Supplementary information

Supplementary Table 1

Table 1 Primer sequences used for quantitative PCR

Primer	Sequences
Homo-GAPDH-F	5'-AACGGATTTGGTCGTATTGGG-3'
Homo-GAPDH-R	5'-CCTGGAAGATGGTGATGGGAT-3'
Homo-ZO-1-F	5'-TGTGAGTCCTTCAGCTGTGGAA-3'
Homo-ZO-1-R	5'-GGAACTCAACACACCATTG-3'
Homo-OCLN-F	5'-ACAAGCGGTTTTATCCAGAGTC-3'
Homo-OCLN-R	5'-GTCATCCACAGGCGAAGTTAAT-3'
Homo-GPX4-F	5'-GAGGCAAGACCGAAGTAAACTAC-3'
Homo-GPX4-R	5'-CCGAACTGGTTACACGGGAA-3'
Homo-xCT-F	5'-ACGGTGGTGTGTTTGCTGTCTC-3'
Homo-xCT-R	5'-GCTGGTAGAGGAGTGTGCTTGC-3'
Mus-GAPDH-F	5'-AACGGATTTGGTCGTATTGGG-3'
Mus-GAPDH-R	5'-TGTAGACCATGTAGTTGAGGTCA-3'
Mus-GZMA-F	5'-GGTGGAAAGGACTCCTGCAA-3'
Mus-GZMA-R	5'-GCCTCGCAAAATACCATCACA-3'
Mus-IL-6-F	5'-AGCCAGAGTCCTTCAGAGAGA-3'
Mus-IL-6-R	5'-GCCACTCCTTCTGTGACTCC-3'

Supplementary Table 2

Table 2 criteria for the Histological Score

	Criteria	Score
amount of inflammation	none	0
	slight	1
	moderate	2
	severe	3
extent of inflammation	none	0
	mucosa	1
	mucosa and submucosa	2
	transmural	3
regeneration	complete regeneration or normal tissue	0
	almost complete regeneration	1
	regeneration with crypt depletion	2
	surface epithelium not intact	3
	no tissue repair	4
crypt damage	none	0
	basal 1/3 damaged	1
	basal 2/3 damaged	2
	only surface epithelium intact	3
	entire crypt and epithelium lost	4

Fig.S1

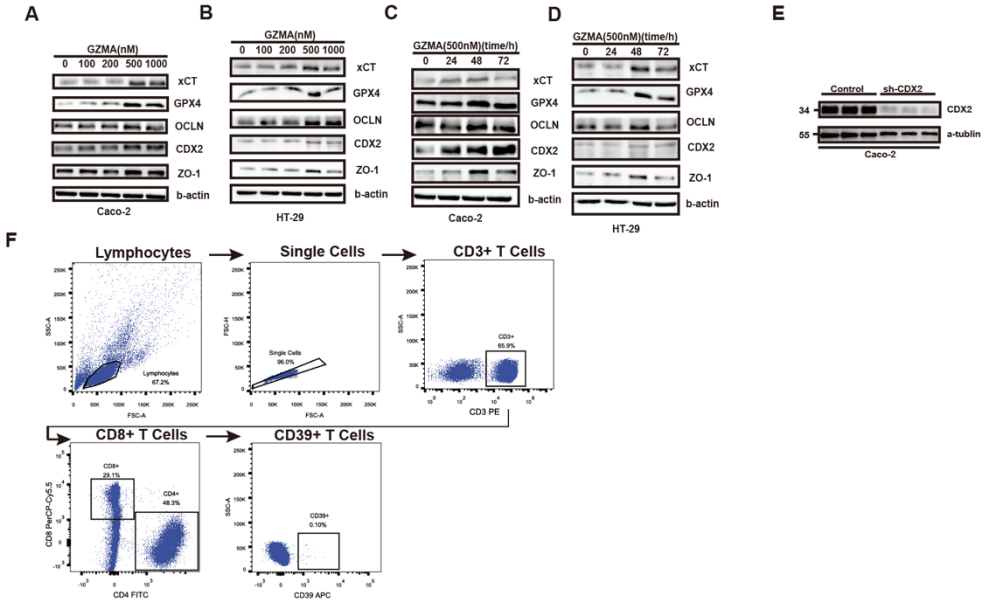

Fig.S1 GZMA modulated intestinal barrier integrity and ferroptosis (A-D) Western blotting was conducted to analyze indicated proteins in HT-29 and Caco-2 cells following stimulation with GZMA (0, 100, 200, 500, 1000nM) for 24/48/72 hours, respectively. **(E)** Western blotting was conducted to confirm the knockdown effect in Caco-2 cells transfected with sh-CDX2 plasmid. **(F)** FACS strategy for sorting $CD8^{+}CD39^{+}$ T cells from peripheral blood of healthy donors.

Fig.S2

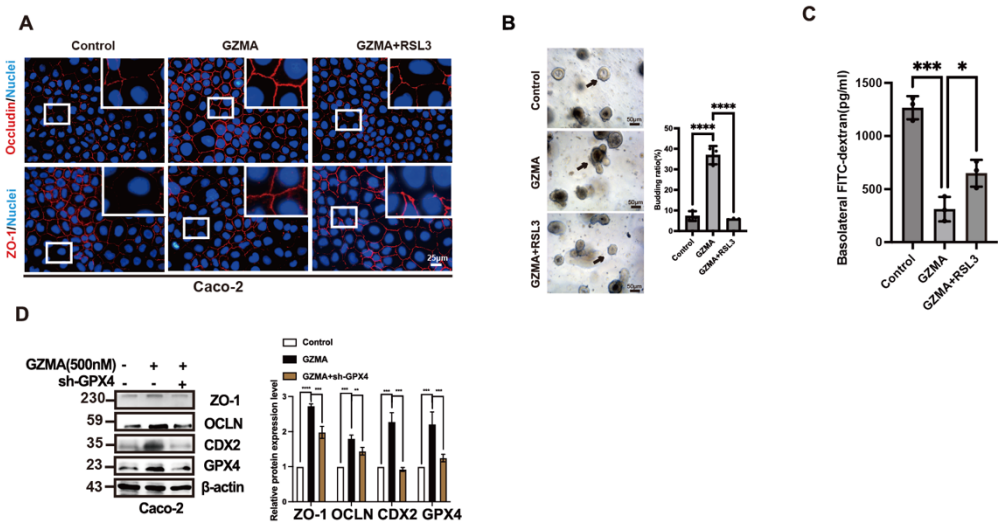

Fig.S2 GZMA modulated intestinal barrier integrity through GPX4. (A) After serum starvation for 24 hours, Caco-2 cells were treated as indicated for 48 hours, following by performance of immunofluorescence staining to detect ZO-1 and OCLN expression, Scale bar: 25 um. **(B)** Intestinal organoid analysis of the effect of GZMA (500 nM) and RSL3 (5 um) for 48 hours on intestinal organoid generation, microscopic examination of organoids was performed to calculate the proportion of budding organoids among every 100 organoids on average. Data was displayed as the means±s.d. of three independent experiments and analyzed by one-way ANOVA and Dunnett's multiple comparison test, ****p<0.0001. Scale bar: 50 um. **(C)** Caco-2 cells were seeded on Transwell polycarbonate membranes and treated with GZMA (500 nM) and RSL3 (5 μm) for 48 hours, following by the assessment of the permeability of the monolayer to FITC-dextran. Data was listed as the means±s.d. of three independent experiments and analyzed by one-way ANOVA and Dunnett's multiple comparison test, *p<0.5, ***p<0.001. **(D)** Caco-2 cells were transfected with sh-GPX4 plasmid for 12 hours following by treatment with GZMA (500 nM) for 48 hours, WB was conducted to analyze indicated protein. Data was presented as means±s.d. of three independent experiments and were analyzed by one-way ANOVA and Dunnett's multiple comparison test, ****p<0.0001, ***p<0.001.

Fig.S3

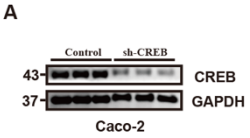

Fig.S3 Immunoblotting analysis of CREB expression. (A) Western blotting was conducted to detect the transfection efficiency of sh-CREB in Caco-2 cells.