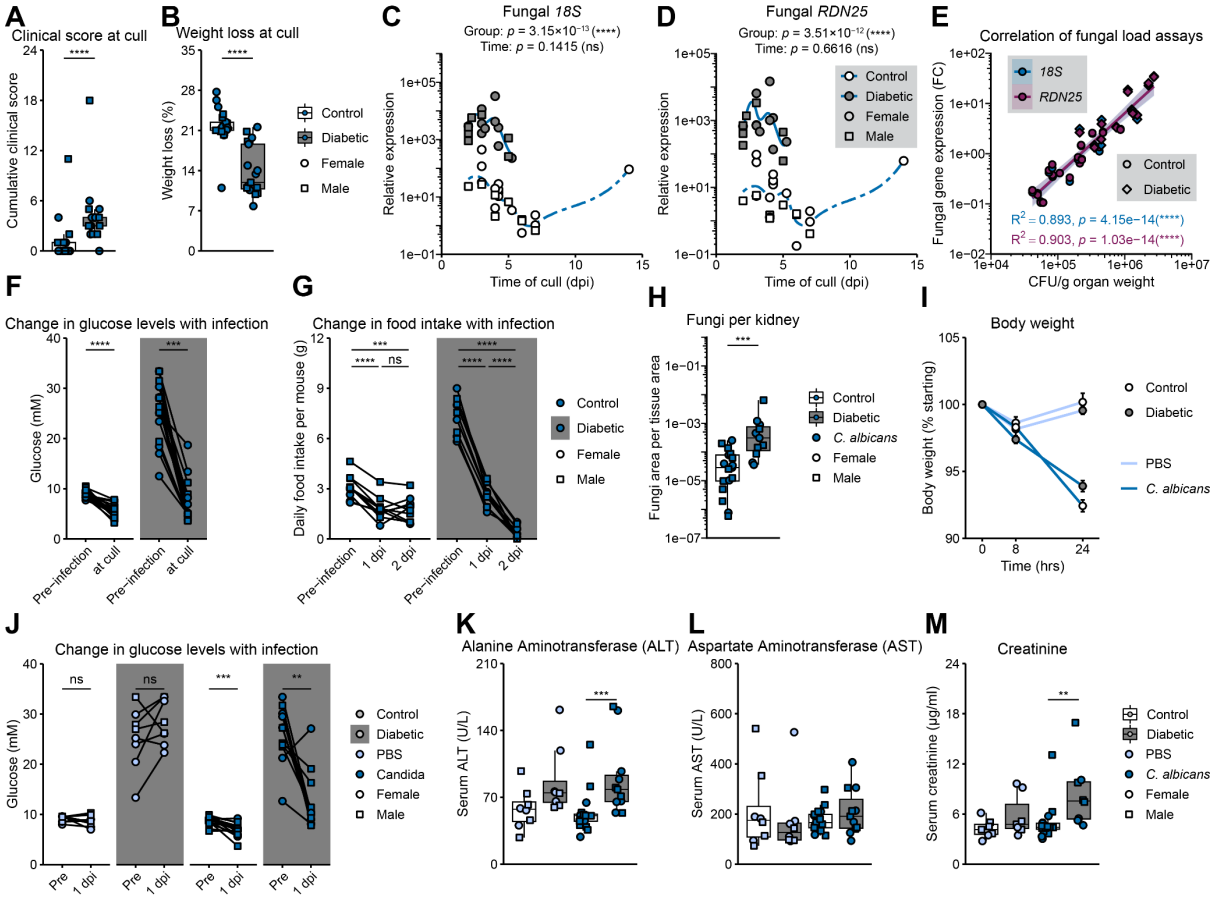



**Figure S1. Further characterisation of *C. albicans* disease in T2D animals. Relates to Figure 1**

(A) Cumulative clinical score at humane endpoint from survival experiment. n=17-22 animals per group. Mann-Whitney *U* test.

(B) Relative weight loss at humane endpoint compared to pre-infection levels from survival experiment. n=17-22 animals per group. Mann-Whitney *U* test.

(C and D) Expression of fungal housekeeping genes *18S* (C) and *RDN25* (D) relative to murine *Tbp* in kidneys collected at humane endpoint. n=17-22 animals per group. ANOVA of $\log_2$-transformed relative expression values.

(E) Correlation between fungal load determination by CFU assay and gene expression (fold change from control) from 24-hr experiment. n=11-17 animals per group. Pearson correlation analysis for each fungal housekeeping gene shown in matching colour.

(F) Blood glucose levels before infection and at humane endpoint from survival study. n=17-22 animals per group. Wilcoxon signed-rank test.

(G) Daily food intake levels before infection and during the first two days of the survival study. n=10 animals per group. Wilcoxon signed-rank test.

(H) Quantification of PAS staining. Relative area of PAS$^+$ fungi per kidney tissue of infected T2D and control mice at 24 hours post-infection. n=11-17 animals per group. Mann-Whitney *U* test.

(I) Relative weight change during 24-hr experiment. Shown are means ± SEM, n=8-17 animals per group.

(J) Blood glucose levels before infection and at cull from 24-hr experiment. n=8-17 animals per group. Wilcoxon signed-rank test.

(K to M) Serum levels of ALT (K), AST (L) and creatinine (M) from 24-hr experiment. n=8-17 animals per group. Dunn's test with Holm correction.

(A to M) Pooled from two independent repeats.

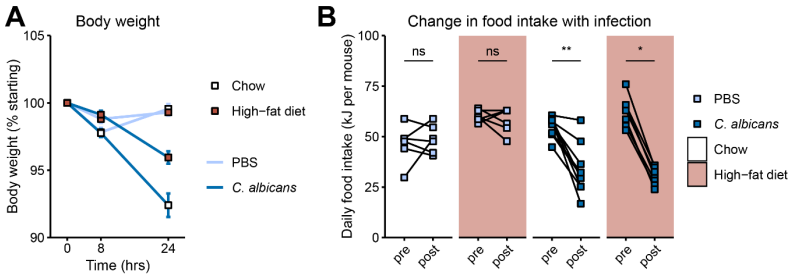



**Figure S2. Further characterisation of *C. albicans* disease in high-fat diet animals. Relates to Figure 2**

(A) Relative weight change of HFD-fed and control mice throughout 24-hr experiment. Shown are means ± SEM, n=7-11 animals per group.

(B) Daily food intake levels before and after infection. n=6-9 animals per group. Wilcoxon signed-rank test.

(A to B) Pooled from two independent infection repeats. Both cohorts were placed on the experimental diet at the same time.

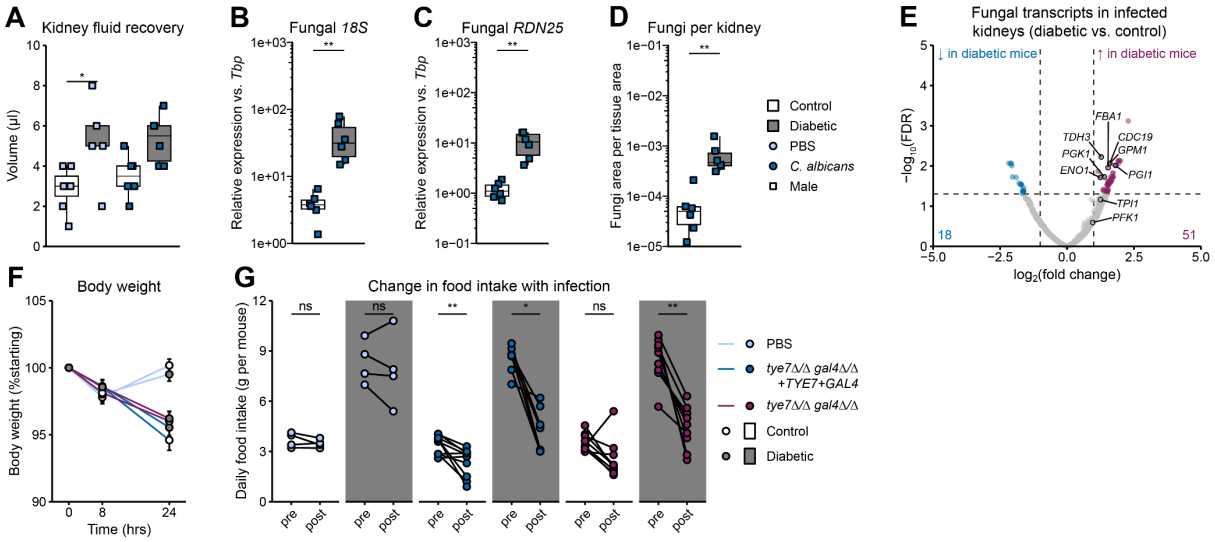



**Figure S3. Further characterisation of the roles of fungal glycolysis in T2D hosts. Relates to Figure 3**

(A) Volume of interstitial kidney fluid recovered through centrifugation. n=5-7 animals per group. Dunn's test with Holm correction.

(B and C) Expression of fungal housekeeping genes *18S* (B) and *RDN25* (C) relative to murine *Tbp* in kidneys of male T2D (db/db) and control mice at 24 hours post-infection. n=6 animals per group. Mann-Whitney *U* test.

(D) Area of PAS$^+$ fungi in PAS-stained kidney section from infected mice relative to total kidney area in male T2D and control mice at 24 hours post-infection. n=6 animals per group. Mann-Whitney *U* test.

(E) Volcano plot showing differences in fungal transcript levels (relative to total fungal transcripts) between T2D and control hosts. Genes involved in *Candida* glycolysis are highlighted in black and labelled.

(F) Relative weight change of T2D and control mice infected with mutant or control strain throughout 24-hr experiment. Shown are means ± SEM, n=4-10 animals per group.

(G) Daily food intake levels before and after infection. n=4-10 animals per group. Wilcoxon signed-rank test.

(A to E) Single experiment. (F and G) Pooled from two independent repeats.

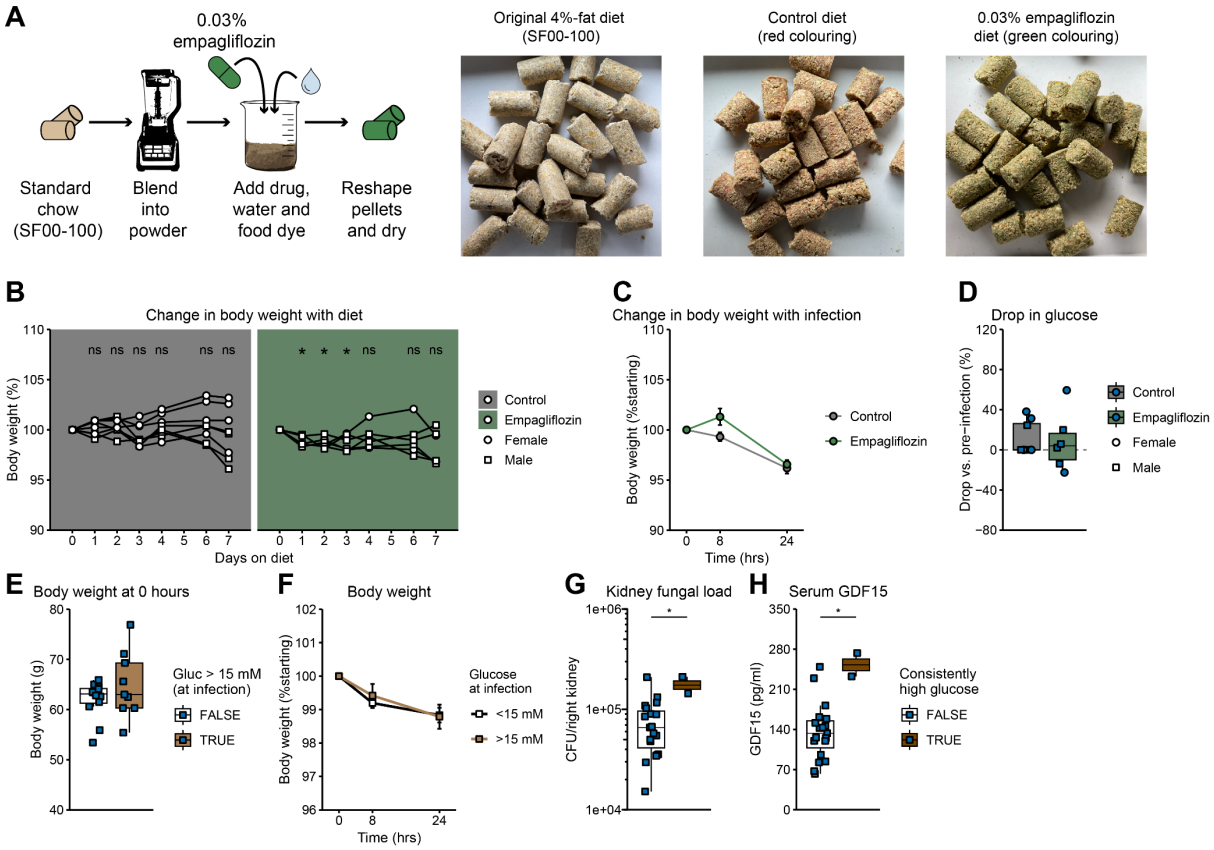



**Figure S4. Further characterisation of empagliflozin-fed and NZO mice. Relates to Figure 4**

(A) Standard 4%-fat-containing chow diet was blended into a powder and empagliflozin was added to a final concentration of 0.03% (w/w). Diet powder was reshaped into food pellets by addition of small amounts of water, and food dye was included for easier identification. A control diet, lacking empagliflozin, was prepared in the same manner. Photographs show original chow pellets and the experimental control and empagliflozin-containing diet pellets.

(B) Relative body weight change throughout the diet feeding period. Wilcoxon signed-rank test compared to the start of the experiment. n=6-8 animals per group.

(C) Relative body weight change following infection. Shown are means ± SEM, n=6-8 animals per group.

(D) Relative drop in blood glucose compared to pre-infection. n=6-8 animals per group. Mann-Whitney *U* test ($p > 0.05$).

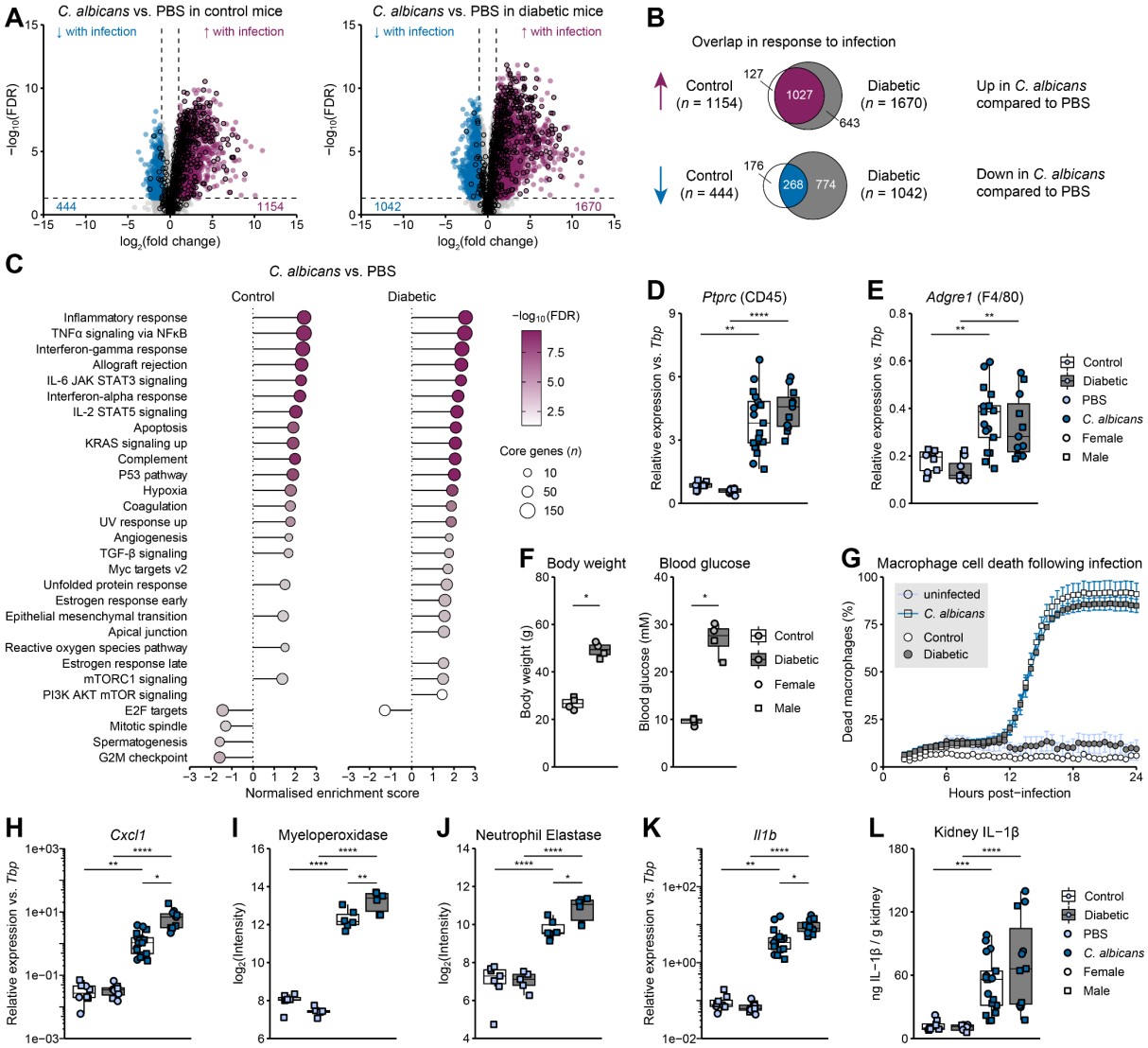
(E) Pre-infection body weight of male NZO mice, stratified by blood glucose levels immediately prior to infection. n=9-11 animals per group. Mann-Whitney *U* test ($p > 0.05$).

(F) Relative body weight change following infection, stratified by blood glucose levels immediately prior to infection. Shown are means ± SEM, n=9-11 animals per group.

(G) Kidney fungal load at 24 hours post-infection, stratified by whether animals displayed consistently high (>20 mM for three measurements) blood glucose levels. n=2-19 animals per group. Mann-Whitney *U* test.

(H) Serum GDF15 levels by ELISA, stratified as in (G). n=2-19 animals per group. Mann-Whitney *U* test.

(A to H) Single experiment.




## Figure S5. Transcriptional response of T2D animals to *C. albicans* infection and further characterisation of immune responses. Relates to Figure 5

(A) Volcano plots showing changes in gene expression with infection in control (left) or T2D (right) mice. Genes involved in immune-related Hallmark pathways (*Complement*, *IL2 STAT5 Signalling*, *IL6 JAK STAT3 Signalling*, *Inflammatory Response*, *Interferon Alpha Response*, *Interferon Gamma Response*, *Reactive Oxygen Species Pathway*, *TNFα Signalling via NFκB*) are highlighted by black outlines. n=5-7 animals per group.

(B) Overlap in genes up- (top) or downregulated (bottom) with infection in control and T2D mice.

(C) Gene set enrichment analysis of changes in gene expression with infection in control (left) and T2D (right) mice, based on murine Hallmark pathways. Only significantly enriched pathways are shown.

(D and E) Gene expression of *Ptprc* (D) and *Adgre1* (E) relative to housekeeping gene *Tbp* in kidneys of T2D and control mice infected with *C. albicans* for 24 hours (same cohort as in Figure 1J-Q). n=8-17 animals per group. Dunn's test with Holm correction.

(F) Body weight and blood glucose levels of T2D and control mice used for bone marrow isolation. n=4 animals per group. Mann-Whitney *U* test.

(G) Bone marrow-derived macrophages from naïve T2D and control mice were infected in vitro with *C. albicans* (MOI 3) and cell death was determined using live imaging. Shown are means ± SEM, n=4 animals per group and n=4 fields of view per condition.

(H) Gene expression of *Cxcl1* relative to housekeeping gene *Tbp* in kidneys of T2D and control mice infected with *C. albicans* for 24 hours (same cohort as in Figure 1I-P). n=8-17 animals per group. Dunn's test with Holm correction.

(I and J) Abundance of myeloperoxidase (I) or neutrophil elastase (J) protein in kidneys of T2D and control mice infected with *C. albicans* for 24 hours, from proteomics data (same cohort as in Figure 3A-E). n=5-7 animals per group. Shown are false-discovery rates from limma statistics.

(I) Gene expression of *Il1b* relative to housekeeping gene *Tbp* in kidneys of T2D and control mice infected with *C. albicans* for 24 hours (same cohort as in Figure 1I-P). n=8-17 animals per group. Dunn's test with Holm correction.
(L) IL-1β levels by ELISA in kidneys of T2D and control mice infected with *C. albicans* for 24 hours (same cohort as in Figure 1J-Q). n=8-17 animals per group. Dunn's test with Holm correction.
(A to C) and (F and G) Single experiment. (D and E) and (H to L) Pooled from two independent repeats.

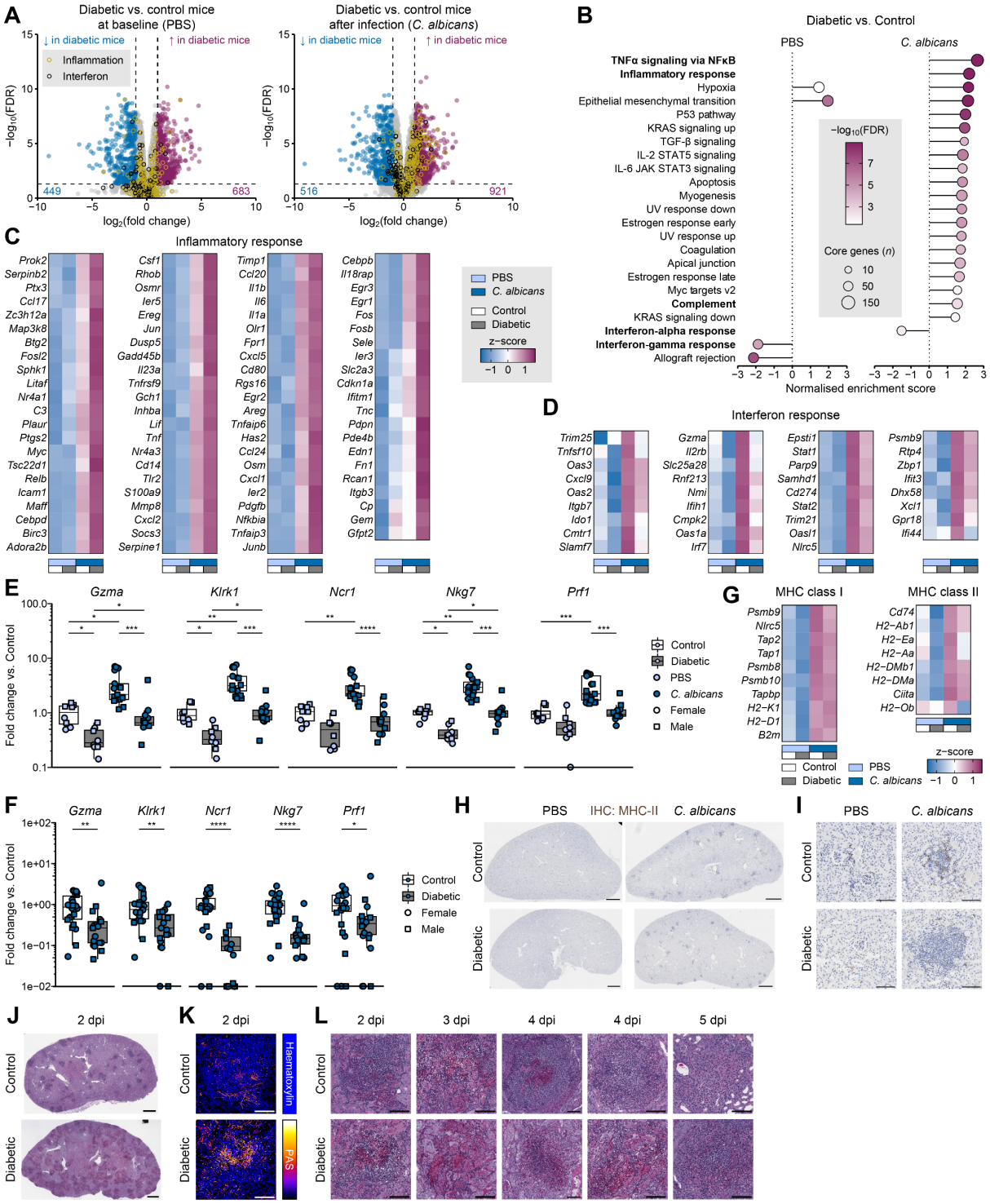



**Figure S6. Differences in the transcriptional and immune response to *C. albicans* infection of T2D versus control animals. Relates to Figure 6**

(A) Volcano plots showing differences in gene expression between uninfected (left) or infected (right) T2D and control animals. Proteins involved in Hallmark pathways related to inflammation (*Complement*, *Inflammatory Response*, *TNFα signalling via NFκB*) or interferon (*Interferon Alpha Response*, *Interferon Gamma Response*) are highlighted by yellow or black outlines, respectively. n=5-7 animals per group.

(B) Gene set enrichment analysis of differences in gene expression between uninfected (left) or infected (right) T2D and control mice, based on murine Hallmark pathways. Only significantly enriched pathways are shown.

(C and D) Heatmaps showing scaled expression levels of genes involved in inflammatory (C) or interferon (D) response. All depicted genes were significantly upregulated in control kidneys with infection (C and D) and expressed at significantly higher (C) or lower (D) levels in infected T2D animals (FDF < 0.05). n=5-7 animals per group.

(E) Expression of indicated NK cell-related genes in kidneys of T2D and control mice infected with *C. albicans* for 24 hours, as shown in Figure 6G, bottom panel. n=8-17 animals per group. Dunn's test with Holm correction.
(F) Expression of indicated NK cell-related genes in kidneys of T2D and control mice infected with *C. albicans* upon reaching humane endpoint. n=17-22 animals per group. Mann-Whitney *U* test.
(G) Heatmap showing scaled expression levels of genes involved in antigen presentation.
(H and I) Immunohistochemical staining for MHC-II in kidney sections from T2D and control mice infected with *C. albicans* for 24 hours (same cohort as in Figure 1J-Q). Size of scale bar: 1 mm, overview (H); 100 µm, zoom (I).
(J) Representative images of PAS staining of kidney sections from T2D or control mice infected with *C. albicans* at humane endpoint (same cohort as in Figure 1A-I). Size of scale bar: 1 mm.
(K) Zoomed-in images of deconvoluted and pseudo-coloured PAS staining of kidneys from T2D and control mice collected at humane endpoint. Colours: blue, haematoxylin; fire scale, PAS. Size of scale bar: 100 µm.
(L) Original PAS images of representations shown in Figure 6P and Figure S6K. Size of scale bar: 100 µm.
(A to D) and (G) Single experiment. (E and F) and (H to L) Pooled from two independent repeats.

**Table S1. Clinical signs severity score**

| Score | 0 | 1 | 2 |
|---|---|---|---|
| Alertness | Explores its surroundings in response to stimulation | Responds slowly to stimulation and makes little attempt to explore its surroundings or engage with cage mates | Does not respond to stimulation |
| Activity | Activity levels are normal and the animal explores its local area. | Not as active as cage mates or conspecifics and tends to remain in the same location with a hunched appearance when disturbed | Has a hunched appearance and remains in the same location when disturbed |
| Movement | Moves around without any evidence of impairment | Shows signs of stiffness as it moves, is lame or does not move in a coordinated manner. | Is conscious, but unable to move one or more limbs |
| Breathing | Breathes rapidly (non-resting) and with minimal effort | Change to the normal breathing rate (faster or slower) with some increase in difficulty (dyspnoea). | Very laboured breathing or gasping to breathe |
| Coat and skin | Coat is sleek and shiny OR “barbering” present | Has a “fluffed up” appearance (piloerection), has a (non-surgical) wound, is observed scratching more frequently than normal or has another type of skin problem | An infected wound with discharge and/or bleeding or skin infection with severe pruritis (itching) or ulcerated skin |
| Eyes | Eyes are clear, moist and glistening | Lens within the eye is white (cataract), a watery discharge from the eye is present or there is pink porphyrin staining (rat) | Surface of the eye is dull and white, there is a white or yellow coloured discharge from the eye, there is evidence of damage to the eye or bleeding from the eye |
| Nose | The nose may have a slightly moist appearance | Clear, watery discharge is present at the nose or there is pink porphyrin staining (rat) | White or yellow discharge is present at the nose or congealed around the nostrils. |
| Faeces | Consistency and colour of the faeces within the cage is normal (taking into consideration any special diets being fed) | Observable diarrhoea or a soiled perineum with poorly formed or watery faeces apparent in the cage | Faeces contain blood and/or mucus or the animal has not defaecated for over 48 hours (if singly housed). |
| Change in body weight | Weight is unchanged, increased or <5% loss | Acute weight loss (over ≤48 hours) >5% <10% body weight<br>Chronic weight loss (over >48 hours) >5% <15% body weight | Acute weight loss (over ≤48 hours) >10% body weight<br>Chronic weight loss (over >48 hours) >15% body weight |

**Table S2. Primers used for gene expression analysis**

| Target | Forward primer | Reverse primer |
|---|---|---|
| Mouse | | |
| *Adgre1* | TCAAATGGATCCAGAAGGCTCCCA | TGCACTGCTTGGCATTGCTGTATC |
| *Cxcl1* | TCCAGAGCTTGAAGGTGTTGCC | AACCAAGGGAGCTTCAGGGTCA |
| *Gzma* | GTGGTGGAAAGGACTCCTGCAA | GAGAGGAAAGTATAGACACCAGG |
| *Il1b* | TGGACCTTCCAGGATGAGGACA | GTTCATCTCGGAGCCTGTAGTG |
| *Klrk1* | CCTATCACTGGATGGGACTGGT | GCTTGAGCCATAGACAGCACAG |
| *Ncr1* | TAGGGCTCACAGAGGGACATAC | GTAGGTGCAAGGCTGCTGTTCT |
| *Nkg7* | CCACAGGTCCTCACTTCTCTGC | CAGCCAGGATACAGAAGCTCTG |
| *Prf1* | ACACAGTAGAGTGTCGCATGTAC | GTGGAGCTGTTAAAGTTGCGGG |
| *Ptprc* | CTTCAGTGGTCCCATTGTGGTG | TCAGACACCTCTGTCGCCTTAG |
| *C. albicans* | | |
| *18S* | GGATTTACTGAAGACTAACTACTG | GAACAACAACCGATCCCTAGT |
| *CDC19* | AAAAACCAACTGCTACCACTGAAAC | TTTCGTTTCTGGTAACCATCAAAAT |
| *ECE1* | TGCCGTCGTCAGATTGCCAGA | AGGCCAACATCTGGAACGCCA |
| *HXK2* | AGGTCAAAACCTTGACAAGTTGAAG | CAAATAGCAGCAATACCACAAACAG |
| *PFK1* | AATGCCAATAAAAGATTTGAAACCA | ATCTCCATGGATACCAATGACAACT |
| *PGI1* | AGAGCCAATGTTTTCACCAACTATC | ACATTCTTTGGTGCAAGTTCTTTTC |
| *RDN25* | GAGAGGAACCGTTCATTCAGATAAT | CTATGGTCCAGCGACTAAAAAGTCT |