

1 **Fig. S1** Effect of addition of hydrolyzed casein to diets with different protein levels on  
2 growth performance of mice. Body weight (A), daily food intake (B), the mRNA levels  
3 of epithelial cell marker genes in the jejunum and ileum (C, D), the mRNA levels of  
4 enteroendocrine cell marker genes in the jejunum and ileum (E, F), the mRNA levels  
5 of enteroendocrine cell transcription factors in the jejunum and ileum (G, H), the  
6 mRNA levels of ghrelin in the stomach (I), and the small intestine length of mouse (J).  
7 Data are presented as mean  $\pm$  SEM. (n = 6-7 per group). \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P$   
8  $< 0.001$ , the hydrolyzed casein group compared with the casein group. Analyzed by  
9 independent-samples T test ( $P < 0.05$ ).

10 **Fig. S2** Effect of addition of hydrolyzed casein to diets on growth performance of mice  
11 after antibiotic drinking water treatment. Body weight (A), and daily food intake (B).  
12 Data are presented as mean  $\pm$  SEM. (n = 6-7 per group). \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  
13  $P < 0.001$ , the hydrolyzed casein group compared with the casein group in vehicle and  
14 ABX. Analyzed by independent-samples T test ( $P < 0.05$ ).

15 **Fig. S3** Hydrolyzed casein changed duodenal microbial composition in mice. The venn  
16 diagram of Casein vs Hydrolyzed Casein (A), principal component analysis (PCA) of  
17 bacterial community (B), and the distribution (%) of bacteria at phylum level and genus  
18 level in the duodenum of mice (C). Data are presented as mean  $\pm$  SEM (n = 4 per group),  
19 \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P < 0.001$ , the hydrolyzed casein group compared with the  
20 casein group. Analyzed by Mann–Whitney U test with Bonferroni-adjusted  $P$ -  
21 values.

22 **Fig. S4** Effect of addition of hydrolyzed casein to diets on the quantities of  
23 *Akkermansia*, *Bifdobacterium* and Total bacteria in duodenal mucosa of mice after  
24 antibiotic drinking water treatment in the duodenal mucosa. The quantities of  
25 *Akkermansia* in the duodenal mucosa (A), the quantities of *Bifdobacterium* in the  
26 duodenal mucosa(B), and the quantities of total bacteria in the duodenal mucosa (C).  
27 Data are presented as mean  $\pm$  SEM. (n = 6-7per group). \*  $P < 0.05$ , \*\*  $P < 0.01$ , \*\*\*  $P$   
28  $< 0.001$ , the hydrolyzed casein group compared with the casein group in normal and  
29 low protein, respectively. Statistical analyses were performed using one or two-way  
30 ANOVA followed by a Tukey post-hoc comparisons.  $P$ -values of general effect for diet  
31 (D) and ABX (A) factors and diet  $\times$  ABX (D  $\times$  A) interaction are recorded under the  
32 title of each graph.

33 **Fig. S5** Effect of addition of hydrolyzed casein to diets on the quantities of  
34 *Akkermansia*, *Bifdobacterium* and Total bacteria in duodenal mucosa of mice after  
35 antibiotic drinking water treatment in the jejunum. The quantities of *Akkermansia* in  
36 the jejunal mucosa and digesta (A, D), the quantities of *Bifdobacterium* in the jejunal  
37 mucosa and digesta (B, E), and the quantities of total bacteria in the jejunal mucosa and  
38 digesta (C, F). Data are presented as mean  $\pm$  SEM. (n = 5-6per group). \*  $P < 0.05$ , \*\*  
39  $P < 0.01$ , \*\*\*  $P < 0.001$ , the hydrolyzed casein group compared with the casein group  
40 in normal and low protein, respectively. Statistical analyses were performed using one  
41 or two-way ANOVA followed by a Tukey post-hoc comparisons.  $P$ -values of general

42 effect for diet (D) and ABX (A) factors and diet  $\times$  ABX (D  $\times$  A) interaction are recorded  
43 under the title of each graph.

44 **Fig. S6** Effect of addition of hydrolyzed casein to diets on the quantities of  
45 *Akkermansia*, *Bifidobacterium* and Total bacteria in duodenal mucosa of mice after  
46 antibiotic drinking water treatment in the ileum. the quantities of *Akkermansia* in the  
47 ileal mucosa and digesta (A, D), the quantities of *Bifidobacterium* in the ileal mucosa  
48 and digesta (B, E), and the quantities of total bacteria in the ileal mucosa and digesta  
49 (C, F). Data are presented as mean  $\pm$  SEM. (n = 5-6per group). \*  $P < 0.05$ , \*\*  $P < 0.01$ ,  
50 \*\*\*  $P < 0.001$ , the hydrolyzed casein group compared with the casein group in normal  
51 and low protein, respectively. Statistical analyses were performed using one or two-  
52 way ANOVA followed by a Tukey post-hoc comparisons.  $P$ -values of general effect  
53 for diet (D) and ABX (A) factors and diet  $\times$  ABX (D  $\times$  A) interaction are recorded  
54 under the title of each graph.

55 **Fig. S7** Effect of addition of hydrolyzed casein to diets on growth performance of mice  
56 after administration of *A. muciniphila* treatment. Body weight (A), and daily food  
57 intake (B). Data are presented as mean  $\pm$  SEM. (n = 8 per group). \*  $P < 0.05$ , \*\*  $P <$   
58 0.01, \*\*\*  $P < 0.001$ , the hydrolyzed casein group compared with the casein group in  
59 normal and low protein, respectively. Analyzed by independent-samples T test ( $P <$   
60 0.05).

61 **Table S1.** Experimental diet composition and nutrient levels. <sup>1</sup>Mineral mixture (per kg  
62 diet): Ca 5 g; P 1.5 g; K 3.6 g; Mg 0.5 g; Fe 45 mg; Cu 6.0 mg; Mn 10.0 mg; Zn 36.6

63 mg; I 0.2 mg; Na 1g; Se 0.18mg; chlorine 1.6 g; fluorine 1 mg; chromium 1 mg;  
64 molybdenum 0.15 mg. <sup>2</sup> Vitamin mix (per kg diet): vitamin A 4000 IU; vitamin D<sub>3</sub>  
65 1000 IU; vitamin K<sub>3</sub> 0.09 mg; vitamin B<sub>12</sub> 25 µg; vitamin B<sub>6</sub> 6 mg; riboflavin 6 mg;  
66 biotin 0.2 mg; folic acid 2.0 mg; nicotinamide 30 mg; D-pantothenic acid 15 mg. <sup>3</sup> The  
67 energy of diets was calculated based on the contents of protein, fat and carbohydrate.

68 **Table S2.** List of primers used in the present study.

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