Supplementary Figure 1: a) m^{6}A signals in the human and mouse *XPO1* gene retrieved from the Metdb v2 database[29]. Blue peaks correspond to meRIP-seq reads, yellow and green boxes are exons and UTR's respectively. Location of the CD-associated rs3087898 SNP is marked in the human transcript. **b)** Secondary structure of both forms of the human *XPO1* 5'UTR as predicted using the Vienna package[30]. **c)** m^{6}A RNA immunoprecipitation (meRIP) followed by RT-qPCR of the 5'UTR of *XPO1* and positive and negative controls in HCT116 intestinal and Jurkat T cell lines, n=3-5. (****p<0.0001; ns: non-significant according to a two-way ANOVA test. Enrichment relative to control IgG #p<0.05, ###p<0.001, ####p<0.0001 according to a two-way ANOVA test). **d)** Left, m^{6}A levels in the 5'UTR of *XPO1* in RNA extracted from human intestinal biopsies as assessed by meRIP-qPCR, n=3. (****p< 0.0001, according to a 2-tailed Student's t-test)**.** Right, m^{6}A RNA immunoprecipitation (meRIP) followed by RT-qPCR of the 5'UTR of *XPO1* in immune (CD45+) and epithelial (CD326+) fractions from human intestinal biopsies, n=pool of 18 individuals. (**p<0.01 according to a two-way ANOVA test. Enrichment relative to control IgG #p<0.05, ns: non-significant according to a two-way ANOVA test). **e)** m^{6}A-RT-qPCR of the 3 m^{6}A motifs in the 5'UTR of *XPO1* and positive and negative controls in intestinal cells, n=4. Significance was calculated relative to the negative control. (*p<0.05,**p<0.01 according to a one-way ANOVA test). **f)** Cellular localization of both *XPO1* mRNA forms *XPO1*C* (C) and *XPO1*T* (T) and *PO* (cytoplasmic) and *MALAT1* (nuclear) controls, n=4. (ns: non-significant according to a one-way ANOVA test). **g)** mRNA stability of both *XPO1* mRNA forms *XPO1*C* (C) and *XPO1*T* (T) in cells treated with actinomycin D for 3 h and 6 h, n=3. (ns: non-significant according to a two-way ANOVA test). All values are means ± SEM.

Supplementary Figure 2: a) Relative expression of *METTL3* measured by RT-qPCR and **b)** overall m^{6}A RNA levels measured by ELISA in cells transfected with an empty vector (EV) and a vector overexpressing METTL3 (ovMETTL3), n=3. (*p<0.05, ****p<0.0001 according to a two-tailed Student's t-test). **c-d)** Relative RNA expression measured by RT-qPCR and quantitative summary of the of *METTL3* and *YTHDF1* immunoblot in Figure 2B, (***p<0.001, ****p<0.0001 according to a two-tailed Student's t-test). **e)** overall m^{6}A RNA levels measured by ELISA, (+p<0.1, ns:non-significant according to a two-tailed Student's t-test). **f)** m^{6}A RNA immunoprecipitation (meRIP) followed by RT-qPCR of the 5'UTR of *XPO1* (*p<0.05; ns: non-significant according to a two-way ANOVA test. Enrichment relative to control IgG +p<0.1,

#p<0.05, ##p<0.01 according to a two-way ANOVA test) and **g)** quantitative summary of the XPO1 immunoblot in Figure 2C, n=3-4. (*p<0.05 according to a two-tailed Student's t-test). **h-i)** METTL3 and YTHDF1 immunoprecipitation RT-qPCR values for *XPO1* 5'UTR and m^6A positive and negative controls, n=3-4. (Enrichment relative to control IgG +p<0.1, #p<0.05, ###p<0.001, ####p<0.0001, ns: non-significant according to a two-way ANOVA test). **j)** m^6A immunoprecipitation (meRIP) RT-qPCR values for *XPO1* 5'UTR and m^6A positive and negative controls in C26 mouse intestinal cells, n=3. (ns: non-significant according to a two-way ANOVA test. Enrichment relative to control IgG ###p<0.001 according to a two-way ANOVA test). **k)** Relative expression measured by RT-qPCR and quantitative summary of YTHDF1 immunoblot in Figure 2E and **l)** relative expression of *Xpo1* measured by RT-qPCR in WT (+/-) and *Ythdf1* knockout mice (DF1 KO), n=7. (**p<0.01, ***p<0.001, ns: non-significant according to a two-tailed Mann Whitney test). All values are means ± S.E.M.

Supplementary Figure 3: a) Schematic representation of the gliadin treatment set up *in vitro* (top) and *in vivo* (bottom). **b)** Left, overall m^6A RNA levels measured by m^6A Dotblot in cells, n=4. Right, quantitative summary of immunoblot in Figure 3A for XPO1, YTHDF1 and METTL3 in HCT116 cells, n=4. (+p<0.1, *p<0.05, **p<0.01, according to a two-tailed Student's t-test). **c)** Quantitative summary of XPO1 and YTHDF1 immunoblot in Figure 3C, n=3. (+p<0.1, ns:non-significant, according to a one-tailed Student's t-test). Silencing efficiency compared to NT cells (#p<0.05, according to a one-tailed Student's t-test). **d)** Left, overall m^6A RNA levels measured by m^6A Dotblot in WT control (NT) or PTG-treated mice (PTG), n=7. Right, quantitative summary of immunoblot in Figure 3D for XPO1 and YTHDF1 , n=7 (+p<0.1, *p<0.05, ns: non-significant according to a one-tailed Mann Whitney test). **e)** Left, overall m^6A RNA levels measured by m^6A Dotblot in humanized HLA-DR3-DQ2 control (NT) or PTG-treated mice (PTG). Right, quantitative summary of immunoblot in Figure 3D for XPO1 and YTHDF1, n=2-5 (+p<0.1, ns: non-significant according to a one-tailed Mann Whitney test). **f)** Quantitative summary of immunoblot in Figure 3F for YTHDF1 and XPO1 in untreated (-) and PTG-treated cells (+PTG) derived from wild type (WT) or *Ythdf1* KO (KO) mice, n=2-4 (+p<0.1, ns:non-significant according to a one-way ANOVA test). All values are means ± S.E.M.

Supplementary Figure 4: a) Quantitative summary of immunoblot in Figure 4A for XPO1 and p50 in cells transfected with an empty vector (EV) and overexpressing both forms of *XPO1* (C

and T), n=3. (*p<0.05, ***p<0.001 according to a two-way ANOVA test). **b)** Relative expression measured by RT-qPCR of *XPO1* and *IL8* in cells transfected with an empty vector (EV), overexpressing both forms of *XPO1* (C and T) and cells overexpressing *XPO1* and treated with the NFkB inhibitor Bay (T+BAY), n=3. (***p<0.001, ****p<0.0001, ns: non-significant according to a two-way ANOVA test)**. c)** Representative immunoblot and quantitative summary of the immunoblot for XPO1 and p50 in untreated cells (NT) and cells treated with PTG, n=4. (*p<0.05, **p<0.01 according to a two-tailed Student's t-test). **d)** Quantitative summary of immunoblot in Figure 4F for YTHDF1, XPO1 and p50 in untreated cells (NT), cells treated with PTG and cells treated with PTG + silenced for YTHDF1 (PTG+siYTH), n=3. (+p<0.1, ns: non-significant according to a one-tailed Student's t-test). Silencing efficiency compared to NT cells (#p<0.05, according to a one-tailed Student's t-test). **e)** Quantitative summary of immunoblot in Figure 4G for XPO1 and p50 in untreated cells (NT), cells treated with PTG and cells treated with + *XPO1* function inhibitor leptomycin B (PTG+LMB), n=3. (+p<0.1, *p<0.05, ns: non-significant according to a two-way ANOVA test). **f)** Relative expression measured by RT-qPCR of *XPO1* and *IL8* in untreated cells (NT), cells treated with PTG and cells treated with PTG and *XPO1* function inhibitor leptomycin B (PTG+LMB), n=3. (*p<0.05, ****p<0.0001, ns: non-significant according to a two-way ANOVA test). Quantitative summary of immunoblot for p50 protein in **g)** WT and **h)** humanized HLA-DR3-DQ2 control mice (NT) or PTG-treated mice (PTG) in Figure 4J and K, respectively. n=7 and n=2-3 (*p<0.05 according to a one-tailed Mann Whitney test). **i)** Relative expression measured by RT-qPCR of mouse *IL8* functional homolog cytokine *Cxcl1* in untreated (-) and PTG-treated cells (+PTG) derived from wild type (WT) or *Ythdf1* KO (KO) mice, n=2-4. All values are means ± S.E.M.

Supplementary Figure 5: a) Expression quantitative trait loci (eQTL) of *XPO1* expression levels compared between individuals with the protection genotype (CC) and individuals harboring the risk allele (CT+TT) n=7-25. Values are means ± S.E.M. (ns: non-significant, according to a two-tailed Mann Whitney test)**. b)** RNA was extracted from untreated and PTG incubated biopsies and expression of *XPO1*, *METTL3* and *YTHDF1* was measured by RT-qPCR, n=15. Values are means of induction ± S.E.M. (+p<0.1, ns: non-significant according to a one-tailed Mann Whitney test). **c)** Correlation of the induction between *YTHDF1* and *XPO1* in PTG treated biopsies. Triangles correspond to *XPO1* mRNA and dots to XPO1 protein induction. n=9-15, R and p were calculated by Pearson correlation.

Supplementary Table1. List of used qPCR primers.

Gene	Primer Sequence
XPO1 (5'UTR)	Fw: TGTTCCAGTCTTTGCTGCTG Rv: AAGGCTCGCCTAAACTTTCC
METTL3	Fw: TCGAGAGCGAAATTTTTCAAC Rv: GGAGATAGAGAGCCTTCTGAACC
YTHDF1	Fw: ACCTGTCCAGCTATTACCCG Rv: TGGTGAGGTATGGAATCGGAG
HPRT	Fw: ACCAGTCAACAGGGGACATAA Rv: CTTCGTGGGGTCCTTTTCACC
TUG1	Fw: ATTCCACGACCATGGTTGTC Rv: ATTCACCACCAACCACACAG
SOCS1	Fw: AGACCCCTTCTCACCTCTTG Rv: AGTTAAGCTGCTACAACAACCAG
IL8	Fw: ACTGAGAGTGATTGAGAGTGGAC Rv: AACCCTCTGCACCCAGTTTTC
5'UTR Xpo1	Fw: GGTGGGAAAACTGTGAAACCC Rv: ACTGCTTCTTCCTTCCTTGTCC
Ythdf1-/-	Fw: CCTGCATTCTCAGCATGG Rv: GCTCCAGACTGTTCATCC
Hprt	Fw: CTGGTGAAAAGGACCTCTCGAAG Rv: CCAGTTTCACTAATGACACAAACG
Mip2a	Fw: CCAACCACCAGGCTACAGG Rv: GCGTCACACTCAAGCTCTG
Cxcl1	Fw: CTGGGATTCACCTCAAGAACATC Rv: CAGGGTCAAGGCAAGCCTC

Supplementary Table 2. List of used qPCR assays.

Gene	**Assay ID**
XPO1	C__16006954_10
MALAT1	Hs00273907_s1
RPLPO	Hs99999902_m1
Mettl3	Mm01316319_m1
Ythdf1	Mm00620538_m1
Rplpo	Mm00725448_s1

Supplementary Table 3. List of human biopsy samples.

	Dx	ORIGIN	AGE (years)	SEX	HLA	Serology	Marsh (0-3)
ADULT INDIVIDUALS	**CD (n=6)**	100% USA	34.2 ± 19.5	83.3% FEMALE 16.7% MALE		100% +	100% 3
	CTR (n=22)	31.8% USA 68.2% SPAIN	45.2 ± 11.3	77.3% FEMALE 22.7% MALE	13.6% DQ2 4.5% DQ8	100% -	100% 0
	GFD (n=6)	100% USA	37.3 ± 11.4	33.3% FEMALE 66.7% MALE		100% -	83.3% 0 16.7% 1
	Dx	**ORIGIN**	**AGE (years)**	**SEX**	**HLA**	**Serology**	**Marsh (0-3)**
PEDIATRIC INDIVIDUALS	**CD (n=28)**	100% SPAIN	4.6 ± 3.7	48.5 FEMALE 51.5 % MALE	69.7% DQ2 9.1% DQ2/DQ8	81.8% + 12.1% -	20% 0 80% 3
	CTR (n=16)	100% SPAIN	8.1± 3.6	68.75% FEMALE 31.25% MALE	-	100% -	100% 0
	GFD (n=12)	100% SPAIN	2 ± 0.7	69.2% FEMALE 30.8% MALE	69.2% DQ2 23.1% DQ2/DQ8	7.7% + 92.3% -	84.6% 0 7.7% 1 7.7% 3