

Supplementary Tables

Table S1. Characteristics of the study participants according to the quartiles of UPFs (% Kcal).

Characteristics	All participants (11765)	Dietary UPF quartiles (% of total energy intake)				p value
		Q1 (0-21.463%)	Q2 (21.450-33.507%)	Q3 (33.507-47.038%)	Q4 (47.038-100%)	
UPF, Cal% (SE)	34.840 (0.167)	12.737 (0.111)	27.669 (0.062)	39.792 (0.071)	59.160 (0.180)	0.0132
Age, % (SE)						
6-12	21.454 (0.375)	23.360 (0.261)	24.651 (0.088)	21.856 (0.087)	15.947 (0.090)	
13-19	17.493 (0.348)	15.199 (0.095)	16.219 (0.091)	17.165 (0.087)	21.387 (0.088)	
20-39	30.667 (0.415)	29.344 (0.094)	29.684 (0.267)	29.980 (0.256)	33.662 (0.269)	
40-59	30.387 (0.417)	32.098 (0.280)	29.446 (0.251)	30.999 (0.253)	29.003 (0.252)	0.2534
Sex, % (SE)						
Male	49.732 (0.005)	50.085 (0.009)	48.113 (0.009)	49.558 (0.009)	51.173 (0.009)	
Female	50.268 (0.005)	49.915 (0.009)	51.887 (0.009)	50.442 (0.009)	48.827 (0.009)	<0.0001
Race/ethnicity, % (SE)						
Mexican American	38.776 (0.004)	33.662 (0.009)	39.714 (0.009)	41.061 (0.009)	40.666 (0.009)	
Non-Hispanic White	21.241 (0.004)	16.287 (0.007)	19.007 (0.007)	22.059 (0.008)	27.610 (0.008)	
Non-Hispanic Black	22.643 (0.004)	30.432 (0.008)	23.461 (0.008)	19.715 (0.007)	16.967 (0.007)	
Others	17.340 (0.003)	19.619 (0.007)	17.818 (0.007)	17.165 (0.007)	14.757 (0.007)	<0.0001
Education, % (SE)						
Below high school	97.136 (0.002)	97.756 (0.003)	97.688 (0.003)	97.281 (0.003)	95.818 (0.002)	
High school	1.479 (0.001)	1.360 (0.002)	1.122 (0.002)	1.292 (0.002)	2.142 (0.003)	
Above High school	1.385 (0.001)	0.884 (0.002)	1.190 (0.002)	1.427 (0.002)	2.040 (0.003)	<0.0001
BMI status, kg/m² (SE)						
Normal weight	20.165 (0.057)	20.087 (0.123)	19.768 (0.119)	20.248 (0.117)	20.464 (0.104)	
Overweight	27.313 (0.026)	27.234 (0.054)	27.251 (0.053)	27.438 (0.051)	27.318 (0.053)	

Characteristics	All participants (11765)	Dietary UPF quartiles (% of total energy intake)				<i>p</i> value
		Q1 (0-21.463%)	Q2 (21.450-33.507%)	Q3 (33.507-47.038%)	Q4 (47.038-100%)	
Obese	35.971 (0.107)	35.773 (0.233)	35.398 (0.213)	35.951 (0.214)	36.489 (0.217)	<0.0001
Dietary fiber, g/day (SE)	15.365 (0.077)	16.757 (0.183)	15.725 (0.154)	15.203 (0.139)	13.776 (0.128)	
CDAI, (SE)	-0.267 (0.071)	-0.478 (0.149)	-0.157 (0.149)	-0.357 (0.141)	-0.075(0.129)	0.3866
Food allergy, % (SE) (self-reported)	8.559 (0.003)	7.719 (0.005)	8.569 (0.005)	8.668 (0.005)	9.283 (0.006)	0.0378
Asthma, % (SE) (self-reported)	16.073 (0.003)	14.485 (0.006)	14.621 (0.007)	16.655 (0.007)	18.531 (0.008)	<0.0001
Wheeze, % (SE) (self-reported)	12.945 (0.003)	11.595 (0.006)	12.377 (0.006)	14.004 (0.006)	13.805 (0.007)	0.0029

Values are mean (standard error) or % (standard error) as indicated.

p value across UPF quartiles was assessed by Pearson chi-square for categorical variables and linear regression for continuous variables. All statistical tests were two-sided.

SE, standard error; UPF, ultra-processed food; BMI, body mass index; CDAI, composite dietary antioxidant index.

Table S2. The ingredient information of diet D12450H.

Product	D12450H	
	gm%	kcal%
Protein	19.2%	20.1%
Carbohydrate	66.8%	69.9%
Fat	4.3%	10.0%
Total		100
kcal/gm	3.83	
Ingredient	gm	kcal
Casein	200	800
L-Cystine	3	12
Corn Starch	452.2	1808.8
Maltodextrin	75	300
Sucrose	176.8	707.2
Cellulose	50	0
Soybean Oil	25	22.5
Lard	20	180
Mineral Mix S10026B	50	0
Vitamin Mix V10001C	1	4
Choline Bitartrate	2	0
FD&C Yellow Dye #5	0.04	0
FD&C Red Dye #40	0.01	0
FD&C Blue Dye #1	0	0
Total	1055.05	4037

Table S3. Criteria for evaluating allergic symptoms score.

	Description	Score
Scratching	No symptoms	0
	Mild scratching; rubbing of nose, head, or feet (<5 episodes)	1
	Intermediate scratching; rubbing of nose, head, or feet (5~10 episodes)	2
	Severe scratching (>10 episodes)	3
Behavior	Normal	0
	Hyperactivity	1
	Aggressive behavior; pain loud after prodding	2
Physical appearance	Normal activity	0
	Significantly reduced mobility; piloerection	2
	Immobility after prodding, tremors, and/or significant respiratory distress	3
Stool consistency	Normal	0
	Loose stool	2
	Diarrhea	4

Table S4. Mass cytometry antibody panel.

	Surface Marker	Metal label
1	CD45	89Y
2	CD3	166Er
3	CD8	113Cd
4	CD4	112Cd
5	CD25	154Gd
6	CD69	153Eu_EQ4
7	CD62L	164Dy
8	CD44	148Sm
9	IL-7Ra	146Nd
10	CD19	158Gd
11	CD27	174Yb
12	CD138	171Yb
13	IgD	147Sm
14	CD11b	173Yb
15	CD11c	150Sm
16	MHCII	209Bi
17	CD103	151Eu_EQ3
18	XCR1	163Dy
19	CD83	155Gd
20	CD317	143Nd
21	FcεR1α+	169Tm
22	F4/80	144 Nd
23	Ly-6G	152Gd
24	Ly6C	162Dy
25	CD90	170Yb
26	RAGE	168Er
27	TLR2*	149Sm
28	TLR4	176Lu_EQ7
29	TCRδ [#]	155Gd
30	CD49b [#]	164Dy
	Intracellular Marker	Metal label
31	T-Bet	160Dy
32	GATA-3	145Nd
33	RoRyT	159Tb
34	IL-9	141Pr
35	Foxp3	165Ho_EQ5
36	p38 [#]	156Gd
37	p-STAT3 [#]	158Gd
38	NF-κB*	142Ce_EQ2
39	MyD88*	156Gd

* Antibodies used only in the orally sensitized model.

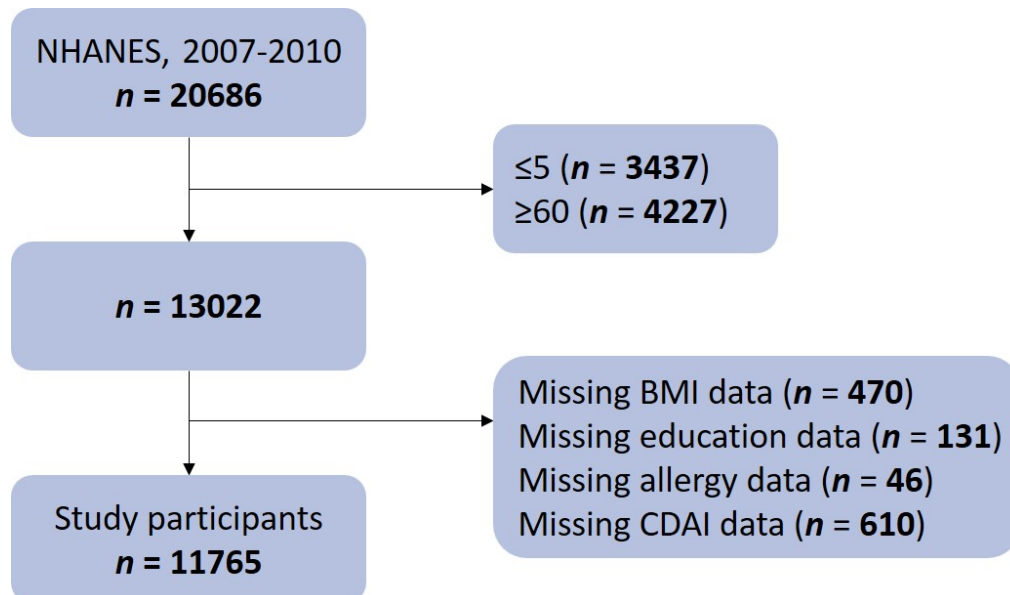
[#] Antibodies used only in the epicutaneously sensitized model.

Table S5. Primers used for qRT-PCR in the study.

Gene	Primer sequence	
	Forward primer	Reverse primer
<i>Ager</i> (RAGE)	CTACCTTCTCCTGCAGTTTCAG	CATCCTTTATCCAGTGGACCTG
<i>Tjp1</i> (ZO-1)	CTGGTGAAGTCTCGGAAAAATG	CATCTCTTGCTGCCAAACTATC
<i>Claudin-2</i>	GGTTCCTGACAGCATGAAATTT	GCCATCATAGTAGTTGGTACGA
<i>Occludin</i>	TGCTTCATCGCTTCCTTAGTAA	GGGTTCACTCCCATTATGTACA
<i>Tlr4</i>	GCCATCATTATGAGTGCCAATT	AGGGATAAGAACGCTGAGAATT
<i>Il25</i>	GGCATTCTACTCAGGAACGGACTC	CAAACAAACACAACAAAAGGCAAAGGG
<i>Il33</i>	ATGCCAAATGCCTCCGCAGATG	AACAAGCACAGGTAACGCCACTC
<i>Tslp</i>	GTGGAATCTGGGAGAAACTGCTGAG	CACGAATTGTACTGTCCTGGGTCTG
<i>Gata3</i>	TCTGGAGGAGGAACGCTAATGGG	CGGGTCTGGATGCCTTCTTTCTTC
<i>Tbet</i>	ATCACTAAGCAAGGACGGCGAATG	ACCAAGACCACATCCACAAACATCC
<i>Foxp3</i>	ACAGAATGCCATCCGCCACAAC	TACGGTCCCACTGCTCCCTTC
<i>Myd88</i>	AGCAGAACCAGGAGTCCGAGAAG	GGGCAGTAGCAGATAAAGGCATCG
<i>Nfkb1</i>	GACACGACAGAATCCTCAGCATCC	CCACCAGCAGCAGCAGACATG
<i>Gapdh</i>	CAGGAGGCATTGCTGATGAT	GAAGGCTGGGGCTCATTT

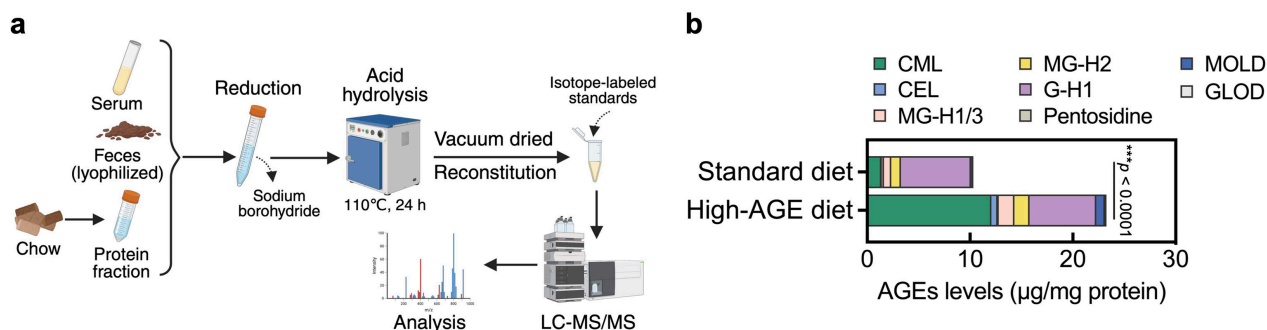
Supplementary Figures

Figure S1. Flow chart of the screening process of eligible participants in NHANES 2007-2010.



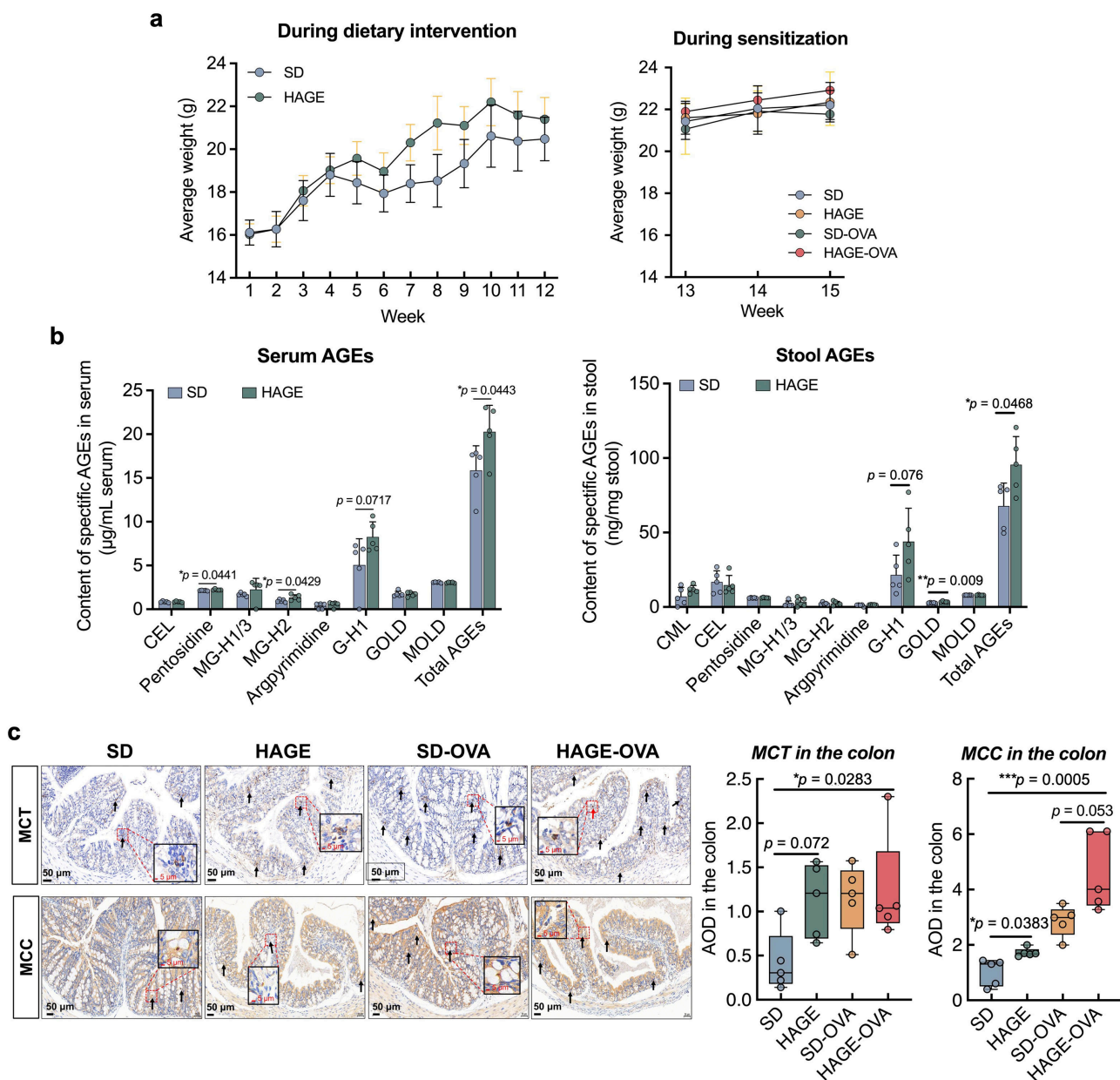
BMI, body mass index; CDAI, composite dietary antioxidant index.

Figure S2. a, Schematic diagram of the extraction and analytical process of AGEs in mouse biological samples and chow diets[#]. **b**, Contents of AGEs in the standard diet and heat-treated high-AGE diet ($n = 5$).



To prepared the high-AGE diet, the standard diet D12450H was baked at 175 °C for 45 min. The two diets were identical in calories and macronutrients level. Results are expressed as the mean value. Pair-wise comparison was conducted by Student's *t* tests (two-tailed). *** $p < 0.001$. AGEs, advanced glycation end-products; CEL, N ϵ -carboxyethyllysine; CML, N ϵ -(carboxymethyl)-lysine; G-H1, glyoxal-derived hydroimidazolone 1; GOLD, glyoxal lysine dimer; MG-H1/2/3, methyglyoxal-derived hydroimidazolone 1/2/3; MOLD, methylglyoxal lysine dimer. [#]Created in BioRender. Zhang, Q. (2025) <https://BioRender.com/pf8iqnb>. Source data are provided as a Source Data file.

Figure S3. Supplementary data for the orally sensitized model: **a**, Changes in mouse body weight during dietary intervention and allergen sensitization phases (left panel: $n = 15-16$; right panel: $n = 7-8$). **b**, Contents of specific AGEs in the serum and stool of mice after 12 weeks of dietary regimen ($n=5$). **c**. Representative images and quantification of immunohistochemistry staining for MCT and MCC in the colon tissue ($n=5$); scale bar: 50 μm .



Mice received either a control standard diet (SD) or a heat-treated high-AGE diet (HAGE) for 12 weeks before induction of experimental food allergy via *i.g.* gavage of model allergen OVA. Serum and stool samples collected at 12 weeks were analyzed for AGEs quantification.

Colon tissue sections were collected upon oral challenge for immunohistochemistry staining. Bar and line graphs show mean $\pm$ SEM (**a, b**) and boxplots represent median with 25th/75th percentiles (box) and 1.5 $\times$ IQR (whiskers) (**c**). **a-b**, Pair-wise comparison was conducted by Student's *t* tests or Mann-Whitney tests (two-tailed); **c**, Comparisons were performed using one-way ANOVA or Kruskal-Wallis test, followed by appropriate post-hoc tests for pairwise comparisons. **p* < 0.05, ***p* < 0.01, ****p* < 0.001. AGEs, advanced glycation end-products; CEL, N ϵ -carboxyethyllysine; CML, N ϵ -(carboxymethyl)-lysine; G-H1, glyoxal-derived hydroimidazolone 1; GOLD, glyoxal lysine dimer; *i.g.*, intragastric; MCT, mast cell tryptase; MCC, mast cell chymase; MG-H1/2/3, methylglyoxal-derived hydroimidazolone 1/2/3; MOLD, methylglyoxal lysine dimer; OVA, ovalbumin. Source data are provided as a Source Data file.

Figure S4. Representative manual gating strategy for **a**, mass cytometry, and **b**, fluorescent flow cytometry.

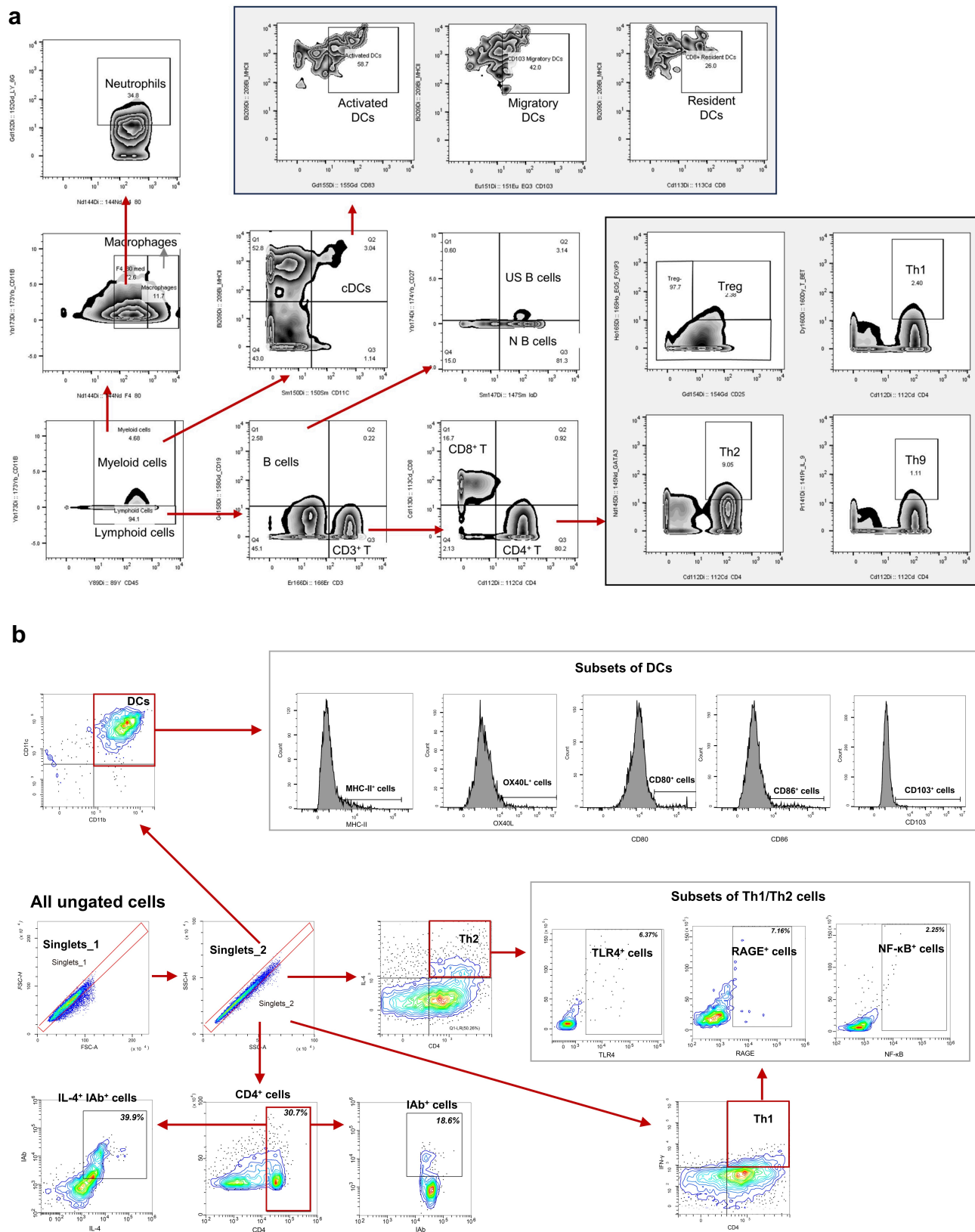
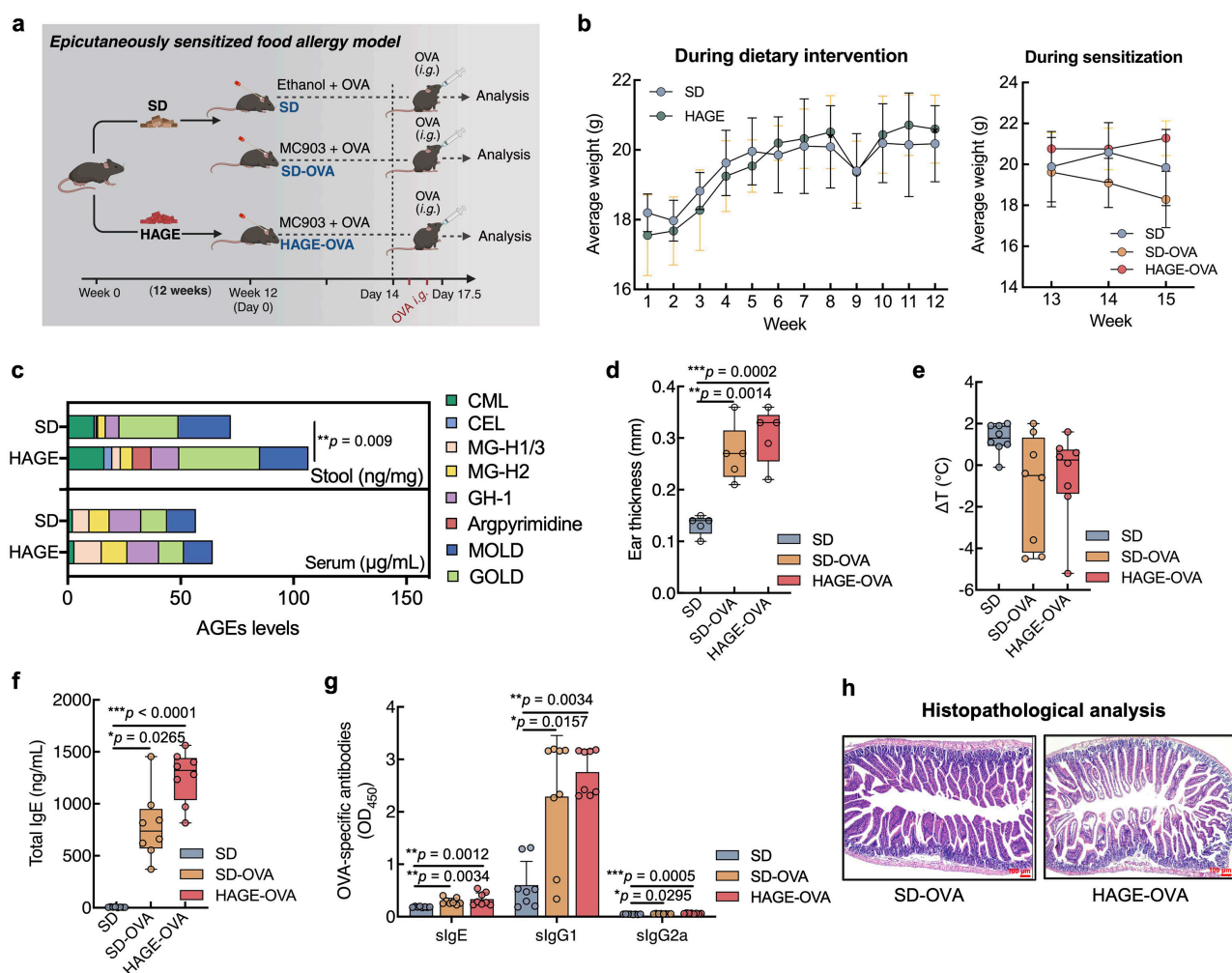


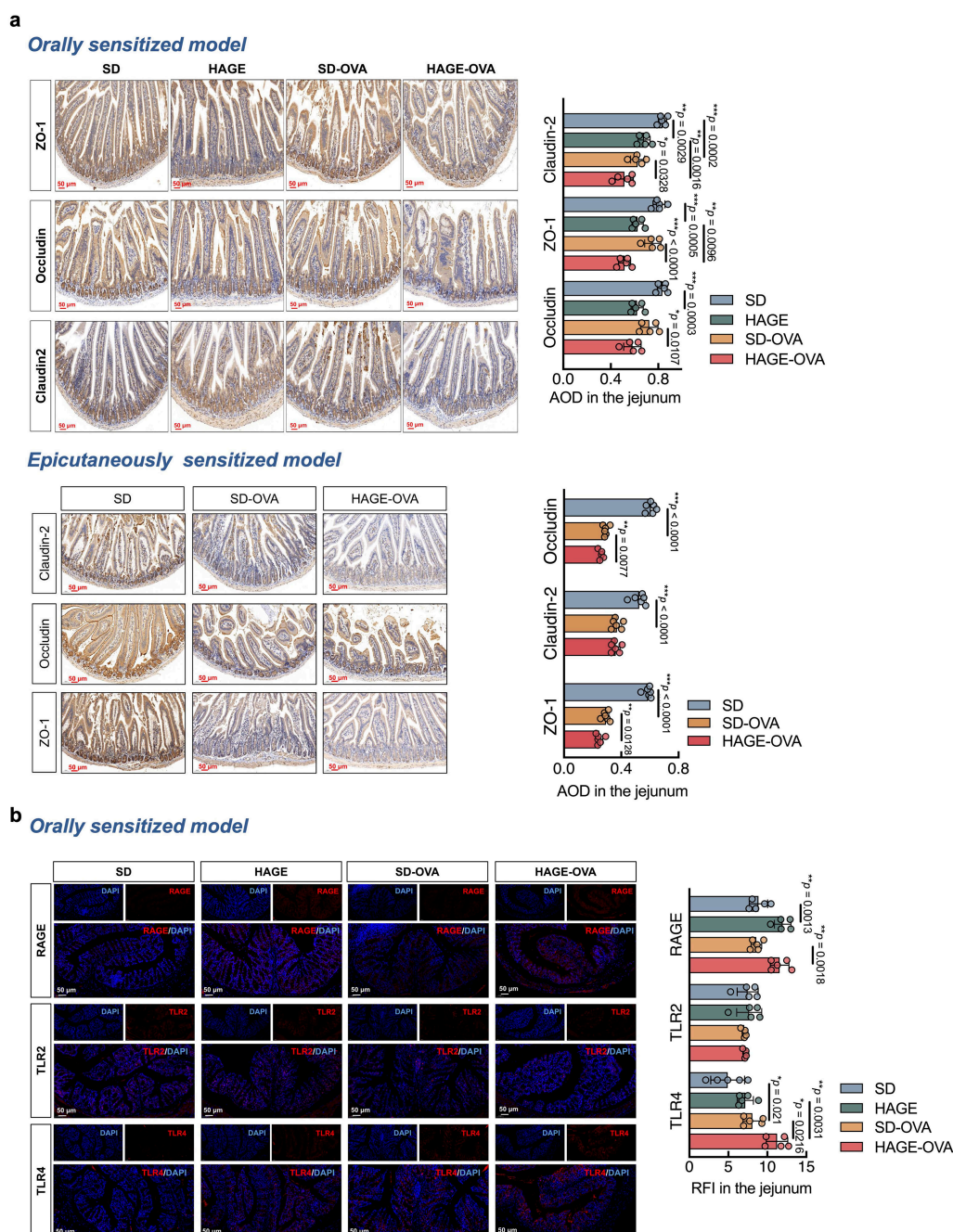
Figure S5. Long-term exposure to dAGEs promoted allergic inflammation in epicutaneously sensitized model of food allergy: a, Schematic illustration of the study design[#]. **b**, Changes in mouse body weight during dietary intervention and allergen sensitization phases ($n = 8-16$). **c**, Contents of AGEs in the serum and feces of mice upon 12 weeks of regimen ($n = 5$). **d**, Ear thickness ($n = 5$). **e**, Rectal temperature change upon last challenge ($n = 8$). **f**, Serum total IgE level ($n = 8$). **g**, Serum OVA-specific antibody level (IgE, IgG1 and IgG2a; $n = 8$). **h**, Representative images of H&E-stained intestinal sections (scale bar: 100 μ m).



Mice received either a control standard diet (SD) or a heat-treated high-AGE diet (HAGE) for 12 weeks before induction of experimental food allergy via epicutaneous sensitization of model allergen OVA. Bar and line graphs show mean $\pm$ SEM (**b**, **c**, **g**) and boxplots represent median with 25th/75th percentiles (box) and $1.5 \times \text{IQR}$ (whiskers) (**d-f**). **b-c**, Pair-wise

comparison was conducted by Student's *t* tests or Mann-Whitney tests (two-tailed); **d-g**, Comparisons were performed using one-way ANOVA or Kruskal-Wallis test, followed by appropriate post-hoc tests for pairwise comparisons. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. AGEs, advanced glycation end-products; AOD, average optical density; H&E, hematoxylin and eosin; OVA, ovalbumin. #Created in BioRender. Zhang, Q. (2025) <https://BioRender.com/pf8iqnb>. Source data are provided as a Source Data file.

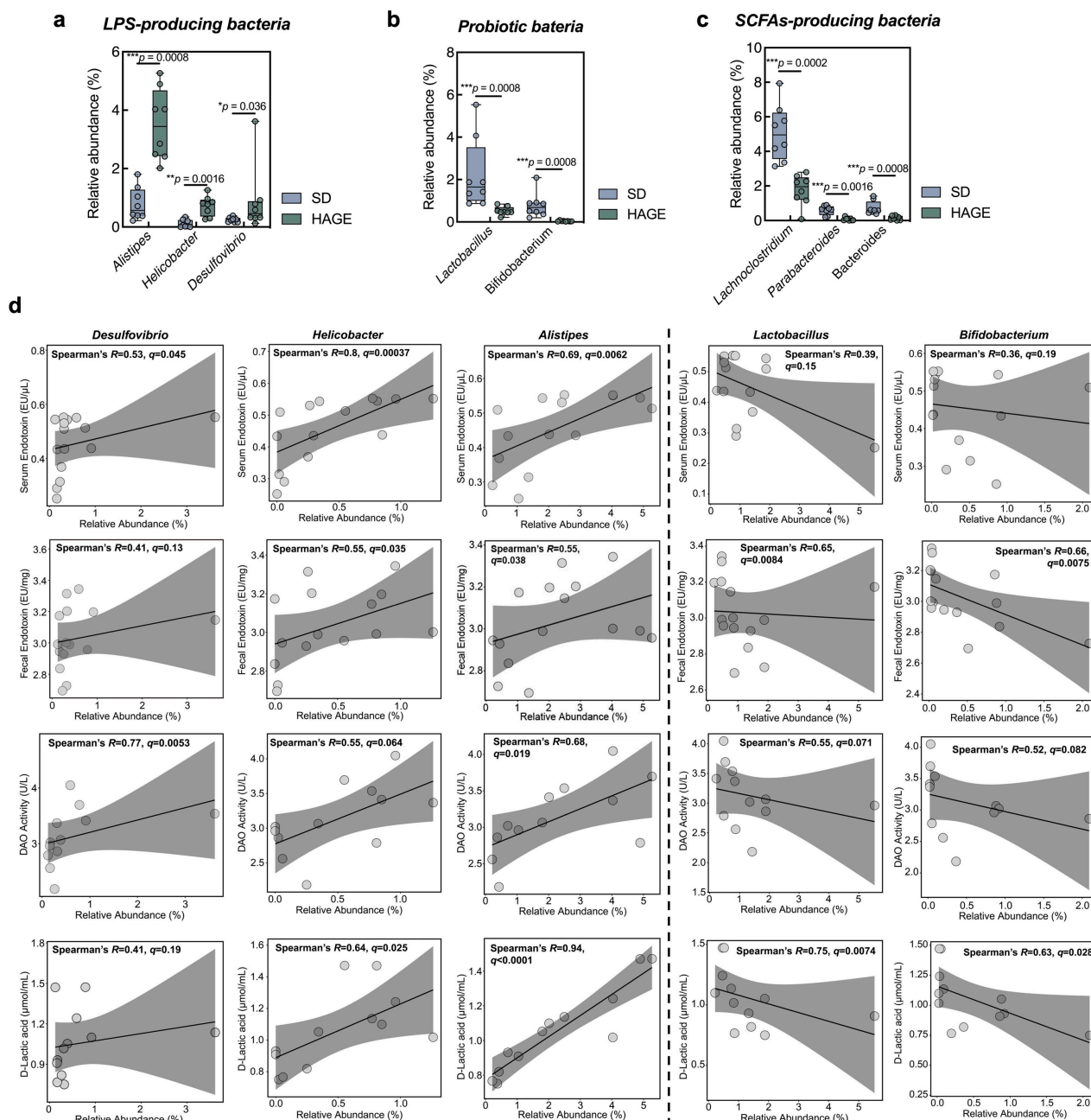
Figure S7. Supplementary data for intestinal barrier dysfunction and receptor signaling analyses ($n = 5$): **a**, Representative images of immunohistochemistry staining for tight-junction proteins in the jejunum tissue; scale bar: 50 μm . **b**, Representative images of immunofluorescence staining for RAGE, TLR2, and TLR4 receptors in the colon tissue; scale bar: 50 μm .



Mice received either a control standard diet (SD) or a heat-treated high-AGE diet (HAGE) for 12 weeks before induction of experimental food allergy via *i.g.* gavage or epicutaneous

sensitization of model allergen OVA. Jejenum tissue was analyzed for expression levels of tight-junction proteins, and colon tissue was analyzed for staining of RAGE and TLRs receptor. Results are expressed as mean $\pm$ SEM. Comparisons were performed using one-way ANOVA or Kruskal-Wallis test, followed by appropriate post-hoc tests for pairwise comparisons. * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. AGEs, advanced glycation end-products; AOD, average optical density; OVA, ovalbumin. Source data are provided as a Source Data file.

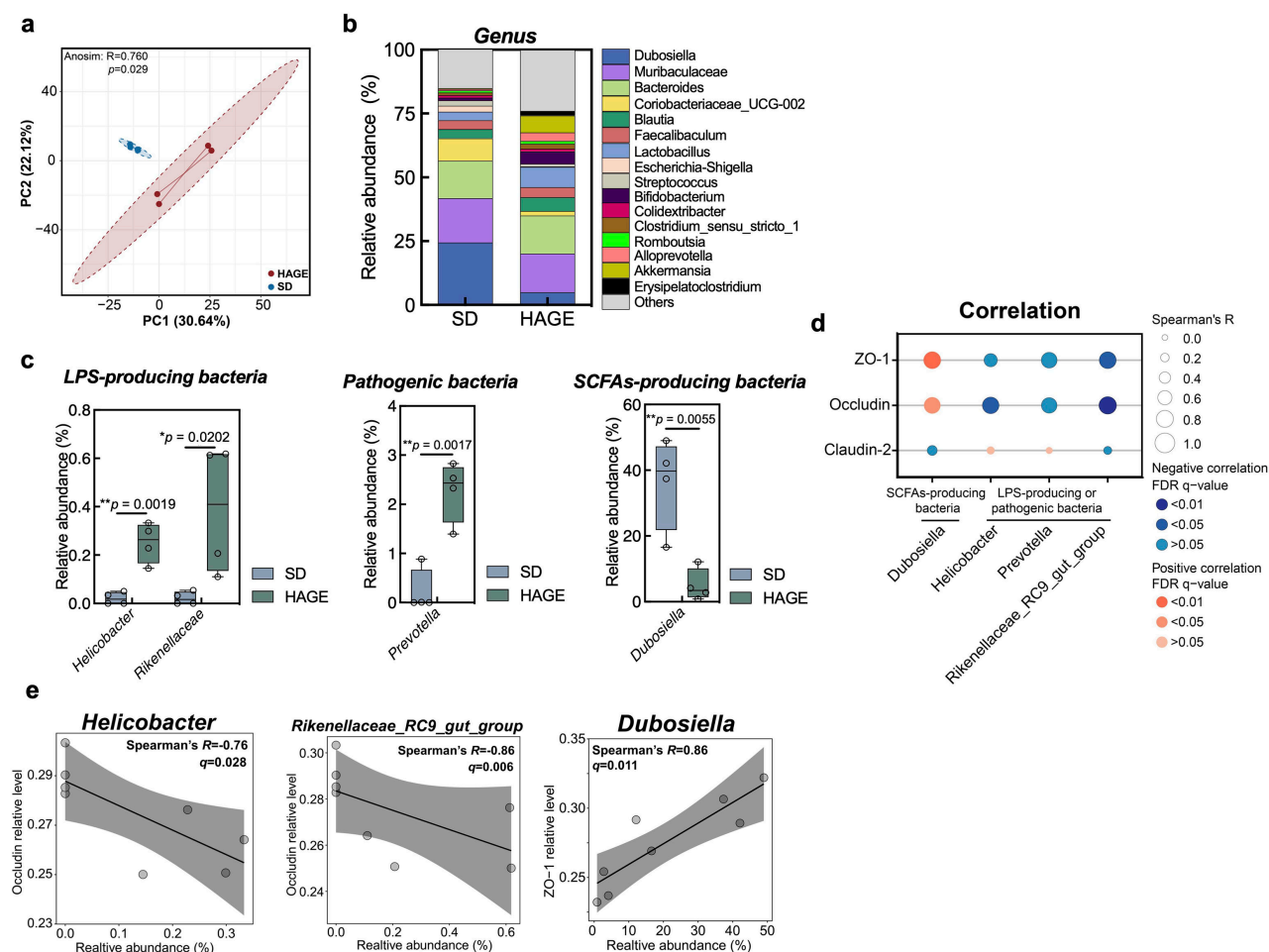
Figure S8. Supplementary data for gut microbiota analysis in the orally sensitized model ($n = 8$): **a-c**, Relative abundance of pathogenic and probiotic bacteria. **d**, Representative correlations between the abundance of specific genera and markers associated with gut barrier integrity.



Mice received either a control standard diet (SD) or a heat-treated high-AGE diet (HAGE) for 12 weeks before induction of experimental food allergy. Feces at 12 weeks were collected for analysis. Results represent median with 25th/75th percentiles (box) and $1.5 \times \text{IQR}$ (whiskers). Pair-wise comparison was conducted by Student's t tests or Mann-Whitney tests

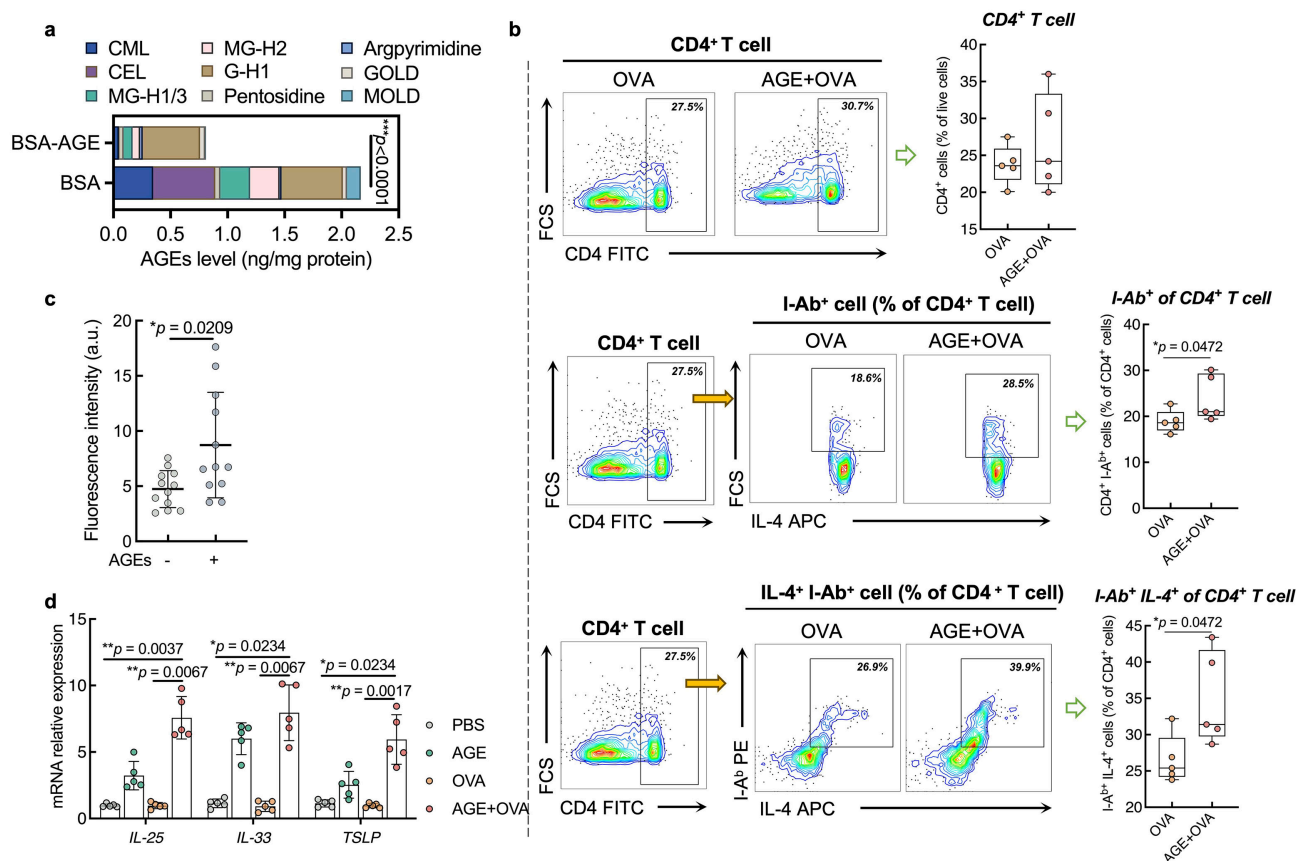
(two-tailed). $*p < 0.05$, $**p < 0.01$, $***p < 0.001$; FDR-corrected q values were presented in correlation analysis. AGEs, advanced glycation end-products; DAO, diamine oxidase; LPS, lipopolysaccharide; SCFAs, short-chain fatty acids. Source data are provided as a Source Data file.

Figure S9. Supplementary data for gut microbiota analysis in the epicutaneously sensitized model ($n = 4$): **a**, PCoA analysis based on Bray Curits distance (Anosim test). **b**, Bacterial relative abundance at the genus level. **c**, Relative abundance of pathogenic and probiotic bacteria. **d-e**, Spearman correlations and representative linear regressions between the abundance of specific genera and expression of TJ-proteins in the jejunum.



Mice received either a control standard diet (SD) or a heat-treated high-AGE diet (HAGE) for 12 weeks before induction of experimental food allergy. Feces at 12 weeks were collected for analysis. Results represent median with 25th/75th percentiles (box) and $1.5 \times \text{IQR}$ (whiskers). Pair-wise comparison was conducted by Student's t tests or Mann-Whitney tests (two-tailed). $*p < 0.05$, $**p < 0.01$; FDR-corrected q values were presented in correlation analysis. AGEs, advanced glycation end-products; LPS, lipopolysaccharide; PCoA, principal coordinate analysis; SCFAs, short-chain fatty acids; TJ, tight-junction. Source data are provided as a Source Data file.

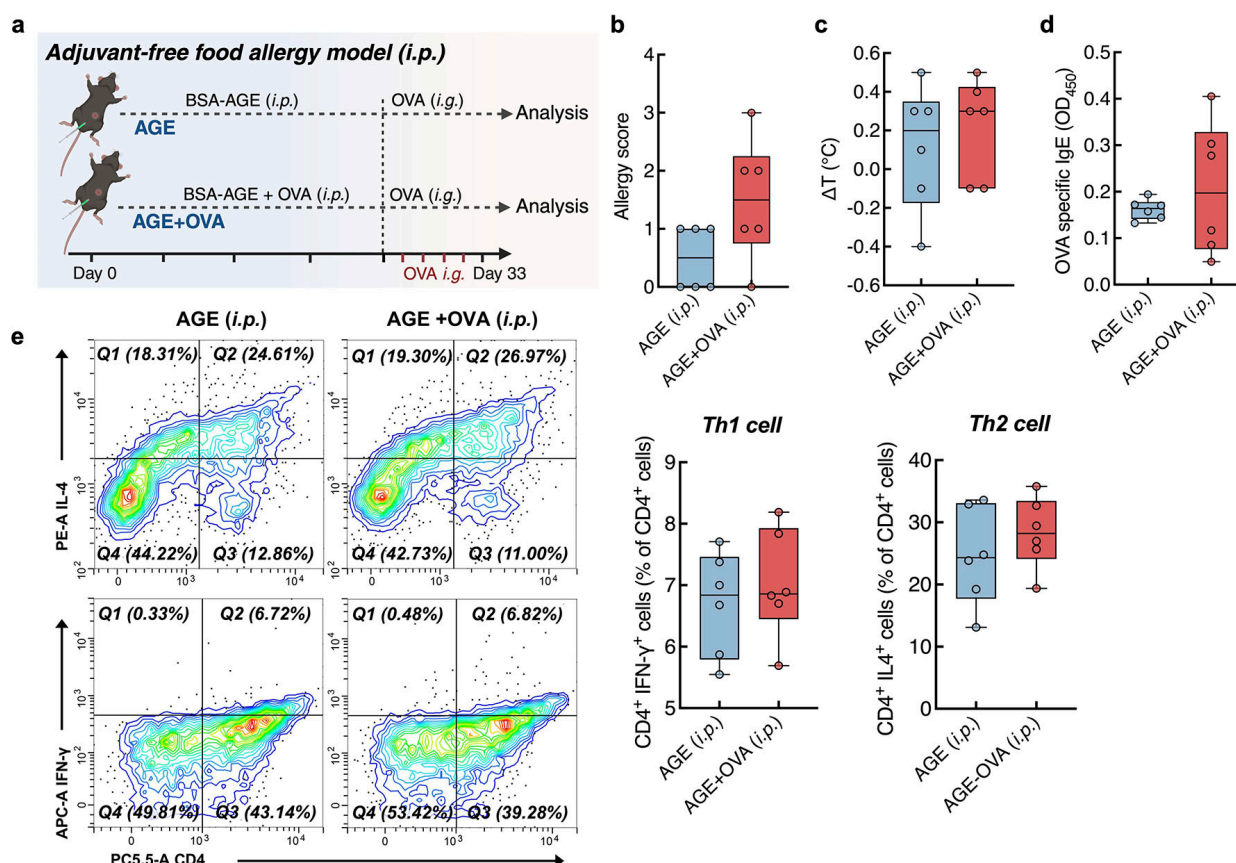
Figure S10. Supplementary data for the adjuvant-free model: a, Contents of AGEs in BSA and BSA-AGE ($n = 5$). **b**, Characterization of OVA-specific T-cell responses by using IAb tetramer staining: representative cell sorting plots and quantification of cell subsets ($n = 5$). **c**, Gut permeability assessed by an FITC-dextran assay ($n = 12$). **d**, Relative gene expression levels of danger signal molecules in the intestine ($n = 5$).



Mice were exposed to BSA-AGE alone or in the presence of model allergen OVA via *i.g.* gavage to establish an adjuvant-free model of food allergy. Splenocytes were harvested, stimulated, and analyzed by flow cytometry for OVA-specific responses by staining with an IAb tetramer that specially recognizes the OVA₃₂₃₋₃₃₉ epitope. Gut permeability was assessed in the 4th week of sensitization. Bar graphs show mean $\pm$ SEM (**a**, **d**) and boxplots represent median with 25th/75th percentiles (box) and 1.5 $\times$ IQR (whiskers) (**b**). **a-c**, Pair-wise comparison was conducted by Mann-Whitney tests (two-tailed); **d**, Comparisons were performed using one-way ANOVA or Kruskal-Wallis test, followed by appropriate post-hoc tests for pairwise comparisons. $*p < 0.05$, $**p < 0.01$. AGEs, advanced glycation end-products;

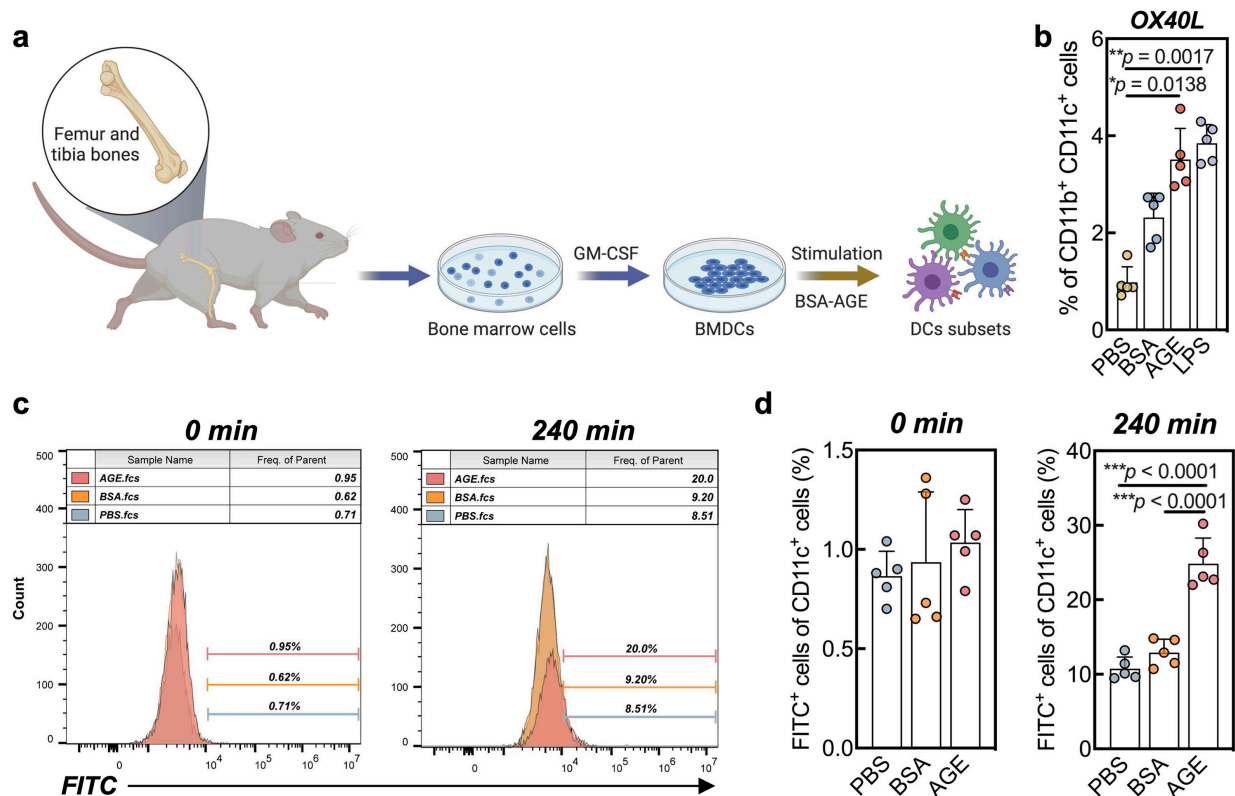
BSA-AGE, methylglyoxal-glycated bovine serum albumin; *i.g.*, intragastric; OVA, ovalbumin; TCRs, T-cell receptors. Source data are provided as a Source Data file.

Figure S11. Administration of BSA-AGE via parenteral route did not elicit adjuvant activity ($n = 6$): **a**, Schematic illustration of the study design[#]. **b**, Clinical allergy score of mice upon last challenge. **c**, Rectal temperature change after last challenge. **d**, Serum OVA-specific IgE level. **e**, Representative cell sorting plots and quantification of Th1 and Th2 cells in MLN lymphocytes by flow cytometry.



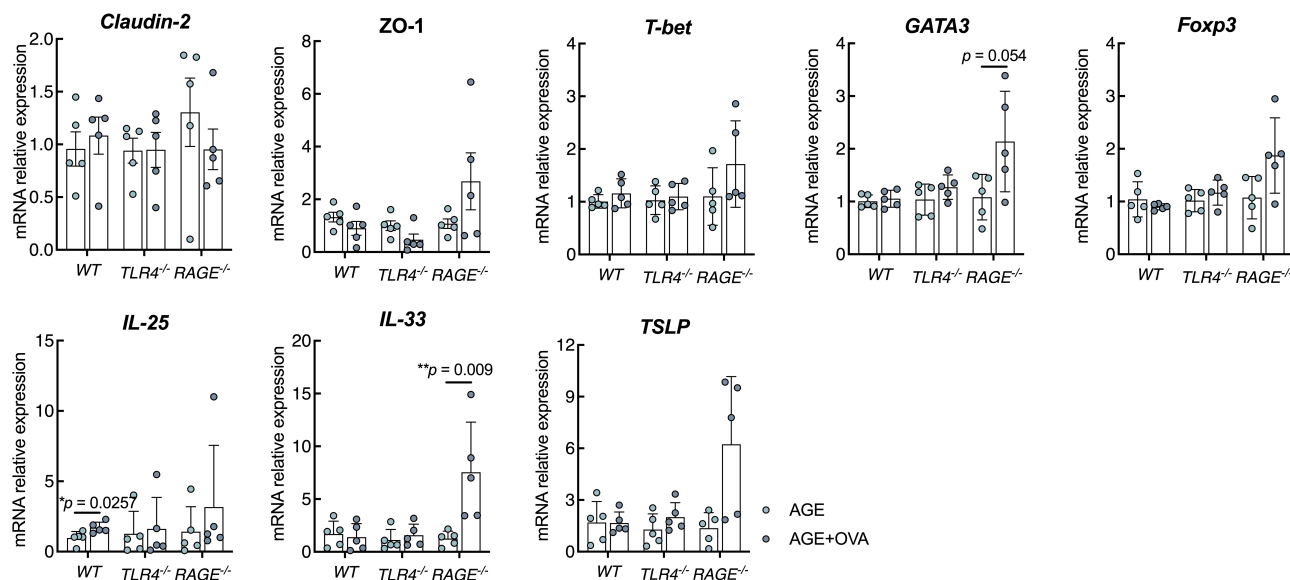
Mice were exposed to BSA-AGE alone or in the presence of model allergen OVA via intraperitoneal injection to assess its adjuvant activity when given parenterally. Results represent median with 25th/75th percentiles (box) and 1.5×IQR (whiskers). Pair-wise comparison was conducted by Student's t tests or Mann-Whitney tests (two-tailed). BSA-AGE, methylglyoxal-glycated bovine serum albumin; MLN, mesenteric lymph nodes; OVA, ovalbumin. [#]Created in BioRender. Zhang, Q. (2025) <https://BioRender.com/pf8iqnb>. Source data are provided as a Source Data file.

Figure S12. Supplementary data for the *in vitro* BMDCs experiments: **a**, Schematic diagram of BMDCs generation from mouse femurs/tibias[#]. **b**, Flow cytometry of OX40L⁺ cells in CD11b⁺ CD11c⁺ cells of treated BMDCs. **c-d**. Uptake of FITC-labeled allergen OVA by treated BMDCs (*n* = 5).



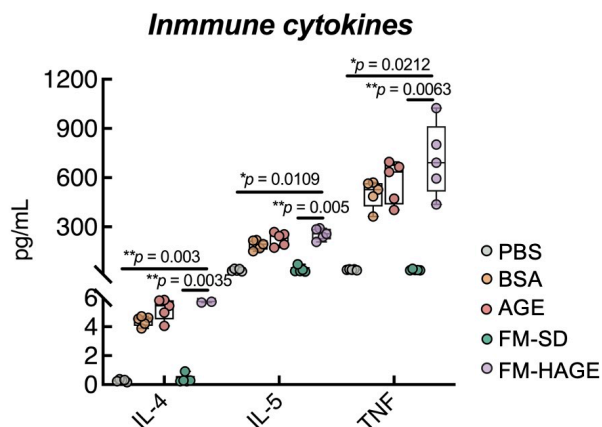
Mouse BMDCs were treated with BSA-AGE to assess its effect on DCs phenotype. PBS-/BSA- and LPS-treated cells serve as the negative and positive control, respectively. To analyze allergen uptake, treated cells were incubated with FITC-labeled OVA and assessed at indicated times. Results are expressed as mean $\pm$ SEM. Comparisons were performed using one-way ANOVA or Kruskal-Wallis test, followed by appropriate post-hoc tests for pairwise comparisons. **p* < 0.05, ***p* < 0.01, ****p* < 0.001. BMDCs, bone marrow-derived dendritic cells; BSA-AGE, methylglyoxal-glycated bovine serum albumin; GM-CSF, granulocyte-macrophage colony stimulating factor; LPS, lipopolysaccharide; OX40L, OX40L ligand. [#]Created in BioRender. Zhang, Q. (2025) <https://BioRender.com/pf8iqnb>. Source data are provided as a Source Data file.

Figure S13. Supplementary data for the knock-out model ($n = 5$): Relative expression levels of genes related to intestinal barrier function, type 2 immunity, and pro-inflammatory molecules in the intestine.



The adjuvant-free model of food allergy was performed in wild type (WT), RAGE-knockout (RAGE^{-/-}), and TLR4-knockout (TLR4^{-/-}) mice. Gene expression levels of markers related to gut barrier function, type 2 immunity and localized inflammation in the intestine of knock-out mice were determined. Results are expressed as mean $\pm$ SEM. Pair-wise comparison was conducted by Student's t tests or Mann-Whitney tests (two-tailed). * $p < 0.05$, ** $p < 0.01$. Source data are provided as a Source Data file.

Figure S14. Supplementary data for the human PBMC experiments ($n = 5$): Concentrations of Th2 and pro-inflammatory cytokines in cell-free supernatants following treatments.



PBMCs from healthy individuals were stimulated with BSA-AGE (AGE) or a fecal supernatant (FM-HAGE) from HAGE-fed mice of the orally sensitized model, followed by collection of cell-free supernatant for cytokine analysis. Cells treated with PBS, BSA, and a fecal extract (FM-SD) from SD-fed mice served as negative controls. Results represent median with 25th/75th percentiles (box) and $1.5 \times \text{IQR}$ (whiskers). Comparisons were performed using one-way ANOVA or Kruskal-Wallis test, followed by appropriate post-hoc tests for pairwise comparisons. $*p < 0.05$, $**p < 0.01$. Source data are provided as a Source Data file.