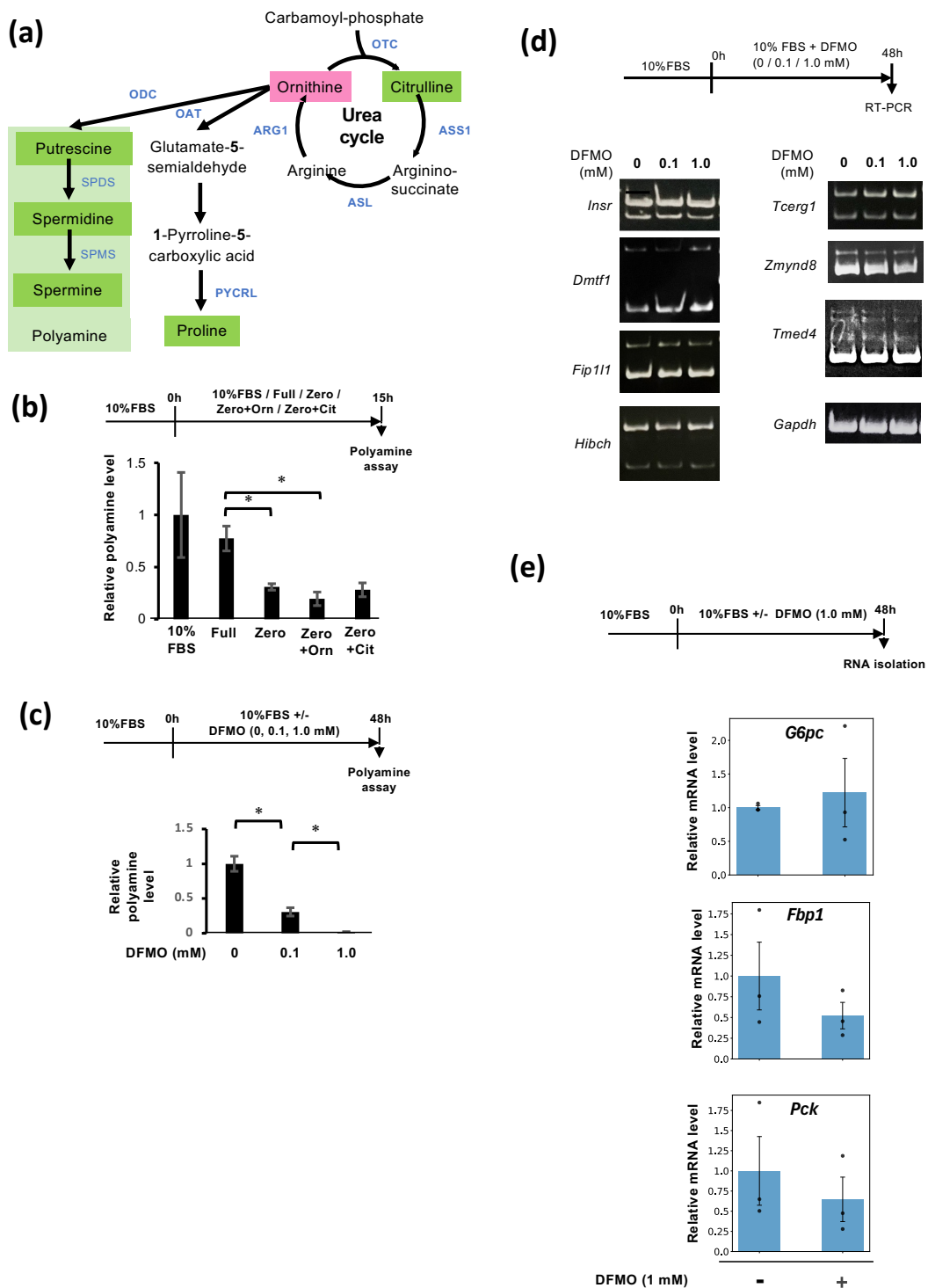


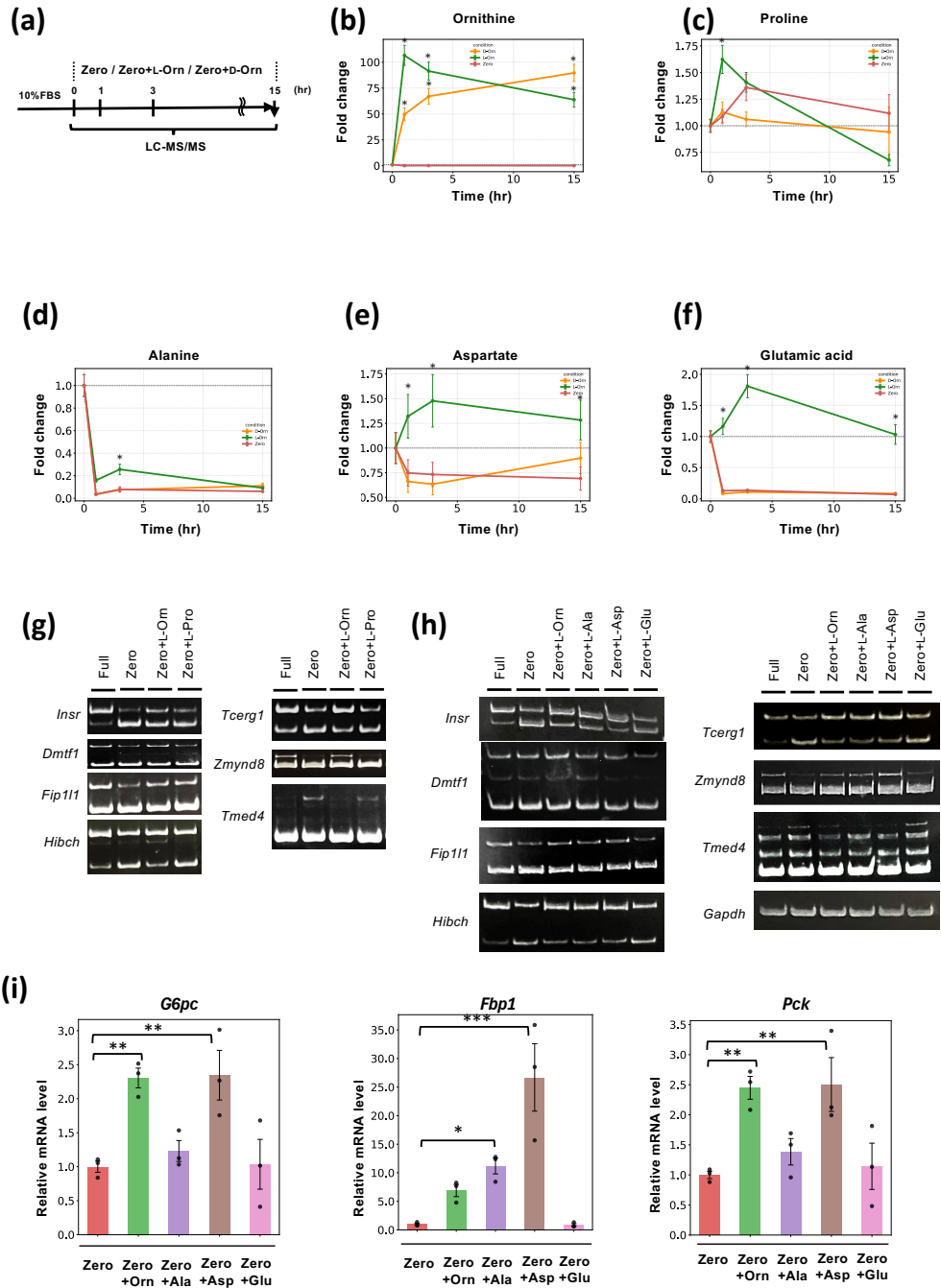
**Extended Data Fig. 1.**

**(a):** Schematic diagram of the target sites of siRNA against PTBP1 are shown. **(b):** H4IIE cells were transfected with siRNA against with NC or siPTBP1 #2. PTBP1 and  $\beta$ -actin, protein levels were analyzed by immunoblotting. *Ira*- and *Irb*-specific primers were designed and used for qPCR analysis. Based on these results, the mRNA ratio of *Ira*/(*Ira*+*Irb*) was calculated. **(c):** *G6pc* mRNA levels were quantified using real-time qPCR and normalized against 18S rRNA levels. **(d):** H4IIE cells were transfected with siRNA against with NC or sihnRNP M. hnRNP M and  $\beta$ -actin protein levels were analyzed by immunoblotting. *Ira*- and *Irb*-specific primers were designed and used for qPCR analysis. Based on these results, the mRNA ratio of *Ira*/(*Ira*+*Irb*) was calculated. **(e):** *G6pc*, *Fbp1*, or *Pck* mRNA levels were quantified using real-time qPCR and normalized against 18S rRNA levels. (b) – (e): Bar: mean  $\pm$  S.E.M., a false discovery rate- (FDR-) adjusted  $p$ -value, \* $p$  < 0.05, \*\* $p$  < 0.01, \*\*\* $p$  < 0.001.  $n$  = 3, Welch's  $t$  test.



**Extended Data Fig. 2. Transcriptional and splicing regulation by L-ornithine metabolites.**

**(a):** A schematic diagram illustrating ornithine metabolites. **(b):** The intracellular polyamine levels were measured in H4IIE cells cultured for 15 h in 10%FBS medium, Full, Zero, Zero supplemented with L-ornithine, or Zero supplemented with L-citrulline. **(c):** The intracellular polyamine levels were measured in H4IIE cells cultured for 48 h in 10%FBS medium containing 0, 0.1, 1.0 mM DFMO. **(d):** H4IIE cells were cultured for 48 hours in 10% FBS medium containing 0, 0.1, 1.0 mM DFMO. RT-PCR analyses were carried out to detect the change in alternative splicing of various genes. **(e):** *G6pc*, *Fbp1*, or *Pck* mRNA levels were quantified using real-time qPCR and normalized against 18S rRNA levels. Bar: mean  $\pm$  S.E.M., \* $p < 0.05$ , \*\* $p < 0.01$ , \*\*\* $p < 0.001$ .  $n = 3$ , Welch's  $t$  test.



**Extended Data Fig. 3. Transcriptional and splicing regulation by L-ornithine metabolites.**

**(a):** H4IIE cells were cultured in Zero, Zero+L-ornithine, Zero+D-ornithine for 1, 3, 15 hours. Intracellular metabolites were quantified by LC-MS/MS analysis. **(b-f):** Intracellular levels of ornithine **(b)**, proline **(c)**, alanine **(d)**, aspartic acid **(e)**, glutamic acid **(f)** were shown. Y-axis indicates the fold change of intracellular levels of those at time point = 0 (hr). A false discovery rate- (FDR-) adjusted  $p$ -value,  $*p < 0.2$  compared to Zero,  $n = 3$ , Welch's  $t$  test. **(g):** H4IIE cells were cultured in Full, Zero, Zero+L-ornithine, or Zero+L-proline. RT-PCR analyses were carried out to detect the change in alternative splicing. **(h):** H4IIE cells were cultured in Full, Zero, Zero+L-ornithine, or Zero+L-alanine, Zero+L-aspartate, Zero+L-glutamate. RT-PCR analyses were carried out to detect the change in alternative splicing. **(i):** H4IIE cells were cultured in Full, Zero, Zero+L-ornithine, or Zero+L-alanine, Zero+L-aspartate, Zero+L-glutamate. *G6pc*, *Fbp1*, or *Pck* mRNA levels were quantified using real-time qPCR and normalized against 18S rRNA levels. Bar: mean  $\pm$  S.E.M., a false discovery rate- (FDR-) adjusted  $p$ -value,  $*p < 0.05$ ,  $**p < 0.01$ ,  $***p < 0.001$ .  $n = 3$ , Welch's  $t$  test.