

## Supplemental Tables

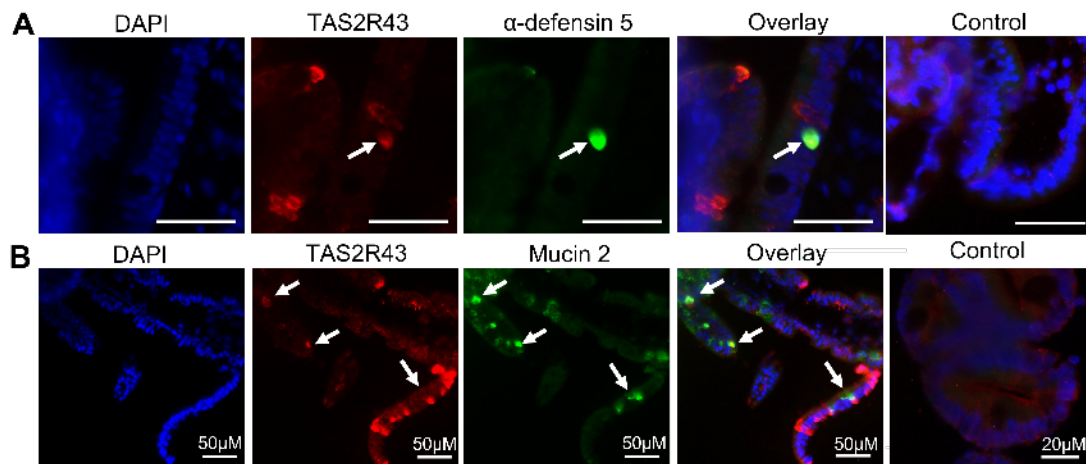
**Supplemental Table 1.** Demographics of lean and obese subjects

<b>Parameter</b>	<b>Lean (n=9)</b>	<b>Obese (n=42)</b>	<b>Lean vs Obese</b>
<b>Male/Female</b>	7/2	8/34	<i>P</i> <0.001
<b>Age (years)</b>	57±3	47±2	<i>P</i> <0.05
<b>BMI (kg/m<sup>2</sup>)</b>	23.9±1.1	40.8±0.7	<i>P</i> <0.001

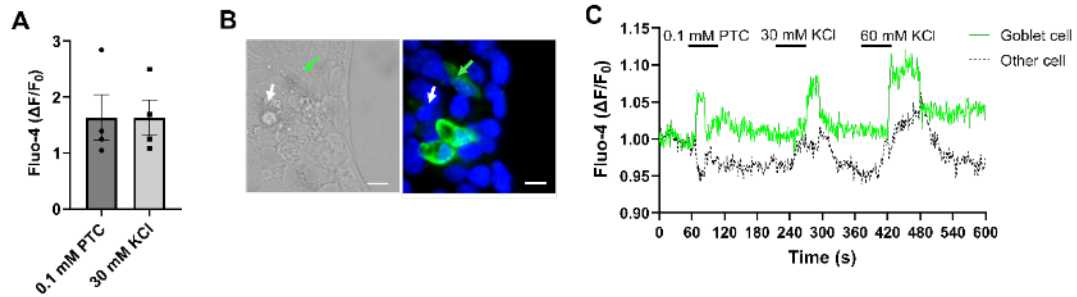
**Supplemental Table 2.** Primers used in qPCR

<b>Genes</b>	<b>Forward primer</b>	<b>Reverse primer</b>	<b>Size (bp)</b>
<i>TAS2R4</i>	GCAGTGCTGGTTTGTGACC	GCGTGATGTACAGGCAAGTG	168
<i>TAS2R5</i>	ACACTCATGGCAGCCTATCC	CGAGCACACACTGTCTTCCA	107
<i>TAS2R7</i>	GCAGGTGTGGATGTCAAACCTC	TCTTGACCCAGTCCATGCAG	167
<i>TAS2R8</i>	ATGTGGATTACCACCTGCCT	GGAAATGGCAAAGCATCCCAG	135
<i>TAS2R10</i>	CCTTTGGAGACACAACAGGC	GACCCCAGGGATAGATGGCT	221
<i>TAS2R13</i>	GAAAGTGCCCTGCCGAGTAT	CCAGATCAGCCCAATTCTGGA	177
<i>TAS2R14</i>	CCAGGTGATGGGAATGGCTTA	AGGGCTCCCCATCTTTGAAC	128
<i>TAS2R16</i>	ATGGCATCACTGACCAAGCA	TTCAACGTAGGGCTGCTCA	255
<i>TAS2R20</i>	ATTTGGGGGAACAAGACGCT	ACTACGGAAAACTTGTGGGAA	183
<i>TAS2R30</i>	GGCTGGAAAAGCAACCTGTC	ACACAATGCCCTCTTGTGA	191
<i>TAS2R31</i>	TTGAGGAGTGCAGTGTACCTTTC	ACGGCACATAACAAGAGGAAAA	218
<i>TAS2R38</i>	AGGCCACATTAAGCCCTC	CAGCTCTCCTCAACTTGGA	216
<i>TAS2R39</i>	TTCTGTGGCTGTCCGTGTTTA	GGGTGGCTGTCAGGATGAAC	207
<i>TAS2R40</i>	CGGTGAACACAGATGCCACAGATA	GTGTTTTGCCCTGGCCCACT	150
<i>TAS2R43</i>	ATATCTGGGCAGTGATCAACC	CCCAACAACATCACCAGAATGAC	148
<i>TAS2R46</i>	ACATGACTTGGAAGATCAAACCTGAG	AGCTTTTATGTGGACCTTCATGC	200
<i>RPS11</i>	CAGCCGACCATCTTTCAAAAC	TCTCGAAGCGGTTGTACTTG	274
<i>RPS18</i>	ACCAACATCGATGGGCGGCG	TGGTGATCACACGTTCCACCTCA	157
<i>GAPDH</i>	AGGTGAAGGTCGGAGTCA	GGTCATTGATGGCAACAA	99
<i>DEFA5</i>	GCCATCCTTGCTGCCATTC	TGATTTACACACCCCCGGAGA	241
<i>DEFA6</i>	CCTCACCATCCTCACTGCTGTTT	CCATGACAGTGCAGGTCCCATA	266
<i>DEFB1</i>	ATGAGAACTTCTACCTTCTG	TCACTTGCAGCACTTGCC	207
<i>DEFB4A</i>	CCAGCC ATCAGCCATGAGGGT	GGAGCCCTTTCTGAAT CCGCA	255
<i>MUC1</i>	CATTGCCTTGGCTGTCTGTC	GCGACGTGCCCTACAAG	246
<i>MUC2</i>	CAGCACCGATTGCTGAGTTG	GCTGGTCATCTCAATGGCAG	140
<i>TAS2R43- Sequencing</i>	CCAGTCTGGTAGTGGTTACA	TCACCCAGTACCTCATTTGCC	876
<i>GDF-15</i>	TCCAGACCTATGATGACTTGT	AACCTTGAGCCCATTCCA	127

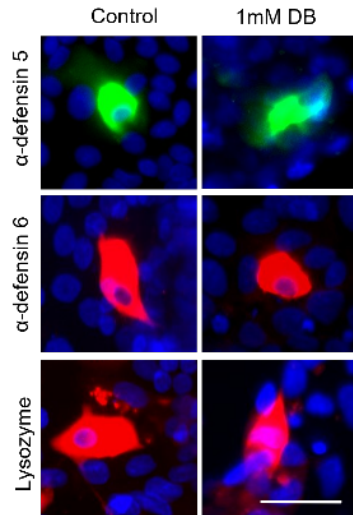
## Supplemental Figures



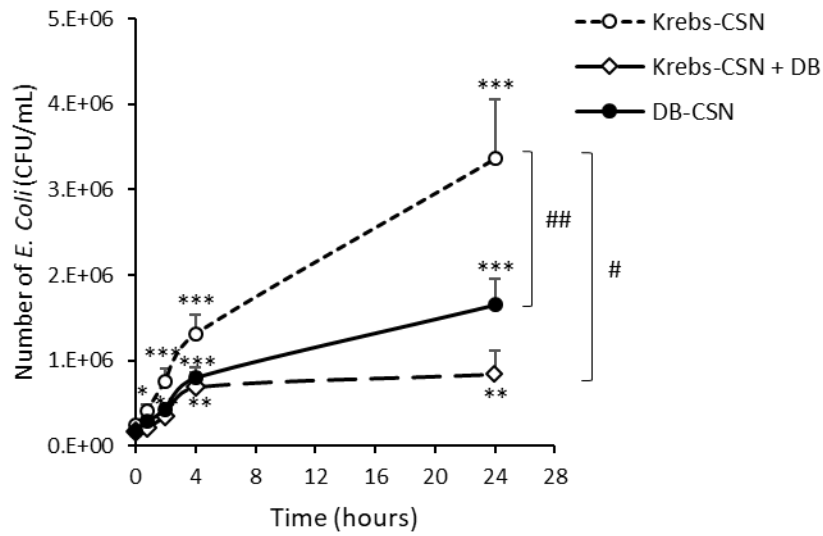
**Supplemental Figure 1. Co-localization of TAS2R43 with Paneth or goblet cells in tissue sections from a lean subject.** Representative double-immunofluorescence staining of jejunal tissue sections from a lean organ donor for TAS2R43 (red) and (A)  $\alpha$ -defensin 5, Paneth cells, or (B) mucin 2, goblet cells, (green). Nuclei were stained by DAPI (blue). Scale bars, (A) 50  $\mu$ m or (B) as indicated. Co-localization was performed in sections from two lean subjects.



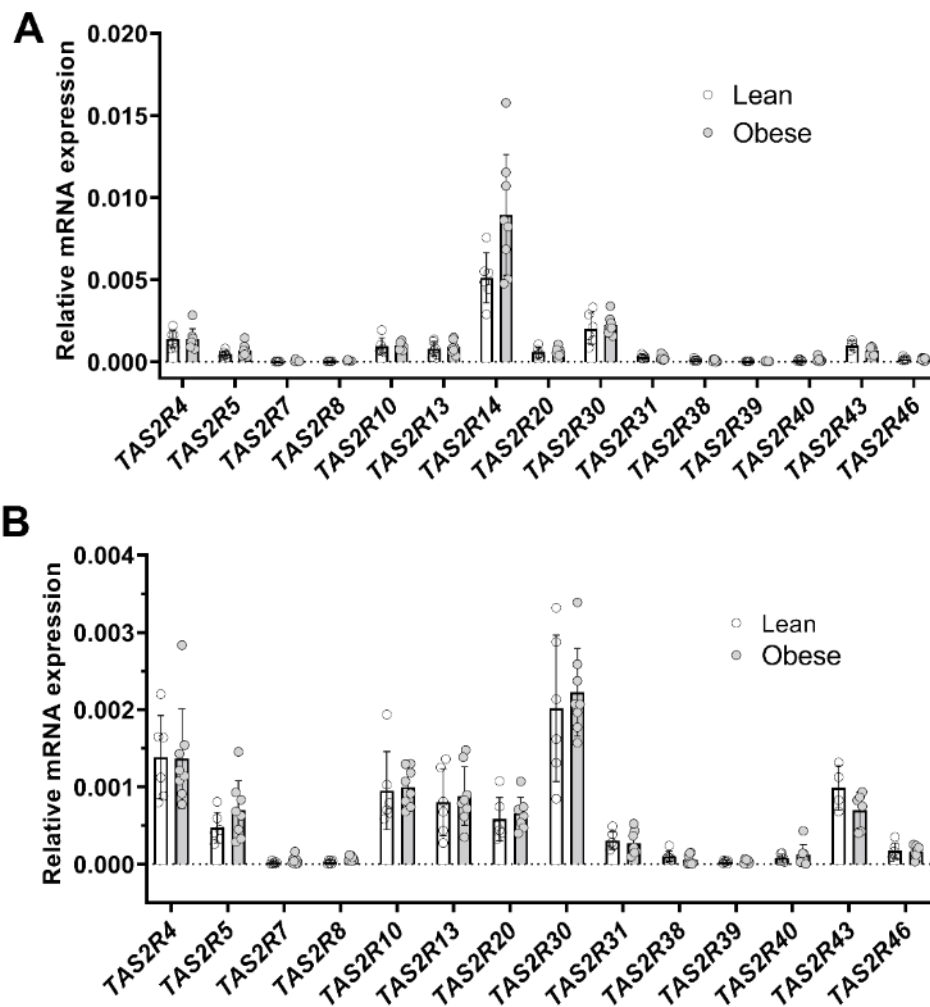
**Supplemental Figure 2. Intracellular  $\text{Ca}^{2+}$  changes in response to PTC and identification of cells in crypts from obese patients by immunostaining.** (A) Relative rise in fluorescence intensity in single cells from primary jejunal crypts from obese patients treated with 0.1 mM PTC or 30 mM KCl. Data represent the mean $\pm$ SEM, n=4 obese subjects. (B) The left picture shows the cells in brightfield of which the tracings of the  $\text{Ca}^{2+}$  changes are depicted. The right picture shows the immunofluorescent staining for mucin 2, a marker for goblet cells. (C) Tracing of a goblet cell responding to 0.1 mM PTC with a  $\text{Ca}^{2+}$  increase and a non-identified, non-responding cell. Scale bars=20  $\mu\text{M}$ .



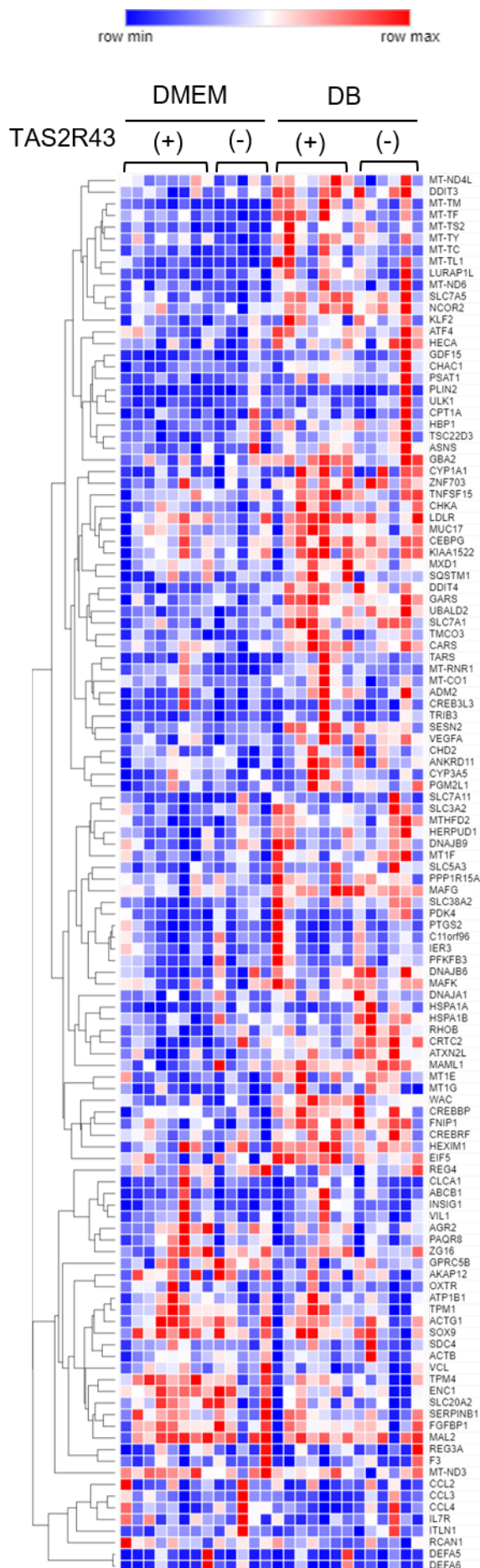
**Supplemental Figure 3. Immunofluorescence study of the effect of DB on protein expression in Paneth cells in a lean subject.** Representative immunofluorescence staining for  $\alpha$ -defensin 5,  $\alpha$ -defensin 6 and lysozyme after 30 min treatment of jejunal crypts from a lean patient with DMEM or 1mM DB. No difference between control and 1 mM DB treatment was detected. Scale bar, 25 $\mu$ m.



**Supplemental Figure 4. Bacteriostatic effects of DB on *E. coli* growth.** Time-dependent effect of the supernatant of jejunal crypts from obese patients stimulated for 4 hours with Krebs (Krebs-CSN) or DB (DB-CSN) on colony forming units (CFU) of *E. coli* and their bacteriostatic control (Krebs-CSN + DB). Data represent the mean $\pm$ SEM, (n=4-6). Statistics: mixed model over time \*:  $P < 0.05$ , \*\*:  $P < 0.01$ , \*\*\*:  $P < 0.001$ , vs. 0h; #:  $P < 0.05$ , ##:  $P < 0.01$ , vs. Krebs-CSN.

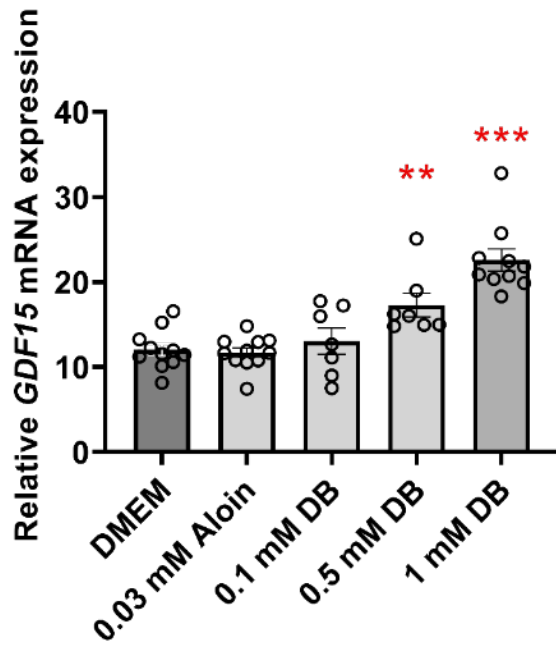


**Supplemental Figure 5. Relative mRNA expression of TAS2Rs in crypts derived from either lean or obese subjects.** (A and B) Relative mRNA expression of single TAS2Rs in primary jejunal crypts from lean (n=4-6) and obese (n=6-8) subjects normalized to the expression of the endogenous controls RPS18, GAPDH and RPS11. (B) Detail of (A) excluding TAS2R14. Data represent the mean $\pm$ SEM. Statistics: Mixed model lean vs. obese. No significant differences between the expression of TAS2Rs in lean vs. obese was detected.

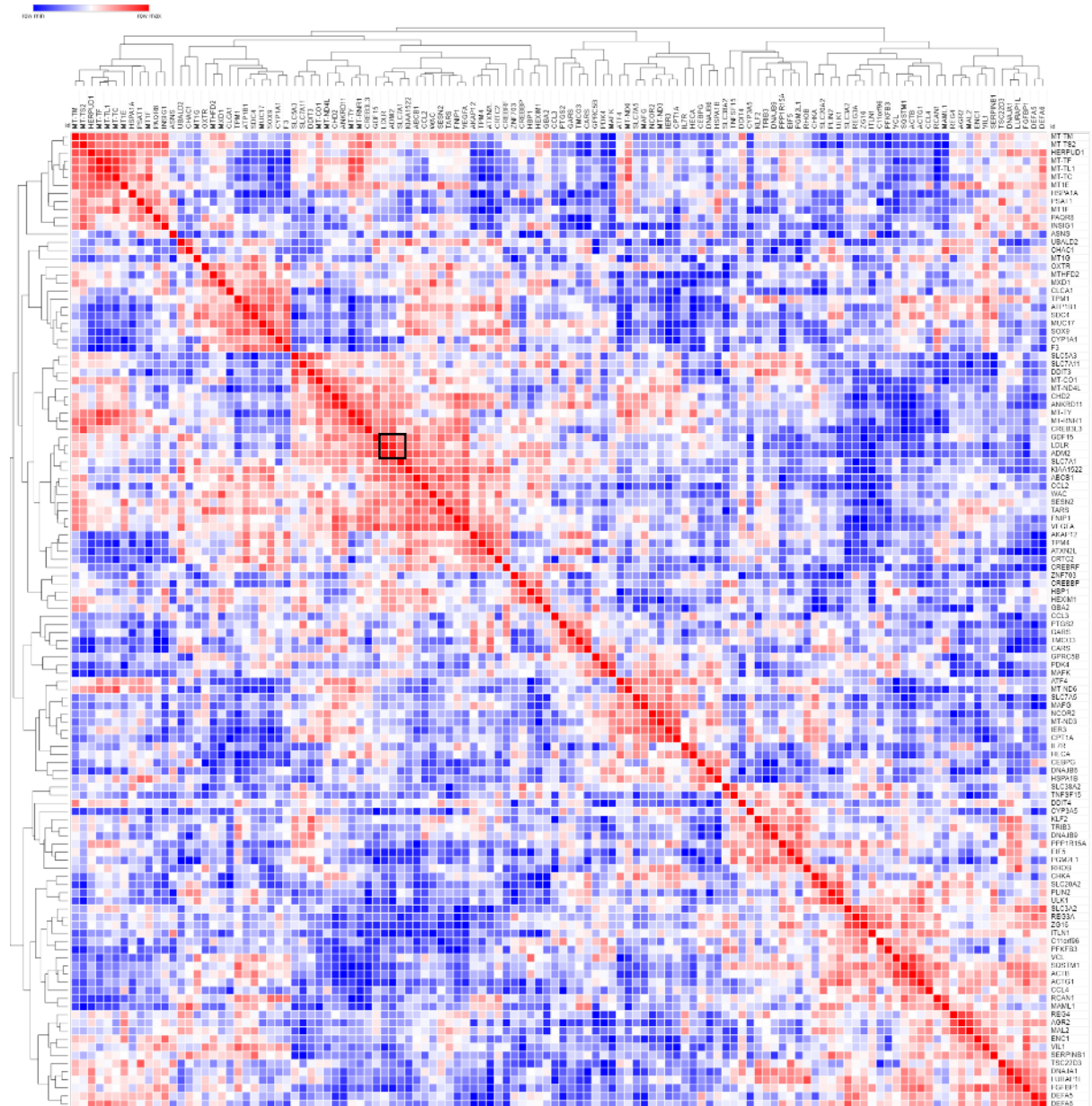


**Supplemental Figure 6. Heatmap of the 120 identified DEGs identified in jejunal crypts from obese TAS2R43(+) and TAS2R43(-) patients after 4 hours treatment with DMEM or 1mM DB. Hierarchical clustering was conducted by one minus Pearson correlation, linkage method average, with the heatmapping tool Morpheus of the Broad Institute.**

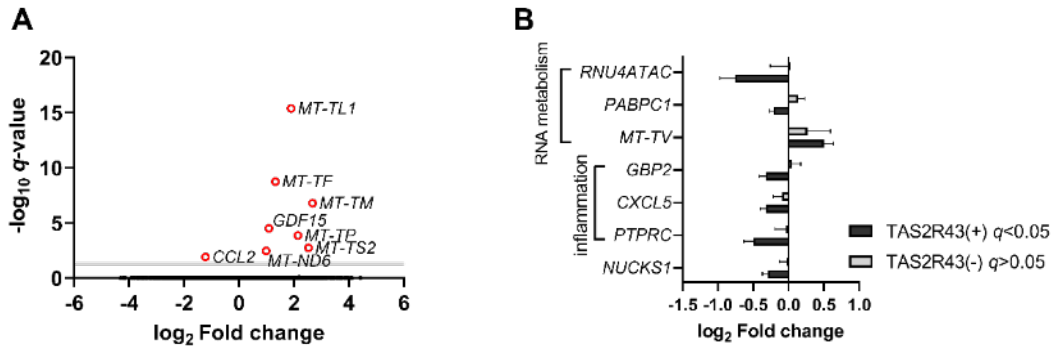




**Supplemental Figure 7. Effect of bitter agonists on *GDF15* mRNA expression in crypts from obese patients.** Concentration-dependent effect of treatment of jejunal crypts from obese patients (n=7-11) for 4 hours with DB (0.1-1 mM) on relative *GDF15* mRNA expression. Treatment with 0.03 mM aloin for 4h had no effect on *GDF15* mRNA expression. Data represent the mean±SEM. Statistics: mixed model. \*\*:  $P < 0.01$ , \*\*\*:  $P < 0.001$ , vs. DMEM.



**Supplemental Figure 8. Correlation matrix of the fold changes of 120 identified DEGs in response to DB in jejunal crypts from obese patients. The most significantly upregulated gene *GDF15* significantly correlated with *ADM2* and *LDLR*, position indicated by a black square (Pearson *r*).**



**Supplemental Figure 9. Transcriptomic analysis of jejunal crypts from lean or obese subjects stimulated with DB. (A)** Volcano plot showing the log<sub>2</sub> fold changes (DB-DMEM) of significantly DEGs indicated in red, after treatment of crypts derived from lean subjects (n=4) with 1 mM DB or DMEM (control). **(B)** Comparison of the log<sub>2</sub> fold changes of the 7 DEGs identified only in the data set of the TAS2R43(+) obese subjects (n=7-8) after treatment with 1 mM DB vs TAS2R43(-) (n=5-6).