

## Supporting Information for

Original article

# **Gut microbiota controls the development of chronic pancreatitis: A critical role of short-chain fatty acids-producing Gram-positive bacteria**

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**Table S1**, related to **Figure 1C**: The characteristics of predominant microbial taxa of control mice, CP mice and broad-spectrum ABX-treated CP mice.

Group	Bacteria	G <sup>+</sup> or G <sup>-</sup>	SCFAs-producer
Con	<i>g__Lactobacillus</i>	G <sup>+</sup>	Yes <sup>1</sup>
	<i>f__Muribaculaceae</i>	G <sup>-</sup>	Yes <sup>2</sup>
	<i>g__Lachnospiraceae NK4A136 group</i>	G <sup>+</sup>	Yes <sup>3,4</sup>
	<i>g__Faecalibaculum</i>	G <sup>+</sup>	Yes <sup>5</sup>
	<i>g__Prevotellaceae NK3B31 group</i>	G <sup>-</sup>	Yes <sup>6</sup>
	<i>g__Alloprevotella</i>	G <sup>-</sup>	
	<i>g__Lachnospiraceae</i>	G <sup>+</sup>	Yes <sup>7</sup>
	<i>g__Ruminococcus 1</i>	G <sup>+</sup>	Yes <sup>5</sup>
	<i>g__Ruminococcaceae UCG_014</i>	G <sup>+</sup>	Yes <sup>4,8</sup>
	<i>f__Lachnospiraceae g_uncultured</i>	G <sup>+</sup>	Yes <sup>3</sup>
	<i>g__Desulfovibrio</i>	G <sup>-</sup>	Yes <sup>4</sup>
	<i>g__Eubacterium_coprostanoligenes group</i>	G <sup>+</sup>	
	<i>g__Roseburia</i>	G <sup>+</sup>	Yes <sup>5</sup>
	<i>g__Rikenellaceae RC9 gut group</i>	G <sup>-</sup>	Yes <sup>9</sup>
	<i>g__A2</i>	G <sup>+</sup>	Yes <sup>3</sup>
	<i>g__Eubacterium_xylanophilum group</i>	G <sup>+</sup>	
	<i>g__Ruminiclostridium 6</i>	G <sup>+</sup>	Yes <sup>7</sup>
	<i>g__ASF356</i>	G <sup>+</sup>	Yes <sup>10</sup>
	<i>g__Ruminococcaceae UCG_009</i>	G <sup>+</sup>	Yes <sup>4,8</sup>
	<i>g__Lachnospiraceae UCG_001</i>	G <sup>+</sup>	Yes <sup>3</sup>
	<i>g__Candidatus Saccharimonas</i>	G <sup>+</sup>	
	<i>g__Ruminococcaceae UCG_010</i>	G <sup>+</sup>	Yes <sup>4,8</sup>
	<i>g__Defluviitaleaceae UCG_011</i>	G <sup>+</sup>	
	<i>g__Acetatifactor</i>	G <sup>+</sup>	
	<i>g__Candidatus Arthromitus</i>	G <sup>+</sup>	
	<i>f__Peptococcaceae g_uncultured</i>	G <sup>+</sup>	Yes <sup>11</sup>
	<i>g__Ruminococcaceae UCG_004</i>	G <sup>+</sup>	Yes <sup>4,8</sup>
	<i>f__Desulfovibrionaceae</i>	G <sup>-</sup>	
	<i>f__Christensenellaceae</i>	G <sup>-</sup>	Yes <sup>12</sup>
	<i>g__Coriobacteriaceae UCG_002</i>	G <sup>+</sup>	Yes <sup>13</sup>
	<i>g__Family XIII UCG_001</i>	G <sup>+</sup>	
	<i>g__Tyzzerella 3</i>	G <sup>+</sup>	
<i>g__Ruminococcaceae NK4A214 group</i>	G <sup>+</sup>	Yes <sup>4,8</sup>	
CAE	<i>g__Bifidobacterium</i>	G <sup>+</sup>	Yes <sup>1</sup>
	<i>f__Clostridiales vadin BB60 group</i>		
	<i>g__Ruminiclostridium 5</i>	G <sup>+</sup>	Yes <sup>7</sup>
	<i>g__Lachnospiraceae FCS020 group</i>	G <sup>+</sup>	Yes <sup>3,4</sup>
	<i>g__Anaerotruncus</i>	G <sup>+</sup>	Yes <sup>4</sup>
ABX+CAE	<i>o__Rhodospirillales</i>	G <sup>-</sup>	Yes <sup>1</sup>
	<i>g__Bacteroides</i>	G <sup>-</sup>	Yes <sup>5</sup>
	<i>g__Escherichia_Shigella</i>	G <sup>-</sup>	
	<i>g__Erysipelatoclostridium</i>	G <sup>+</sup>	
	<i>o__Gastranaerophilales</i>	G <sup>-</sup>	
	<i>g__Clostridioides</i>	G <sup>+</sup>	Yes <sup>5</sup>
	<i>g__Enterococcus</i>	G <sup>+</sup>	Yes <sup>14</sup>
	<i>g__Proteus</i>	G <sup>-</sup>	

G<sup>+</sup>: Gram-positive bacteria; G<sup>-</sup>: Gram-negative bacteria

**Table S2**, related to **Figure S3**: The characteristics of predominant microbial taxa of CP mice and broad-spectrum ABX-treated CP mice.

Group	Bacteria	G <sup>+</sup> or G <sup>-</sup>	SCFAs-producer
CAE	<i>f__Peptococcaceae g_uncultured</i>	G <sup>+</sup>	Yes <sup>11</sup>
	<i>g__Ruminococcaceae UCG_009</i>	G <sup>+</sup>	Yes <sup>4,8</sup>
	<i>g__Anaerotruncus</i>	G <sup>+</sup>	Yes <sup>4</sup>
	<i>g__Lachnospiraceae FCS020group</i>	G <sup>+</sup>	Yes <sup>3,4</sup>
	<i>g__Defluviitaleaceae UCG_011</i>	G <sup>+</sup>	
	<i>g__Ruminococcaceae UCG_010</i>	G <sup>+</sup>	Yes <sup>4,8</sup>
	<i>g__Enterorhabdus</i>	G <sup>+</sup>	
	<i>g__ASF356</i>	G <sup>+</sup>	Yes <sup>10</sup>
	<i>g__Butyricoccus</i>	G <sup>+</sup>	Yes <sup>15</sup>
	<i>g__Lachnospiraceae UCG_001</i>	G <sup>+</sup>	Yes <sup>3</sup>
	<i>g__A2</i>	G <sup>+</sup>	Yes <sup>3</sup>
	<i>g__Eubacterium_coprostanoligenes group</i>	G <sup>+</sup>	
	<i>g__Lachnoclostridium</i>	G <sup>+</sup>	Yes <sup>7</sup>
<i>g__Ruminiclostridium 5</i>	G <sup>+</sup>	Yes <sup>7</sup>	
<i>g__Lactobacillus</i>	G <sup>+</sup>	Yes <sup>1</sup>	
ABX+CAE	<i>o__Rhodospirillales</i>	G <sup>-</sup>	Yes <sup>1</sup>
	<i>g__Bacteroides</i>	G <sup>-</sup>	Yes <sup>5</sup>
	<i>g__Erysipelatoclostridium</i>	G <sup>+</sup>	
	<i>o__Gastranaerophilales</i>	G <sup>-</sup>	
	<i>g__Parabacteroides</i>	G <sup>-</sup>	Yes <sup>16</sup>
	<i>g__Odoribacter</i>	G <sup>-</sup>	
	<i>f__Ruminococcaceae g_uncultured</i>	G <sup>+</sup>	Yes <sup>4,8</sup>
	<i>g__Lachnospiraceae UCG_006</i>	G <sup>+</sup>	Yes <sup>3</sup>
	<i>g__Clostridioides</i>	G <sup>+</sup>	Yes <sup>5</sup>
	<i>g__Ruminiclostridium 6</i>	G <sup>+</sup>	Yes <sup>7</sup>
<i>g__Enterococcus</i>	G <sup>+</sup>	Yes <sup>14</sup>	

G<sup>+</sup>: Gram-positive bacteria; G<sup>-</sup>: Gram-negative bacteria

**Table S3**, related to **Figure 1E**: The characteristics of predominant microbial taxa of healthy participants and CP patients.

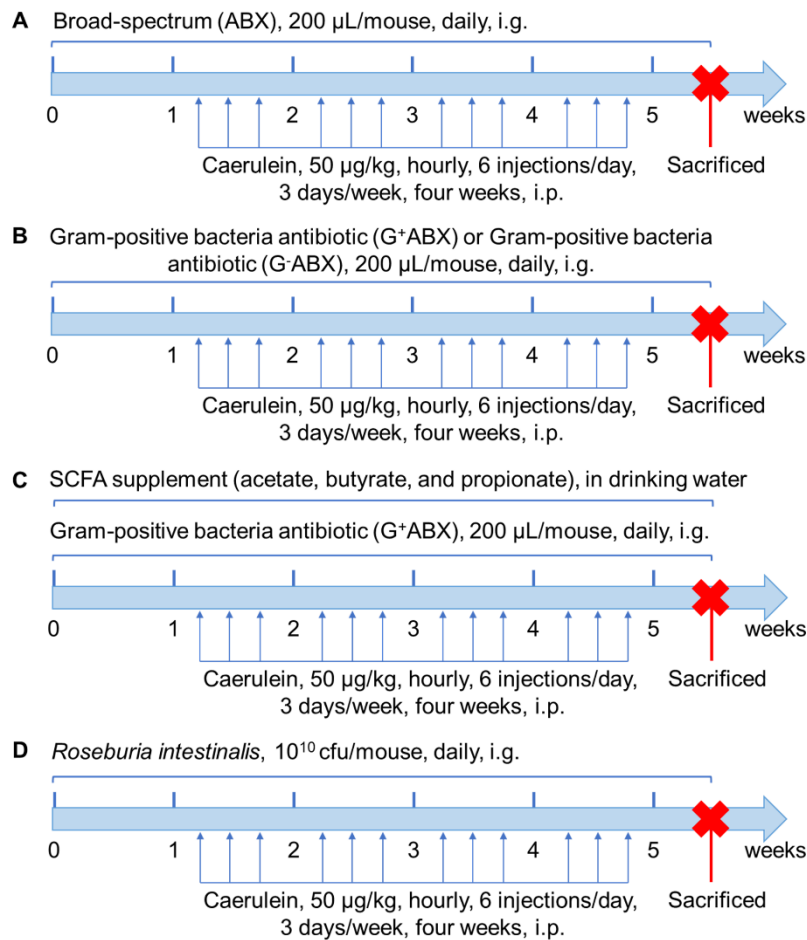
Group	Bacteria	G <sup>+</sup> or G <sup>-</sup>	SCFAs-producer
Healthy participants	<i>g__Candidatus Bacilloplasma</i>	G <sup>+</sup>	
	<i>g__Lachnospiraceae FCS020 group</i>	G <sup>+</sup>	Yes <sup>3,4</sup>
	<i>f__Streptomycetaceae</i>	G <sup>+</sup>	
	<i>g__Lactococcus</i>	G <sup>+</sup>	
	<i>g__Anaerorhabdus furcosa group</i>	G <sup>-</sup>	
	<i>g__Bacillus</i>	G <sup>+</sup>	Yes <sup>17</sup>
	<i>g__Ruminiclostridium 5</i>	G <sup>+</sup>	Yes <sup>7</sup>
	<i>g__Sphingomonas</i>	G <sup>-</sup>	
	<i>g__Ruminococcus gauvreauii group</i>	G <sup>+</sup>	Yes <sup>18</sup>
	<i>g__Cupriavidus</i>	G <sup>-</sup>	
	<i>g__Acidibacter</i>	G <sup>-</sup>	
	<i>g__Lachnospiraceae NC2004 group</i>	G <sup>+</sup>	Yes <sup>18</sup>
	<i>g__Romboutsia</i>	G <sup>+</sup>	
	<i>g__Weissella</i>	G <sup>+</sup>	
	<i>g__Barnesiella</i>	G <sup>-</sup>	Yes <sup>19</sup>
	<i>g__Dorea</i>	G <sup>+</sup>	Yes <sup>20</sup>
	<i>f__Brucellaceae</i>	G <sup>-</sup>	
	<i>g__Desulfovibrio</i>	G <sup>-</sup>	Yes <sup>4</sup>
	<i>g__Pelomonas</i>	G <sup>-</sup>	
	<i>g__Haemophilus</i>	G <sup>-</sup>	
	<i>g__Microbacterium</i>	G <sup>+</sup>	
	<i>g__Coprococcus 3</i>	G <sup>+</sup>	Yes <sup>4</sup>
	<i>f__Lachnospiraceae g_uncultured</i>	G <sup>+</sup>	Yes <sup>3</sup>
	<i>f__Peptococcaceae g_uncultured</i>	G <sup>+</sup>	Yes <sup>11</sup>
	<i>g__Erysipelotrichaceae UCG 003</i>	G <sup>+</sup>	Yes <sup>21</sup>
	<i>g__Subdoligranulum</i>	G <sup>+</sup>	Yes <sup>22</sup>
	<i>g__Prevotella 9</i>	G <sup>-</sup>	Yes <sup>23</sup>
	<i>g__Faecalibacterium</i>	G <sup>+</sup>	Yes <sup>24</sup>
CP patients	<i>g__Escherichia_Shigella</i>	G <sup>-</sup>	
	<i>g__Parabacteroides</i>	G <sup>-</sup>	Yes <sup>16</sup>
	<i>g__Eubacterium_hallii_group</i>	G <sup>+</sup>	Yes <sup>24</sup>
	<i>g__Sutterella</i>	G <sup>-</sup>	
	<i>o__Selenomonadales</i>	G <sup>-</sup>	
	<i>g__Lachnospiraceae ND3007 group</i>	G <sup>+</sup>	Yes <sup>18</sup>

G<sup>+</sup>: Gram-positive bacteria; G<sup>-</sup>: Gram-negative bacteria

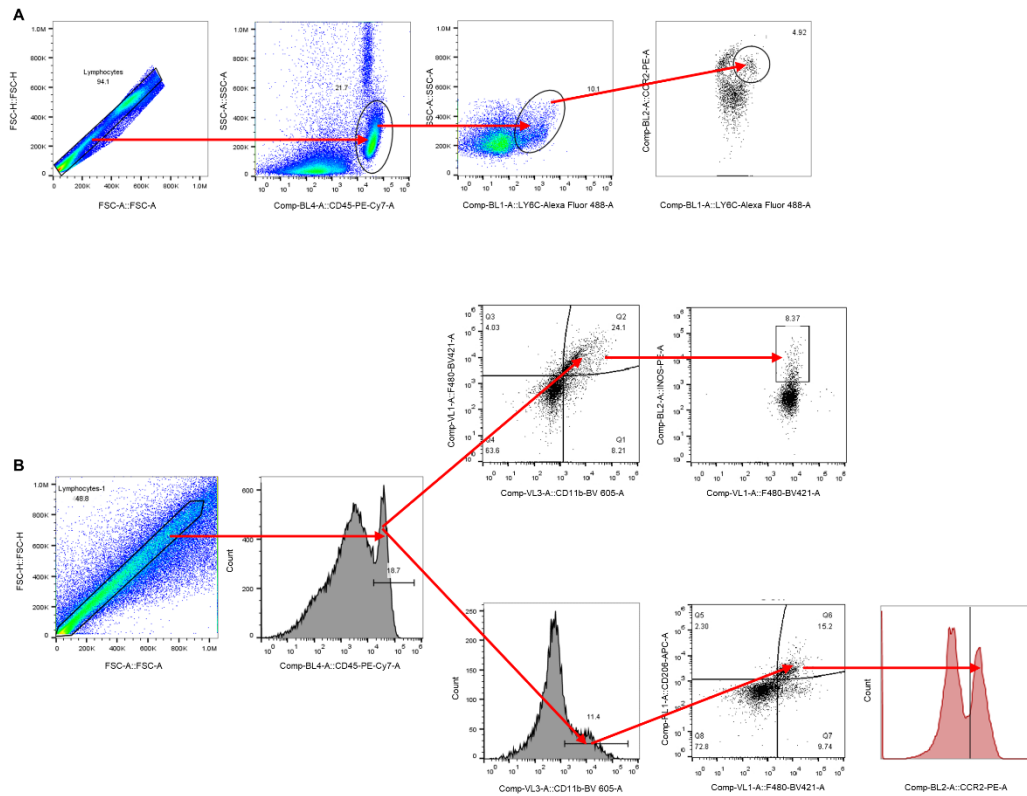
**Table S4**, related to **Figure S4**: The characteristics of predominant microbial taxa of control mice, CP mice, G<sup>+</sup>ABX-treated CP mice and G<sup>-</sup> ABX-treated CP mice.

Group	Bacteria	G <sup>+</sup> or G <sup>-</sup>	SCFAs-producer
Con	f__Muribaculaceae	G <sup>-</sup>	Yes <sup>2</sup>
	g__Lactobacillus	G <sup>+</sup>	Yes <sup>1</sup>
	g__Faecalibaculum	G <sup>+</sup>	Yes <sup>5</sup>
	g__Prevotellaceae NK3B31 group	G <sup>-</sup>	Yes <sup>6</sup>
	g__Alloprevotella	G <sup>-</sup>	
	g__Ruminococcus 1	G <sup>+</sup>	Yes <sup>5</sup>
	g__Desulfovibrio	G <sup>-</sup>	Yes <sup>4</sup>
	g__Rikenellaceae RC9 gut group	G <sup>-</sup>	Yes <sup>9</sup>
	g__ASF356	G <sup>+</sup>	Yes <sup>10</sup>
	g__Candidatus Saccharimonas	G <sup>+</sup>	
	g__Ruminococcaceae UCG_009	G <sup>+</sup>	Yes <sup>4,8</sup>
	g__Enterorhabdus	G <sup>+</sup>	
	g__Candidatus Arthromitus	G <sup>+</sup>	
	g__Negativebacilli	G <sup>-</sup>	
	g__Tyzzerella 3	G <sup>+</sup>	
	f__Desulfovibrionaceae	G <sup>-</sup>	
g__Family XIII UCG_001	G <sup>+</sup>		
CAE	g__Bifidobacterium	G <sup>+</sup>	Yes <sup>1</sup>
	g__Escherichia_Shigella	G <sup>-</sup>	
	g__Prevotellaceae UCG_001	G <sup>-</sup>	Yes <sup>25</sup>
	g__Odoribacter	G <sup>-</sup>	
	o__Rhodospirillales	G <sup>-</sup>	Yes <sup>1</sup>
	o__Gastranaerophilales	G <sup>-</sup>	
	g__Clostridiumsensustricto 1	G <sup>+</sup>	
	f__Christensenellaceae	G <sup>-</sup>	Yes <sup>12</sup>
	g__Defluviitaleaceae UCG_011	G <sup>+</sup>	
	g__Alistipes	G <sup>-</sup>	Yes <sup>26</sup>
G <sup>-</sup> ABX+CAE	g__Lachnospiraceae NK4A136 group	G <sup>+</sup>	Yes <sup>3,4</sup>
	f__Clostridialesvadin BB60 group		
	g__Parabacteroides	G <sup>-</sup>	Yes <sup>16</sup>
	g__Ruminiclostridium 6	G <sup>+</sup>	Yes <sup>7</sup>
	g__Erysipelatoclostridium	G <sup>+</sup>	
	g__Angelakisella	G <sup>-</sup>	
	g__Coprococcus 3	G <sup>+</sup>	Yes <sup>4</sup>
g__Coriobacteriaceae UCG_002	G <sup>+</sup>	Yes <sup>13</sup>	

G<sup>+</sup>: Gram-positive bacteria; G<sup>-</sup>: Gram-negative bacteria

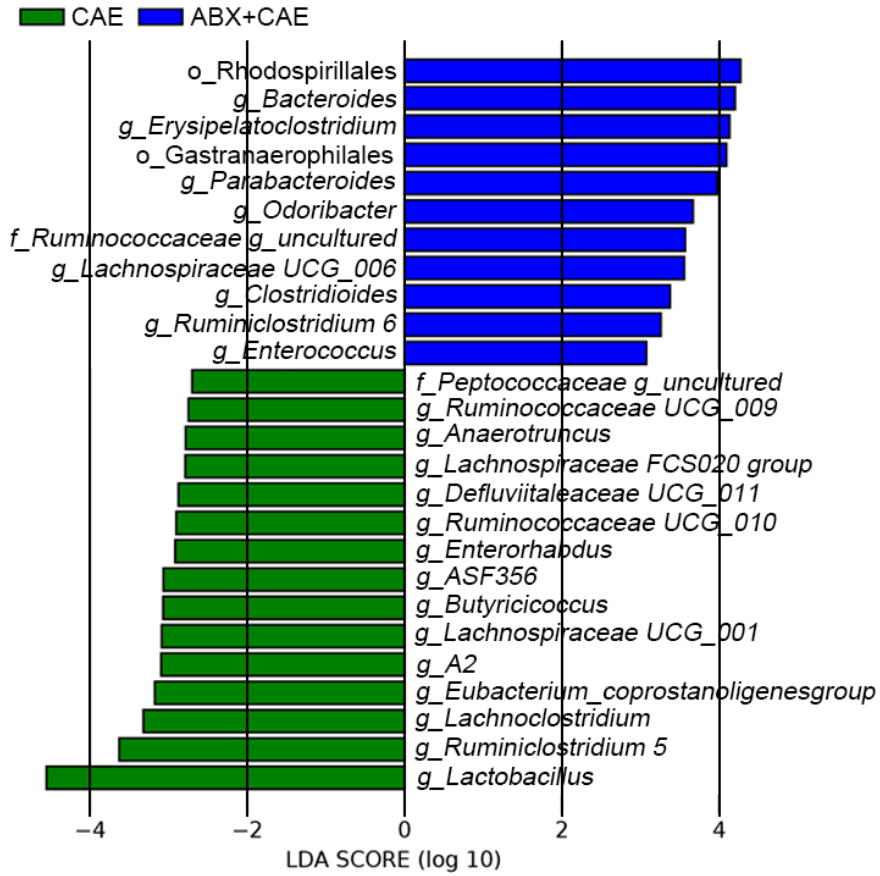


**Figure S1**, related to **Methods**: Schematic diagram showing the experimental design and timeline of CP mice with different treatments. (A) Animal protocol for chronic pancreatitis mice treated with broad spectrum antibiotic. (B) Animal protocol for chronic pancreatitis mice treated with Gram-positive bacteria antibiotic or Gram-negative bacteria probiotic. (C) Animal protocol for chronic pancreatitis mice treated with Gram-positive bacteria antibiotic and SCFA supplement. (D) Animal protocol for chronic pancreatitis mice treated with *Roseburia intestinalis*.

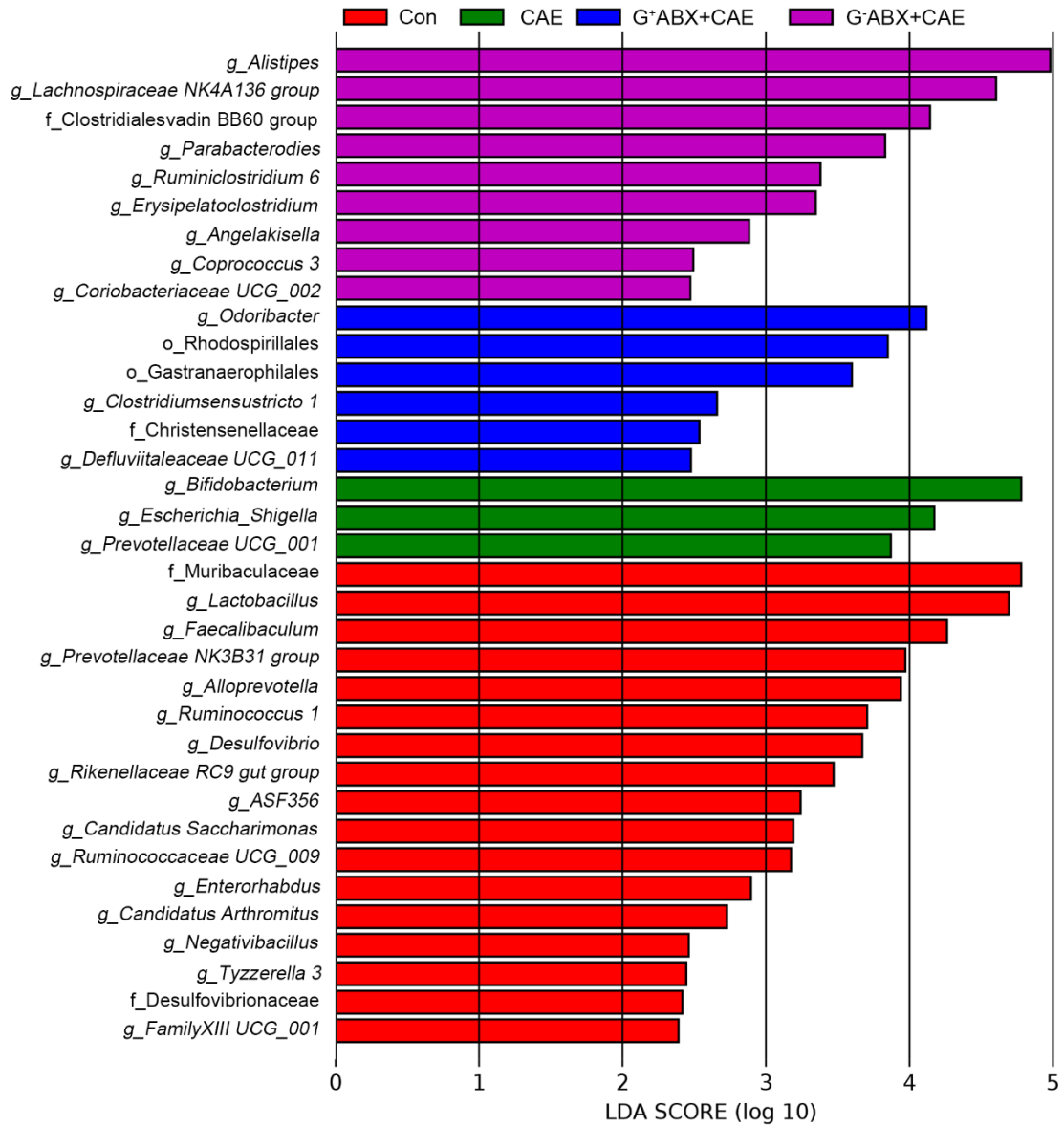


**Figure S2**, related to **Methods**: Gating strategies for flow cytometry. (A) Gating strategy for CCR2<sup>+</sup> monocytes (CD45<sup>+</sup>CD11b<sup>+</sup>Ly6C<sup>hi</sup>CCR2<sup>+</sup>). (B) Gating strategy for M1 macrophages (CD45<sup>+</sup>CD11b<sup>+</sup>F4/80<sup>+</sup>iNOS<sup>+</sup>), M2 macrophages (CD45<sup>+</sup>CD11b<sup>+</sup>F4/80<sup>+</sup>CD206<sup>+</sup>) and CCR2<sup>+</sup> M2 macrophages (CD45<sup>+</sup>CD11b<sup>+</sup>F4/80<sup>+</sup>CD206<sup>+</sup>CCR2<sup>+</sup>).

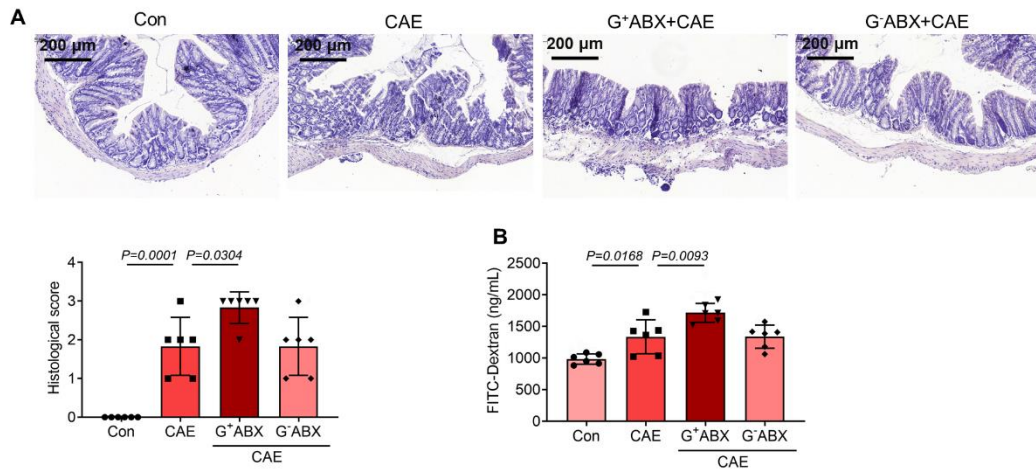




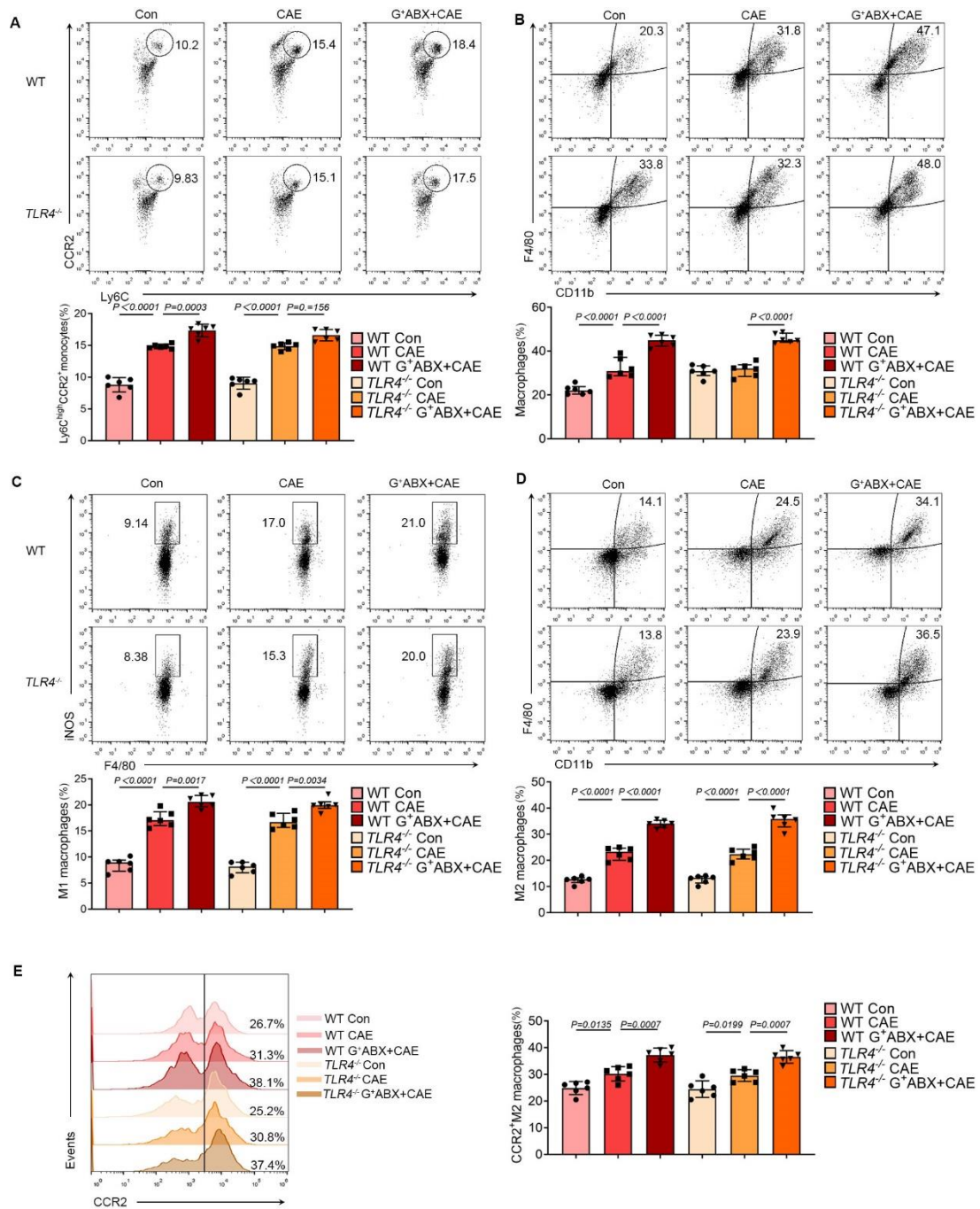
**Figure S3**, related to **Figure 1**. The LEfSe analyses of microbiome composition distribution of CP mice and broad-spectrum ABX-treated CP mice (CAE,  $n = 10$ ; ABX+CAE,  $n = 10$ ).



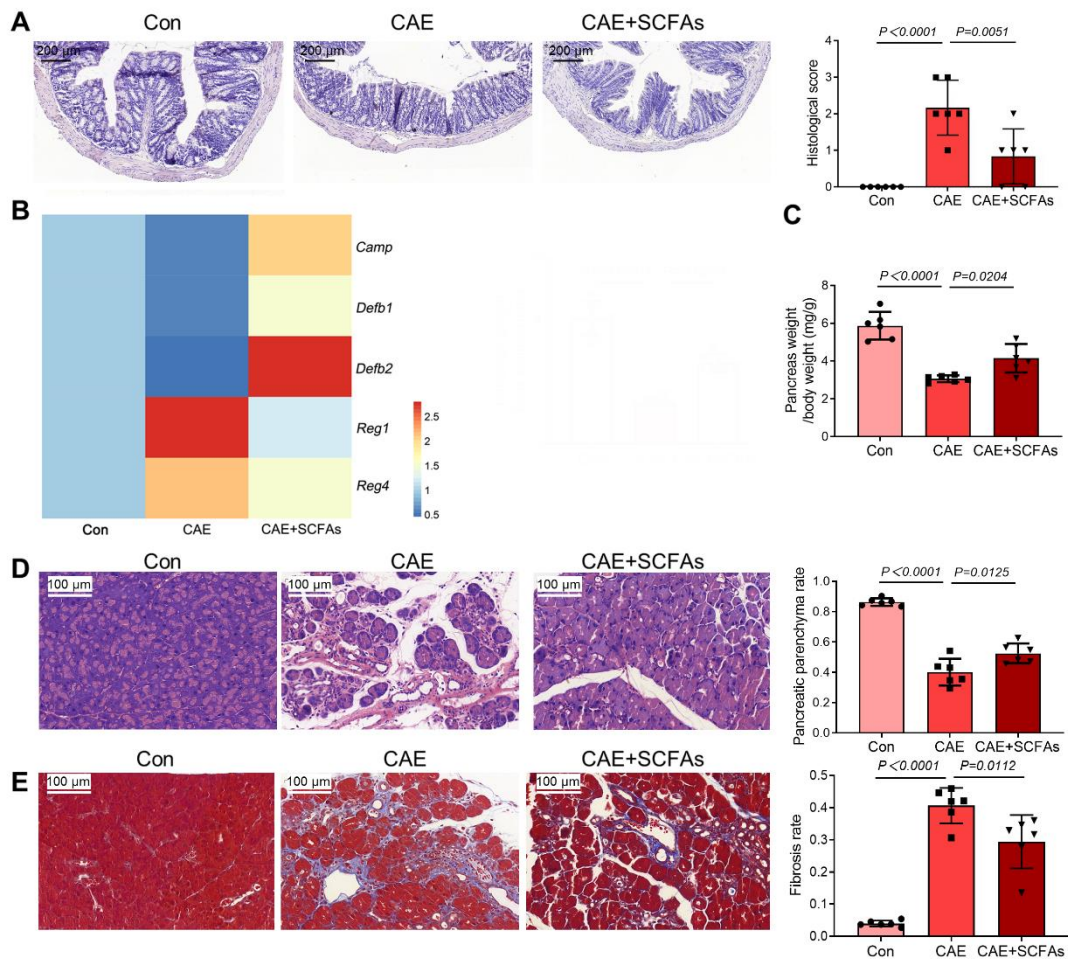
**Figure S4**, related to **Figure 3**. The LEfSe analyses of microbiome composition of control mice, CP mice, G<sup>+</sup>ABX-treated CP mice and G<sup>-</sup> ABX-treated CP mice (Con,  $n = 8$ ; CAE,  $n = 10$ ; G<sup>+</sup> ABX+CAE,  $n = 10$ ; G<sup>-</sup> ABX+CAE,  $n = 10$ ).



**Figure S5**, related to **Figure 3**. Depletion of G<sup>+</sup> bacteria but not G<sup>-</sup> bacteria compromises gut barrier function in mice with CP. (A) The representative images and histological scores of the colon by H&E staining ( $n = 6$ ). Scale bar: 200  $\mu$ m. (B) Intestinal permeability assessment by measuring FITC-dextran ( $n = 6$ ). Data are representative and were the mean  $\pm$  SD from three independent experiments.  $P$  values were calculated by one-way ANOVA followed by Tukey's *post hoc* test for multiple comparisons.



**Figure S6**, related to **Figure 4**. TLR4 deficiency does not affect the frequency of monocytes and macrophages. (A) The frequency of Ly6C<sup>hi</sup>CCR2<sup>+</sup> monocytes among CD45<sup>+</sup>CD11b<sup>+</sup> population. (B) The frequency of CD11b<sup>+</sup>F4/80<sup>+</sup> macrophages among CD45<sup>+</sup> population. (C) The frequency of iNOS<sup>+</sup> M1 macrophages among CD45<sup>+</sup>CD11b<sup>+</sup>F4/80<sup>+</sup> population. (D) The frequency of F4/80<sup>+</sup>CD206<sup>+</sup> M2 macrophages among CD45<sup>+</sup>CD11b<sup>+</sup> population. (E) The frequency of CCR2<sup>+</sup> M2 macrophages among CD45<sup>+</sup>CD11b<sup>+</sup> F4/80<sup>+</sup>CD206<sup>+</sup> population ( $n = 6$ ). Data are representative and were the median  $\pm$  interquartile range from three independent experiments.  $P$  values were calculated by one-way ANOVA followed by Tukey's *post hoc* test for multiple comparisons.



**Figure S7**, related to **Figure 5**. SCFAs improve gut barrier dysfunction and alleviates the severity of CP. (A) The representative images and histological scores of the colon by H&E staining ( $n = 6$ ). Scale bar: 200  $\mu\text{m}$ . (B) The mRNA expression of antimicrobial peptides (*Camp*, *Defb1*, *Defb2*, *Reg1* and *Reg4*,  $n = 6$ ). (C) The ratio of pancreatic weight and body weight ( $n = 6$ ). (D) The representative images and parenchyma rates of the pancreas by H&E staining ( $n = 6$ ). Scale bar: 100  $\mu\text{m}$ . (E) The representative images and fibrosis rates of the pancreas by Masson's Trichrome staining ( $n = 6$ ). Scale bar: 100  $\mu\text{m}$ . Data are representative and were the mean  $\pm$  SD from three independent experiments.  $P$  values were calculated by one-way ANOVA followed by Tukey's *post hoc* test for multiple comparisons.

## References

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