Akkermansia muciniphila administration ameliorates streptozotocin-induced hyperglycemia and muscle atrophy by promoting IGF2 secretion from mouse intestine

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Background

Type 1 diabetes

Insulin Absolute Deficiency, Infections, Genetic or Immune Factors	Cause of Disease
Adolescents or children under the age of 20	Age Range
Normal weight or slightly underweight	Body Weight
Increased eating, increased urination, increased drinking, and weight loss	Symptoms
Acute complications, coma, and shock	Complications
Methods of Insulin Injection	Treatment Methods

Results

Figure 1

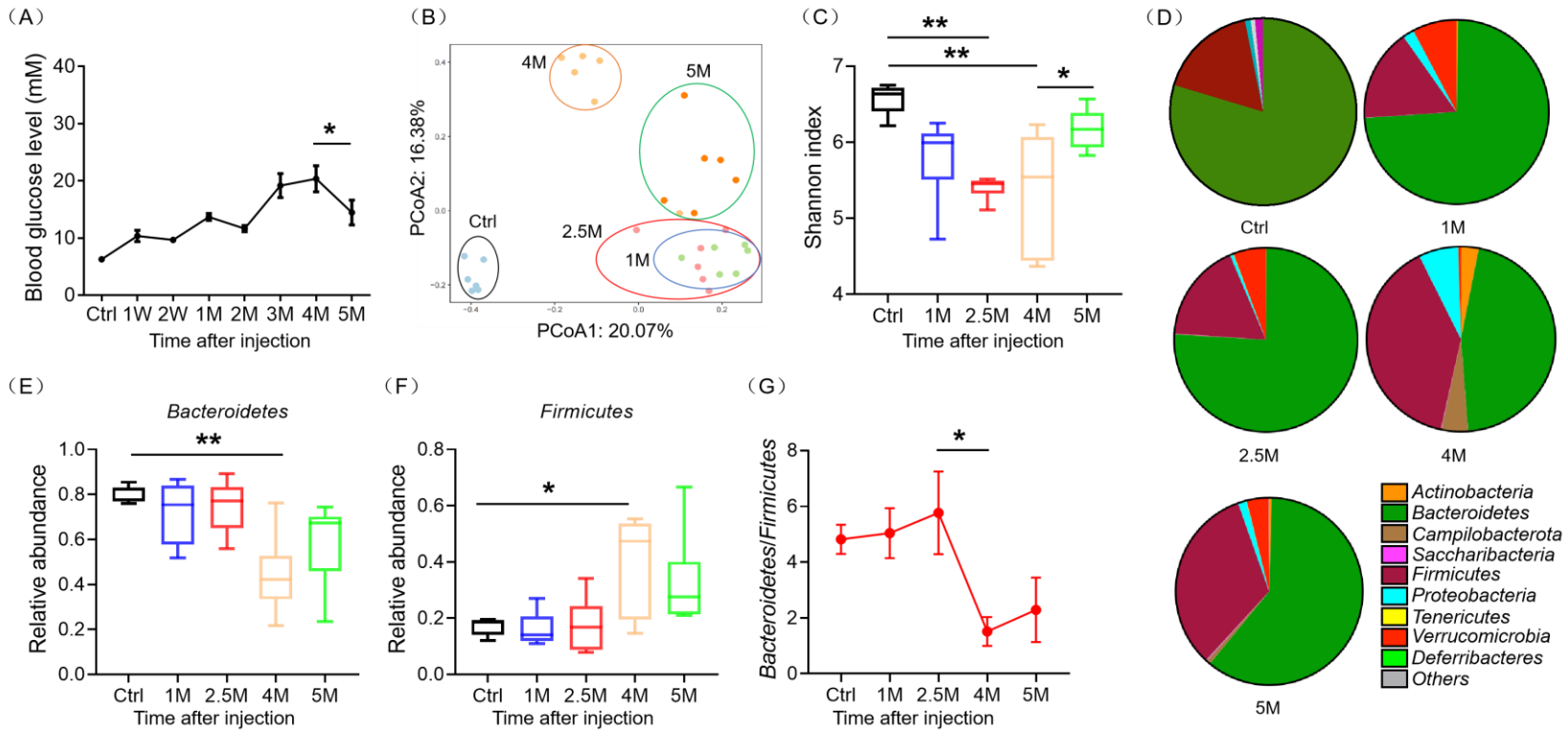
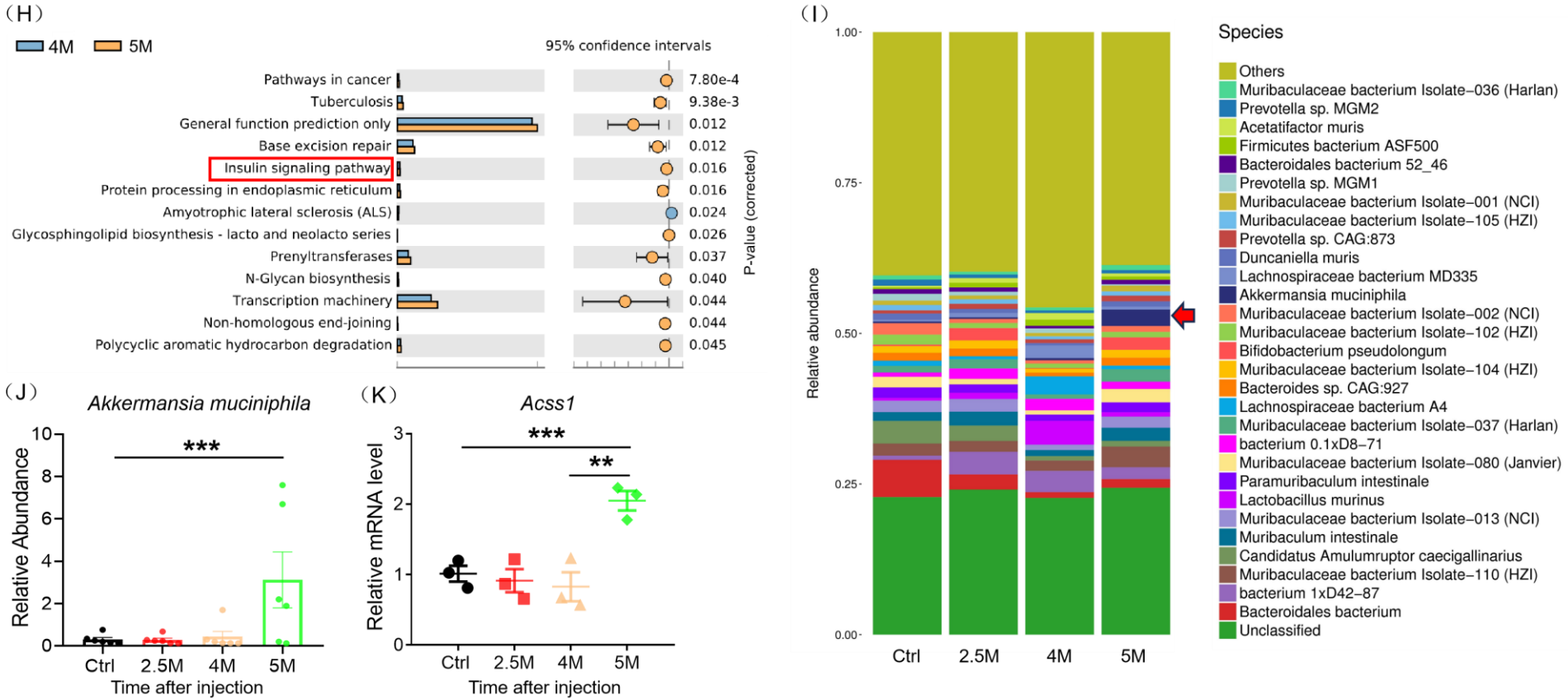


Figure 1 **Mice survived after long-term streptozotocin injection has decreased glucose level, altered intestinal microbiota and increased *Akkermansia muciniphila*.** (A) Fasting blood glucose levels of mice before and after 1-week, 2-week, 1-month, 2-month, 3-month, 4-month and 5-month of streptozotocin (STZ) injection. (B) PCA analysis of 16s rRNA sequencing data of cecal contents from mice after 1-month, 2.5-month 4-month and 5-month of STZ injection, $n = 6$. (C) Shannon index of the 16s rRNA sequencing data, $n = 6$. (D) Bacterial community structure analysis at phyla level, $n = 6$. (E-G) Relative abundances of *Bacteroidetes* (E) and *Firmicutes* (F), and the ratio of *Bacteroidetes*/*Firmicutes* (G) at 1-month, 2.5-month 4-month and 5-month after STZ injection, $n = 6$.

Results

Figure 1



(H) KEGG pathway analysis of bacterial communities between 4-month and 5-month after STZ injection, $n = 6$. (I) Bacterial community structure analysis at phyla level, $n = 6$. Red arrow indicated *Akkermansia muciniphila* (*A. muciniphila*). (J) Relative abundances of *A. muciniphila* at different time post STZ injection, $n = 6$. (K) qRT-PCR detection of *Acss1* at 2.5-month 4-month and 5-month post STZ injection. Data represent mean ± SEM. (*t*-test: * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$).

Results

Figure 2

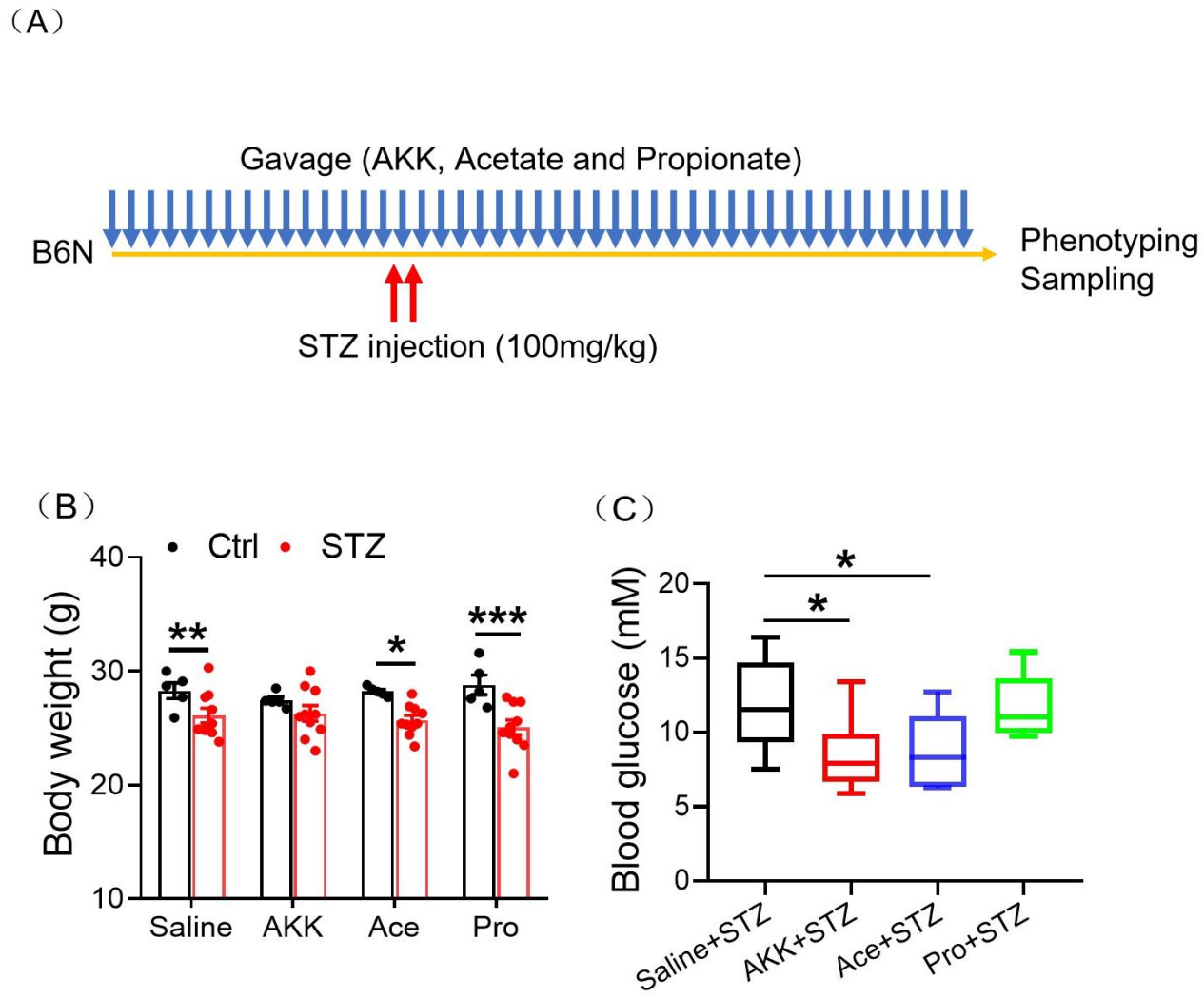
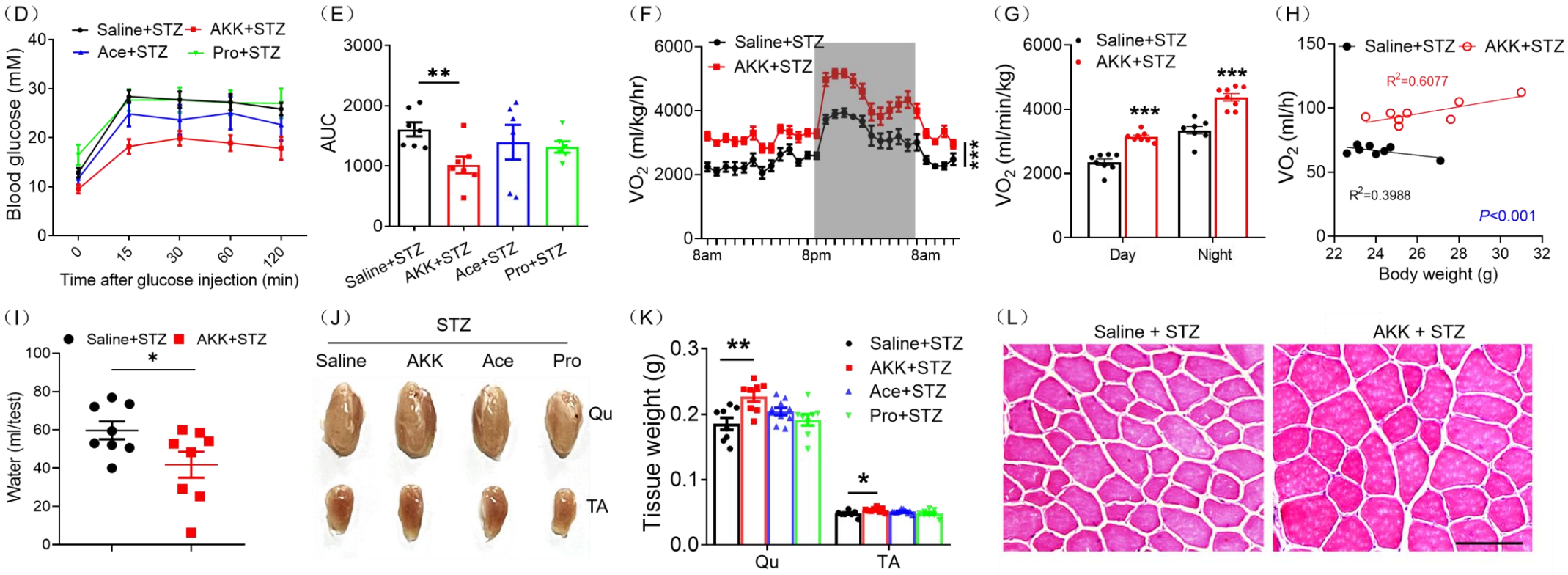


Figure 2 *A. muciniphila* gavage protects mice from STZ-induced muscle atrophy through promoting intestinal IGF2 secretion. (A) A scheme showing the gavage and STZ injection on wild-type C57BL/6J mice. (B) Body weight of mice received gavage of Saline, *A. muciniphila* (AKK), sodium acetate (Ace) and sodium propionate (Pro) after 5-week of STZ induced T1D, n = 5 and 10 of mice with/without STZ injection. (C) Fasting glucose levels of mice after 5-week of STZ injection, n = 10, 6, 5 and 5 for each group, respectively.

Results

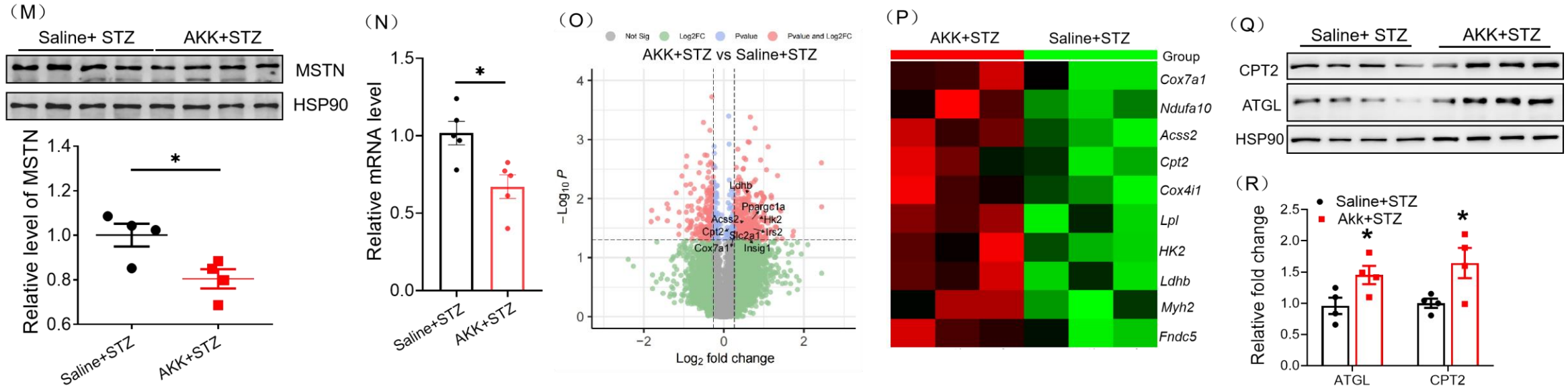
Figure 2



(D) Blood glucose levels during glucose tolerance test (GTT) on mice after STZ injection. (E) Area under curve (AUC) calculated from GTT. (F-H) O_2 consumption (F), average day and night O_2 consumption (G) and correlation between O_2 consumption and body weight (H) from AKK and Saline groups, $n = 8$. (I) Water consumption of mice from AKK and Saline groups after STZ injection, $n = 8$. (J, K) Representative images (K) and weights (K) of Quadriceps (Qu) and Tibialis Anterior (TA) muscles isolated from mice received gavage of Saline, AKK, Ace and Pro after STZ induced T1D. (L) Representative H&E staining image of muscle cross-section from Saline and AKK groups.

Results

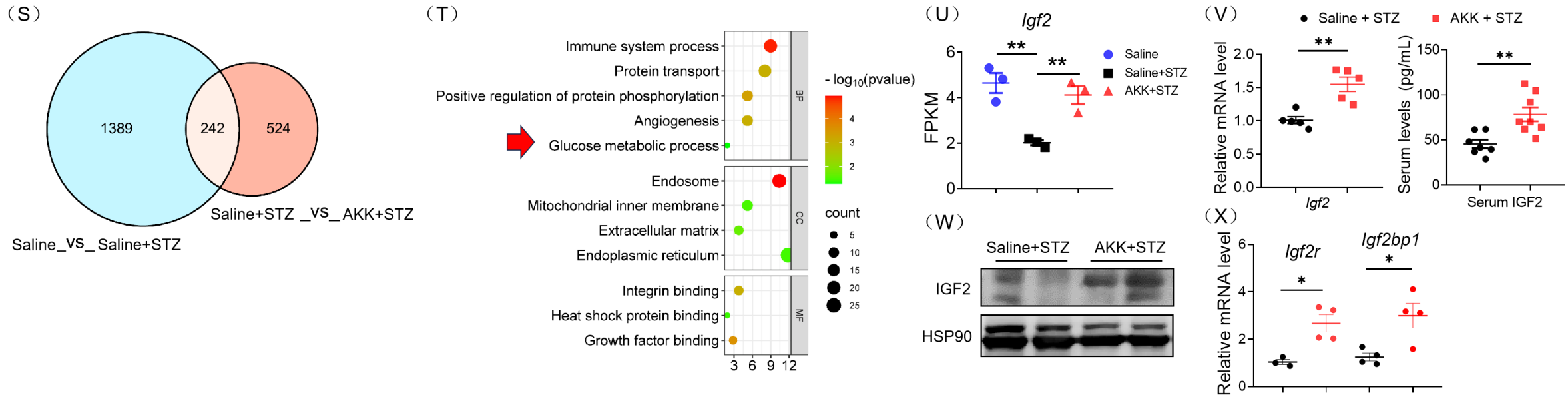
Figure 2



(M) Western blot and calculation of MSTN protein expression level in TA muscles, $n = 4$. (N) Relative mRNA levels of *Mstn* TA muscles from Saline and AKK groups after STZ injection, $n = 5$. (O) Volcano plot showing the Log_2 fold change and $-Log_{10}P$ of all genes by RNA-sequencing using TA muscles from AKK and Saline groups, red dots represented significant differential gene expression (DEGs) with fold change > 1.3 while green dots represented unchanged genes. (P) Heatmap of key DEGs involved in lipid and glucose metabolism from AKK and Saline groups after STZ injection, $n = 3$. (Q, R) Western blot (Q) and calculation (R) of CPT2 and ATGL protein expression levels in TA muscles, $n = 4$.

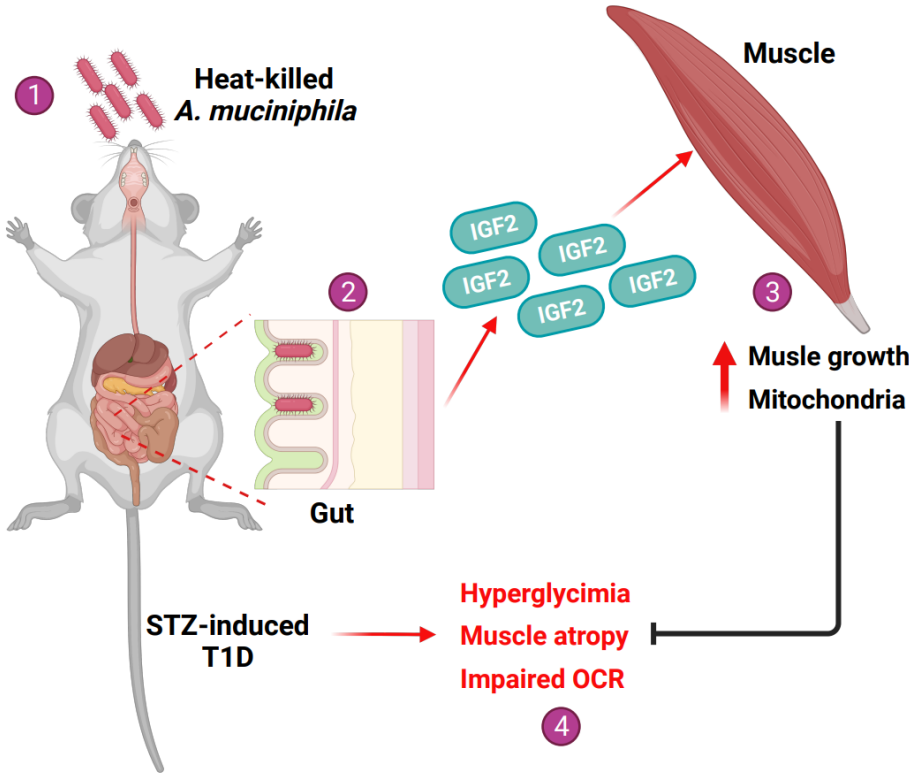
Results

Figure 2



(S) Venn diagram of overlapping DEGs from untreated VS Saline and Saline VS AKK. (T) GO enrichment of all overlapping DEGs indicating the specific changed in glucose metabolic process, *n* = 3. (U) Gene expression levels of *Igf2* from untreated, Saline and AKK groups, *n* = 3. (V) qRT-PCR validation of *Igf2* expression from intestine and serum concentrations of IGF2 protein of Saline and AKK groups after STZ injection, *n* = 5 and 8, respectively. (W) Western blot of IGF2 from intestine of AKK and Saline groups after STZ injection. (X) Relative mRNA levels of *Igf2r* and *Igf2bp1* in TA muscles from Saline and AKK groups after STZ injection, *n* = 4.

Summary



- The mice surviving after 5-month of streptozotocin (STZ) injection had reduced blood glucose level and recovered gut microbiota with increased *A. muciniphila* proportion.
- Gavage of heat-killed *A. muciniphila* increased the diversity of gut microbiota and elevated immune and metabolic signaling pathways in intestine.
- Mechanistically, *A. muciniphila* treatment promoted the secretion of IGF2 from which subsequently activated IGF2 signaling in skeletal muscle and enhanced muscle and global metabolism.

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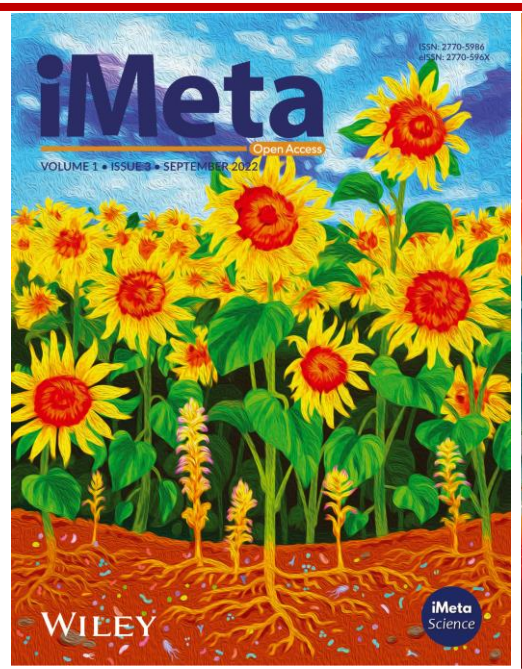

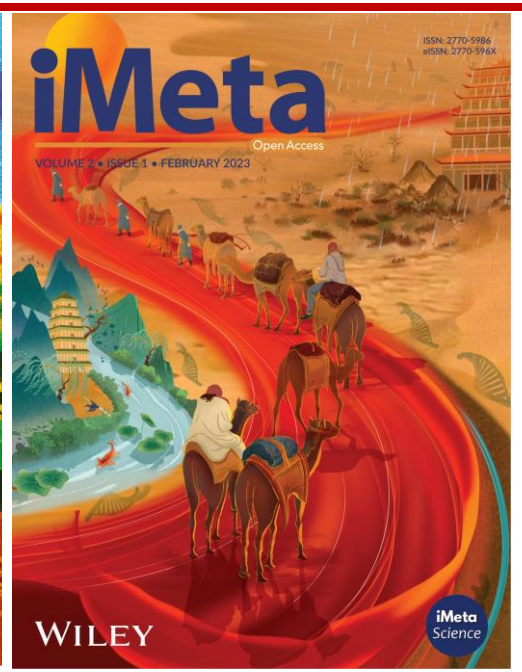

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