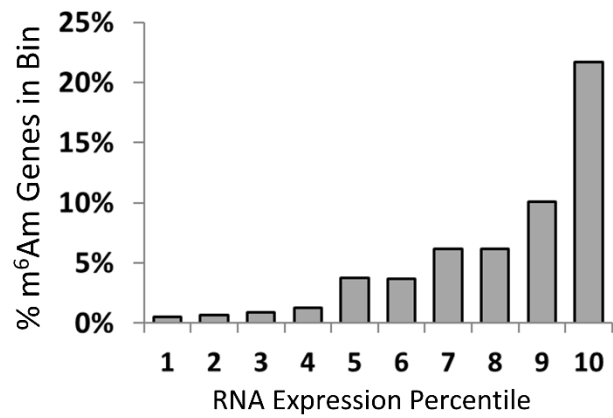
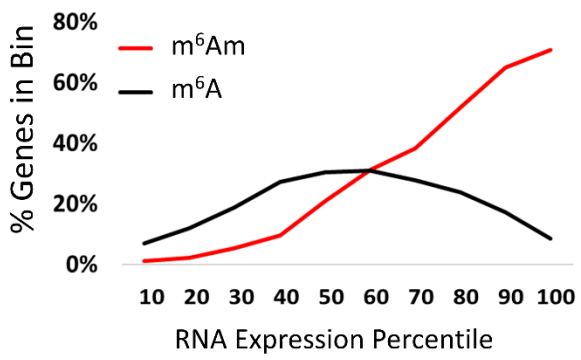


Supplementary Information File

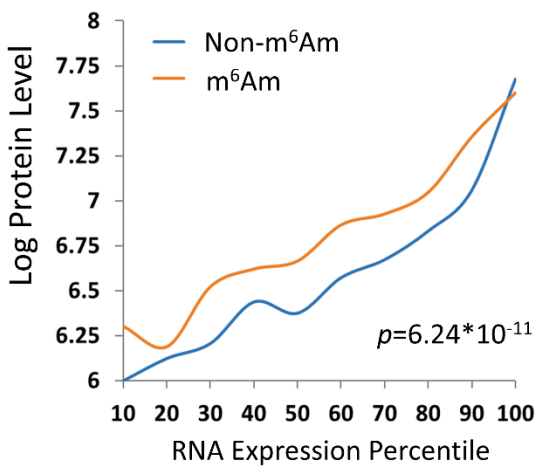
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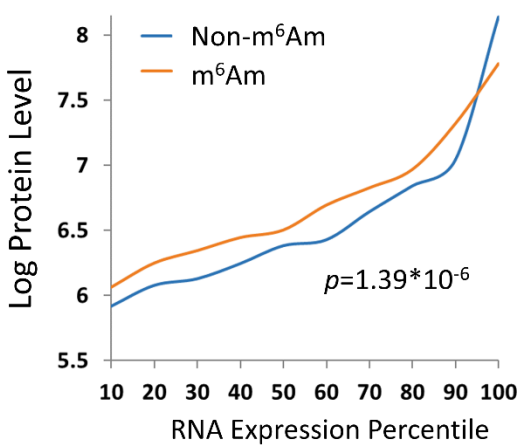
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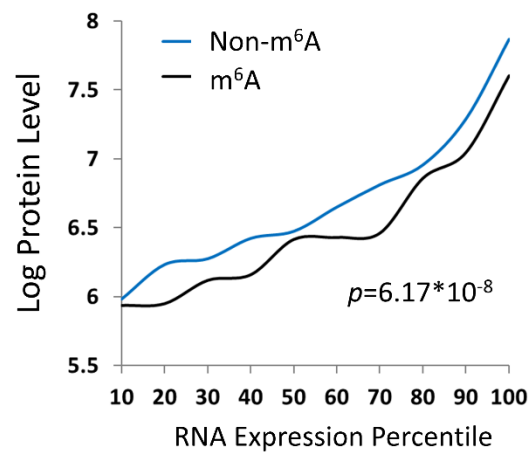
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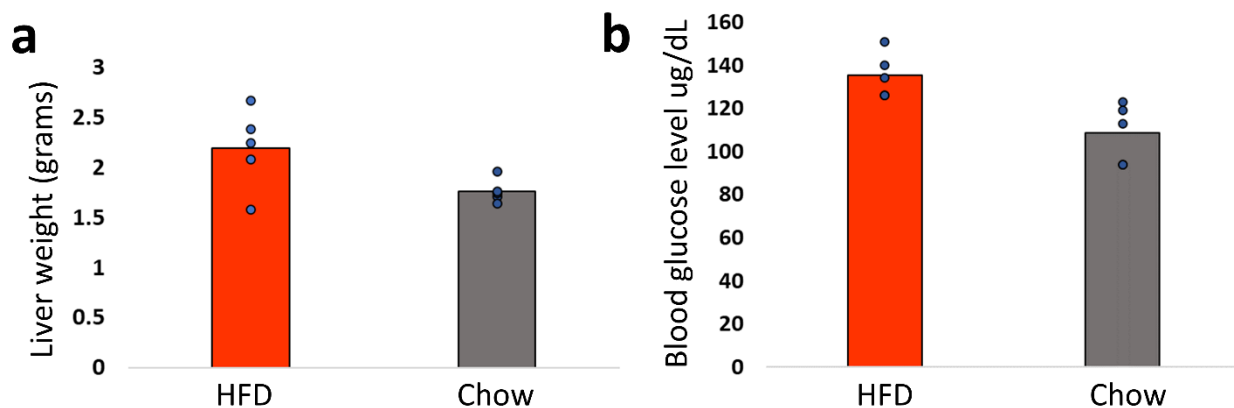
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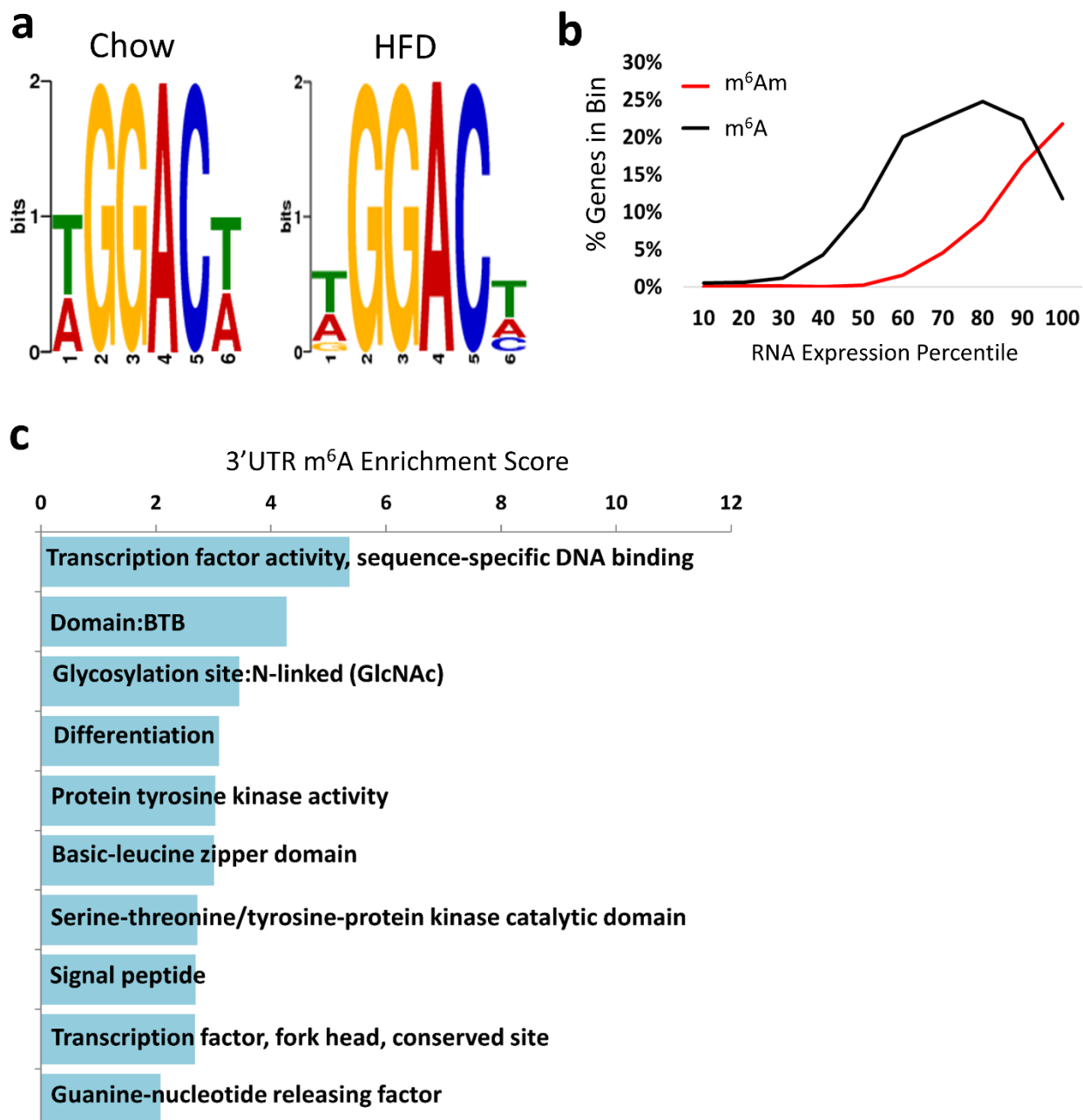
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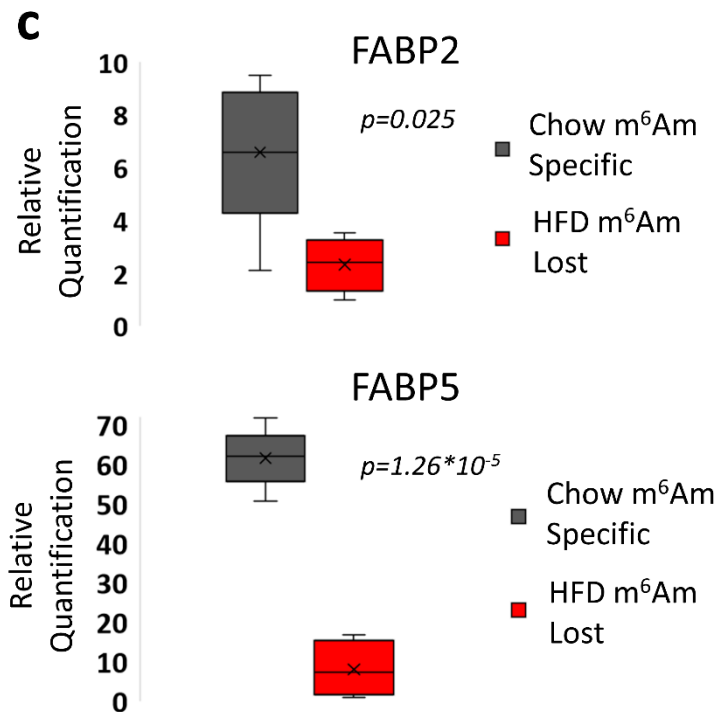
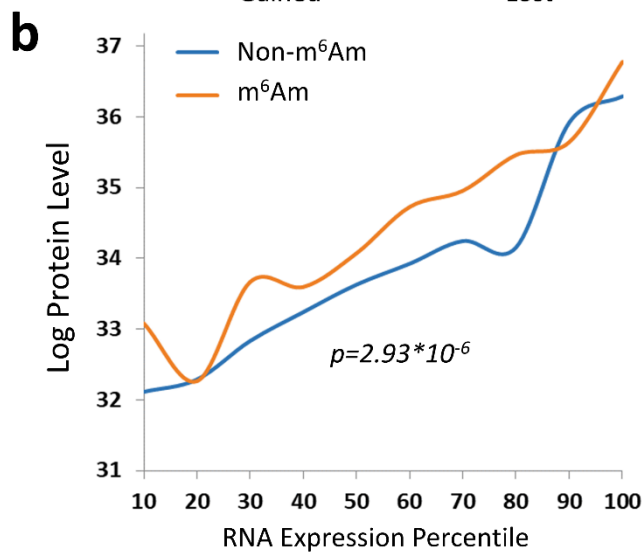
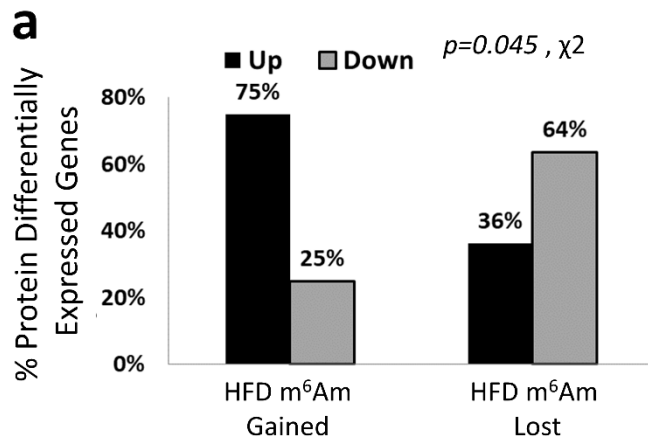
Supplementary Fig. 1 Protein and mRNA expression profiles of m⁶Am- and non-5' UTR m⁶A-modified genes in WT and *Mettl3* KO mESCs. **a** Fraction of m⁶Am methylated genes across their RNA expression percentile bins after removing genes that were identified as m⁶A decorated (sites located outside the 5' UTR) in WT mESCs. **b** Fraction of m⁶Am and non- 5' UTR m⁶A-methylated genes as a function of their RNA expression level in ES WT cells. **c** High-throughput protein expression of m⁶Am- and non-m⁶Am-methylated genes as a function of their RNA expression level in *Mettl3* KO mESCs. Two-tailed *p*-value of an ANCOVA analysis controlling for RNA levels of each gene as covariates is reported, $F(1,3765)=42.99, p=6.24 \times 10^{-11}$. **d** High-throughput protein expressions of m⁶Am- and non-m⁶Am-methylated genes as a function of their RNA expression level in WT mESCs. Two-tailed *p*-value of an ANCOVA analysis controlling for RNA levels of each gene as covariates is reported, $F(1,3691)=23.36, p=1.39 \times 10^{-6}$. **e** High-throughput protein expression of non- 5' UTR m⁶A- and non-m⁶A-methylated genes as a function of their RNA expression level in WT mESCs. Two-tailed *p*-value of an ANCOVA analysis controlling for RNA levels of each gene as covariates is reported, $F(1,3691)=29.43, p=6.17 \times 10^{-8}$. Source data are provided as a Source Data file.



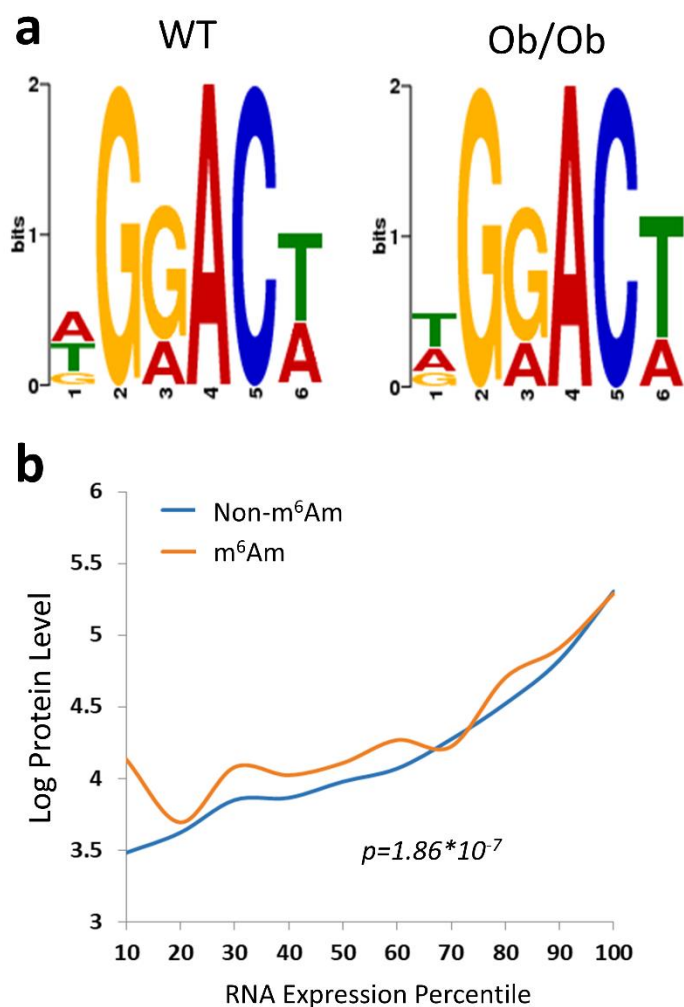
Supplementary Fig. 2 High fat diet mice physiologic parameters. **a** Liver weight of HFD mice and lean control chow diet mice. N=10 (5 HFD mice, and 5 Chow lean control mice). **b** Blood glucose levels of mice consuming HFD and control chow diet after 6-hour fasting. N=10 (5 HFD mice, and 5 Chow lean control mice). Source data are provided as a Source Data file.



Supplementary Fig. 3 Extended profile of methylation characteristics of lean and HFD mice. a MEME RNA consensus motif of m^6A peaks in HFD and regular chow diet mice. **b** Fraction of m^6Am - and non- 5' UTR m^6A -methylated genes as a function of their RNA expression level in regular chow diet control mice. **c** Gene ontology analysis of m^6A 3' UTR showing an enrichment for non-metabolic processes. Source data are provided as a Source Data file.



Supplementary Fig. 4 Extended protein regulation data of m⁶Am genes in HFD mice. **a** High throughput proteomic profiling proportions of genes with protein differential expression (>1.5 fold) which gained or lost m⁶Am upon HFD, after removing all >1.5 fold RNA differentially expressed genes. Two-tailed *p*-values are indicated (Chi-square test). **b** High-throughput protein expressions of m⁶Am and non-m⁶Am methylated genes as a function of their RNA expression level in regular chow diet control mice. Two-tailed *p*-value of an ANCOVA analysis controlling for RNA levels of each gene as covariates is reported, $F(1,2176)=21.98, p=2.93 \times 10^{-6}$. **c** Quantification of FABBP2 and FABP5 western blots signal relative to the normalizing gene HSP-70. The results show a clear repeating pattern of overexpression across all lean biological replicates (N=5) versus all fat biological replicates (N=4). *p*-values are indicated (two tailed student t-test). Box plot surrounds the 1-3 quartiles, whiskers denote 1.5 interquartile range. Source data are provided as a Source Data file.



Supplementary Fig. 5 Extended characteristics of m⁶Am genes in ob/ob and WT control mice. a MEME RNA consensus motif of m⁶A peaks in ob/ob and their WT littermates mice. **b** High-throughput protein expressions of m⁶Am and non-m⁶Am methylated genes as a function of their RNA expression level in the WT control mice. Two-tailed *p*-value of an ANCOVA analysis controlling for RNA levels of each gene as covariates is reported. Source data are provided as a Source Data file.

Supplementary Table 1 Gene ontology enrichment terms identified for m⁶Am genes in lean and HFD mice in this study (Fig. 2e) and their co-occurrence in *Pcif1* KO studies.

Enriched m ⁶ Am Process	Enriched in Reference
Mitochondrion	22,23,24,25
Oxidation-reduction process	23,24,25
Endoplasmic reticulum	23,24,25
Fatty acid metabolism	23,24,25
Citrate cycle (TCA cycle)	23,24
Pyridoxal phosphate-dependent transferase	23,25
Peroxisome	23,25
Drug metabolism - cytochrome P450	23,24,25
Iron ion binding; Cytochrome P450; Monooxygenase activity; Linoleic acid metabolism	23,24,25
Non-Alcoholic Fatty Liver Disease (NAFLD); Alzheimer's disease; Respiratory chain	23,24,25