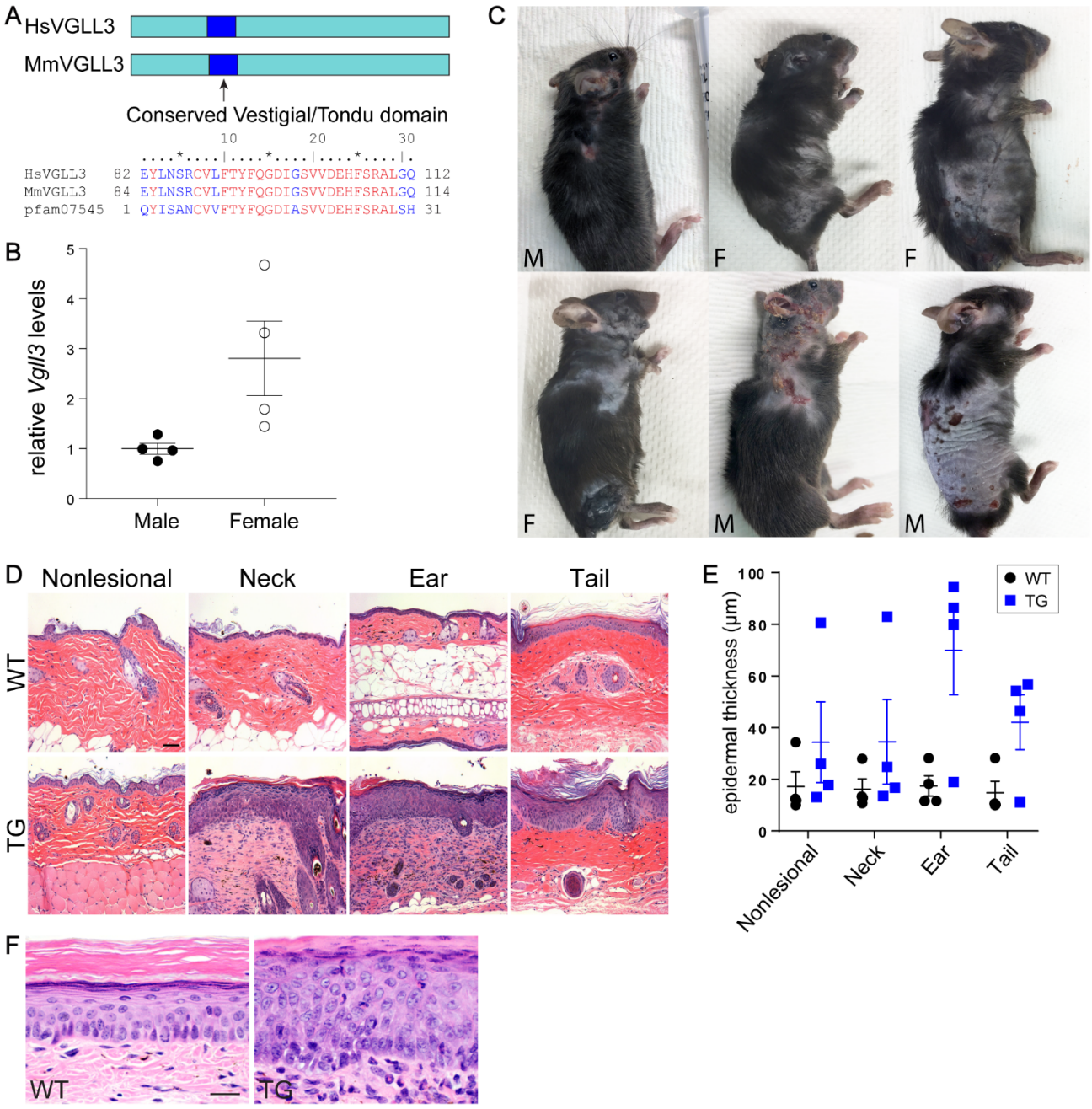

Figure S1. Skin-directed *Vgll3* overexpression leads to epidermal hyperplasia and cutaneous inflammation. A. Murine and human VGLL3 show 87% protein sequence homology, including 100% sequence identity of the Vestigial/Tondu putative transcription cofactor domain (pfam07545). **B.** Detection of endogenous *Vgll3* mRNA in skin of male (N=4) and female (N=4) WT mice by quantitative reverse transcription PCR (qRT-PCR). Error bars, mean and SEM. P=0.053 by two-tailed student t test. **C.** Additional images of transgenic (TG) mice at time of euthanasia. TG mice often required euthanasia at 3-4 months of age due to severity of cutaneous lesions. All mice pictured were from different founder lines. M, male. F, female. **D.** H&E staining of additional site-matched WT and TG sections showing characteristic changes of epidermal acanthosis, pigmentary incontinence, and variable inflammation. Scale bar, 50 µm. **E.** Average epidermal thickness in WT (N=4) and TG (N=4) skin from the specified sites (nonlesional, grossly normal posterior dorsal skin). Error bars, mean and SEM. **F.** Volar sections demonstrating neutrophilic dermal infiltration and exocytosis into the epidermis occasionally seen in TG lesional sections. Scale bar, 20 µm.

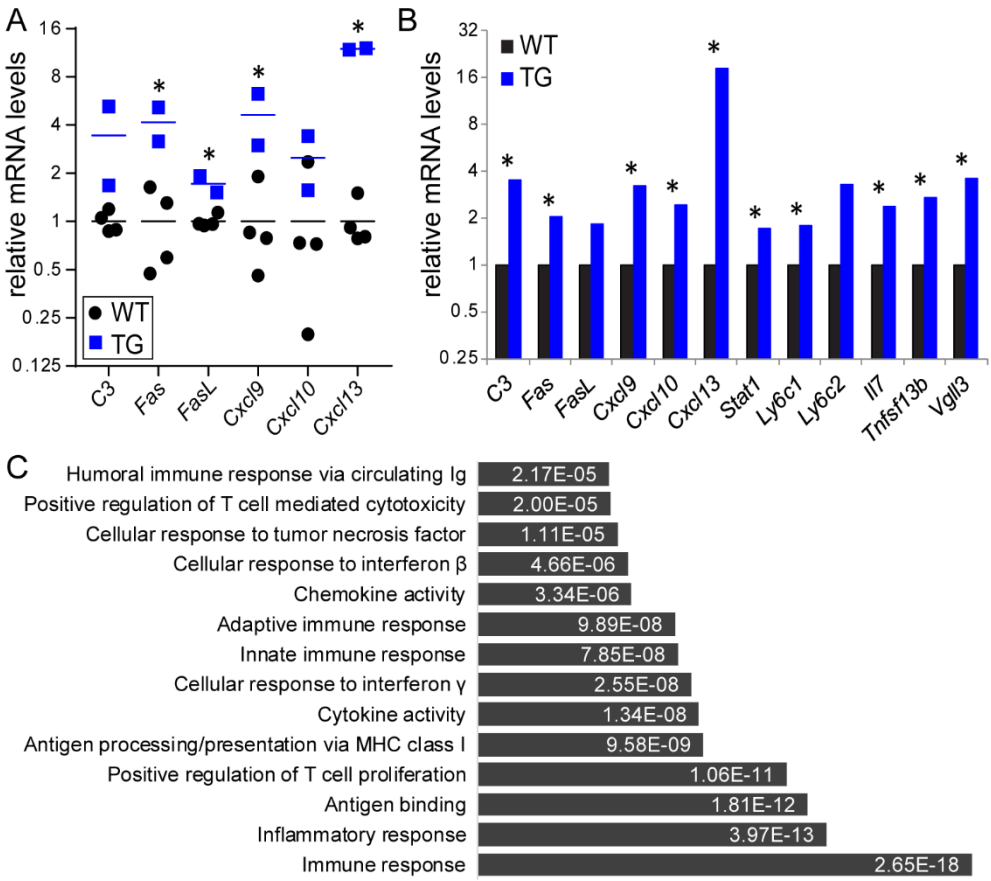

Figure S2. Genes dysregulated in skin of *K5-Vgll3* TG mice are enriched for immunological functions. A. Detection of additional immune transcripts by qRT-PCR in nonlesional dorsal skin of WT (N=4) and TG (N=2) mice with high *Vgll3* expression (more than tenfold WT average). Error bars, mean ± SEM. *, p<0.05 by two-tailed student t test. **B.** Relative detection of *Vgll3* and additional immune transcripts by RNA-seq of nonlesional, normal-appearing dorsal skin of age- and sex-matched WT (N=4) and TG (N=4) mice. *, Q<0.1. See **Methods** for additional statistical details. **C.** Select immunological Gene Ontology terms highly enriched in TG non-lesional skin. P values are indicated in white text. False discovery rate <0.05 for all. Ig, immunoglobulin.

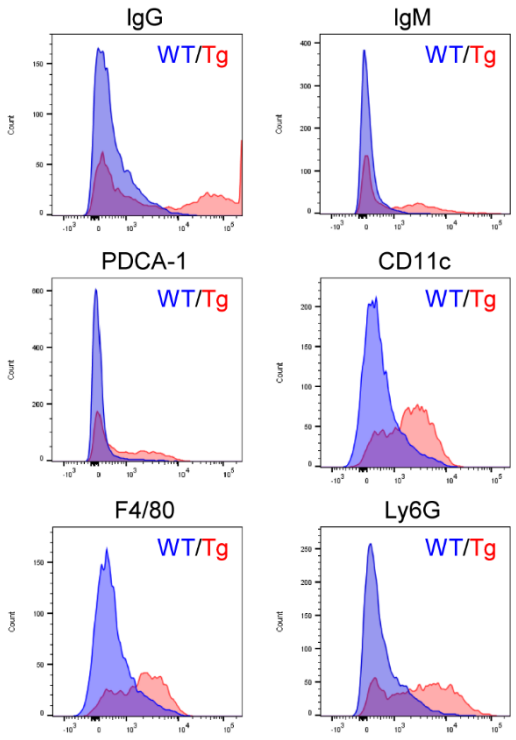

Figure S3. Expansion of immune cell populations in *K5-Vgll3* transgenic mouse skin. Detection of the indicated markers by flow cytometry of total cell suspensions prepared from WT and TG ear tissue. PDCA-1, marker of plasmacytoid dendritic cells. CD11c, marker of dendritic cells. F4/80, marker of macrophages. Ly6G, marker of neutrophils and other granulocytes. Data shown correspond to 1 WT and 1 TG animal and are representative of 2 independent experiments.

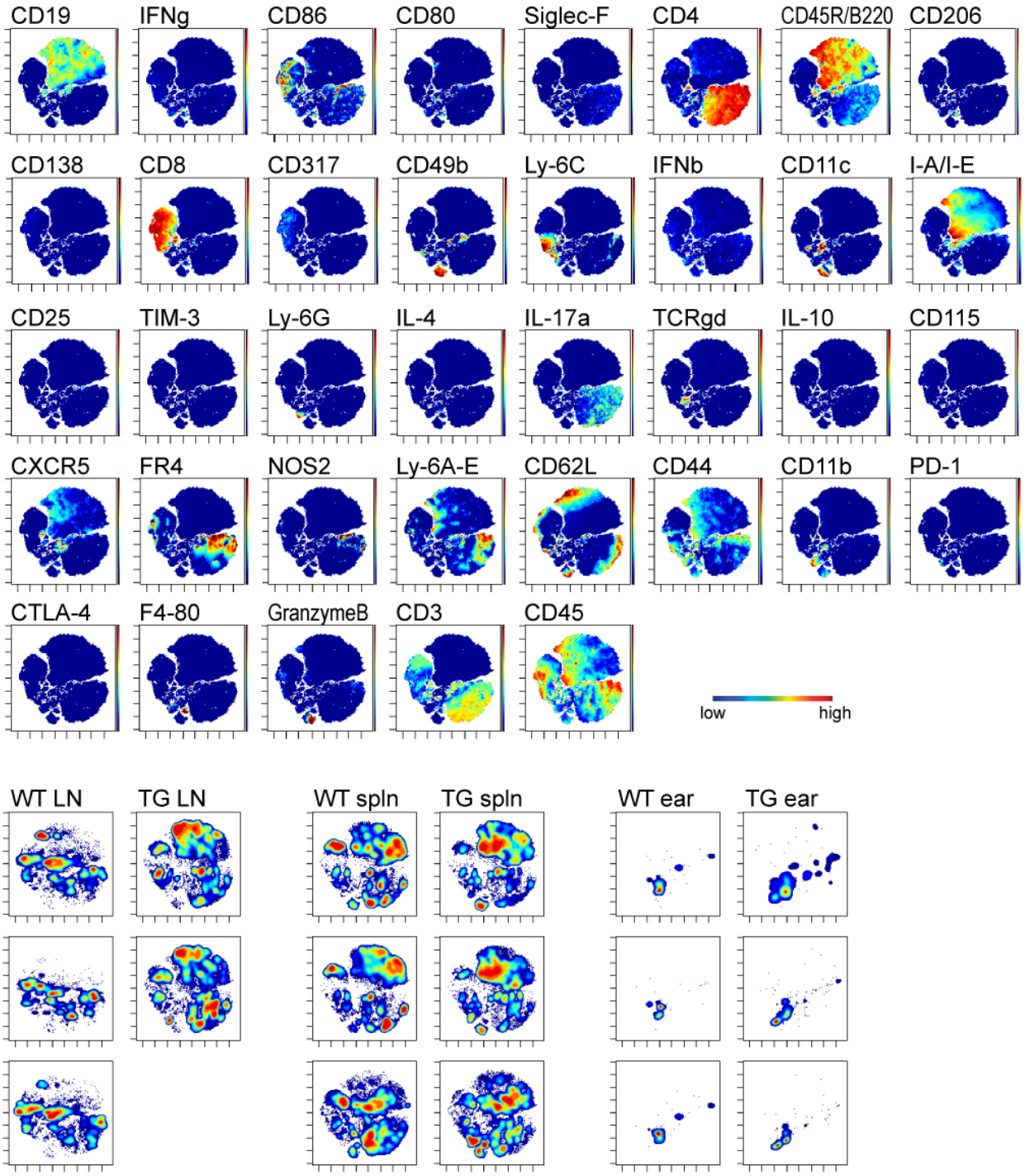

Figure S4. Characterization of systemic inflammation in the *K5-Vgll3* transgenic mouse by CyTOF, complete panel. Comprehensive CyTOF data for single experiment consisting of 3 age- and sex-matched WT and TG mice visualized by viSNE. Top, viSNE maps depicting expression of all markers. Each dot is a cell. Color reflects level of expression of marker from low (blue) to high (red). Bottom, contour plot of viSNE maps colored by density of cells isolated from the specified tissues in WT and TG mice. Here, color reflects cell density from low (blue) to high (red). Data shown correspond to one WT and one TG mouse that are representative of the experiment. LN and spleen data represent ~20,000 CD45+ live singlets per sample. Ear skin samples represent all recorded CD45+ live singlets (between 262 and 1234) for each sample. Data are representative of two independent CyTOF experiments. LN, lymph node. Spln, spleen.

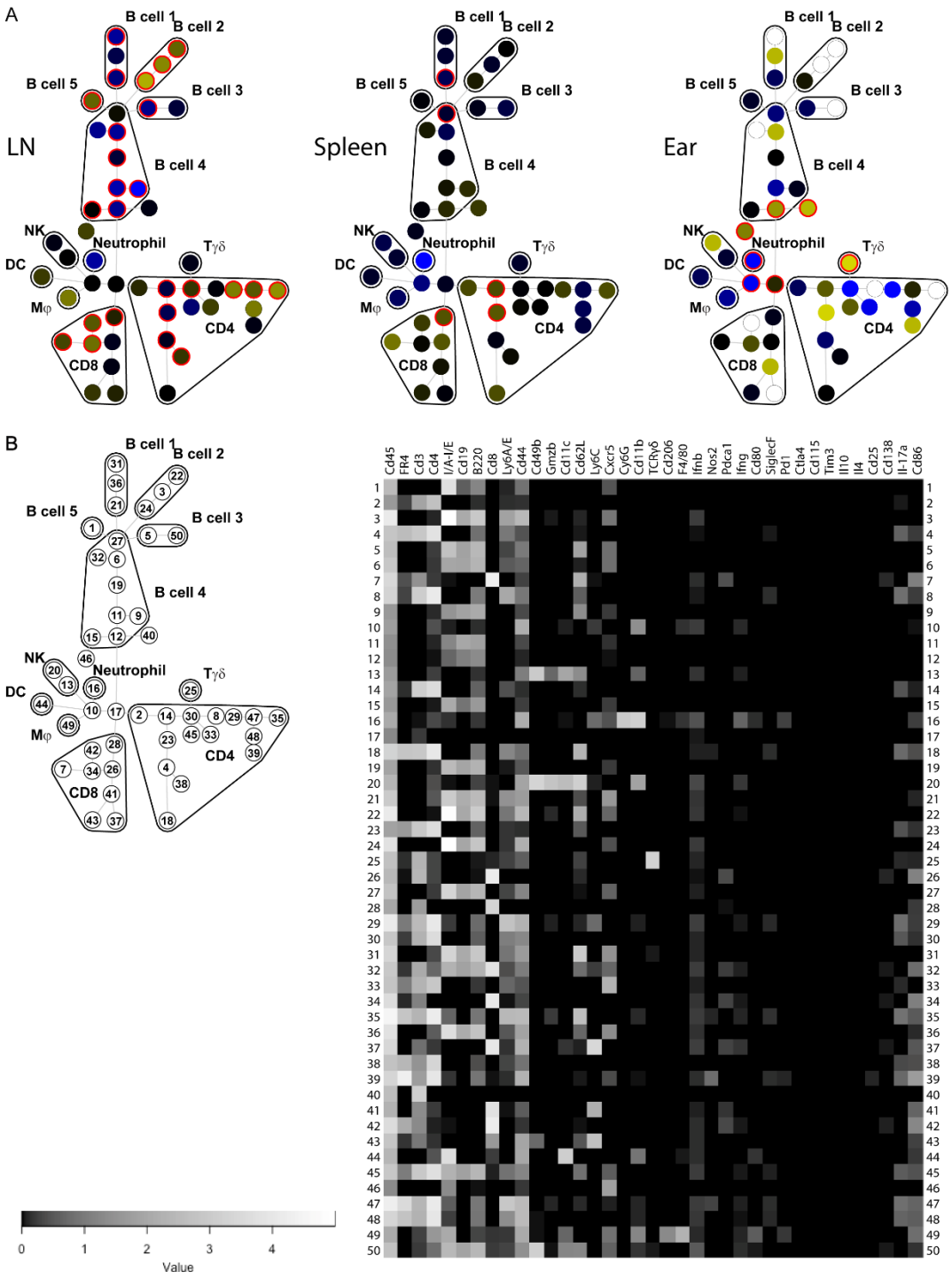

Figure S5. Comparison of CyTOF-derived SPADE populations in WT and TG by tissue. A. SPADE trees for the indicated tissue types colored to show whether the relative number of cells in each node is enriched in WT (yellow) or TG (blue) samples. For each node, the percentage of the total population was calculated in WT and TG samples of that tissue and the log ratio represented by color scale. Nodes have been sized equally to better show color. Red border, significantly (Q<0.1) upregulated in WT (yellow interior) or TG (blue interior). For populations not detected in either WT or TG, the minimum nonzero value for WT or TG, respectively, was assigned in place of zero; for these populations, ratio was not allowed to exceed the maximum or minimum ratios to avoid color skewing. White node, population detected in neither WT nor TG samples in the indicated tissue. **B.** Heat map for all markers with populations numbered according to SPADE tree key.

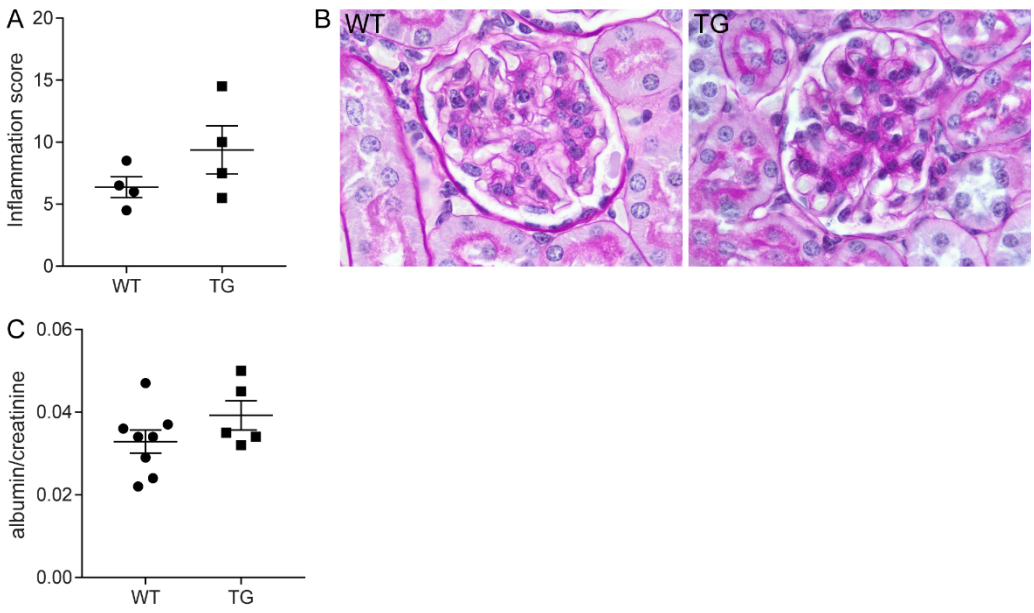

Figure S6. Fulminant nephritis is not detected in *K5-Vgll3* transgenic animals at euthanasia. A. Histological scoring of sections from WT (N=4) and TG (N=4) kidneys (see Methods for scoring criteria). Error bars, mean ± SEM. P=0.20 by two-tailed student t test. **B.** H&E staining of representative sections from WT and TG kidneys scored in **A**. **C.** Albumin to creatinine ratio in the urine of WT (N=8) and TG (N=5) mice. Error bars, mean ± SEM. P=0.19 by two-tailed student t test.

Table S1. Table of transgenic DEGs identified in WT versus TG nonlesional, grossly normal-appearing dorsal skin.

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Table S2. CyTOF labels and antibodies used

	Label	Target	Clone	Company	Cat No
1	112Cd	CD19	6D5	Life Technologies	Q10379
2	141Pr	IFNg	XMG1.2	Biolegend	505812
3	142Nd	CD86	GL-1	Biolegend	105002
4	143Nd	CD80	16-10A1	Biolegend	104702
5	144Nd	Siglec-F	E50-2440	BD	552125
6	145Nd	CD4	RM4-5	Biolegend	100520
7	146Nd	CD45R (B220)	RA3-6B2	Biolegend	103202
8	147Sm	CD206	C068C2	Biolegend	141701
9	148Nd	CD138	281-2	Biolegend	142502
10	149Sm	CD8	53-6.7	Biolegend	100716
11	150Nd	PDCA-1 (CD317)	129C1	Biolegend	127102
12	151Eu	CD49b	DX5	Biolegend	108902
13	152Sm	Ly-6C	HK1.4	Novus	NBP1-28046
14	153Eu	IFNb	7F-D3	Abcam	ab24324
15	154Sm	CD11c	N418	Biolegend	117302
16	155Gd	I-A/I-E	M5/114.15.2	Biolegend	107602
17	156Gd	CD25	3C7	Biolegend	101902
18	158Gd	Tim-3 (CD366)	RMT3-23	Biolegend	119702
19	159Tb	Ly-6G	1A8	Biolegend	127637
20	160Gd	IL-4	11B11	Biolegend	504102
21	161Dy	IL-17A	TC11-18H10.1	Biolegend	506935
22	162Dy	TCR γ/δ	GL3	Biolegend	118101
23	163Dy	IL-17F	316016	Novus Biologicals	MAB2057
24	164Dy	IL-10	JES5-16E3	Biolegend	505002
25	165Ho	CSF-1R (CD115)	AFS98	Biolegend	135502
26	166Er	CXCR5	614641	Novus Biologicals	MAB6198
27	167Er	FR4	TH6	Biolegend	125102
28	168Er	NOS2	5C1B52	Biolegend	690902
29	169Tm	Ly-6A/E (Sca-1)	D7	Biolegend	108135
30	170Er	CD62L	MEL-14	Biolegend	104402
31	171Yb	CD44	IM7	Biolegend	103014
32	172Yb	CD11b	M1/70	Fluidigm	3172012B
33	173Yb	PD-1 (CD279)	RMP1-30	Biolegend	109113
34	174Yb	CTLA-4	UC10-4B9	Biolegend	106302
35	175Lu	F4/80	BM8	Biolegend	123143
36	176Yb	Granzyme B	GB11	Abcam	ab10912
37	191/193Ir	DNA		Fluidigm	201192B
38	195Pt	Live/Dead		Fluidigm	201064
39	209Bi	CD3	145-2C11	Biolegend	100314
40	89Y	mCD45	30-F11	Fluidigm	3089005B

Table S3. Table of genes differentially enriched in WT versus TG blood.

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Table S4. qRT-PCR primers used

Transcript	Assay
C3	Mm1232779_m1
Cxcl9	Mm00434946_m1
Cxcl10	Mm00445236_m1
Cxcl13	Mm04214185_s1
Fas	Mm1204974_m1
FasL	Mm00438864_m1
Ifnb1	Mm00439552_s1
Ifnk	Mm02529417_s1
Il7	Mm01295803_m1
Ly6c2	Mm00841873_m1
Rn 18s	Mm04277571_s1
Stat1	Mm00439531_m1
Tnfsf13b	Mm00446345_m1
Vgll3	Mm01170279_m1