

Supplementary Table S1. Mouse key intestinal epithelial, tight junction protein and inflammatory markers primer sequence

| Sl. No. | Gene          | Gene sequence (5'-3')      | GenBank Accession number/Ref |
|---------|---------------|----------------------------|------------------------------|
| 1       | <i>Notch1</i> | F: GATGGCCTCAATGGGTACAAG   | NM_008714                    |
|         |               | R: TCGTTGTTGTTGATGTCACAGT  |                              |
| 2       | <i>Wnt3</i>   | F: CTCGCTGGCTACCCAATTTG    | NM_009521                    |
|         |               | R: CTTACACCTTCTGCTACGCT    |                              |
| 3       | <i>Ocln</i>   | F: TTGAAAGTCCACCTCCTTACAGA | NM_008756                    |
|         |               | R: CCGGATAAAAAGAGTACGCTGG  |                              |
| 4       | <i>Tjp1</i>   | F: GCCGCTAAGAGCACAGCAA     | M_00116357                   |
|         |               | R: GCCCTCCTTTAACACATCAGA   |                              |
| 5       | <i>Pcna</i>   | F: TTTGAGGCACGCCTGATCC     | NM_011045                    |
|         |               | R: GGAGACGTGAGACGAGTCCAT   |                              |
| 6       | <i>Ccnd1</i>  | F: GCGTACCCTGACACCAATCTC   | NM_007631                    |
|         |               | R: CTCCTCTTCGACTTCTGCTC    |                              |
| 7       | <i>Kir67</i>  | F: ATCATTGACCGCTCCTTTAGGT  | M_00108111                   |
|         |               | R: GCTCGCCTTGATGGTTCCT     |                              |
| 8       | <i>Lyz1</i>   | F: GAGACCGAAGCACCGACTATG   | MID: 2615969                 |
|         |               | R: CGGTTTTGACATTGTGTTTCGC  |                              |
| 9       | <i>Gp2</i>    | F: ACAGTGTCAACCATCTTGCTC   | NM_025989                    |
|         |               | R: CCCGATTATAGTCAATGGCTGG  |                              |
| 10      | <i>Tff3</i>   | F: TTGCTGGGTCCTCTGGGATAG   | MID: 1918584                 |
|         |               | R: TACACTGCTCCGATGTGACAG   |                              |
| 11      | <i>Elf3</i>   | F: GCTGCCACCTGTGAGATCAG    | M_00116313                   |
|         |               | R: GTGCCAAAGGTAGTCGGAGG    |                              |
| 12      | <i>Spdef</i>  | F: AAGGCAGCATCAGGAGCAATG   | NM_013891                    |
|         |               | R: CTGTCAATGACGGGACACTG    |                              |
| 13      | <i>Gfi1</i>   | F: AGAAGGCGCACAGCTATCAC    | NM_010278                    |
|         |               | R: GGCTCCATTTTCGACTCGC     |                              |
| 14      | <i>Math1</i>  | F: GAGTGGGCTGAGGTAAAAGAGT  | NM_007500                    |
|         |               | R: GGTCGGTGCTATCCAGGAG     |                              |
| 15      | <i>Muc2</i>   | F: TTCGGCACGAGCAACTTTG     | MID: 3291612                 |
|         |               | R: GGCAGGACACCTTGTCAATTG   |                              |
| 16      | <i>Muc6</i>   | F: CGGCTGCGTCTGTCCTAAG     | NM_181729                    |
|         |               | R: GCATAGTCACATGGGCATTCT   |                              |
| 17      | <i>Muc13</i>  | F: GATCTCTGCAACCCTAACCCC   | NM_010739                    |
|         |               | R: TCCTTTCACACATGACGACAG   |                              |
| 18      | <i>Il10</i>   | F: GCTCTTACTGACTGGCATGAG   | MID: 3230229                 |
|         |               | R: CGCAGCTCTAGGAGCATGTG    |                              |
| 19      | <i>Tgfβ1</i>  | F: CTCCCGTGGCTTCTAGTGC     | NM_011577                    |
|         |               | R: GCCTTAGTTTGGACAGGATCTG  |                              |
| 20      | <i>Il1R</i>   | F: GCAACTGTTCTGAACTCAACT   | NM_008261                    |

|    |                 |                            |              |
|----|-----------------|----------------------------|--------------|
| 20 |                 | R: ATCTTTTGGGGTCCGTCAACT   | NM_008304    |
| 21 | <i>Il6</i>      | F: CCAAGAGGTGAGTGCTTCCC    | MID: 3230229 |
|    |                 | R: CTGTTGTTCCAGACTCTCTCCCT |              |
| 22 | <i>Tnfa</i>     | F: CCCTCACACTCAGATCATCTTCT | NM_013693    |
|    |                 | R: GCTACGACGTGGGCTACAG     |              |
| 23 | <i>Sis</i>      | F: GCTATCGCTCTTGTTGTGGTT   | M_00108113   |
|    |                 | R: TTCCAGGACTAGGGGTTGAAG   |              |
| 24 | <i>Call</i>     | F: TCCCACCACTGGGGATACAG    | NM_009801    |
|    |                 | R: CTCTTGACGCAGCTTTATCATA  |              |
| 25 | <i>Hes1</i>     | F: CCAGCCAGTGTC AACACGA    | NM_008235    |
|    |                 | R: AATGCCGGGAGCTATCTTTCT   |              |
| 26 | <i>Casp3</i>    | F: ATGGAGAACAACAAAACCTCAGT | NM_009810    |
|    |                 | R: TTGCTCCCATGTATGGTCTTTAC |              |
| 27 | <i>Casp8</i>    | F: TGCTTGGACTACATCCCACAC   | NM_009812    |
|    |                 | R: TGCAGTCTAGGAAGTTGACCA   |              |
| 28 | <i>Bad</i>      | F: GAGGAGGAGCTTAGCCCTTT    | MID: 3229443 |
|    |                 | R: AGGAACCCTCAAACCTCATCG   |              |
| 29 | <i>Myc</i>      | F: GCTGTTTGAAGGCTGGATTTC   | MID: 3255000 |
|    |                 | R: GATGAAATAGGGCTGTACGGAG  |              |
| 30 | <i>Bax</i>      | F: TAGCAAACCTGGTGCTCAAGG   | MID: 2528875 |
|    |                 | R: TCTTGATCCAGACAAGCAG     |              |
| 31 | <i>Bcl2l2</i>   | F: GCGGAGTTCACAGCTCTATAC   | NM_007537    |
|    |                 | R: AAAAGGCCCTACAGTTACCA    |              |
| 32 | <i>Bcl2</i>     | F: GATGACTGAGTACCTGAACCG   | MID: 2583008 |
|    |                 | R: CAGAGACAGCCAGGAGAAATC   |              |
| 33 | <i>Villin1</i>  | F: TCAAAGGCTCTCTCAACATCAC  | NM_009509    |
|    |                 | R: AGCAGTCACCATCGAAGAAGC   |              |
| 34 | <i>Epcam</i>    | F: GCGGCTCAGAGAGACTGTG     | NM_008532    |
|    |                 | R: CCAAGCATTTAGACGCCAGTTT  |              |
| 35 | <i>Vimentin</i> | F: CGTCCACACGCACCTACAG     | NM_011701    |
|    |                 | R: GGGGGATGAGGAATAGAGGCT   |              |
| 36 | <i>Lgr5</i>     | F: CCTACTCGAAGACTTACCCAGT  | NM_010195    |
|    |                 | R: GCATTGGGGTGAATGATAGCA   |              |
| 37 | <i>Olfm4</i>    | F: AAACAATGTCCTTAGCATTGCGC | M_00103029   |
|    |                 | R: GCTTCCAAGGGCCAATGAAAC   |              |
| 38 | <i>Sox9</i>     | F: AGTACCCGCATCTGCACAAC    | NM_011448    |
|    |                 | R: ACGAAGGGTCTTTCTCGCT     |              |
| 39 | <i>Sox4</i>     | F: GACCTGCTCGACCTGAACC     | NM_009238    |
|    |                 | R: ACTCCAGCCAATCTCCCGA     |              |
| 40 | <i>Neurog3</i>  | F: CCAAGAGCGAGTTGGCACT     | NM_009719    |
|    |                 | R: CGGGCCATAGAAGCTGTGG     |              |
| 41 | <i>Chga</i>     | F: ATCCTCTCTATCCTGCGACAC   | NM_007693    |
|    |                 | R: GGGCTCTGGTTCTCAAACACT   |              |
| 42 | <i>Cck</i>      | F: AAGAGCGGCGTATGTCTGTG    | NM_031161    |
|    |                 | R: CATCCAGCCCATGTAGTCCC    |              |

|    |                 |                           |              |
|----|-----------------|---------------------------|--------------|
| 43 | <i>Ffar2</i>    | F: CTTGATCCTCACGGCCTACAT  | NM_146187    |
|    |                 | R: CCAGGGTCAGATTAAGCAGGAG |              |
| 44 | <i>Ffar3</i>    | F: CTAAACCTGACCATTTCCGACC | M_00103331   |
|    |                 | R: GATAGGCCACGCTCAGAAAAC  |              |
| 45 | <i>Mct2</i>     | F: GCTGGGTCGTAGTCTGTGC    | NM_011391    |
|    |                 | R: ATCCAAGCGATCTGACTGGAG  |              |
| 46 | <i>Mct1</i>     | F: TGTTAGTCGGAGCCTTCATTTT | NM_009196    |
|    |                 | R: CACTGGTCGTTGCACTGAATA  |              |
| 47 | <i>Glp1r</i>    | F: ACGGTGTCCCTCTCAGAGAC   | NM_021332    |
|    |                 | R: ATCAAAGGTCCGGTTGCAGAA  |              |
| 48 | <i>Neurogd2</i> | F: AACTCCACGTCCCCATACAG   | NM_009718    |
|    |                 | R: GAGGCGCATAACGATGCTTCT  |              |
| 49 | <i>Gcg</i>      | F: TTACTTTGTGGCTGGATTGCTT | NM_008100    |
|    |                 | R: AGTGCGGTTTGTCTTCATTCA  |              |
| 50 | <i>Pcsk1</i>    | F: AGTTGGAGGCATAAGAATGCTG | NM_013628    |
|    |                 | R: GCCTTCTGGGCTAGTCTGC    |              |
| 51 | <i>Pcsk2</i>    | F: AGAGAGACCCAGGATAAAGATG | NM_008792    |
|    |                 | R: CTTGCCAGTGTTGAACAGGT   |              |
| 52 | <i>Slc5a1</i>   | F: AATGCGGCTGACATCTCAGTC  | NM_019810    |
|    |                 | R: ACCAAGGCGTTCCATTCAAAG  |              |
| 53 | <i>Arid3a</i>   | F: GCTTGGGACATCCGTCCTC    | NM_007880    |
|    |                 | R: CAAATGCCTATCTCCCTCAGC  |              |
| 54 | <i>18s</i>      | F: GCAATTATTCCCATGAACG    | MID: 3230229 |
|    |                 | R: GGCCTCACTAAACCATCAA    |              |

**Supplementary Table S2.** RFA (Random forest analysis) of intestinal specific marker gene expression in mice intestinal organoid treated with obese FCM (Fecal conditioned media) and mice administration with obese FMT (fecal microbiome transplant)

| FCM treatment to mice organoid |                |        |           |         |                 |               |
|--------------------------------|----------------|--------|-----------|---------|-----------------|---------------|
| Sl. No.                        | Gene           | B6 FCM | db/db FCM | DIO FCM | p-Value         |               |
|                                |                |        |           |         | B6 vs db/db FCM | B6 vs DIO FCM |
| 1                              | <i>Tjp1</i>    | 1.024  | 0.042     | 0.062   | 0               | 0             |
| 2                              | <i>Tgfb1</i>   | 0.996  | 0.557     | 0.469   | 0.002           | 0             |
| 3                              | <i>Ocln</i>    | 1.002  | 0.129     | 0.082   | 0               | 0             |
| 4                              | <i>Il1β</i>    | 1.017  | 1.955     | 2.485   | 0               | 0             |
| 5                              | <i>Bax</i>     | 1.031  | 5.353     | 5.116   | 0               | 0             |
| 6                              | <i>Mct1</i>    | 1.036  | 3.062     | 5.301   | 0.047           | 0.001         |
| 7                              | <i>Ffar2</i>   | 0.996  | 0.686     | 0.794   | 0.019           | 0.029         |
| 8                              | <i>Kir67</i>   | 0.983  | 2.648     | 2.2     | 0               | 0             |
| 9                              | <i>Epcam</i>   | 1.026  | 1.693     | 1.687   | 0.029           | 0.003         |
| 10                             | <i>Casp3</i>   | 1.028  | 4.924     | 2.962   | 0.001           | 0             |
| 11                             | <i>Sox9</i>    | 0.99   | 1.903     | 1.622   | 0.003           | 0.014         |
| 12                             | <i>Sis</i>     | 1.002  | 1.053     | 2.302   | 0.058           | 0.007         |
| 13                             | <i>Cck</i>     | 0.993  | 0.95      | 0.696   | 0.273           | 0.01          |
| 14                             | <i>Casp8</i>   | 1.057  | 3.549     | 2.76    | 0               | 0             |
| 15                             | <i>Slc5a1</i>  | 1.032  | 0.669     | 0.614   | 0.019           | 0.012         |
| 16                             | <i>Pcna</i>    | 0.982  | 1.739     | 2.348   | 0.015           | 0.039         |
| 17                             | <i>Glp1r</i>   | 0.993  | 0.714     | 0.631   | 0.019           | 0.044         |
| 18                             | <i>Il10</i>    | 1.014  | 0.506     | 0.646   | 0               | 0.02          |
| 19                             | <i>Ccnd1</i>   | 1.074  | 5.432     | 3.231   | 0.018           | 0.018         |
| 20                             | <i>Pcsk1</i>   | 1.011  | 0.669     | 0.784   | 0.037           | 0.147         |
| 21                             | <i>Ffar3</i>   | 1.055  | 0.975     | 0.894   | 0.384           | 0.282         |
| 22                             | <i>Elf3</i>    | 1.004  | 0.481     | 0.452   | 0               | 0             |
| 23                             | <i>Notch1</i>  | 1.004  | 2.809     | 2.654   | 0.012           | 0.035         |
| 24                             | <i>Sox4</i>    | 1.064  | 1.609     | 1.042   | 0.014           | 0.437         |
| 25                             | <i>Wnt3</i>    | 0.989  | 4.744     | 4.529   | 0               | 0             |
| 26                             | <i>Hes1</i>    | 1.016  | 1.615     | 1.771   | 0.013           | 0.004         |
| 27                             | <i>Bad</i>     | 1.078  | 2.182     | 1.59    | 0.021           | 0.011         |
| 28                             | <i>Gp2</i>     | 1.103  | 0.862     | 1.039   | 0.19            | 0.404         |
| 29                             | <i>Villin1</i> | 1.048  | 1.855     | 2.018   | 0.004           | 0             |
| 30                             | <i>Math1</i>   | 1.03   | 0.585     | 0.469   | 0.001           | 0             |
| FMT administration to mice     |                |        |           |         |                 |               |

| Sl. No. | Gene                         | B6 FMT | db/db FMT | DIO FMT | p-Value         |               |
|---------|------------------------------|--------|-----------|---------|-----------------|---------------|
|         |                              |        |           |         | B6 vs db/db FMT | B6 vs DIO FMT |
| 1       | <i>Tjp1</i>                  | 0.993  | 0.29      | 0.352   | 0               | 0.001         |
| 2       | <i>Tgfb1</i>                 | 0.989  | 0.484     | 0.374   | 0.046           | 0.031         |
| 3       | <i>Ocln</i>                  | 1.014  | 0.253     | 0.336   | 0.002           | 0             |
| 4       | <i>Il1<math>\beta</math></i> | 0.998  | 1.533     | 1.752   | 0               | 0             |
| 5       | <i>Bax</i>                   | 1.007  | 1.905     | 2.863   | 0.032           | 0.004         |
| 6       | <i>Mct1</i>                  | 0.988  | 1.755     | 1.995   | 0.018           | 0.006         |
| 7       | <i>Ffar2</i>                 | 0.989  | 0.623     | 0.52    | 0.034           | 0.014         |
| 8       | <i>Kir67</i>                 | 0.994  | 2.858     | 4.474   | 0.031           | 0.001         |
| 9       | <i>Epcam</i>                 | 1.029  | 3.243     | 7.717   | 0.031           | 0             |
| 10      | <i>Casp3</i>                 | 1.018  | 3.973     | 5.12    | 0.004           | 0.001         |
| 11      | <i>Sox9</i>                  | 1.005  | 1.892     | 2.583   | 0.048           | 0             |
| 12      | <i>Sis</i>                   | 1.024  | 1.754     | 2.775   | 0.045           | 0.006         |
| 13      | <i>Cck</i>                   | 0.982  | 0.57      | 0.438   | 0.043           | 0.014         |
| 14      | <i>Casp8</i>                 | 0.981  | 1.398     | 1.796   | 0.05            | 0.007         |
| 15      | <i>Slc5a1</i>                | 0.983  | 0.486     | 0.592   | 0.029           | 0.03          |
| 16      | <i>Pcna</i>                  | 1.026  | 1.927     | 2.046   | 0.041           | 0.028         |
| 17      | <i>Glp1r</i>                 | 1.054  | 0.688     | 0.826   | 0.042           | 0.109         |
| 18      | <i>Il10</i>                  | 1.012  | 0.625     | 0.19    | 0.045           | 0.032         |
| 19      | <i>Ccnd1</i>                 | 0.984  | 1.866     | 2.251   | 0.032           | 0.021         |
| 20      | <i>Pcsk1</i>                 | 0.99   | 0.684     | 0.264   | 0.014           | 0.002         |
| 21      | <i>Ffar3</i>                 | 0.984  | 0.525     | 0.564   | 0.036           | 0.02          |
| 22      | <i>Elf3</i>                  | 1.015  | 0.709     | 0.348   | 0.003           | 0             |
| 23      | <i>Notch1</i>                | 1.014  | 2.282     | 5.186   | 0.002           | 0.001         |
| 24      | <i>Sox4</i>                  | 0.986  | 1.705     | 2.236   | 0.017           | 0             |
| 25      | <i>Wnt3</i>                  | 0.995  | 2.747     | 3.645   | 0               | 0.001         |
| 26      | <i>Hes1</i>                  | 1.006  | 2.386     | 4.405   | 0.151           | 0.001         |
| 27      | <i>Bad</i>                   | 1.008  | 1.796     | 2.86    | 0.029           | 0.006         |
| 28      | <i>Gp2</i>                   | 0.985  | 1.401     | 1.344   | 0.046           | 0.214         |
| 29      | <i>Villin1</i>               | 1.001  | 3.543     | 5.673   | 0.004           | 0             |
| 30      | <i>Math1</i>                 | 0.987  | 0.544     | 0.615   | 0.004           | 0.002         |

Supplementary table S3. Correlation of ethanolamine utilizing operon gene with ethanolamine metabolite, Tjp1 and leaky gut and inflammatory markers in obese mice

Correlations

|             | <i>ine</i>          | <i>Tjp1</i>        | <i>FITC</i>         | <i>Il1b</i>         | <i>Il6</i>          | <i>Trfa</i>         | <i>LBP</i>          | <i>CD14</i>         |
|-------------|---------------------|--------------------|---------------------|---------------------|---------------------|---------------------|---------------------|---------------------|
| <i>eutA</i> | -.514               | .413               | -.430               | -.577 <sup>*</sup>  | -.589 <sup>*</sup>  | -.572               | -.556               | -.647 <sup>*</sup>  |
| <i>eutB</i> | -.851 <sup>**</sup> | .899 <sup>**</sup> | -.900 <sup>**</sup> | -.871 <sup>**</sup> | -.766 <sup>**</sup> | -.899 <sup>**</sup> | -.966 <sup>**</sup> | -.980 <sup>**</sup> |
| <i>eutC</i> | -.854 <sup>**</sup> | .952 <sup>**</sup> | -.923 <sup>**</sup> | -.868 <sup>**</sup> | -.779 <sup>**</sup> | -.910 <sup>**</sup> | -.986 <sup>**</sup> | -.981 <sup>**</sup> |
| <i>eutD</i> | -.559               | .521               | -.619 <sup>*</sup>  | -.904 <sup>**</sup> | -.651 <sup>*</sup>  | -.807 <sup>**</sup> | -.701 <sup>*</sup>  | -.722 <sup>**</sup> |
| <i>eutP</i> | -.295               | .352               | -.366               | -.005               | .123                | -.068               | -.230               | -.201               |
| <i>eutQ</i> | -.854 <sup>**</sup> | .815 <sup>**</sup> | -.858 <sup>**</sup> | -.895 <sup>**</sup> | -.702 <sup>*</sup>  | -.879 <sup>**</sup> | -.922 <sup>**</sup> | -.933 <sup>**</sup> |
| <i>eutS</i> | -.616 <sup>*</sup>  | .581 <sup>*</sup>  | -.696 <sup>*</sup>  | -.923 <sup>**</sup> | -.610 <sup>*</sup>  | -.805 <sup>**</sup> | -.734 <sup>**</sup> | -.731 <sup>**</sup> |
| <i>eutT</i> | -.832 <sup>**</sup> | .932 <sup>**</sup> | -.895 <sup>**</sup> | -.742 <sup>**</sup> | -.707 <sup>*</sup>  | -.814 <sup>**</sup> | -.935 <sup>**</sup> | -.937 <sup>**</sup> |



Supplementary table S4. Non-targeted metabolomic analysis of obese human subject verses lean human

| Participant ID         | hCnt_1_3_1 | hCnt_1_0_3_1 | hCnt_1_1_3_1 | hCnt_2_3_1 | hCnt_3_3_1 | hCnt_4_3_1 | hCnt_5_3_1 | hCnt_7_3_1 | hCnt_8_3_1 | hCnt_9_3_1 | hOb_10_3_1 | hOb_2_3_1 | hOb_4_3_1 |
|------------------------|------------|--------------|--------------|------------|------------|------------|------------|------------|------------|------------|------------|-----------|-----------|
| Normal weight (1),     | 1          | 1            | 1            | 1          | 1          | 1          | 1          | 1          | 1          | 1          | 2          | 2         | 2         |
| Obese (2)              |            |              |              |            |            |            |            |            |            |            |            |           |           |
| Metabolites            |            |              |              |            |            |            |            |            |            |            |            |           |           |
| 1,3-Dihydroxyacetone   | 0.0007     | 0.0005       | 0.0006       | 0.0006     | 0.0006     | 0.0007     | 0.0005     | 0.0007     | 0.0007     | 0.0007     | 0.0004     | 0.0007    | 0.0006    |
| 3-Methyl-2-oxovalerate | 0.0006     | 0.0005       | 0.0008       | 0.0004     | 0.0006     | 0.0007     | 0.0006     | 0.0006     | 0.0005     | 0.0006     | 0.0006     | 0.0004    | 0.0009    |
| 4-Hydroxyphenylacetate | 0.0003     | 0.0004       | 0.0002       | 0.0003     | 0.0004     | 0.0004     | 0.0002     | 0.0005     | 0.0003     | 0.0004     | 0.0002     | 0.0005    | 0.0004    |
| Acetate                | 0.0809     | 0.1235       | 0.1193       | 0.1481     | 0.0729     | 0.0717     | 0.0860     | 0.0850     | 0.0697     | 0.0905     | 0.1049     | 0.0823    | 0.0658    |
| Alanine                | 0.0051     | 0.0074       | 0.0084       | 0.0054     | 0.0077     | 0.0065     | 0.0114     | 0.0056     | 0.0080     | 0.0073     | 0.0095     | 0.0054    | 0.0076    |
| Allantoin              | 0.0001     | 0.0000       | 0.0001       | 0.0000     | 0.0000     | 0.0000     | 0.0000     | 0.0000     | 0.0001     | 0.0001     | 0.0001     | 0.0001    | 0.0001    |
| Arabinose              | 0.0006     | 0.0005       | 0.0007       | 0.0006     | 0.0005     | 0.0008     | 0.0005     | 0.0007     | 0.0006     | 0.0006     | 0.0004     | 0.0008    | 0.0006    |
| Aspartate              | 0.0018     | 0.0017       | 0.0013       | 0.0014     | 0.0018     | 0.0019     | 0.0017     | 0.0021     | 0.0020     | 0.0021     | 0.0013     | 0.0016    | 0.0021    |
| Butyrate               | 0.0111     | 0.0119       | 0.0105       | 0.0169     | 0.0095     | 0.0185     | 0.0121     | 0.0010     | 0.0976     | 0.0119     | 0.0103     | 0.0067    | 0.0099    |
| Choline                | 0.0014     | 0.0013       | 0.0041       | 0.0013     | 0.0015     | 0.0029     | 0.0016     | 0.0017     | 0.0016     | 0.0025     | 0.0014     | 0.0019    | 0.0018    |
| Citrulline             | 0.0008     | 0.0012       | 0.0011       | 0.0009     | 0.0010     | 0.0010     | 0.0012     | 0.0011     | 0.0099     | 0.0011     | 0.0024     | 0.0021    | 0.0012    |
| Ethanol                | 0.0055     | 0.0035       | 0.0021       | 0.0002     | 0.0033     | 0.0038     | 0.0037     | 0.0048     | 0.0032     | 0.0061     | 0.0059     | 0.0085    | 0.0039    |
| Ethanolamine           | 0.0013     | 0.0019       | 0.0013       | 0.0017     | 0.0019     | 0.0017     | 0.0019     | 0.0016     | 0.0019     | 0.0020     | 0.0019     | 0.0194    | 0.0018    |
| Formate                | 0.0000     | 0.0000       | 0.0000       | 0.0000     | 0.0000     | 0.0000     | 0.0000     | 0.0000     | 0.0000     | 0.0000     | 0.0000     | 0.0000    | 0.0001    |
| Fumarate               | 0.0002     | 0.0005       | 0.0008       | 0.0005     | 0.0003     | 0.0007     | 0.0004     | 0.0005     | 0.0003     | 0.0003     | 0.0002     | 0.0001    | 0.0003    |
| Galactose              | 0.0001     | 0.0000       | 0.0001       | 0.0000     | 0.0001     | 0.0001     | 0.0000     | 0.0001     | 0.0001     | 0.0000     | 0.0000     | 0.0001    | 0.0001    |
| Glucose                | 0.0014     | 0.0018       | 0.0021       | 0.0013     | 0.0013     | 0.0024     | 0.0011     | 0.0015     | 0.0014     | 0.0019     | 0.0023     | 0.0060    | 0.0012    |
| Glutamate              | 0.0050     | 0.0062       | 0.0058       | 0.0055     | 0.0051     | 0.0072     | 0.0055     | 0.0060     | 0.0062     | 0.0053     | 0.0035     | 0.0043    | 0.0057    |
| Glutamine              | 0.0010     | 0.0010       | 0.0009       | 0.0007     | 0.0011     | 0.0012     | 0.0014     | 0.0012     | 0.0012     | 0.0011     | 0.0007     | 0.0009    | 0.0011    |
| Glycerol               | 0.0076     | 0.0071       | 0.0036       | 0.0040     | 0.0044     | 0.0063     | 0.0024     | 0.0051     | 0.0048     | 0.0038     | 0.0047     | 0.0078    | 0.0050    |
| Glycine                | 0.0018     | 0.0036       | 0.0022       | 0.0016     | 0.0019     | 0.0027     | 0.0021     | 0.0019     | 0.0026     | 0.0022     | 0.0021     | 0.0037    | 0.0022    |



|                                    |        |        |        |        |        |        |        |        |        |        |        |        |        |
|------------------------------------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|--------|
| Isoleucine                         | 0.0034 | 0.0057 | 0.0041 | 0.0033 | 0.0051 | 0.0050 | 0.0061 | 0.0035 | 0.0058 | 0.0047 | 0.0082 | 0.0041 | 0.0055 |
| Lactate                            | 0.0097 | 0.0056 | 0.0051 | 0.0044 | 0.0080 | 0.0066 | 0.0054 | 0.0068 | 0.0059 | 0.0052 | 0.0042 | 0.0045 | 0.0124 |
| Lactulose                          | 0.0003 | 0.0002 | 0.0004 | 0.0004 | 0.0003 | 0.0004 | 0.0003 | 0.0004 | 0.0003 | 0.0004 | 0.0002 | 0.0004 | 0.0003 |
| Leucine                            | 0.0021 | 0.0034 | 0.0030 | 0.0024 | 0.0041 | 0.0031 | 0.0043 | 0.0020 | 0.0040 | 0.0033 | 0.0055 | 0.0026 | 0.0032 |
| Lysine/5-<br>Aminopentanoate       | 0.0026 | 0.0039 | 0.0084 | 0.0038 | 0.0037 | 0.0037 | 0.0092 | 0.0033 | 0.0047 | 0.0043 | 0.0061 | 0.0029 | 0.0034 |
| Malonate                           | 0.0038 | 0.0051 | 0.0053 | 0.0044 | 0.0062 | 0.0050 | 0.0049 | 0.0059 | 0.0055 | 0.0062 | 0.0041 | 0.0052 | 0.0036 |
| Methanol                           | 0.0013 | 0.0018 | 0.0018 | 0.0016 | 0.0013 | 0.0020 | 0.0009 | 0.0016 | 0.0013 | 0.0015 | 0.0015 | 0.0021 | 0.0010 |
| Methylamine                        | 0.0011 | 0.0014 | 0.0013 | 0.0012 | 0.0014 | 0.0013 | 0.0011 | 0.0015 | 0.0013 | 0.0017 | 0.0011 | 0.0009 | 0.0020 |
| N,N-<br>Dimethylformamid           | 0.0013 | 0.0014 | 0.0013 | 0.0014 | 0.0019 | 0.0014 | 0.0010 | 0.0014 | 0.0011 | 0.0014 | 0.0016 | 0.0009 | 0.0015 |
| Nicotinate                         | 0.0000 | 0.0000 | 0.0001 | 0.0001 | 0.0000 | 0.0000 | 0.0001 | 0.0001 | 0.0000 | 0.0000 | 0.0001 | 0.0000 | 0.0001 |
| Phenylalanine                      | 0.0008 | 0.0012 | 0.0008 | 0.0009 | 0.0012 | 0.0010 | 0.0014 | 0.0009 | 0.0013 | 0.0011 | 0.0016 | 0.0009 | 0.0011 |
| Propionate                         | 0.0169 | 0.0195 | 0.0196 | 0.0207 | 0.0239 | 0.0113 | 0.0237 | 0.0185 | 0.0163 | 0.0160 | 0.0246 | 0.0139 | 0.0145 |
| Pyruvate                           | 0.0017 | 0.0021 | 0.0020 | 0.0019 | 0.0018 | 0.0023 | 0.0022 | 0.0021 | 0.0021 | 0.0018 | 0.0012 | 0.0014 | 0.0019 |
| Sarcosine                          | 0.0020 | 0.0014 | 0.0018 | 0.0014 | 0.0021 | 0.0020 | 0.0014 | 0.0023 | 0.0019 | 0.0018 | 0.0012 | 0.0011 | 0.0020 |
| Succinate                          | 0.0007 | 0.0006 | 0.0006 | 0.0006 | 0.0006 | 0.0008 | 0.0006 | 0.0008 | 0.0007 | 0.0007 | 0.0004 | 0.0005 | 0.0008 |
| Taurine                            | 0.0075 | 0.0010 | 0.0012 | 0.0087 | 0.0096 | 0.0012 | 0.0010 | 0.0010 | 0.0011 | 0.0010 | 0.0010 | 0.0021 | 0.0009 |
| Threonine                          | 0.0007 | 0.0007 | 0.0006 | 0.0007 | 0.0008 | 0.0009 | 0.0007 | 0.0008 | 0.0009 | 0.0008 | 0.0006 | 0.0010 | 0.0007 |
| total bile acid and<br>cholesterol | 0.0004 | 0.0003 | 0.0002 | 0.0002 | 0.0005 | 0.0004 | 0.0003 | 0.0004 | 0.0003 | 0.0003 | 0.0003 | 0.0003 | 0.0005 |
| total bile acid and<br>cholesterol | 0.0004 | 0.0004 | 0.0004 | 0.0003 | 0.0007 | 0.0004 | 0.0004 | 0.0004 | 0.0002 | 0.0004 | 0.0004 | 0.0003 | 0.0004 |
| Tyrosine                           | 0.0008 | 0.0012 | 0.0009 | 0.0010 | 0.0012 | 0.0010 | 0.0011 | 0.0010 | 0.0015 | 0.0011 | 0.0009 | 0.0010 | 0.0011 |
| Uracil                             | 0.0001 | 0.0003 | 0.0002 | 0.0001 | 0.0000 | 0.0002 | 0.0001 | 0.0001 | 0.0002 | 0.0002 | 0.0001 | 0.0001 | 0.0002 |
| Valerate                           | 0.0112 | 0.0036 | 0.0058 | 0.0037 | 0.0078 | 0.0082 | 0.0032 | 0.0073 | 0.0063 | 0.0050 | 0.0038 | 0.0029 | 0.0143 |
| Valine                             | 0.0024 | 0.0034 | 0.0030 | 0.0022 | 0.0036 | 0.0033 | 0.0040 | 0.0024 | 0.0037 | 0.0031 | 0.0063 | 0.0025 | 0.0035 |

| Participant ID         | hOb_5_3_1 | hOb_6_3_1 | hOb_7_3_1 | hOb_8_3_1 | hOb_9_3_1 | hob_11_3_1 | hob_3_3_1 |
|------------------------|-----------|-----------|-----------|-----------|-----------|------------|-----------|
| Normal weight (1),     | 2         | 2         | 2         | 2         | 2         | 2          | 2         |
| Obese (2)              |           |           |           |           |           |            |           |
| Metabolites            |           |           |           |           |           |            |           |
| 1,3-Dihydroxyacetone   | 0.0006    | 0.0009    | 0.0006    | 0.0004    | 0.0009    | 0.0006     | 0.0008    |
| 3-Methyl-2-oxovalerate | 0.0008    | 0.0006    | 0.0010    | 0.0006    | 0.0007    | 0.0006     | 0.0005    |
| 4-Hydroxyphenylacetate | 0.0004    | 0.0003    | 0.0005    | 0.0003    | 0.0004    | 0.0002     | 0.0002    |
| Acetate                | 0.0617    | 0.0766    | 0.1503    | 0.1022    | 0.0635    | 0.0989     | 0.1448    |
| Alanine                | 0.0072    | 0.0061    | 0.0078    | 0.0077    | 0.0087    | 0.0089     | 0.0061    |
| Allantoin              | 0.0001    | 0.0002    | 0.0000    | 0.0001    | 0.0000    | 0.0001     | 0.0000    |
| Arabinose              | 0.0006    | 0.0009    | 0.0006    | 0.0005    | 0.0009    | 0.0005     | 0.0006    |
| Aspartate              | 0.0017    | 0.0013    | 0.0014    | 0.0018    | 0.0026    | 0.0019     | 0.0013    |
| Butyrate               | 0.0095    | 0.0052    | 0.0078    | 0.0012    | 0.0074    | 0.0028     | 0.0012    |
| Choline                | 0.0038    | 0.0020    | 0.0020    | 0.0034    | 0.0018    | 0.0014     | 0.0026    |
| Citrulline             | 0.0008    | 0.0012    | 0.0018    | 0.0012    | 0.0019    | 0.0014     | 0.0011    |
| Ethanol                | 0.0055    | 0.0080    | 0.0024    | 0.0045    | 0.0031    | 0.0055     | 0.0056    |
| Ethanolamine           | 0.0018    | 0.0157    | 0.0020    | 0.0217    | 0.0025    | 0.0021     | 0.0015    |
| Formate                | 0.0001    | 0.0000    | 0.0000    | 0.0000    | 0.0000    | 0.0000     | 0.0000    |
| Fumarate               | 0.0009    | 0.0002    | 0.0008    | 0.0005    | 0.0004    | 0.0001     | 0.0001    |
| Galactose              | 0.0001    | 0.0001    | 0.0000    | 0.0000    | 0.0000    | 0.0000     | 0.0000    |
| Glucose                | 0.0015    | 0.0023    | 0.0014    | 0.0017    | 0.0015    | 0.0017     | 0.0021    |
| Glutamate              | 0.0057    | 0.0044    | 0.0055    | 0.0062    | 0.0073    | 0.0068     | 0.0048    |
| Glutamine              | 0.0010    | 0.0007    | 0.0012    | 0.0010    | 0.0012    | 0.0011     | 0.0007    |
| Glycerol               | 0.0052    | 0.0059    | 0.0034    | 0.0036    | 0.0035    | 0.0033     | 0.0031    |
| Glycine                | 0.0028    | 0.0027    | 0.0023    | 0.0019    | 0.0026    | 0.0033     | 0.0021    |

|                                    |        |        |        |        |        |        |        |
|------------------------------------|--------|--------|--------|--------|--------|--------|--------|
| Isoleucine                         | 0.0053 | 0.0046 | 0.0049 | 0.0045 | 0.0073 | 0.0070 | 0.0047 |
| Lactate                            | 0.0056 | 0.0042 | 0.0045 | 0.0074 | 0.0062 | 0.0057 | 0.0042 |
| Lactulose                          | 0.0004 | 0.0004 | 0.0003 | 0.0003 | 0.0005 | 0.0003 | 0.0003 |
| Leucine                            | 0.0033 | 0.0032 | 0.0043 | 0.0028 | 0.0049 | 0.0050 | 0.0034 |
| Lysine/5-<br>Aminopentanoate       | 0.0034 | 0.0046 | 0.0066 | 0.0032 | 0.0042 | 0.0048 | 0.0035 |
| Malonate                           | 0.0047 | 0.0041 | 0.0048 | 0.0057 | 0.0062 | 0.0049 | 0.0055 |
| Methanol                           | 0.0013 | 0.0015 | 0.0047 | 0.0010 | 0.0016 | 0.0021 | 0.0027 |
| Methylamine                        | 0.0012 | 0.0011 | 0.0014 | 0.0014 | 0.0017 | 0.0015 | 0.0013 |
| N,N-<br>Dimethylformamide          | 0.0009 | 0.0009 | 0.0014 | 0.0013 | 0.0016 | 0.0016 | 0.0016 |
| Nicotinate                         | 0.0001 | 0.0001 | 0.0000 | 0.0001 | 0.0001 | 0.0000 | 0.0000 |
| Phenylalanine                      | 0.0011 | 0.0011 | 0.0010 | 0.0007 | 0.0016 | 0.0014 | 0.0009 |
| Propionate                         | 0.0200 | 0.0193 | 0.0289 | 0.0182 | 0.0138 | 0.0217 | 0.0257 |
| Pyruvate                           | 0.0021 | 0.0013 | 0.0016 | 0.0022 | 0.0024 | 0.0023 | 0.0017 |
| Sarcosine                          | 0.0019 | 0.0011 | 0.0012 | 0.0021 | 0.0025 | 0.0014 | 0.0016 |
| Succinate                          | 0.0007 | 0.0005 | 0.0005 | 0.0006 | 0.0008 | 0.0007 | 0.0005 |
| Taurine                            | 0.0009 | 0.0019 | 0.0010 | 0.0008 | 0.0011 | 0.0010 | 0.0011 |
| Threonine                          | 0.0009 | 0.0015 | 0.0006 | 0.0006 | 0.0011 | 0.0008 | 0.0006 |
| total bile acid and<br>cholesterol | 0.0003 | 0.0003 | 0.0004 | 0.0003 | 0.0003 | 0.0003 | 0.0003 |
| total bile acid and<br>cholesterol | 0.0004 | 0.0005 | 0.0007 | 0.0004 | 0.0004 | 0.0005 | 0.0005 |
| Tyrosine                           | 0.0014 | 0.0011 | 0.0016 | 0.0011 | 0.0015 | 0.0013 | 0.0008 |
| Uracil                             | 0.0003 | 0.0002 | 0.0001 | 0.0002 | 0.0001 | 0.0001 | 0.0001 |
| Valerate                           | 0.0036 | 0.0025 | 0.0037 | 0.0079 | 0.0035 | 0.0032 | 0.0045 |
| Valine                             | 0.0035 | 0.0028 | 0.0035 | 0.0032 | 0.0048 | 0.0041 | 0.0032 |

**Supplementary table S5.** RFA (Random forest analysis) of differential miRNA expression in organoids treated with obese (db/db and DIO [diet induced obese]) FCM (fecal conditioned media) vs control (B6-NC [normal chow]) FCM

| SI. No | miRNA                  | Organoid |           |         |                 |               |
|--------|------------------------|----------|-----------|---------|-----------------|---------------|
|        |                        | B6 FCM   | db/db FCM | DIO FCM | p-Value         |               |
|        |                        |          |           |         | B6 vs db/db FCM | B6 vs DIO FCM |
| 1      | <i>mmu-miR-101a-3p</i> | 1        | 1.857     | 1.748   | 0               | 0             |
| 2      | <i>mmu-miR-21</i>      | 1        | 1.413     | 1.452   | 0               | 0             |
| 3      | <i>mmu-miR-574-5p</i>  | 1        | 0.754     | 0.702   | 0.001           | 0             |
| 4      | <i>mmu-miR-10a</i>     | 1        | 1.23      | 1.193   | 0.002           | 0.009         |
| 5      | <i>mmu-miR-665</i>     | 1        | 0.704     | 0.616   | 0               | 0             |
| 6      | <i>mmu-miR-465c-5p</i> | 1        | 0.864     | 0.875   | 0.045           | 0.056         |
| 7      | <i>mmu-miR-466c-5p</i> | 1        | 0.599     | 0.816   | 0.002           | 0             |
| 8      | <i>mmu-miR-485</i>     | 1        | 0.846     | 0.728   | 0.018           | 0.001         |
| 9      | <i>mmu-miR-770-5p</i>  | 1        | 0.597     | 0.626   | 0               | 0             |
| 10     | <i>mmu-miR-871</i>     | 1        | 0.974     | 0.81    | 0.336           | 0.013         |
| 11     | <i>mmu-miR-1188</i>    | 1        | 0.578     | 0.565   | 0               | 0             |
| 12     | <i>mmu-miR-542-5p</i>  | 1        | 0.76      | 0.741   | 0.001           | 0             |
| 13     | <i>mmu-miR-1951</i>    | 1        | 1.047     | 1.037   | 0.006           | 0.008         |
| 14     | <i>mmu-miR-340-5p</i>  | 1        | 0.884     | 0.885   | 0.038           | 0.037         |
| 15     | <i>mmu-miR-719</i>     | 1        | 2.011     | 1.348   | 0               | 0.001         |
| 16     | <i>mmu-miR-208a</i>    | 1        | 0.752     | 0.765   | 0               | 0.001         |
| 17     | <i>mmu-miR-675-3p</i>  | 1        | 1.385     | 1.252   | 0               | 0.002         |
| 18     | <i>mmu-miR-214</i>     | 1        | 0.811     | 0.495   | 0               | 0             |
| 19     | <i>mmu-miR-298</i>     | 1        | 1.378     | 1.309   | 0               | 0             |
| 20     | <i>mmu-miR-687</i>     | 1        | 1.556     | 1.561   | 0               | 0.001         |
| 21     | <i>mmu-miR-191</i>     | 1        | 0.886     | 0.888   | 0.042           | 0.066         |
| 22     | <i>mmu-miR-107</i>     | 1        | 1.239     | 1.241   | 0.019           | 0.009         |
| 23     | <i>mmu-miR-1</i>       | 1        | 0.84      | 0.861   | 0.191           | 0.238         |
| 24     | <i>mmu-miR-204-3p</i>  | 1        | 0.745     | 0.85    | 0.023           | 0.131         |
| 25     | <i>mmu-miR-674</i>     | 1        | 0.722     | 0.715   | 0.003           | 0.011         |
| 26     | <i>mmu-miR-324-5p</i>  | 1        | 1.279     | 1.162   | 0.001           | 0.008         |
| 27     | <i>mmu-miR-212</i>     | 1        | 0.585     | 0.607   | 0.047           | 0.076         |
| 28     | <i>mmu-miR-465a-5p</i> | 1        | 0.962     | 0.913   | 0.073           | 0.108         |
| 29     | <i>mmu-miR-142-5p</i>  | 1        | 1.185     | 1.133   | 0.014           | 0.073         |
| 30     | <i>mmu-miR-342-3p</i>  | 1        | 0.911     | 0.905   | 0.072           | 0.044         |

Supplementary Table 6a. Correlation network between miRNA and mRNA differential expression in intestinal mice organoid tre:

| miRNA/Gene             | <i>Cck</i> | <i>Elf3</i> | <i>Ffar2</i> | <i>Ffar3</i> | <i>Gp2</i> | <i>Math1</i> | <i>Tgfb1</i> | <i>Tjp1</i> | <i>Notch1</i> |
|------------------------|------------|-------------|--------------|--------------|------------|--------------|--------------|-------------|---------------|
| <i>mmu-miR-1</i>       | .059       | -.083       | -.039        | -.049        | .106       | .141         | .050         | .195        | -.298         |
| <i>mmu-miR-101a-3p</i> | -.659**    | -.604**     | -.552*       | -.474*       | -.390      | -.664**      | -.650**      | -.776**     | .714**        |
| <i>mmu-miR-107</i>     | -.121      | -.279       | -.287        | .003         | -.346      | -.368        | -.303        | -.323       | .461          |
| <i>mmu-miR-1188</i>    | .207       | .459        | .223         | -.021        | .279       | .385         | .230         | .320        | -.393         |
| <i>mmu-miR-142-5p</i>  | -.361      | -.257       | -.073        | -.081        | -.033      | -.312        | -.118        | -.312       | .324          |
| <i>mmu-miR-191</i>     | .110       | .174        | -.078        | -.147        | .160       | .190         | .116         | .209        | -.272         |
| <i>mmu-miR-1951</i>    | -.136      | -.234       | -.145        | .062         | -.403      | -.365        | -.262        | -.399       | .537*         |
| <i>mmu-miR-204-3p</i>  | -.068      | .315        | .179         | -.080        | .151       | .114         | .086         | -.003       | -.010         |
| <i>mmu-miR-208a</i>    | .130       | .329        | .047         | -.139        | .406       | .346         | .222         | .404        | -.501*        |
| <i>mmu-miR-21</i>      | -.254      | -.453       | -.287        | -.022        | -.319      | -.451        | -.285        | -.382       | .483*         |
| <i>mmu-miR-212</i>     | .299       | .313        | .253         | .035         | .147       | .411         | .313         | .218        | -.334         |
| <i>mmu-miR-214</i>     | .210       | .340        | .222         | .002         | .397       | .425         | .274         | .432        | -.546*        |
| <i>mmu-miR-298</i>     | -.133      | -.381       | -.077        | .116         | -.383      | -.339        | -.211        | -.371       | .446          |
| <i>mmu-miR-324-5p</i>  | -.059      | -.254       | .038         | .181         | -.454      | -.285        | -.184        | -.404       | .500*         |
| <i>mmu-miR-340-5p</i>  | -.020      | .076        | -.364        | -.242        | .112       | -.030        | -.103        | .131        | -.110         |
| <i>mmu-miR-342-3p</i>  | -.022      | .034        | -.036        | -.149        | .363       | .182         | .147         | .286        | -.407         |
| <i>mmu-miR-465a-5p</i> | -.010      | -.076       | -.296        | -.209        | .303       | .072         | .027         | .324        | -.374         |
| <i>mmu-miR-465c-5p</i> | .249       | .062        | -.061        | -.005        | -.006      | .189         | .063         | .215        | -.254         |
| <i>mmu-miR-466c-5p</i> | .115       | .223        | -.091        | -.089        | .101       | .139         | -.006        | .163        | -.210         |
| <i>mmu-miR-485</i>     | .050       | .388        | .247         | -.017        | .127       | .206         | .141         | .051        | -.079         |
| <i>mmu-miR-542-3p</i>  | .371       | .381        | .467         | .219         | .168       | .487*        | .293         | .348        | -.441         |
| <i>mmu-miR-574-5p</i>  | .283       | .496*       | .386         | .102         | .197       | .433         | .268         | .284        | -.353         |
| <i>mmu-miR-665</i>     | .147       | .347        | .101         | -.075        | .404       | .348         | .217         | .406        | -.480*        |
| <i>mmu-miR-674</i>     | -.057      | .288        | -.014        | -.202        | .422       | .186         | .138         | .272        | -.317         |
| <i>mmu-miR-675-3p</i>  | -.158      | -.313       | -.006        | .133         | -.385      | -.340        | -.197        | -.417       | .502*         |
| <i>mmu-miR-687</i>     | -.260      | -.395       | -.270        | -.037        | -.346      | -.449        | -.284        | -.430       | .537*         |
| <i>mmu-miR-719</i>     | -.244      | -.395       | -.159        | .031         | -.336      | -.414        | -.241        | -.418       | .503*         |
| <i>mmu-miR-770-5p</i>  | .204       | .398        | .195         | -.010        | .352       | .388         | .239         | .392        | -.463         |
| <i>mmu-miR-10a</i>     | -.378      | -.391       | -.331        | -.148        | -.149      | -.456        | -.254        | -.346       | .428          |
| <i>mmu-miR-871</i>     | -.259      | -.027       | -.085        | -.217        | .373       | -.020        | .062         | .093        | -.165         |

significant level; \* =  $p < 0.05$ , \*\* =  $p < 0.01$

ated with db/db FCM (fecal conditioned media) vs control (B6-NC [normal chow]) FCM

| miRNA/Gene             | <i>Pcsk1</i> | <i>Slc5a1</i> | <i>Sox4</i> | <i>Sox9</i> | <i>Wnt3</i> | <i>Villin</i> | <i>Epcam</i> | <i>Il-1β</i> | <i>Glp1r</i> | <i>Ocln1</i> |
|------------------------|--------------|---------------|-------------|-------------|-------------|---------------|--------------|--------------|--------------|--------------|
| <i>mmu-miR-1</i>       | .145         | .044          | -.099       | .002        | .265        | -.465         | .022         | .221         | -.202        | -.106        |
| <i>mmu-miR-101a-3p</i> | -.694**      | -.530*        | .434        | .083        | .522*       | .529*         | .607**       | .437         | -.211        | -.318        |
| <i>mmu-miR-107</i>     | -.482*       | -.102         | .105        | -.142       | .120        | .205          | .022         | -.145        | -.127        | -.150        |
| <i>mmu-miR-1188</i>    | .668**       | .119          | -.008       | .497*       | -.445       | .191          | .099         | -.154        | .478*        | .452         |
| <i>mmu-miR-142-5p</i>  | -.524*       | -.255         | .114        | -.297       | .173        | .093          | -.018        | .180         | -.330        | -.421        |
| <i>mmu-miR-191</i>     | .286         | .041          | -.016       | .183        | -.188       | -.156         | -.016        | -.210        | .071         | -.015        |
| <i>mmu-miR-1951</i>    | -.503*       | -.092         | .111        | -.204       | .103        | .358          | .039         | -.103        | -.020        | -.083        |
| <i>mmu-miR-204-3p</i>  | .300         | -.098         | .176        | .435        | -.436       | .547*         | .195         | -.073        | .428         | .302         |
| <i>mmu-miR-208a</i>    | .562*        | .045          | -.028       | .408        | -.322       | -.162         | .000         | -.100        | .145         | .150         |
| <i>mmu-miR-21</i>      | -.725**      | -.172         | .071        | -.443       | .369        | -.067         | -.071        | .059         | -.448        | -.465        |
| <i>mmu-miR-212</i>     | .446         | .267          | -.167       | .034        | -.163       | -.041         | -.004        | -.107        | .348         | .243         |
| <i>mmu-miR-214</i>     | .647**       | .145          | -.107       | .357        | -.224       | -.173         | .012         | .069         | .220         | .315         |
| <i>mmu-miR-298</i>     | -.591**      | -.044         | -.005       | -.486*      | .413        | -.014         | -.038        | .146         | -.267        | -.257        |
| <i>mmu-miR-324-5p</i>  | -.485*       | .013          | .004        | -.389       | .265        | .265          | .021         | .065         | .002         | -.033        |
| <i>mmu-miR-340-5p</i>  | .136         | -.109         | .133        | .364        | -.267       | -.035         | .023         | -.381        | -.021        | -.085        |
| <i>mmu-miR-342-3p</i>  | .193         | -.035         | -.078       | .044        | .047        | -.476*        | -.080        | .139         | -.273        | -.226        |
| <i>mmu-miR-465a-5p</i> | .120         | -.059         | -.033       | .098        | .079        | -.644**       | -.135        | -.001        | -.422        | -.312        |
| <i>mmu-miR-465c-5p</i> | .335         | .166          | -.065       | .129        | .023        | -.300         | -.005        | -.104        | .096         | .134         |
| <i>mmu-miR-466c-5p</i> | .411         | .031          | .071        | .421        | -.279       | .096          | .115         | -.298        | .280         | .230         |
| <i>mmu-miR-485</i>     | .400         | .008          | .097        | .410        | -.458       | .539*         | .172         | -.137        | .532*        | .401         |
| <i>mmu-miR-542-3p</i>  | .696**       | .311          | -.201       | .264        | -.158       | .040          | .069         | .147         | .494*        | .618**       |
| <i>mmu-miR-574-5p</i>  | .711**       | .207          | -.058       | .444        | -.420       | .307          | .121         | -.083        | .627**       | .620**       |
| <i>mmu-miR-665</i>     | .590**       | .070          | -.030       | .443        | -.336       | -.086         | .011         | -.063        | .203         | .264         |
| <i>mmu-miR-674</i>     | .372         | -.112         | .094        | .448        | -.407       | .056          | .028         | -.103        | .090         | .061         |
| <i>mmu-miR-675-3p</i>  | -.574*       | -.063         | .027        | -.430       | .309        | .193          | -.002        | .127         | -.142        | -.171        |
| <i>mmu-miR-687</i>     | -.708**      | -.187         | .107        | -.376       | .266        | .118          | -.022        | -.011        | -.323        | -.409        |
| <i>mmu-miR-719</i>     | -.682**      | -.148         | .064        | -.451       | .342        | .067          | -.035        | .098         | -.324        | -.370        |
| <i>mmu-miR-770-5p</i>  | .652**       | .125          | -.048       | .455        | -.360       | .013          | .039         | -.059        | .334         | .396         |
| <i>mmu-miR-10a</i>     | -.712**      | -.295         | .142        | -.331       | .226        | -.016         | -.070        | .029         | -.500*       | -.576*       |
| <i>mmu-miR-871</i>     | -.069        | -.224         | .059        | .022        | -.041       | -.206         | -.064        | .142         | -.344        | -.372        |

| miRNA/Gene           | <i>Il-10</i> | <i>Hes1</i> | <i>Mct1</i> | <i>Sis</i> |
|----------------------|--------------|-------------|-------------|------------|
| <i>mmu-miR-1</i>     | -.068        | -.102       | .280        | .148       |
| <i>mmu-miR-</i>      | -.529*       | .651**      | .444        | -.602**    |
| <i>mmu-miR-107</i>   | -.119        | .192        | .187        | -.173      |
| <i>mmu-miR-</i>      | .237         | -.435       | -.381       | .093       |
| <i>mmu-miR-142-</i>  | -.295        | .403        | -.057       | -.197      |
| <i>mmu-miR-191</i>   | .026         | -.322       | -.125       | .102       |
| <i>mmu-miR-</i>      | -.047        | .338        | .147        | -.185      |
| <i>mmu-miR-204-</i>  | .068         | -.131       | -.476*      | -.136      |
| <i>mmu-miR-</i>      | .041         | -.509*      | -.327       | .126       |
| <i>mmu-miR-21</i>    | -.269        | .424        | .315        | -.151      |
| <i>mmu-miR-212</i>   | .313         | -.146       | -.116       | .232       |
| <i>mmu-miR-214</i>   | .157         | -.419       | -.230       | .176       |
| <i>mmu-miR-298</i>   | -.084        | .520*       | .404        | -.088      |
| <i>mmu-miR-324-</i>  | .067         | .516*       | .292        | -.109      |
| <i>mmu-miR-340-</i>  | -.148        | -.459       | -.144       | -.044      |
| <i>mmu-miR-342-</i>  | -.159        | -.226       | -.085       | .117       |
| <i>mmu-miR-</i>      | -.250        | -.388       | .083        | .127       |
| <i>mmu-miR-465c-</i> | .141         | -.269       | .276        | .164       |
| <i>mmu-miR-466c-</i> | .083         | -.402       | -.085       | .005       |
| <i>mmu-miR-485</i>   | .191         | -.168       | -.465       | -.063      |
| <i>mmu-miR-542-</i>  | .424         | -.224       | -.103       | .206       |
| <i>mmu-miR-574-</i>  | .380         | -.321       | -.344       | .110       |
| <i>mmu-miR-665</i>   | .083         | -.501*      | -.333       | .120       |
| <i>mmu-miR-674</i>   | -.100        | -.432       | -.510*      | -.018      |
| <i>mmu-miR-675-</i>  | -.048        | .548*       | .267        | -.136      |
| <i>mmu-miR-687</i>   | -.237        | .418        | .208        | -.194      |
| <i>mmu-miR-719</i>   | -.193        | .505*       | .272        | -.158      |
| <i>mmu-miR-770-</i>  | .183         | -.465       | -.327       | .129       |
| <i>mmu-miR-10a</i>   | -.398        | .329        | .065        | -.206      |
| <i>mmu-miR-871</i>   | -.322        | -.073       | -.311       | -.066      |

Supplementary Table 6b. Correlation network between miRNA and mRNA differential expression in int

| miRNA/Genes            | <i>Cck</i> | <i>Elf3</i> | <i>Ffar2</i> | <i>Ffar3</i> | <i>Gp2</i> | <i>Math1</i> | <i>Tgf-β1</i> |
|------------------------|------------|-------------|--------------|--------------|------------|--------------|---------------|
| <i>mmu-miR-1</i>       | -.071      | -.129       | -.365        | -.090        | -.004      | -.083        | -.169         |
| <i>mmu-miR-101a-3p</i> | -.382      | -.628**     | -.245        | -.213        | .319       | -.619**      | -.606**       |
| <i>mmu-miR-107</i>     | .186       | -.273       | -.040        | -.109        | -.038      | -.392        | -.444         |
| <i>mmu-miR-1188</i>    | -.070      | .433        | .030         | .256         | .134       | .529*        | .575*         |
| <i>mmu-miR-142-5p</i>  | -.191      | -.306       | -.020        | -.188        | -.272      | -.249        | -.354         |
| <i>mmu-miR-191</i>     | -.170      | .153        | .011         | .013         | -.037      | .251         | .272          |
| <i>mmu-miR-1951</i>    | .170       | -.305       | .045         | -.025        | -.311      | -.325        | -.531*        |
| <i>mmu-miR-204-3p</i>  | -.212      | .095        | .096         | .109         | .170       | .162         | .312          |
| <i>mmu-miR-208a</i>    | -.237      | .285        | -.090        | .086         | .039       | .399         | .444          |
| <i>mmu-miR-21</i>      | .082       | -.431       | -.048        | -.266        | -.128      | -.532*       | -.578*        |
| <i>mmu-miR-212</i>     | .026       | .227        | .117         | .039         | .317       | .238         | .335          |
| <i>mmu-miR-214</i>     | -.170      | .372        | .032         | .206         | .210       | .451         | .596**        |
| <i>mmu-miR-298</i>     | .165       | -.335       | .138         | -.115        | -.136      | -.415        | -.476*        |
| <i>mmu-miR-324-5p</i>  | .332       | -.189       | .183         | .082         | -.228      | -.238        | -.421         |
| <i>mmu-miR-340-5p</i>  | -.105      | .106        | -.258        | -.086        | .218       | .089         | .159          |
| <i>mmu-miR-342-3p</i>  | -.273      | .054        | -.217        | -.128        | -.064      | .140         | .147          |
| <i>mmu-miR-465a-5p</i> | -.053      | -.036       | -.331        | -.058        | -.020      | -.007        | -.101         |
| <i>mmu-miR-465c-5p</i> | -.085      | .114        | .020         | .136         | -.233      | .257         | .095          |
| <i>mmu-miR-466c-5p</i> | -.124      | .393        | .046         | .245         | .057       | .513*        | .540*         |
| <i>mmu-miR-485</i>     | .016       | .399        | .024         | .225         | .203       | .454         | .498*         |
| <i>mmu-miR-542-5p</i>  | -.063      | .371        | -.064        | .177         | .152       | .448         | .480*         |
| <i>mmu-miR-574-5p</i>  | .041       | .446        | .099         | .313         | .177       | .511*        | .549*         |
| <i>mmu-miR-665</i>     | -.120      | .323        | -.080        | .125         | .240       | .368         | .460          |
| <i>mmu-miR-674</i>     | -.291      | .098        | -.130        | .032         | -.128      | .226         | .167          |
| <i>mmu-miR-675-3p</i>  | .258       | -.240       | .142         | -.046        | -.022      | -.359        | -.389         |
| <i>mmu-miR-687</i>     | .105       | -.432       | -.096        | -.250        | -.189      | -.511*       | -.616**       |
| <i>mmu-miR-719</i>     | .181       | -.375       | -.086        | -.210        | -.109      | -.487*       | -.573*        |
| <i>mmu-miR-770-5p</i>  | -.127      | .389        | .026         | .229         | .160       | .467         | .561*         |
| <i>mmu-miR-10a</i>     | -.109      | -.441       | -.166        | -.330        | -.237      | -.465        | -.551*        |
| <i>mmu-miR-871</i>     | -.294      | .093        | -.212        | -.055        | -.084      | .201         | .184          |

significant level; \* =  $p < 0.05$ , \*\* =  $p < 0.01$



intestinal mice organoid treated with DIO (diet induced obese) FCM (fecal conditioned media) vs control (B6

| <i>miRNA/Genes</i>     | <i>Tjp1</i> | <i>Notch1</i> | <i>Pcsk1</i> | <i>Slc5a1</i> | <i>Sox4</i> | <i>Sox9</i> | <i>Wnt3</i> |
|------------------------|-------------|---------------|--------------|---------------|-------------|-------------|-------------|
| <i>mmu-miR-1</i>       | .024        | -.160         | -.161        | .108          | .114        | .230        | -.152       |
| <i>mmu-miR-101a-3p</i> | -.739**     | .492*         | -.414        | -.287         | .214        | -.320       | .556*       |
| <i>mmu-miR-107</i>     | -.352       | .544*         | -.129        | -.021         | -.091       | -.209       | .510*       |
| <i>mmu-miR-1188</i>    | .459        | -.510*        | .252         | .254          | .136        | .434        | -.639**     |
| <i>mmu-miR-142-5p</i>  | -.199       | -.129         | -.185        | -.376         | -.160       | -.336       | .425        |
| <i>mmu-miR-191</i>     | .212        | -.404         | .069         | -.084         | .019        | .036        | -.267       |
| <i>mmu-miR-1951</i>    | -.347       | .216          | -.076        | -.058         | -.269       | -.297       | .554*       |
| <i>mmu-miR-204-3p</i>  | .092        | -.127         | .075         | -.103         | .129        | -.035       | -.153       |
| <i>mmu-miR-208a</i>    | .440        | -.611**       | .104         | .008          | .122        | .332        | -.596**     |
| <i>mmu-miR-21</i>      | -.459       | .529*         | -.255        | -.241         | -.131       | -.425       | .735**      |
| <i>mmu-miR-212</i>     | .029        | .099          | .117         | .211          | .162        | .055        | -.297       |
| <i>mmu-miR-214</i>     | .428        | -.410         | .197         | .116          | .192        | .345        | -.638**     |
| <i>mmu-miR-298</i>     | -.470*      | .519*         | -.118        | -.148         | -.188       | -.473*      | .705**      |
| <i>mmu-miR-324-5p</i>  | -.383       | .388          | .050         | .111          | -.275       | -.315       | .515*       |
| <i>mmu-miR-340-5p</i>  | .202        | -.091         | -.071        | .092          | .230        | .347        | -.380       |
| <i>mmu-miR-342-3p</i>  | .280        | -.501*        | -.087        | -.163         | .079        | .178        | -.304       |
| <i>mmu-miR-465a-5p</i> | .120        | -.209         | -.105        | .116          | .087        | .309        | -.234       |
| <i>mmu-miR-465c-5p</i> | .164        | -.535*        | .125         | .026          | -.132       | .055        | -.224       |
| <i>mmu-miR-466c-5p</i> | .448        | -.587*        | .241         | .162          | .088        | .358        | -.669**     |
| <i>mmu-miR-485</i>     | .354        | -.310         | .229         | .328          | .159        | .415        | -.673**     |
| <i>mmu-miR-542-5p</i>  | .416        | -.447         | .178         | .260          | .165        | .458        | -.708**     |
| <i>mmu-miR-574-5p</i>  | .388        | -.352         | .730**       | .358          | .125        | .428        | -.701**     |
| <i>mmu-miR-665</i>     | .392        | -.346         | .116         | .193          | .230        | .464        | -.661**     |
| <i>mmu-miR-674</i>     | .294        | -.614**       | .017         | -.140         | .002        | .178        | -.322       |
| <i>mmu-miR-675-3p</i>  | -.440       | .647**        | -.052        | .001          | -.136       | -.366       | .595**      |
| <i>mmu-miR-687</i>     | -.445       | .453          | -.248        | -.185         | -.160       | -.386       | .697**      |
| <i>mmu-miR-719</i>     | -.455       | .580*         | -.203        | -.093         | -.132       | -.346       | .658**      |
| <i>mmu-miR-770-5p</i>  | .458        | -.467         | .212         | .168          | .159        | .418        | -.678**     |
| <i>mmu-miR-10a</i>     | -.304       | .144          | -.636**      | -.366         | -.123       | -.335       | .588*       |
| <i>mmu-miR-871</i>     | .341        | -.605**       | -.046        | -.134         | .069        | .249        | -.384       |

## i-NC [normal chow]) FCM

| miRNA/Genes            | Villin | Epcam  | Il-1 $\beta$ | Glp1r   | Ocln1 | Il-10 | Hes1    | Mct1   | Sis     |
|------------------------|--------|--------|--------------|---------|-------|-------|---------|--------|---------|
| <i>mmu-miR-1</i>       | -.091  | .024   | .002         | -.282   | -.088 | -.055 | -.143   | .011   | -.060   |
| <i>mmu-miR-101a-3p</i> | .257   | .349   | .592**       | -.306   | -.316 | -.413 | .643**  | .686** | -.634** |
| <i>mmu-miR-107</i>     | .312   | .107   | .396         | -.024   | .084  | -.046 | .500*   | .343   | -.270   |
| <i>mmu-miR-1188</i>    | -.322  | -.409  | -.349        | .186    | .174  | .199  | -.683** | -.404  | .411    |
| <i>mmu-miR-142-5p</i>  | .140   | .649** | -.089        | -.347   | -.346 | -.189 | .307    | .145   | -.309   |
| <i>mmu-miR-191</i>     | -.238  | .051   | -.321        | -.039   | -.193 | -.015 | -.293   | -.219  | .141    |
| <i>mmu-miR-1951</i>    | .570*  | .564*  | .166         | -.048   | .109  | .121  | .543*   | .309   | -.340   |
| <i>mmu-miR-204-3p</i>  | -.090  | .073   | -.080        | .170    | -.130 | -.057 | -.068   | -.036  | .049    |
| <i>mmu-miR-208a</i>    | -.466  | -.198  | -.424        | -.112   | -.139 | -.021 | -.653** | -.405  | .295    |
| <i>mmu-miR-21</i>      | .307   | .387   | .362         | -.191   | -.172 | -.199 | .678**  | .412   | -.407   |
| <i>mmu-miR-212</i>     | -.147  | -.437  | .043         | .286    | .121  | .064  | -.169   | -.053  | .216    |
| <i>mmu-miR-214</i>     | -.394  | -.346  | -.280        | .157    | .034  | .053  | -.595** | -.343  | .352    |
| <i>mmu-miR-298</i>     | .512*  | .432   | .333         | .071    | .006  | -.014 | .735**  | .406   | -.362   |
| <i>mmu-miR-324-5p</i>  | .706** | .402   | .255         | .259    | .320  | .294  | .608**  | .344   | -.261   |
| <i>mmu-miR-340-5p</i>  | -.484* | -.510* | -.007        | -.209   | -.081 | -.161 | -.427   | -.148  | .176    |
| <i>mmu-miR-342-3p</i>  | -.471* | -.001  | -.343        | -.385   | -.353 | -.198 | -.442   | -.272  | .108    |
| <i>mmu-miR-465a-5p</i> | -.189  | -.123  | -.051        | -.301   | -.029 | -.040 | -.286   | -.075  | .025    |
| <i>mmu-miR-465c-5p</i> | .087   | .303   | -.381        | -.018   | -.007 | .196  | -.241   | -.196  | .061    |
| <i>mmu-miR-466c-5p</i> | -.286  | -.238  | -.413        | .139    | .092  | .176  | -.640** | -.406  | .360    |
| <i>mmu-miR-485</i>     | -.268  | -.527* | -.200        | .236    | .251  | .211  | -.579*  | -.303  | .386    |
| <i>mmu-miR-542-5p</i>  | -.373  | -.472* | -.285        | .082    | .137  | .139  | -.669** | -.364  | .379    |
| <i>mmu-miR-574-5p</i>  | -.187  | -.486* | -.233        | .708**  | .341  | .292  | -.588*  | -.331  | .409    |
| <i>mmu-miR-665</i>     | -.462  | -.549* | -.195        | .008    | .092  | .012  | -.646** | -.324  | .351    |
| <i>mmu-miR-674</i>     | -.278  | .144   | -.413        | -.273   | -.242 | -.074 | -.451   | -.300  | .090    |
| <i>mmu-miR-675-3p</i>  | .498*  | .171   | .423         | .217    | .156  | .058  | .668**  | .391   | -.275   |
| <i>mmu-miR-687</i>     | .347   | .457   | .326         | -.219   | -.136 | -.134 | .643**  | .417   | -.412   |
| <i>mmu-miR-719</i>     | .355   | .270   | .406         | -.101   | -.044 | -.088 | .637**  | .425   | -.364   |
| <i>mmu-miR-770-5p</i>  | -.371  | -.388  | -.311        | .124    | .117  | .102  | -.655** | -.389  | .377    |
| <i>mmu-miR-10a</i>     | .099   | .539*  | .117         | -.660** | -.376 | -.300 | .438    | .263   | -.389   |
| <i>mmu-miR-871</i>     | -.445  | .013   | -.401        | -.371   | -.300 | -.151 | -.527*  | -.329  | .133    |

**Supplementary table S7.** Predictive abundance of Eut operon expressing bacterial species and the abundance of bacterial species itself that were different in obese/T2D (both db/db and DIO) compared to Lean normal chow fed controls

| Targeted Bacterial Species          | Cumulative eut operon gene Correlation with Bacterial Species |      |      |       | Relative Abundance (R.A) |       |      |       | p-Value |      |       | FC   |      |      |       | Lean abundance ranking |
|-------------------------------------|---|------|------|-------|--------------------------|-------|------|-------|---------|------|-------|------|------|------|-------|------------------------|
|                                     | Lean  | dbdb | DIO  | Obese | Lean                     | dbdb  | DIO  | Obese | dbdb    | DIO  | Obese | Lean | dbdb | DIO  | Obese |                        |
| <i>Pedobacter kwangyangensis</i>    | -0.78   | 0.77 | 0.89 | 0.83  | 21.00                    | 12.54 | 0.05 | 6.30  | 0.00    | 0.00 | 0.00  | 1.00 | 0.60 | 0.00 | 0.30  | 1                      |
| <i>Akkermansia muciniphila</i>      | -0.83   | 0.81 | 0.87 | 0.84  | 18.90                    | 0.19  | 2.16 | 1.17  | 0.00    | 0.00 | 0.00  | 1.00 | 0.01 | 0.11 | 0.06  | 2                      |
| <i>Alkaliphilus crotonatoxidans</i> | -0.53   | 0.71 | 0.85 | 0.78  | 5.56                     | 1.33  | 0.04 | 0.69  | 0.00    | 0.00 | 0.00  | 1.00 | 0.24 | 0.01 | 0.12  | 3                      |
| <i>Johnsonella ignava</i>           | -0.44   | 0.71 | 0.84 | 0.77  | 2.26                     | 0.54  | 0.24 | 0.39  | 0.00    | 0.00 | 0.00  | 1.00 | 0.24 | 0.11 | 0.17  | 4                      |
| <i>Bacteroides thetaiotaomicron</i> | -0.48   | 0.21 | 0.80 | 0.51  | 2.09                     | 1.73  | 0.00 | 0.87  | 0.07    | 0.00 | 0.00  | 1.00 | 0.83 | 0.00 | 0.42  | 5                      |
| <i>Clostridium termitidis</i>       | -0.53   | 0.32 | 0.85 | 0.59  | 0.49                     | 0.43  | 0.01 | 0.22  | 0.03    | 0.00 | 0.00  | 1.00 | 0.86 | 0.01 | 0.44  | 6                      |
| <i>Clostridium frigidis</i>         | -0.52   | 0.65 | 0.84 | 0.74  | 0.40                     | 0.18  | 0.01 | 0.10  | 0.00    | 0.00 | 0.00  | 1.00 | 0.45 | 0.04 | 0.24  | 7                      |
| <i>Lachnospira pectinoschiza</i>    | -0.43   | 0.47 | 0.57 | 0.52  | 0.26                     | 0.11  | 0.10 | 0.11  | 0.01    | 0.01 | 0.01  | 1.00 | 0.44 | 0.38 | 0.41  | 8                      |
| <i>Coprobacillus cateniformis</i>   | -0.49   | 0.64 | 0.85 | 0.75  | 0.16                     | 0.07  | 0.00 | 0.04  | 0.00    | 0.00 | 0.00  | 1.00 | 0.47 | 0.02 | 0.24  | 9                      |
| <i>Luteolibacter algae</i>          | -0.53   | 0.77 | 0.89 | 0.83  | 0.14                     | 0.00  | 0.02 | 0.01  | 0.00    | 0.00 | 0.00  | 1.00 | 0.02 | 0.14 | 0.08  | 10                     |
| <i>Peptococcus niger</i>            | -0.51   | 0.62 | 0.78 | 0.70  | 0.07                     | 0.02  | 0.01 | 0.02  | 0.00    | 0.00 | 0.00  | 1.00 | 0.33 | 0.23 | 0.28  | 11                     |
| <i>Bifidobacterium choerinum</i>    | -0.43   | 0.44 | 0.10 | 0.27  | 0.04                     | 0.02  | 0.04 | 0.03  | 0.01    | 0.03 | 0.03  | 1.00 | 0.41 | 0.89 | 0.65  | 12                     |

**Supplementary table S8a.** Control Diet nutrient profile

| Ingredient                                | Control Diet (gm/100 gm) |
|---|--------------------------|
| Casein, USP                               | 13                       |
| Whey Protein 895                          | 13                       |
| Dextrin                                   | 15                       |
| Sucrose                                   | 15                       |
| Wheat Flour, Southern Biscuit self-rising | 26                       |
| Alphacel                                  | 5                        |
| Lard                                      | 20                       |
| Corn Oil                                  | 0                        |
| Mineral Mix, TD93144 w/o Ca, P            | 3.1                      |
| Calcium Carbonate                         | 0.3                      |
| Calcium Phosphate, Monobasic              | 0.1                      |
| Vitamin Mix, Envigo 85529 for Primates    | 2.5                      |
| TOTAL                                     | 100                      |

**Supplementary table S8b. Meat Supplementary Diet (MSD) nutrient profile**

| Ingredient                                | MSD (gm/100 gm) |
|---|-----------------|
| Meat Protein                              | 50              |
| Dextrin                                   | 15              |
| Sucrose                                   | 15              |
| Wheat Flour, Southern Biscuit self-rising | 14              |
| Alphacel                                  | 0               |
| Lard                                      | 0               |
| Corn Oil                                  | 0               |
| Mineral Mix, TD93144 w/o Ca, P            | 3.1             |
| Calcium Carbonate                         | 0.3             |
| Calcium Phosphate, Monobasic              | 0.1             |
| Vitamin Mix, Envigo 85529 for Primates    | 2.5             |
| TOTAL                                     | 100             |

| Supplementary Table S9. Ethanolamine operon specific gene primer sequence |      |   |   |
|---|------|---|---|
| Sl. No  | Gene | Gene sequence (5`-3`)                     | GenBank Accession number/Ref.   |
| 1   | 16s  | 27F: AGAGTTTGATCMTGGCTCAG                 |   |
|   |      | 1492R: TACGGYTACCTTGTTACGACTT             |   |
| 2   | eutA | F: GCCAACACTCGCCAGCTATTGAG                | PMID:16769691   |
|   |      | R: CCGGAAGGAAATGCGAGTGATTT                |   |
| 3   | eutB | F: GCCAAACTAAAGACCACATTGTT                | PMID:16769691   |
|   |      | R: CCGAAGAACAGTGACGGATCGCC                |   |
| 4   | eutC | F: GCCGATCAAAAACAGATTGAAGA                | PMID:16769691   |
|   |      | R: CCTCGGGTCATGTTGATGCCGGA                |   |
| 5   | eutD | F: AATCTGCTACGCACCAAAGTG                  | <a href="https://doi.org/10.1038/s41522-019-0092-7">https://doi.org/10.1038/s41522-019-0092-7</a> |
|   |      | R: GGCTTTACAGGCTGCAACATC                  |   |
| 6   | eutP | F: NNGCTCTTCNTTCATGAAACGTATTGCTTTTGTCG    | PMID: 26448059  |
|   |      | R: NNGCTCTTCNTTATTAGCTGTGATAAGTTTTTACCTG  |   |
| 7   | eutQ | F: NNGCTCTTCNTTCGTGAAAAAATTATCACAGCTAACGA | PMID: 26448059  |
|   |      | R: NNGCTCTTCNTTATCATACGGATTGCCAGTTTG      |   |
| 8   | eutS | F: TTGGTCATTTCACAAAGCGT                   | DOI: 10.1128/JB.00937-13  |
|   |      | R: GCGCAGTAGAAGAAGCGTT                    |   |
| 9   | eutT | F: GCGGCTCTCAGTGAACAGGA                   | DOI: 10.1128/JB.186.17.570  |
|   |      | R: CGCTGCAATCGGCGAACC                     |   |
|   |      |   |   |

| Supplementary Table S10. Human inflammatory and tight junction protein markers primer sequence |               |  |                |
|--|---------------|--|----------------|
| 1  | <i>Ocln</i>   | F: ACAAGCGGTTTTATCCAGAGTC<br>R: GTCATCCACAGGCGAAGTTAAT   | NM_001205254   |
| 2  | <i>Tjp1</i>   | F: CAACATACAGTGACGCTTCACA<br>R: CACTATTGACGTTTCCCCTC     | NM_003257      |
| 3  | <i>Il10</i>   | F: CTGTGAAAACAAGAGCAAGGC<br>R: GAAGCTTCTGTTGGCTCCC       | PMID: 32302292 |
| 4  | <i>Tgf-β1</i> | F: GCAGCACGTGGAGCTGTA<br>R: CAGCCGGTTGCTGAGGTA           | PMID: 32302292 |
| 5  | <i>Il-1β</i>  | F: ATGATGGCTTATTACAGTGGCAA<br>R: GTCGGAGATTCGTAGCTGGA    | NM_000576      |
| 6  | <i>Il6</i>    | F: ACTCACCTTTCAGAACGAATTG<br>R: CCATCTTTGGAAGGTTTCAGGTTG | NM_000600      |
| 7  | <i>Tnf-α</i>  | F: GAGGCCAAGCCCTGGTATG<br>R: CGGGCCGATTGATCTCAGC         | NM_000594      |
| 8  | <i>Arid3a</i> | F: ACCACGGCGACTGGACTTA<br>R: CACAGGTGTCCTCGCTTC          | NM_005224      |

| <b>Supplementary Table S11. siRNA, miRNA and miR101a-3p promoter sequences</b> |  |   |  |
|--|--|---|--|
| <b>Sl. No.</b>   | <b>siRNA/miRNA/miR101a-3p promoter</b>   | <b>Nucleotide sequence (5`-3`)</b>  | <b>GenBank Accession number/Ref./Catalog No.</b> |
| 1  | <i>RNU6B</i>                             | CGCAAGGATGACACGCAAATTCGTGAAGCGTTCCATATTTTT  | Assay ID: 001093                                 |
| 2  | <i>miR101a-3p</i>                        | Mature miRNA sequence-<br>UACAGUACUGUGAU AACUGAA  | Assay ID: 002253                                 |
| 3  | <i>Mimic-miR101a-3p</i>                  | Chr.1: 65058434 - 65058508 [-] on Build GRCh38; Product type- mirVana® miRNA mimic                              | Assay ID: MC11414                                |
| 4  | <i>Inhibitor miR101a-3p</i>              | Chr.1: 65058434 - 65058508 [-] on Build GRCh38; Product type- mirVana® miRNA inhibitor                          | Assay ID: MH11414                                |
| 5  | Scrambled <i>miR101a-3p</i> lentivirus   | SMARTvector Non-targeting mCMV-TurboGFP Control Particles, 50 µL, 10 <sup>8</sup> TU/mL                         | S01-005000-01                                    |
| 6  | Mimic <i>miR101a-3p</i> lentivirus       | shMIMIC Mouse Lentiviral microRNA mmu-miR-101a-3p ,100 µL, 10 <sup>8</sup> TU/mL                                | VSM6213-213647697                                |
| 7  | Negative Control for <i>Arid3a</i> siRNA | STEALTH RNAI NEG CTRL MED GC#2; Invitrogen Stealth RNAi siRNA Negative Control Med GC Duplex #2,                | 12935112   |
| 8  | <i>Arid3a</i> siRNA                      | Ambion Human Single, Format: Tube(s), Stealth RNAi Pre-designed siRNA- Chr. 19: 925733 - 975934 on Build GRCh38 | Assay ID HSS102931                               |
| 9  | NC <i>cel-miR-67</i> : Custom miRNA      | NC cel-miR-67: Length: 24   | CTM-545375                                       |
|  | Mimic, Standard 0.05 µmol                | Active: 5' 5'-<br>P.U.C.A.C.A.A.C.C.U.C.C.U.A.G.A.A.A.G.A.G.U.A.G.A 3'  |  |
|  | miRIDIAN mimic                           | Passenger: 5'<br>U.A.C.U.C.U.U.U.C.U.A.G.G.A.G.G.U.U.G.U.G.A.U.U.3'-LCBi 3'                                     |  |
| 10   | 3-Biotin LC <i>mmu-miR101a-3p</i> :      | 3-Biotin LC mmu-miR101a-3p: Length: 21  | CTM-545376                                       |
|  | Custom miRNA Mimic, Standard             | Active: 5' 5'-<br>P.U.A.C.A.G.U.A.C.U.G.U.G.A.U.A.A.C.U.G.A.A 3'  |  |
|  | 0.05 µmol miRIDIAN mimic                 | Passenger: 5'<br>C.A.G.U.U.A.U.C.A.C.A.G.U.A.C.U.G.U.A.U.U.3'-LCBi 3'   |  |
| 11   | Promoter- <i>miR-101-1-500_to-1</i>      | 19AEPDPC_miR-101-1-500_to-1_pMCSRedFireLuc  | Project ID-2019AAMC7C                            |
| 12   | Promoter- <i>miR-101-1-1000_to-1</i>     | 19AEPDQC_miR-101-1-1000_to-1_pMCSRedFireLuc   | Project ID-2019AAMC7C                            |
| 13   | Promoter- <i>miR-101-1-1500_to-1</i>     | 19AEPDRC_miR-101-1-1500_to-1_pMCSRedFireLuc   | Project ID-2019AAMC7C                            |
| 14   | Promoter- <i>miR-101-1-2000_to-1</i>     | 19AEPDRC_miR-101-1-2000_to-1_pMCSRedFireLuc   | Project ID-2019AAMC7C                            |



| Sl. No. | siRNA/miRNA/miR10 1a-3p promoter          | Nucleotide sequence (5'-3')   | GenBank Accession number/Ref./Catalog No. |
|---------|---|---|---|
| 15      | scrambled <i>miR101-1</i> (-1000 to -500) | 5'- ATC CCT ATA CTT CCG GGT TTT AAG ATT<br>TAC AAT CGT ATA CAT CGC AAG ATC TAA ACT<br>GCC CTT AAG CTG CGT ATA TAG CCA GAC<br>ACG TTC AAT GTG TTA GAA GGA AGT AAC<br>TTA GAC TCC TTA GAA ATT AAT ACC CAA CAG<br>TTC AAT ACA TAA ATA AAA TAG GTT GCC<br>GCG AGA ACC GAA CTT ATA TAT AAT CAA<br>GTC CGT ACT CGA GCT TGG TGC CCA AGG<br>CGA TCG AAA AGT GTC GTA GTG TTA GAC<br>GAT TAC ACT GCA GCA CAG GGG AAT AAA<br>AAG CAG TAA TGC GGA GAA GAA CTG AGT<br>GGA CTC GAC CTC CTC GGA CCA CAA AAT<br>AAT ACG CTA ACA ACG CAC CTG TTT AAA<br>AGG AGG GAA GAT ATG AAT TCC AGA TAT<br>ACG AGA CGC ATA AAG GTT TGT TGG AGA<br>CAC AAC GAG GAT TAT GCT TGG ACT AAA<br>ATC CAC ATC TCG CAC GCG GGT TAC TTA<br>GTC ACT CCT AAA TCT TAC TAC ACT CTC ACT<br>CAC GA - 3' | 16739056                                  |
| 16      | <i>miR-101-1</i> (-1000 to -500)          | 5'- ACT CAC GAA AAA CAA AAG TGA AAG TGC<br>CTG AAG GGA ACC CAG TAG TAA ACA AGA<br>GTA CAA AAT TCT ATA TCT CAC CGG AAA<br>ACA GTG GCA GAG TTC CCA AAT ATT TTT TTT<br>TCA GCA ACT GTG AAC TTC GGA AAG AAT<br>GAA ATG TCT ATC ACT CCC TTT GAA TGT GAA<br>TAA GAT CAG TGT AAC ACG AAT CCA CCT<br>TGC TCT ATG CAA CTG TCT TCT GAA ACA ATC<br>CTC TGA CCC TGA ACA CCA CTT ATT TAA ATA<br>AGC GGT TCT TAA ATC AAT CAA TCC GTA<br>GTG AAT GGT CCA TCC CCA CAA AAC CAA<br>TCC CCA TTG AAG ACC ACA CCA AGT TGT<br>GCC CCA CTT TGG GAA AAG GGG GAA AGC<br>GGG GGT AGA GAA AGA GGG GAA GGA TTG<br>GAA CCA ACA TTA GAT TGT GCC TGG TGT<br>TGC CAC GCG GTT GTC ATA AAC AAC GGC<br>GTC GAA GCA AAC TGT TTT AAA ACT TAG<br>AAA ATA CGG CGG CCT TTA AAC TCT ATT AT -<br>3' | 16739056                                  |
| 17      | Control for ZO1_KI                        | Precision lentiORF RFP positive control viral particles   | OHS5833                                   |
| 18      | ZO1_KI                                    | Precision LentiORF TJP1 w/Stop Codon, 2 x 25 µl viral particles   | OHS5899-202624463                         |