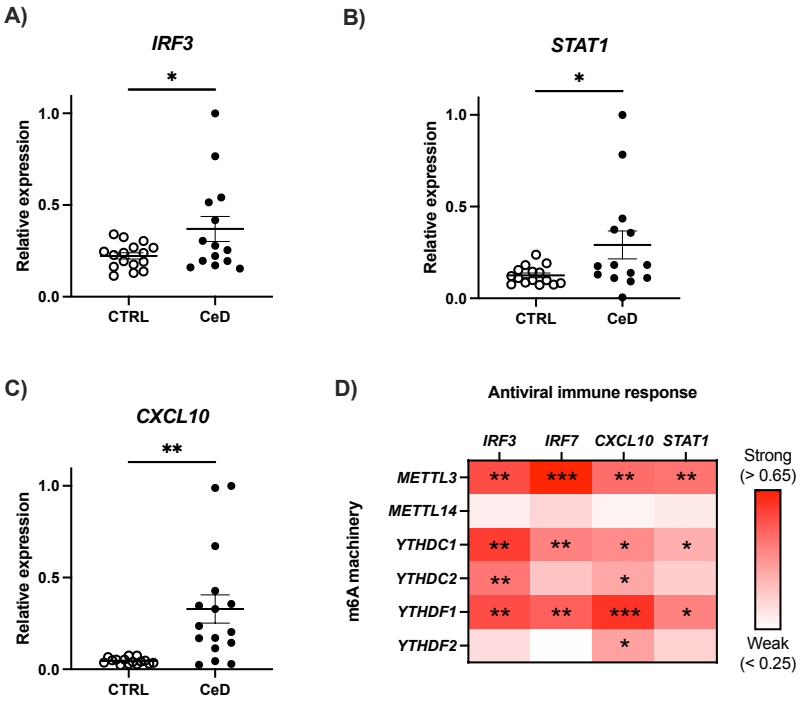
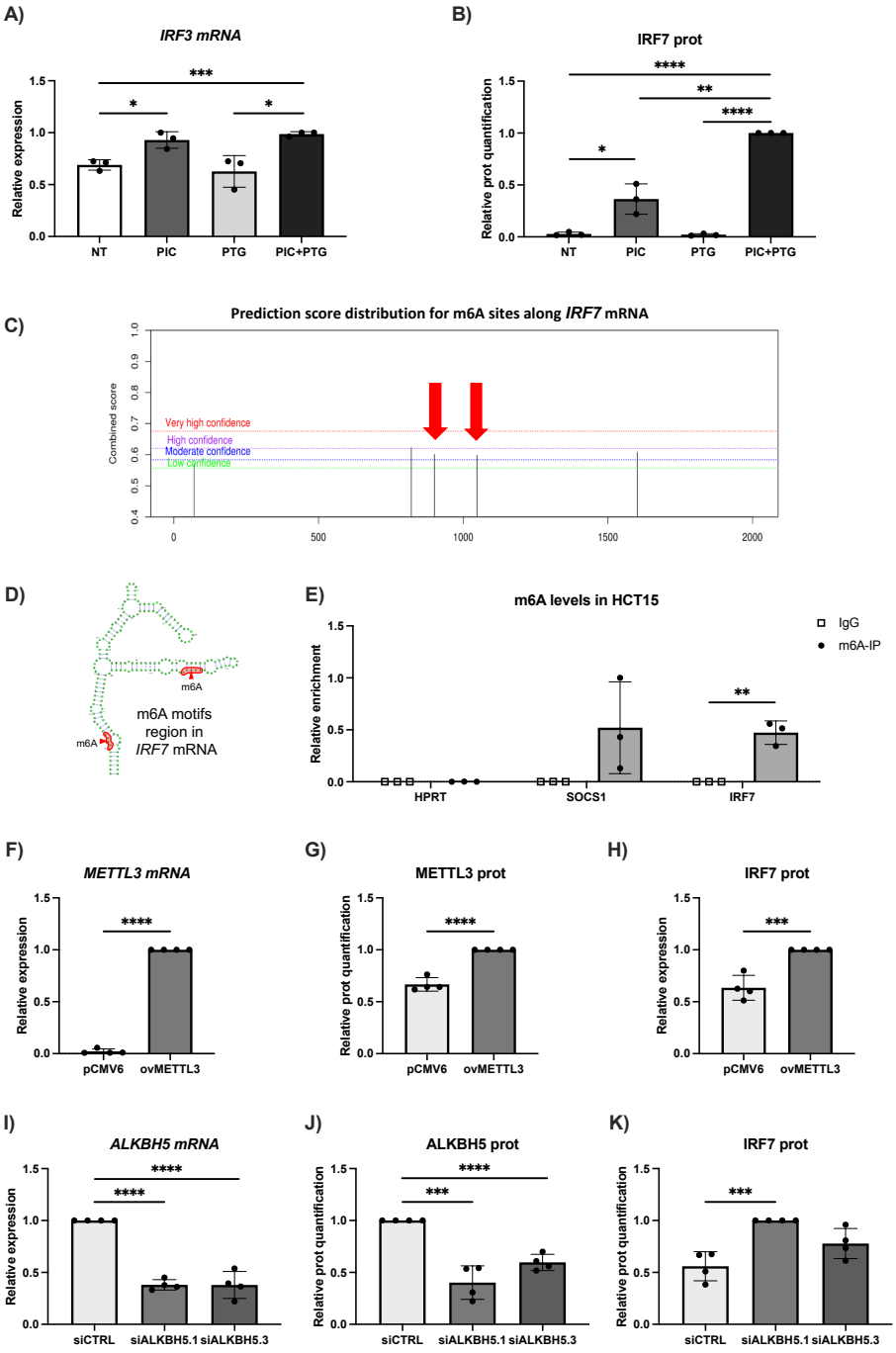
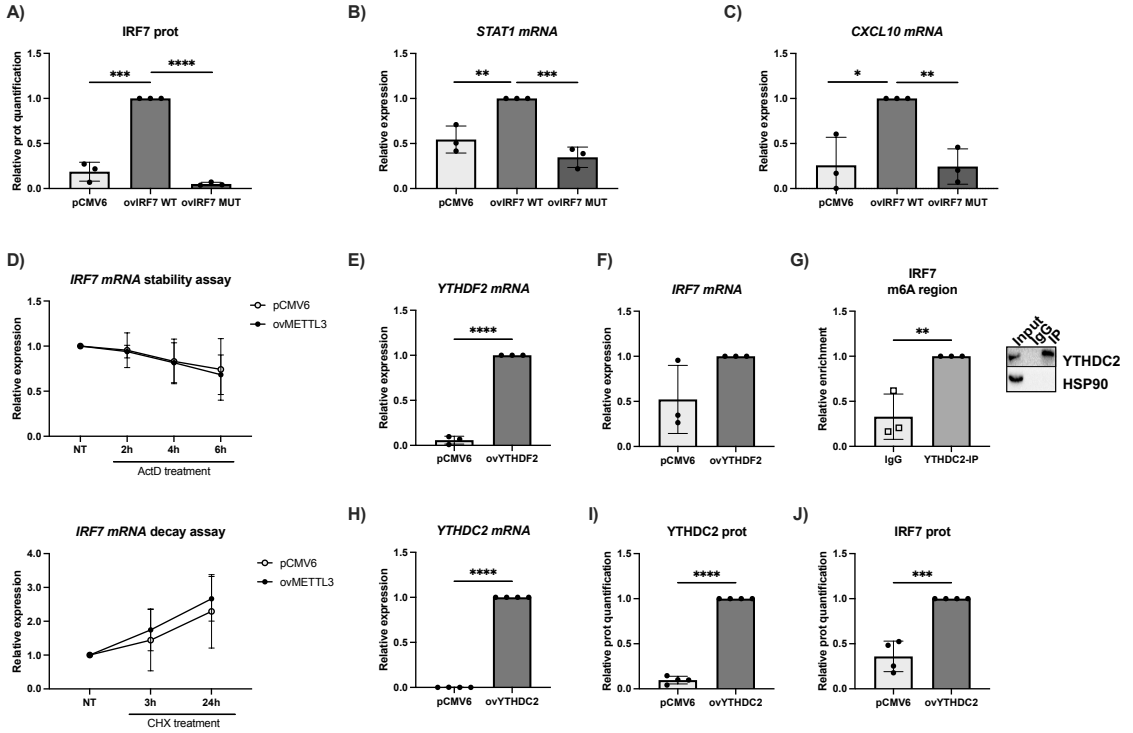
SUPPLEMENTARY FIGURES AND LEGENDS



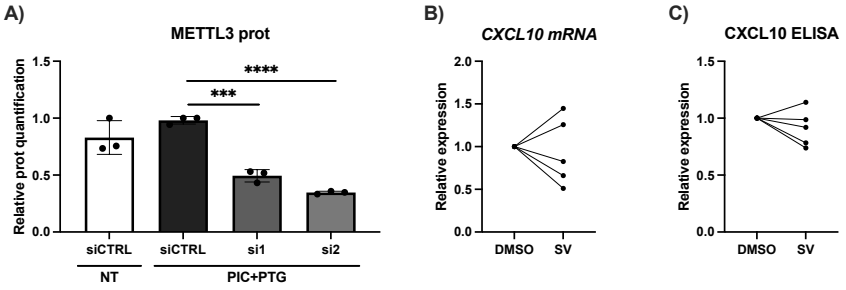
Supplementary Figure 1. A) *IRF3*, **B)** *STAT1* and **C)** *CXCL10* expression in intestinal biopsies of celiac (CeD) and non-celiac (CTRL) individuals. **D)** Spearman correlation analysis between the expression of antiviral and proinflammatory immune-related transcripts, and the expression of m6A machinery members in intestinal biopsies. Red and white color represent strong and weak correlation, respectively. ***p<0.001;**p<0.01;*p<0.05 based on t-test and Spearman correlation analyses.



Supplementary Figure 2. A) *IRF3* expression and **B)** IRF7 protein quantification in non-treated (NT) HCT-15 cells and in cells treated with PIC treatment, stimulated with gliadin (PTG) or with both PIC treatment and PTG stimulation (PIC+PTG). **C)** Prediction scores of m6A motifs using mature *IRF7* mRNA as input, obtained using SRAMP prediction server. Red arrows indicate the two m6A motifs selected as candidates. **D)** Secondary structure of the region where candidate m6A sites are predicted. **E)** Comparison of relative m6A methylation on *IRF7* mRNA with *HPRT* and *SOCS1* mRNAs, negative and positive controls, respectively. m6A methylation was assessed by m6A-RNA immunoprecipitation followed by qPCR (MeRIP-qPCR) in RNAs from HCT-15 cells. **F)** *METTL3* expression and **G)** METTL3 and **H)** IRF7 protein quantification in mock-transfected (pCMV6) and METTL3-overexpressing (ovMETTL3) cells. **I)** *ALKBH5* expression and **J)** ALKBH5 and **K)** IRF7 protein quantification in cells transfected with control siRNA (siCTRL) and ALKBH5-specific siRNAs (si1 or si3). ****p<0.0001;***p<0.001;**p<0.01;*p<0.05 based on t-test and ANOVA analyses.



Supplementary Figure 3. A) IRF7 protein quantification and **B)** *STAT1* and **C)** *CXCL10* expression in cells transfected with m6A-containing (WT) and m6A-truncated (MUT) *IRF7* overexpression plasmid and in mock-transfected cells (pCMV6). **D)** Relative expression of *IRF7* in mock-transfected (pCMV6) and *METTL3*-overexpressing (ovMETTL3) upon actinomycin D (ActD) treatment for 2h, 4h, and 6h (above) and cycloheximide (CHX) treatment for 3h and 24h (below). **E)** *YTHDF2* and **F)** *IRF7* expression in mock-transfected (pCMV6) and *YTHDF2*-overexpressing (ovYTHDF2) cells. **G)** YTHDC2 RNA immunoprecipitation (RIP) and *IRF7* interaction enrichment quantification by qPCR. **H)** *YTHDC2* expression and **I)** YTHDC2 and **J)** IRF7 protein quantification in mock-transfected (pCMV6) and YTHDC2-overexpressing (ovYTHDC2) cells. ****p<0.0001;***p<0.001;**p<0.01;*p<0.05 based on t-test and ANOVA analyses.



Supplementary Figure 4. A) METTL3 protein levels in non-treated (NT) HCT-15 cells or in cells treated with PIC and stimulated with gliadin (PIC+PTG) and transfected with specific siRNAs for METTL3 silencing (si1 or si2) or control siRNA (siCTRL). **B)** *CXCL10 mRNA* expression in cell lysates and **C)** CXCL10 levels in cell supernatant of intestinal biopsies after SV or DMSO incubation. ****p<0.0001;***p<0.001; based on ANOVA analyses.

Supplementary Table 1. Patient details for analyzed biopsy samples.

Dx	Number of samples	Age (years, Mean ± Standard deviation)	Sex	Positivity for celiac serology	Positivity for CeD-risk associated HLA	Marsh classification (0-3)
Active CeD	n = 16	5.7 ± 4.2	Female 58.3% Male 41.7%	100%	HLA-DQ2 83.3% HLA-DQ2/DQ8 16.7%	3 – 100% ⇒ 3a – 25.0% ⇒ 3b – 33.3% ⇒ 3c – 41.7%
Non-CeD (Controls)	n = 16	8.1 ± 3.6	Female 68.8% Male 31.3%	0%	N/A	0 – 100%

Supplementary Table 2: Patient details for analyzed serum samples.

Dx	Number of samples	Age (years, Mean ± Standard deviation)	Sex	Positivity for celiac serology
CeD	n = 44	5.5 ± 3.6	Female 59.1% Male 40.9%	100%
Non-CeD (Controls)	n = 44	9.6 ± 2.7	Female 47.7% Male 52.3%	0%

Supplementary Table 3. Primers used for MUT IRF7 plasmid construction and their sequences.

NAME	PRIMER SEQUENCE (5'→3')
IRF7 Fw + *Sfi*I	AGGGTGGGCCCCCAGGGCCATT
IRF7 Rv + *Bsm*BI	GGGTCGTCTCTACTGCCCACCC
IRF7 Fw + *Sfi*I + 1st m6A mutation	GGTGGGCCCCCAGGGCCATTCCTGGCACACACACATGCTGGCCT
IRF7 Fw + 2nd m6A mutation	GAGAGGGCCAAGAAGGGCTT
IRF7 Rv + 2nd m6A mutation	AAGCCCTTCTTGGCCCTCTC

Supplementary Table 4. Specific primers for gene expression analysis by qPCR.

GENE	FORWARD PRIMER SEQUENCE	REVERSE PRIMER SEQUENCE
ALKBH5	CGGCGAAGGCTACACTTSCG	CCACCAGCTTTTGGATCACCA
CXCL10	GTGGCATTCAAGGAGTACCTC	TGATGGCCTTCGATTCTGGATT
HPRT	ACCAGTCAACAGGGGACATAA	CTTCGTGGGGTCCTTTTCACC
IRF3	AGAGGCTCGTGATGGTCAAG	AGGTCCACAGTATTCTCCAGG
IRF7	CCCACGCTATACCATCTACCT	GATGTCGTCATAGAGGCTGTTG
IRF7 (m6A motifs)	CATTCCTGGCACACACACAT	AAGCCCTTCTTGTCCCTCTC
METTL14	GAGTGTGTTTACGAAAATGGGGT	CCGTCTGTGCTACGCTTCA
METTL3	TCGAGAGCGAAATTTTTCAAC	GGAGATAGAGAGCCTTCTGAACC
RPLP0	GCAGCATCTACAACCCTGAAG	CACTGGCAACATTGCGGAC
SOCS1	AGACCCCTTCTCACCTCTTG	AGTTAAGCTGCTACAACAACCAG

STAT1	CGGCTGAATTTCGGCACCT	CAGTAACGATGAGAGGACCCT
YTHDC1	CTTCTGATGAGCAAGGGAACAA	GGCCTCACTTCGAGTGTCATAA
YTHDC2	CTCCGGAACTTTTGAGAATGCC	TTAAAGCTGGTGGAGGTTCAGG
YTHDF1	ACCTGTCCAGCTATTACCCG	TGGTGAGGTATGGAATCGGAG
YTHDF2	TGAACCTTACTTGAGTCCACAGG	AAGCCAATGGAGGGACTGTAG