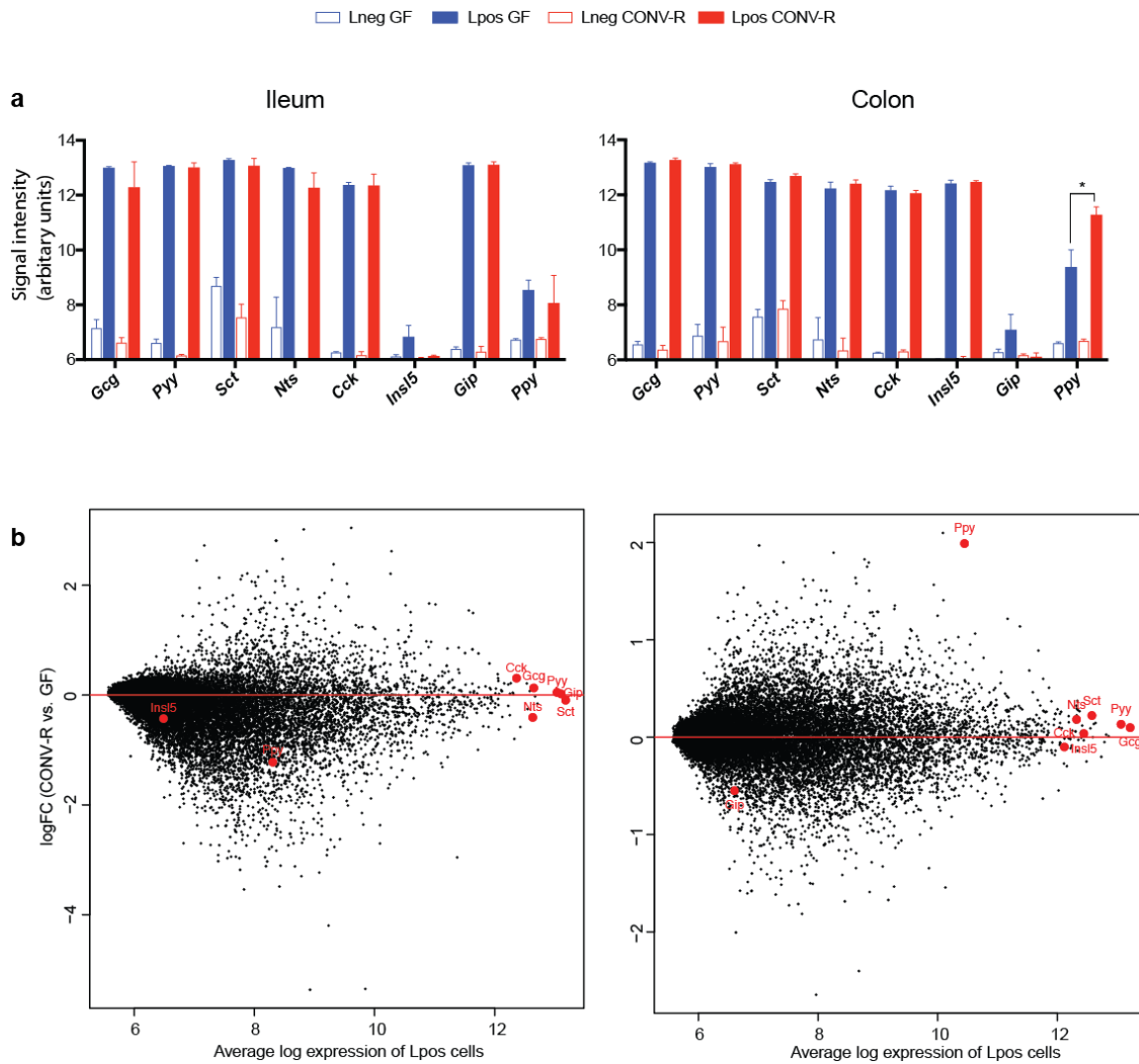


## **Supplementary figures and legends**

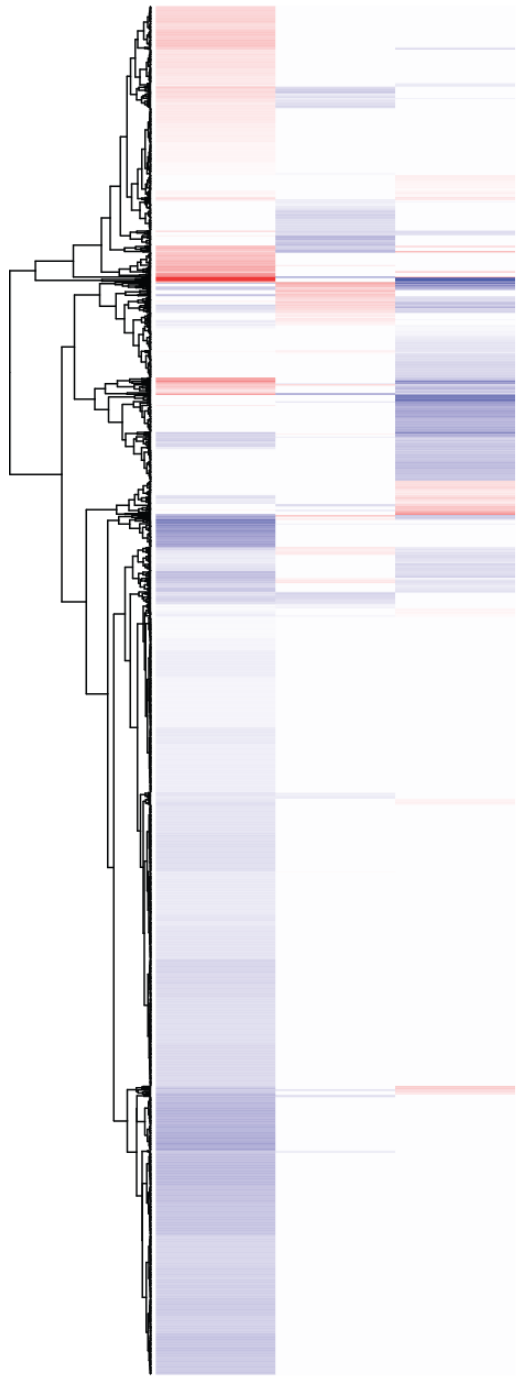
### **Microbial regulation of the L cell transcriptome**

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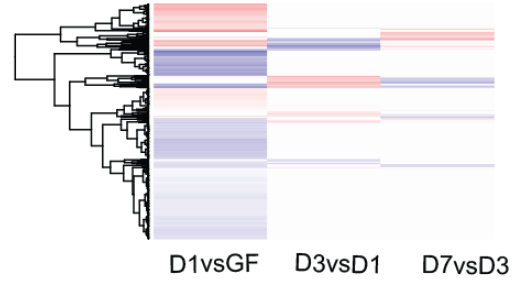
Supplementary figure S1. (a) The expression of genes (expressed as signal intensity) encoding hormones (Gcg, Pyy, Nts, Cck, Insl5, Gip and Ppy) in Lneg and Lpos populations from ileum and colon in GF and CONV-R GLU-Venus mice. \* $p < 0.05$  indicates CONV-R versus GF comparison. (b) MA plots showing average log expression of genes against log fold change (log FC) in CONV-R versus GF comparison in Lpos cells from ileum and colon. Each dot represents a gene and the genes encoding L cell hormones are labelled in red.

Ileum

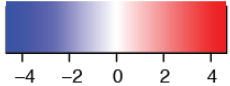


D1vsGF D3vsD1 D7vsD3

Colon



D1vsGF D3vsD1 D7vsD3



-4 -2 0 2 4

Log fold change

Supplementary figure S2. Expression of microbiota-dependent genes in Lpos populations from ileum and colon (obtained in Fig 2) was monitored over D1, 3 and 7 colonization period. Heat map indicates log fold change in expression of significantly altered genes ( $p < 0.05$ ) genes in D1 versus GF, D3 versus D1 and D7 versus D3 comparisons in Lpos populations from ileum and colon.

| <b>Genes encoding different receptor groups</b> |                    |  |              |                  |
|---|--------------------|--|--------------|------------------|
| <b>ID</b>                                       | <b>Gene Symbol</b> | <b>Description</b>                     | <b>logFC</b> | <b>adj.P.Val</b> |
| 17214162  | Gpbar1             | G protein-coupled bile acid receptor 1 | -3.2336      | 0.0000           |
| 17362138  | Gpr137             | G protein-coupled receptor 137         | -1.3305      | 0.0003           |
| 17541465  | Gpr119             | G-protein coupled receptor 119         | -0.8849      | 0.0002           |
| 17337770  | Gpr116             | G protein-coupled receptor 116         | -0.7207      | 0.0003           |
| 17534982  | Gpr112             | G protein-coupled receptor 112         | -0.5121      | 0.0017           |
| 17357630  | Gpr44              | G protein-coupled receptor 44          | -0.4916      | 0.0022           |
| 17284247  | Gpr132             | G protein-coupled receptor 132         | -0.2734      | 0.0171           |
| 17369340  | Gpr107             | G protein-coupled receptor 107         | -0.1879      | 0.0126           |
| 17535353  | Gpr50              | G-protein-coupled receptor 50          | 0.1459       | 0.0136           |
| 17331212  | Gpr15              | G protein-coupled receptor 15          | 0.1817       | 0.0163           |
| 17538960  | Gpr143             | G protein-coupled receptor 143         | 0.2061       | 0.0381           |
| 17533446  | Gpr34              | G protein-coupled receptor 34          | 0.2144       | 0.0461           |
| 17294485  | Gpr150             | G protein-coupled receptor 150         | 0.2751       | 0.0085           |
| 17541919  | Gpr101             | G protein-coupled receptor 101         | 0.2856       | 0.0048           |
| 17504207  | Gpr97              | G protein-coupled receptor 97          | 0.3627       | 0.0027           |
| 17280571  | Gpr22              | G protein-coupled receptor 22          | 0.8624       | 0.0000           |
| 17248911  | Olfir56            | olfactory receptor 56                  | -0.3573      | 0.0011           |
| 17370376  | Olfir368           | olfactory receptor 368                 | -0.2214      | 0.0118           |
| 17387578  | Olfir988           | olfactory receptor 988                 | -0.2057      | 0.0432           |
| 17357940  | Olfir1495          | olfactory receptor 1495                | -0.1587      | 0.0168           |
| 17514916  | Olfir835           | olfactory receptor 835                 | -0.1520      | 0.0249           |
| 17457981  | Olfir448           | olfactory receptor 448                 | -0.1425      | 0.0222           |
| 17299512  | Olfir748           | olfactory receptor 748                 | 0.1011       | 0.0267           |
| 17249258  | Olfir54            | olfactory receptor 54                  | 0.1157       | 0.0372           |
| 17494208  | Olfir69            | olfactory receptor 69                  | 0.1289       | 0.0282           |
| 17246392  | Olfir767           | olfactory receptor 767                 | 0.1306       | 0.0262           |
| 17372912  | Olfir1188          | olfactory receptor 1188                | 0.1323       | 0.0431           |
| 17331230  | Olfir178           | olfactory receptor 178                 | 0.1331       | 0.0304           |
| 17337625  | Olfir133           | olfactory receptor 133                 | 0.1424       | 0.0364           |
| 17363062  | Olfir1426          | olfactory receptor 1426                | 0.1427       | 0.0338           |
| 17246416  | Olfir777           | olfactory receptor 777                 | 0.1427       | 0.0155           |
| 17493121  | Olfir309           | olfactory receptor 309                 | 0.1452       | 0.0392           |
| 17219762  | Olfir414           | olfactory receptor 414                 | 0.1470       | 0.0480           |
| 17481328  | Olfir659           | olfactory receptor 659                 | 0.1519       | 0.0362           |
| 17372771  | Olfir1022          | olfactory receptor 1022                | 0.1528       | 0.0365           |
| 17514920  | Olfir837           | olfactory receptor 837                 | 0.1541       | 0.0148           |
| 17252749  | Olfir59            | olfactory receptor 59                  | 0.1550       | 0.0443           |
| 17494203  | Olfir630           | olfactory receptor 630                 | 0.1585       | 0.0378           |
| 17372931  | Olfir1212          | olfactory receptor 1212                | 0.1595       | 0.0035           |
| 17481153  | Olfir564           | olfactory receptor 564                 | 0.1605       | 0.0416           |

|          |          |                             |         |        |
|----------|----------|-----------------------------|---------|--------|
| 17246422 | Olf801   | olfactory receptor 801      | 0.1614  | 0.0153 |
| 17525720 | Olf945   | olfactory receptor 945      | 0.1623  | 0.0393 |
| 17285641 | Olf1367  | olfactory receptor 1367     | 0.1647  | 0.0358 |
| 17525799 | Olf985   | olfactory receptor 985      | 0.1655  | 0.0191 |
| 17387902 | Olf1223  | olfactory receptor 1223     | 0.1689  | 0.0257 |
| 17374184 | Olf1284  | olfactory receptor 1284     | 0.1705  | 0.0132 |
| 17372906 | Olf1184  | olfactory receptor 1184     | 0.1755  | 0.0390 |
| 17387636 | Olf1040  | olfactory receptor 1040     | 0.1801  | 0.0481 |
| 17357887 | Olf1444  | olfactory receptor 1444     | 0.1881  | 0.0222 |
| 17372927 | Olf1204  | olfactory receptor 1204     | 0.1890  | 0.0298 |
| 17494815 | Olf517   | olfactory receptor 517      | 0.1986  | 0.0059 |
| 17494688 | Olf695   | olfactory receptor 695      | 0.1988  | 0.0135 |
| 17337604 | Olf124   | olfactory receptor 124      | 0.1993  | 0.0117 |
| 17372759 | Olf1014  | olfactory receptor 1014     | 0.1994  | 0.0049 |
| 17481510 | Olf716   | olfactory receptor 716      | 0.2015  | 0.0282 |
| 17387720 | Olf1098  | olfactory receptor 1098     | 0.2019  | 0.0306 |
| 17534667 | Olf1320  | olfactory receptor 1320     | 0.2036  | 0.0226 |
| 17462133 | Olf212   | olfactory receptor 212      | 0.2053  | 0.0035 |
| 17494254 | Olf66    | olfactory receptor 66       | 0.2065  | 0.0373 |
| 17494467 | Olf684   | olfactory receptor 684      | 0.2100  | 0.0012 |
| 17265802 | Olf398   | olfactory receptor 398      | 0.2108  | 0.0304 |
| 17481250 | Olf633   | olfactory receptor 633      | 0.2138  | 0.0225 |
| 17290906 | Olf1368  | olfactory receptor 1368     | 0.2172  | 0.0076 |
| 17486096 | Olf1349  | olfactory receptor 1349     | 0.2208  | 0.0084 |
| 17466416 | Olf458   | olfactory receptor 458      | 0.2208  | 0.0014 |
| 17337608 | Olf125   | olfactory receptor 125      | 0.2256  | 0.0090 |
| 17238642 | Olf763   | olfactory receptor 763      | 0.2264  | 0.0115 |
| 17263185 | Olf323   | olfactory receptor 323      | 0.2397  | 0.0410 |
| 17494443 | Olf666   | olfactory receptor 666      | 0.2427  | 0.0079 |
| 17265761 | Olf1     | olfactory receptor 1        | 0.2525  | 0.0017 |
| 17516120 | Olf145   | olfactory receptor 145      | 0.2621  | 0.0006 |
| 17336071 | Olf55    | olfactory receptor 55       | 0.2637  | 0.0023 |
| 17457977 | Olf449   | olfactory receptor 449      | 0.3191  | 0.0248 |
| 17481141 | Olf557   | olfactory receptor 557      | 0.3348  | 0.0000 |
| 17341326 | Vmn2r109 | vomeronasal 2, receptor 109 | -0.1597 | 0.0120 |
| 17246473 | Vmn2r84  | vomeronasal 2, receptor 84  | 0.1042  | 0.0309 |
| 17467181 | Vmn1r21  | vomeronasal 1 receptor 21   | 0.1288  | 0.0204 |
| 17459248 | Vmn1r37  | vomeronasal 1 receptor 37   | 0.1305  | 0.0316 |
| 17458928 | Vmn1r5   | vomeronasal 1 receptor 5    | 0.1321  | 0.0482 |
| 17493053 | Vmn2r67  | vomeronasal 2, receptor 67  | 0.1322  | 0.0144 |
| 17234873 | Vmn2r81  | vomeronasal 2, receptor 81  | 0.1369  | 0.0398 |
| 17450904 | Vmn2r14  | vomeronasal 2, receptor 14  | 0.1388  | 0.0339 |
| 17460749 | Vmn1r41  | vomeronasal 1 receptor 41   | 0.1408  | 0.0466 |

| 17333769   | Vmn2r95            | vomeronasal 2, receptor 95                | 0.1456       | 0.0245           |
|--|--------------------|---|--------------|------------------|
| 17488090   | Vmn1r185           | vomeronasal 1 receptor 185                | 0.1461       | 0.0497           |
| 17291064   | Vmn1r189           | vomeronasal 1 receptor 189                | 0.1484       | 0.0347           |
| 17486527   | Vmn1r84            | vomeronasal 1 receptor 84                 | 0.1499       | 0.0154           |
| 17346591   | Vmn2r120           | vomeronasal 2, receptor 120               | 0.1507       | 0.0251           |
| 17486055   | Vmn1r60            | vomeronasal 1 receptor 60                 | 0.1608       | 0.0133           |
| 17462816   | Vmn2r23            | vomeronasal 2, receptor 23                | 0.1616       | 0.0412           |
| 17479952   | Vmn2r77            | vomeronasal 2, receptor 77                | 0.1753       | 0.0092           |
| 17467187   | Vmn1r22            | vomeronasal 1 receptor 22                 | 0.1762       | 0.0057           |
| 17486314   | Vmn2r42            | vomeronasal 2, receptor 42                | 0.1842       | 0.0396           |
| 17458936   | Vmn1r8             | vomeronasal 1 receptor 8                  | 0.1885       | 0.0403           |
| 17490031   | Vmn2r59            | vomeronasal 2, receptor 59                | 0.1902       | 0.0006           |
| 17479967   | Vmn2r79            | vomeronasal 2, receptor 79                | 0.2045       | 0.0404           |
| 17474863   | Vmn1r174           | vomeronasal 1 receptor 174                | 0.2249       | 0.0082           |
| 17487619   | Vmn1r149           | vomeronasal 1 receptor 149                | 0.2372       | 0.0041           |
| 17434167   | Vmn2r122           | vomeronasal 2, receptor, 122              | 0.3261       | 0.0017           |
| 17232172   | Taar1              | trace amine-associated receptor 1         | 0.1301       | 0.0416           |
| 17232195   | Taar7f             | trace amine-associated receptor 7F        | 0.1524       | 0.0405           |
| 17232178   | Taar3              | trace amine-associated receptor 3         | 0.1884       | 0.0240           |
| <b>Genes groups involved in synaptic vesicle cycle</b> |                    |   |              |                  |
| <b>ID</b>  | <b>Gene Symbol</b> | <b>Description</b>                        | <b>logFC</b> | <b>adj.P.Val</b> |
| 17532879   | Syp                | synaptophysin                             | -0.7412      | 0.0047           |
| 17357486   | Syt7               | synaptotagmin VII                         | -1.9621      | 0.0000           |
| 17533234   | Syt15              | synaptotagmin-like 5                      | -1.5187      | 0.0000           |
| 17246163   | Esyt1              | extended synaptotagmin-like protein 1     | -1.1727      | 0.0011           |
| 17279584   | Esyt2              | extended synaptotagmin-like protein 2     | -1.1419      | 0.0013           |
| 17373530   | Syt13              | synaptotagmin XIII                        | -0.6979      | 0.0121           |
| 17231174   | Syt14              | synaptotagmin XIV                         | -0.3572      | 0.0428           |
| 17340532   | Syt13              | synaptotagmin-like 3                      | 0.1687       | 0.0112           |
| 17217536   | Syt2               | synaptotagmin II                          | 0.2947       | 0.0323           |
| 17485815   | Syt5               | synaptotagmin V                           | 0.9105       | 0.0000           |
| 17376822   | Snap25             | synaptosomal-associated protein 25        | -1.6392      | 0.0000           |
| 17375083   | Snap23             | synaptosomal-associated protein 23        | -1.3474      | 0.0032           |
| 17263401   | Snap47             | synaptosomal-associated protein, 47       | -0.9653      | 0.0130           |
| 17529417   | Snap91             | synaptosomal-associated protein 91        | -0.7167      | 0.0000           |
| 17279737   | Rab10              | RAB10, member RAS oncogene family         | -1.4537      | 0.0003           |
| 17468705   | Rab7               | RAB7, member RAS oncogene family          | -1.3400      | 0.0005           |
| 17306835   | RabggtA            | Rab geranylgeranyl transferase, a subunit | -1.0574      | 0.0000           |
| 17515340   | Rab3d              | RAB3D, member RAS oncogene family         | -1.0374      | 0.0003           |
| 17342496   | Rab40c             | Rab40c, member RAS oncogene family        | -1.0242      | 0.0183           |
| 17348238   | Rab18              | RAB18, member RAS oncogene family         | -0.9455      | 0.0210           |
| 17416764   | Rab3b              | RAB3B, member RAS oncogene family         | -0.9226      | 0.0000           |

|          |           |   |         |        |
|----------|-----------|---|---------|--------|
| 17524827 | Rab3d     | RAB3D, member RAS oncogene family             | -0.9129 | 0.0000 |
| 17397462 | Rab33b    | RAB33B, member of RAS oncogene family         | -0.8971 | 0.0319 |
| 17547998 | Rab11b    | RAB11B, member RAS oncogene family            | -0.8626 | 0.0008 |
| 17228751 | Rabgap11  | RAB GTPase activating protein 1-like          | -0.8615 | 0.0020 |
| 17342559 | Rab11fip3 | RAB11 family interacting protein 3 (class II) | -0.8528 | 0.0004 |
| 17282074 | Rab15     | RAB15, member RAS oncogene family             | -0.8482 | 0.0040 |
| 17411635 | Rab2a     | RAB2A, member RAS oncogene family             | -0.7770 | 0.0115 |
| 17480205 | Rab30     | RAB30, member RAS oncogene family             | -0.7277 | 0.0000 |
| 17247533 | Rab1      | RAB1, member RAS oncogene family              | -0.6711 | 0.0183 |
| 17306274 | Rab2b     | RAB2B, member RAS oncogene family             | -0.6137 | 0.0031 |
| 17346840 | Rab12     | RAB12, member RAS oncogene family             | -0.5779 | 0.0226 |
| 17225460 | Rab17     | RAB17, member RAS oncogene family             | -0.5039 | 0.0011 |
| 17380251 | Rab22a    | RAB22A, member RAS oncogene family            | -0.4714 | 0.0181 |
| 17530231 | Rab6b     | RAB6B, member RAS oncogene family             | -0.3752 | 0.0380 |
| 17535984 | Rab39b    | RAB39B, member RAS oncogene family            | -0.3162 | 0.0019 |
| 17527166 | Rab39     | RAB39, member RAS oncogene family             | -0.2207 | 0.0184 |
| 17366055 | Rab11fip2 | RAB11 family interacting protein 2 (class I)  | -0.2054 | 0.0168 |
| 17520922 | Rab6b     | RAB6B, member RAS oncogene family             | -0.1781 | 0.0250 |
| 17544779 | Rab9b     | RAB9B, member RAS oncogene family             | 0.3470  | 0.0020 |
| 17502039 | Rab3a     | RAB3A, member RAS oncogene family             | 0.9580  | 0.0075 |

Supplementary table S1. List of gene groups ( $p < 0.05$ ) encoding receptors, and involved in synaptic vesicle cycling in Lpos cells from ileum. LogFC indicate log fold change of gene in GF versus CONV-R comparison



| <b>ID</b>  | <b>Description</b>                        | <b>p-value</b> | <b>Adj. p-value</b> | <b>z-score</b> |
|------------|---|----------------|---------------------|----------------|
| GO:0008015 | Blood circulation                         | 0.00866        | 0.30081             | 0.00000        |
| GO:0030031 | Cell projection assembly                  | 0.01125        | 0.31714             | 0.20851        |
| GO:0042060 | Wound healing                             | 0.02925        | 0.4412              | 0.47141        |
| GO:1901361 | Organic cyclic compound catabolic process | 0.01915        | 0.37754             | 0.72761        |
| GO:0006936 | Muscle contraction                        | 0.0058         | 0.28599             | 0.72761        |
| GO:0016050 | Vesicle organization                      | 0.01136        | 0.31714             | 0.50000        |
| GO:0031667 | Response to nutrient levels               | 0.03076        | 0.44794             | 2.32380        |
| GO:0010038 | Response to metal ion                     | 0.0088         | 0.30081             | 0.53452        |
| GO:0003015 | Heart process                             | 0.01079        | 0.31323             | -0.27735       |
| GO:0098780 | Response to mitochondrial depolarisation  | 0.00131        | 0.18782             | 2.30940        |
| GO:0006839 | Mitochondrial transport                   | 0.04692        | 0.49775             | -1.15470       |
| GO:0009743 | Response to carbohydrate                  | 0.04494        | 0.49775             | -0.90453       |
| GO:0051648 | Vesicle localization                      | 0.03999        | 0.48394             | 1.50756        |

Supplementary table S2. Gene ontology (GO) enrichment analysis of microbiota-regulated genes in CONV-R versus GF comparison in Lpos population from colon.