Electronic Supplementary Material (ESI) for Food & Function.


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

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

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

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

**Fig. S5** Effect of addition of hydrolyzed casein to diets on the quantities of *Akkermansia*, *Bifdobacterium* and Total bacteria in duodenal mucosa of mice after antibiotic drinking water treatment in the jejunum. The quantities of *Akkermansia* in the jejunal mucosa and digesta (A, D), the quantities of *Bifdobacterium* in the jejunal mucosa and digesta (B, E), and the quantities of total bacteria in the jejunal mucosa and digesta (C, F). Data are presented as mean ± SEM. (n = 5-6per group). * $P < 0.05$, ** $P < 0.01$, *** $P < 0.001$, the hydrolyzed casein group compared with the casein group in normal and low protein, respectively. Statistical analyses were performed using one or two-way ANOVA followed by a Tukey post-hoc comparisons. *P*-values of general effect for diet (D) and ABX (A) factors and diet × ABX (D × A) interaction are recorded under the title of each graph.

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

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

**Table S1.** Experimental diet composition and nutrient levels. [1] Mineral mixture (per kg 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

mg; I 0.2 mg; Na 1g; Se 0.18mg; chlorine 1.6 g; fluorine 1 mg; chromium 1 mg; molybdenum 0.15 mg. [2] Vitamin mix (per kg diet)：vitamin A 4000 IU; vitamin $D_3$ 1000 IU; vitamin $K_3$ 0.09 mg; vitamin $B_{12}$ 25 μg; vitamin $B_6$ 6 mg; riboflavin 6 mg; biotin 0.2 mg; folic acid 2.0 mg; nicotinamide 30 mg; D-pantothenic acid 15 mg. [3] The energy of diets was calculated based on the contents of protein, fat and carbohydrate.

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