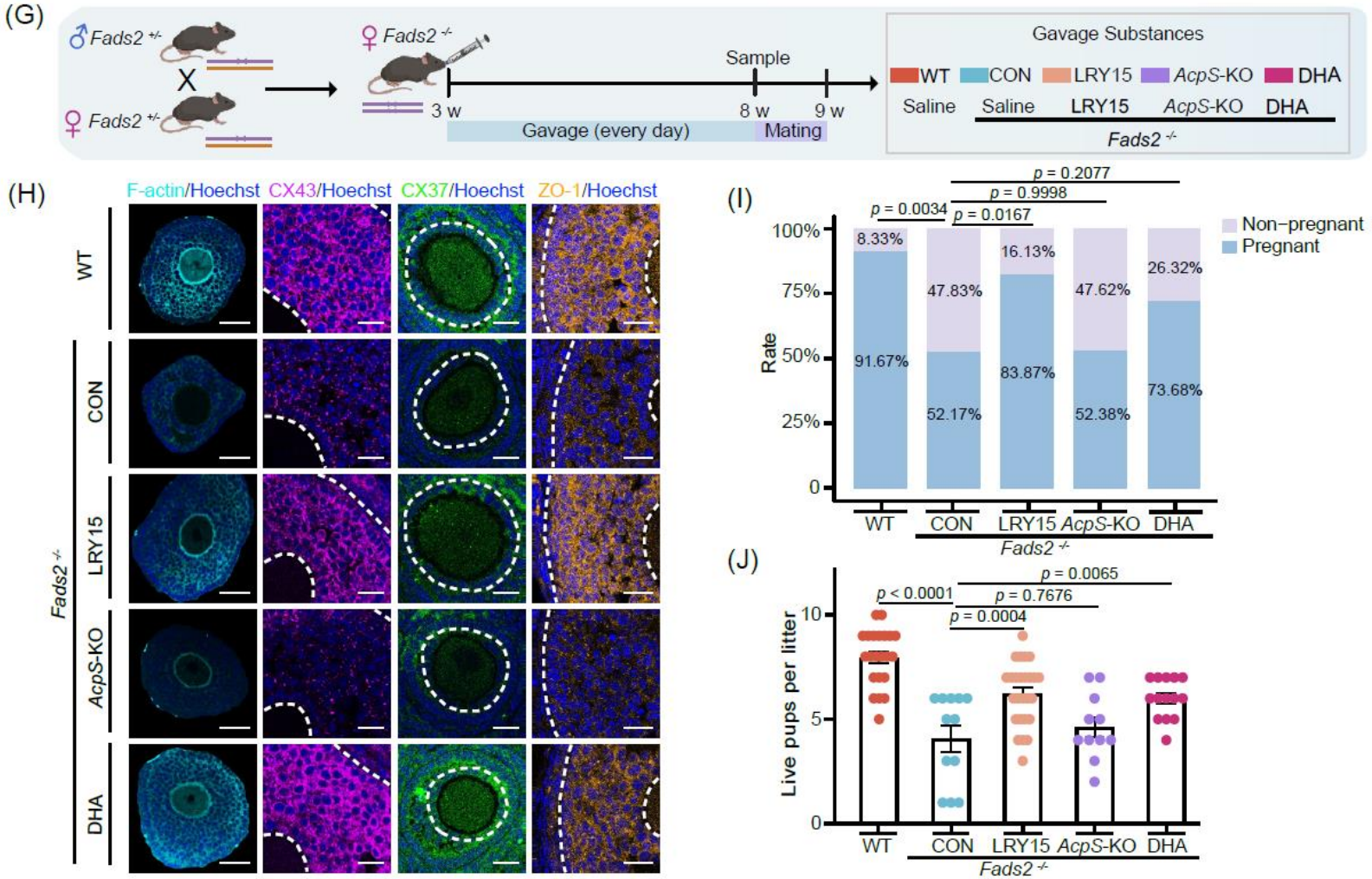


Figure 2 LRY15 recovers ovarian cell-cell junctions via PUFA pathways to enhance ovarian function and female fertility.

(G) Schematic showing the strategy of obtainment of *Fads2* knockout mice (*Fads2*$^{-/-}$), and the treatment schedule for LRY15, *AcpS*-KO, and DHA. (H) Representative images of immunofluorescence staining for F-actin, CX43, CX37, and ZO-1 in ovarian sections. (I) The pregnant rate. (J) The number of live pups per litter.

Summary

- Our study demonstrates that LRY15-derived PUFAs reconstitute disrupted ovarian cell-cell junctions, thereby restoring follicle development and function to improve female fertility.
- These findings provide insights into the gut-ovary axis and offer a promising strategy for improving ovarian function, reproductive health, and fertility.
- Importantly, administration of the probiotic LRY15 represents a cost-effective intervention that could be particularly useful in low-resource settings.

Yongsheng Hao, Yukang Li, Shen Li, Juanli Huo, Ninghang You, Lei Li, Yue Jiang, et al. 2026. *Limosilactobacillus reuteri* enhances ovarian function and female fertility. ***iMeta*** 5: e70164. https://doi.org/10.1002/imt2.70164

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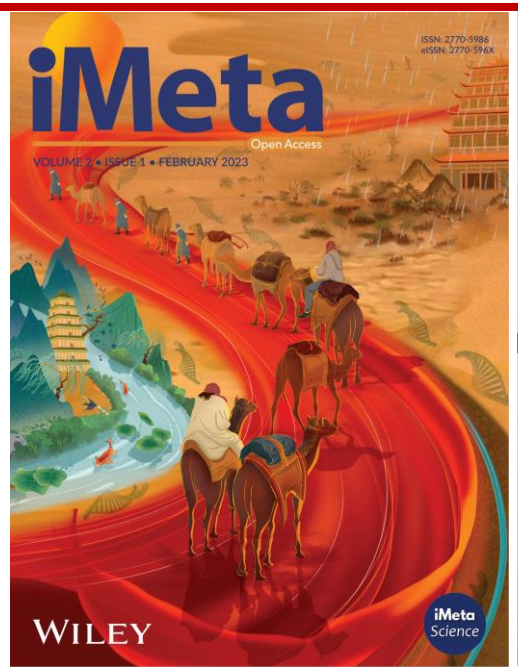

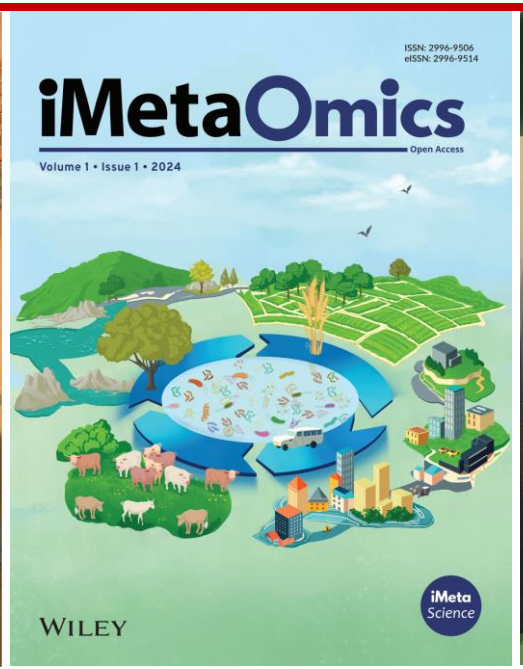

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