Molecular and cellular characterization of pyoderma gangrenosum: Implications for the use of gene expression

Alex G. Ortega-Loayza, Marcia A. Friedman, Ashley M. Reese, Yuangang Liu, Teri M. Greiling, Pamela B. Cassidy, Angelo V. Marzano, Lina Gao, Suzanne S. Fei, James T. Rosenbaum

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Table S3: Pathways associated with differentially expressed genes in the dermis of perilesional PG vs dermis of HC

Significant genes were defined as having an FC >4 and an FDR p-value of <0.05. 2907 differentially expressed genes were identified and entered into Cytoscape. 92 pathways were significantly enriched (FDR <0.05).

Table S3: Dermis of perilesional PG vs dermis of HC pathways			
Pathway	P-value	FDR	Nodes
Extracellular matrix organization(R)	1.11E-16	1.15E-14	CAPNS2,ADAMTS14,FN1,BGN,MMP10,MMP12,MMP11,MMP13,PXDN,MMP19,SPP1,COL22A1,COL3A1,COL17A1,ITGAM,ITGB3,ITGB2,ITGAL,ITGAX,ITGA4,ITGA1,ITGAD,ITGA5,ICAM2,ICAM5,ICAM1,SDC4,SDC1,DDR1,ADAM19,ADAM12,FBN2,VCAM1,FBN1,BCAN,COL10A1,TIMP1,TNC,P4HA3,ADAMTS4,ADAMTS2,PECAM1,MATN4,SCUBE3,COL6A2,COL6A1,COL6A3,NRXN1,THBS1,LUM,COL1A1,COL1A2,COL28A1,COL15A1,LRP4,A2M,CTSS,CTSL,CTSK,CTSB,TMPRSS6,PCOLCE,BMP7,BMP1,COL5A1,COL5A2,MMP1,MMP2,MMP3,MMP8,MMP9,VCAN,SERPINE1,COL12A1,SERPINH1,CDH1,ADAM8,CEACAM6,COL4A2,COL4A1,COL4A4,COL4A6,NID1,NID2,TGFB1,ACAN
Neutrophil degranulation(R)	1.11E-16	1.15E-14	GMFG,C3AR1,JUP,ARHGAP9,SIGLEC9,MMP25,OLR1,PTAFR,PKP1,SLC27A2,FTL,ITGAM,ITGB2,ITGAL,ITGAX,TNFRSF1B,ANPEP,SYNGR1,PPBP,BST2,FCER1G,TYROBP,ADA2,TNFAIP6,RETN,PTX3,CDA,PRSS3,CFD,PLAC8,NCKAP1L,TCN1,ALOX5,RAB31,TCIRG1,FCAR,CR1,PECAM1,CALML5,FTH1,TBC1D10C,KRT1,VNN1,TLR2,LAIR1,FCN1,COTL1,SELL,HK3,PLAUR,RNASE2,FPR1,FPR2,LYZ,PIGR,ARG1,LRRC7,HP,STK10,DSC1,S100A9,S100A8,S100A7,GPR84,PTPRB,PTPRC,FCGR3B,DSP,DSG1,FCGR2A,CD14,ARSB,CTSZ,CTSS,CTSB,CD53,MME,MPO,CD93,CYBB,CYBA,OSCAR,DOK3,SIRPB1,MMP8,MMP9,UNC13D,BIN2,S100A12,SERPINA1,LPCAT1,SERPINB3,SERPINB1,NFAM1,CD177,CLEC4C,CLEC4D,ADAM8,KCNAB2,MNDA,SLC11A1,MGST1,SIGLEC14,CEACAM3,CEACAM6,CXCR1,CXCR2,LILRB2,LILRB3,CD300A,ARHGAP45,C5AR1,CXCL1,SLC2A5,FGR,DOCK2

Staphylococcus aureus infection(K)	1.11E-16	1.15E-14	C3AR1,PTAFR,ITGAM,ITGB2,ITGAL,C1S,C1R,ICAM1,C4B,IL10,SELPLG,CFD,CFI,FCAR,KRT9,KRT33B,KRT33A,C1QB,C1QA,C1QC,SELP,FPR1,FPR3,FPR2,C2,HLA-DMA,FCGR3A,FCGR3B,DSG1,FCGR1A,FCGR2A,FCGR2B,MASP1,KRT28,KRT27,KRT26,KRT25,KRT35,KRT34,KRT32,KRT31,KRT39,KRT38,KRT36,KRT10,KRT19,KRT18,KRT15,C5AR1,KRT40
Binding and Uptake of Ligands by Scavenger Receptors(R)	1.11E-16	1.15E-14	IGHV3-23,IGHV3-7,IGHV3-30,IGHV3-33,IGHV3-11,COL3A1,FTL,IGHV3-48,IGHV3-53,MSR1,IGKC,IGKV1-5,IGLV3-1,IGKV1-16,IGKV1-17,IGKV1-12,IGHA1,IGHA2,APOL1,IGHV4-59,IGLV1-40,IGLV1-47,IGLV1-44,IGHV4-34,IGHV4-39,FTH1,SAA1,IGHV1-69,COL1A1,COL1A2,IGHV1-46,HP,IGLV2-11,IGLV2-14,IGLV2-23,IGHV1-2,SCARA5,MASP1,IGLV6-57,IGKV3-15,IGKV3-11,IGKV3-20,IGLC3,IGLC2,SCARF1,IGLV3-19,IGLV3-25,IGLV3-21,CD163,IGKV3D-20,IGHV2-70,IGHV2-5,IGLV2-8,IGKV4-1,MARCO,JCHAIN,STAB1,COL4A2,COL4A1,IGLV7-43,IGKV2-30
Complement cascade(R)	1.11E-16	1.15E-14	IGHV3-23,C3AR1,IGHV3-7,IGHV3-30,IGHV3-33,IGHV3-11,C1S,C1R,IGHV3-48,IGHV3-53,C4B,IGKC,IGKV1-5,IGLV3-1,IGKV1-16,IGKV1-17,IGKV1-12,CFD,CFI,IGHG3,IGHG4,IGHG1,IGHG2,IGHV4-59,IGLV1-40,IGLV1-47,IGLV1-44,IGHV4-34,IGHV4-39,CR1,C1QB,C1QA,C1QC,FCN1,FCN3,IGHV1-69,C2,IGHV1-46,IGLV2-11,IGLV2-14,IGLV2-23,IGHV1-2,CD19,MASP1,IGLV6-57,IGKV3-15,IGKV3-11,IGKV3-20,IGLC3,IGLC2,IGLV3-19,IGLV3-25,IGLV3-21,IGKV3D-20,IGHV2-70,IGHV2-5,IGLV2-8,IGKV4-1,C5AR2,C5AR1,IGLV7-43,IGKV2-30
Cell surface interactions at the vascular wall(R)	1.11E-16	1.15E-14	IGHV3-23,IGHV3-7,IGHV3-30,IGHV3-33,IGHV3-11,FN1,OLR1,SLC7A7,JAML,ITGAM,ITGB3,ITGB2,ITGAL,ITGAX,ITGA4,ITGA5,IGHV3-48,IGHV3-53,CD244,SDC4,SDC1,IGHM,FCER1G,SELPLG,IGKC,IGKV1-5,IGLV3-1,CD2,IGKV1-16,IGKV1-

			17,IGKV1-12,IGHA1,IGHA2,EPCAM,IGHV4-59,IGLV1-40,IGLV1-47,IGLV1-44,IGHV4-34,IGHV4-39,LCK,PECAM1,ANGPT2,SELE,SELP,SELL,IGHV1-69,LYN,IGHV1-46,SLC16A3,IGLV2-11,IGLV2-14,TNFRSF10D,IGLV2-23,IGHV1-2,CD48,GPC1,CD84,DOK2,IGLV6-57,IGKV3-15,IGKV3-11,IGKV3-20,IGLC3,IGLC2,MMP1,IGLV3-19,IGLV3-25,IGLV3-21,GRB14,CD177,ESAM,TREM1,IGKV3D-20,IGHV2-70,IGHV2-5,IGLV2-8,IGKV4-1,INPP5D,JCHAIN,CEACAM3,CEACAM6,CEACAM5,SIRPG,TGFB1,IGLV7-43,IGKV2-30
Cytokine-cytokine receptor interaction(K)	1.11E-16	1.15E-14	IL31RA,IL12RB1,BMP8A,CRLF2,TNFRSF4,TNFRSF17,TNFRSF9,TNFSF13B,TNFRSF19,TNFRSF1B,TNFRSF21,IL2RG,IL2RA,TNFSF18,TNFSF14,IL36G,PPBP,IL1F10,IL24,IL10,IL15,IL19,IL1A,IL1B,IL32,IL34,OSM,IL7R,IL1RL1,IL1RL2,CD4,IL10RA,CSF3,IFNAR2,XCL2,IL21R,LEP,CD40LG,LTB,IL20RA,IL20RB,CXCL13,CXCL14,TNFRSF11B,TNFRSF10C,TNFRSF10D,CXCL10,CXCL11,FASLG,CCL8,CCL5,CCL4,CCL3,CCL2,CCR1,CD27,CCR8,CCR7,CCR5,CCR4,CCR2,IL17D,INHBA,BMP7,BMP5,BMP3,IL6,ACVR1C,CNTFR,TNFSF4,TNFSF8,CCL11,CCL18,CCL24,CCL23,CCL20,CSF3R,IL3RA,IL17RE,CXCR4,CXCR6,CXCR1,CXCR3,CXCR2,GDF15,IL18RAP,CSF2RB,CSF2RA,TGFB1,CXCL6,CXCL9,CXCL8,CXCL1,CXCL3,CXCL2,CXCL5
Keratinization (R)	1.11E-16	1.15E-14	JUP,CASP14,PKP1,PKP3,TGM5,TCHH,PRSS8,PI3,KRT4,KRT2,KRT1,KRT8,KRT7,KRT5,KRT9,SPRR2E,SPRR2G,PPL,KRT33B,KRT33A,SPRR2A,SPRR2B,SPRR1A,DSC1,DSC3,DSP,DSG1,DSG2,DSG4,EVPL,PERP,KRT28,KRT27,KRT26,KRT25,KRT35,KRT34,KRT32,KRT31,KRT39,KRT38,KRT36,KRT10,KRT19,KRT18,KRT15,KRT6C,KRT71,KRT79,KRT77,KRT75,KRT74,KRT73,KRT72,KRT40,KRT82,KRT81,KRT80,KRT86,KRT85,KRT84,KRT83
Immunoregulatory interactions between a	1.11E-16	1.15E-14	IGHV3-23,IGHV3-7,IGHV3-30,IGHV3-33,IGHV3-11,SIGLEC9,HCST,SIGLEC7,JAML,ITGB2,ITGAL,ITGA4,IGHV3-48,IGHV3-

Lymphoid and a non-Lymphoid cell(R)			53,CD247,ICAM2,ICAM5,ICAM1,CD226,IGKC,IGKV1-5,TYROBP,TRAV19,VCAM1,CRTAM,IGLV3-1,IGKV1-16,IGKV1-17,IGKV1-12,TRBV7-9,IGHV4-59,IGLV1-40,IGLV1-47,IGLV1-44,CD300LB,IGHV4-34,IGHV4-39,IFITM1,SH2D1A,SH2D1B,LAIR1,CD40LG,SELL,TRBC1,IGHV1-69,IGHV1-46,IGLV2-11,IGLV2-14,IGLV2-23,IGHV1-2,FCGR3A,FCGR1A,FCGR2B,CD1D,CD1A,CD19,SLAMF7,SLAMF6,PILRA,CD3G,CD3E,CD3D,MICB,CD96,OSCAR,CD8B,CD8A,IGLV6-57,IGKV3-15,IGKV3-11,IGKV3-20,IGLC3,IGLC2,IGLV3-19,IGLV3-25,IGLV3-21,CDH1,CLEC4G,CD160,TREM2,TREM1,IGKV3D-20,IGHV2-70,IGHV2-5,IGLV2-8,IGKV4-1,LILRA1,LILRB1,LILRB2,CD300A,CD300E,CD300C,KLRB1,KLRC1,IGLV7-43,KLRD1,IGKV2-30,KLRG1
Viral protein interaction with cytokine and cytokine receptor(K)	2.22E-16	2.09E-14	TNFRSF1B,IL2RG,IL2RA,TNFSF14,PPBP,IL24,IL10,IL19,IL34,IL10RA,XCL2,IL20RA,IL20RB,CXCL13,CXCL14,TNFRSF10C,TNFRSF10D,CXCL10,CXCL11,CCL8,CCL5,CCL4,CCL3,CCL2,CCR1,CCR8,CCR7,CCR5,CCR4,CCR2,IL6,CCL11,CCL18,CCL24,CCL23,CCL20,CXCR4,CXCR1,CXCR3,CXCR2,IL18RAP,CXCL6,CXCL9,CXCL8,CXCL1,CXCL3,CXCL2,CXCL5
Fcgamma receptor (FCGR) dependent phagocytosis(R)	3.21E-14	2.73E-12	IGHV3-23,IGHV3-7,IGHV3-30,IGHV3-33,IGHV3-11,IGHV3-48,IGHV3-53,CD247,IGKC,IGKV1-5,IGLV3-1,WIPF1,IGKV1-16,IGKV1-17,IGKV1-12,NCKAP1L,ARPC1B,IGHG3,IGHG4,IGHG1,IGHG2,IGHV4-59,IGLV1-40,IGLV1-47,IGLV1-44,IGHV4-34,IGHV4-39,VAV1,HCK,IGHV1-69,LYN,IGHV1-46,IGLV2-11,IGLV2-14,IGLV2-23,IGHV1-2,FCGR3A,FCGR1A,FCGR2A,CD3G,IGLV6-57,IGKV3-15,IGKV3-11,IGKV3-20,IGLC3,IGLC2,IGLV3-19,IGLV3-25,IGLV3-21,IGKV3D-20,IGHV2-70,IGHV2-5,IGLV2-8,IGKV4-1,WAS,IGLV7-43,FGR,IGKV2-30
Cell adhesion molecules (CAMs)(K)	4.30E-14	3.35E-12	SIGLEC1,CD274,IGSF11,ITGAM,ITGB2,ITGAL,ITGA4,PDCD1,ICAM2,ICAM1,CD226,SDC4,SDC1,SELPLG,VCAM1,CNTN2,CD2,CD4,CD6,ICOS,PE

			CAM1,NECTIN1,PDCD1LG2,CLDN10,CLDN19,CLDN16,CD40LG,NRCAM,SELE,SELP,SELL,CDH15,NRXN1,NRXN2,CLDN1,CLDN3,CLDN8,CTLA4,HLA-DMA,PTPRC,CNTNAP1,CD28,CD22,PTPRF,CD86,CD80,CD8B,CD8A,VCAN,CDH5,CDH4,CDH1,ESAM,TIGIT,OCLN
Class A/1 (Rhodopsin-like receptors)(R)	1.90E-12	1.37E-10	C3AR1,PTAFR,ADORA3,ADORA1,HTR2A,APLN,LPAR4,PPBP,OXGR1,GAL,MC5R,CNR2,PROK2,PROK1,CMKLR1,XCL2,P2RY6,P2RY4,EDN1,SAA1,F2RL2,F2RL3,HRH2,FPR1,FPR3,FPR2,GPR17,GPR18,GPR37,P2RY10,GPR65,CXCL13,CXCL10,CXCL11,CCL5,CCL4,CCL3,CCL2,CCR1,CCR8,CCR7,CCR5,CCR4,CCR2,XK,CCRL2,GPR183,PNOC,GPR132,CCL11,CCL23,CCL20,GPR4,GPR143,CHRM3,CHRM1,TBXA2R,OXTR,NMU,FFAR2,AVPR1A,CCKBR,CXCR4,CXCR6,CXCR1,CXCR3,CXCR2,NPY1R,APLNR,C5AR2,C5AR1,ADRB1,CXCL6,CXCL9,CXCL8,CXCL1,CXCL3,CXCL2,CXCL5,PTGIR,NPY5R,S1PR1,S1PR5,S1PR4
Interleukin-10 signaling(R)	3.37E-11	2.26E-09	PTAFR,TNFRSF1B,ICAM1,IL10,IL1A,IL1B,TIMP1,IL10RA,CSF3,FPR1,PTGS2,CXCL10,CCL5,CCL4,CCL3,CCL2,CCR1,CCR5,CCR2,CD86,CD80,IL6,CCL20,CXCL8,CXCL1,CXCL2
Signaling by the B Cell Receptor (BCR)(R)	4.05E-11	2.51E-09	IGHV3-23,IGHV3-7,IGHV3-30,IGHV3-33,IGHV3-11,BLK,IGHV3-48,IGHV3-53,PIK3AP1,BTK,IGHM,IGHD,IGKC,IGKV1-5,CARD11,IGLV3-1,IGKV1-16,IGKV1-17,IGKV1-12,IGHV4-59,IGLV1-40,IGLV1-47,IGLV1-44,IGHV4-34,IGHV4-39,CD79B,CD79A,VAV1,IGHV1-69,LYN,IGHV1-46,IGLV2-11,IGLV2-14,IGLV2-23,IGHV1-2,PIK3CD,CD19,CD22,IGLV6-57,IGKV3-15,IGKV3-11,IGKV3-20,IGLC3,IGLC2,IGLV3-19,IGLV3-25,IGLV3-21,IGKV3D-20,IGHV2-70,IGHV2-5,IGLV2-8,IGKV4-1,IGLV7-43,IGKV2-30
Rheumatoid arthritis(K)	1.16E-10	6.87E-09	ITGB2,ITGAL,TNFSF13B,ACP5,ICAM1,IL15,IL1A,IL1B,ATP6V1B1,TCIRG1,ATP6V0D2,ATP6V0A4,TLR4,TLR2,LTB,CTLA4,HLA-DMA,FLT1,CCL5,CCL3,CCL2,CD28,CTSL,CTSK,CD86,CD80,IL6,MMP1,MMP3,CCL20,TGFB1,CXCL6,CXCL8,CXCL1,CXCL3,CXCL2,CXCL5

Interleukin-4 and Interleukin-13 signaling(R)	1.18E-09	6.51E-08	GATA3,FN1,JAK3,ITGAM,ITGB2,ITGAX,TNFRSF1B,IL2RG,ICAM1,IL10,IL1A,IL1B,OSM,VCAM1,HMOX1,TIMP1,ALOX5,IGHG4,IGHG1,LBP,SAA1,COL1A2,PTGS2,RORC,F13A1,SOCS3,FASLG,CCL2,CCND1,IL6,MMP1,MMP2,MMP3,MMP9,CCL11,BATF,TGFB1,CXCL8,S1PR1
Hematopoietic cell lineage(K)	2.13E-09	1.11E-07	ITGAM,ITGB3,ITGA4,ITGA1,ITGA5,IL2RA,ANPEP,IL1A,IL1B,IL7R,MS4A1,CD2,CD4,CD5,CD7,CSF3,CR1,HLA-DMA,FCGR1A,CD1D,CD1A,CD19,CD14,CD22,CD3G,CD3E,CD3D,CD38,CD37,MME,CD8B,CD8A,IL6,CSF3R,IL3RA,CSF2RA
Chemokine signaling pathway(K)	3.49E-09	1.71E-07	JAK3,PPBP,RAC2,ADCY2,ADCY8,XCL2,VAV1,HCK,PREX1,LYN,NCF1,CXCL13,CXCL14,CXCL10,CXCL11,PIK3CD,ARRB2,CCL8,CCL5,CCL4,CCL3,CCL2,PIK3R5,CCR1,GNGT2,CCR8,CCR7,CCR5,CCR4,CCR2,RASGRP2,ITK,PLCB2,CCL11,CCL18,CCL24,CCL23,CCL20,WAS,CXCR4,CXCR6,CXCR1,CXCR3,CXCR2,CXCL6,CXCL9,CXCL8,CXCL1,CXCL3,CXCL2,CXCL5,FGR,DOCK2
Osteoclast differentiation(K)	1.76E-08	8.26E-07	SPI1,ITGB3,ACP5,LCP2,BTK,IL1A,IL1B,TYROBP,FOSL1,IFNAR2,LCK,NCF1,NCF2,NCF4,TNFRSF11B,SOCS3,PIK3CD,FCGR3A,FCGR3B,FCGR1A,FCGR2A,FCGR2B,CTSK,CYBA,OSCAR,SIRPB1,MAPK12,TREM2,LILRA6,LILRA1,LILRA2,LILRA5,LILRB1,LILRB2,LILRB3,LILRB4,LILRB5,CAMK4,SIRPG,TGFB1
G alpha (i) signaling events(R)	3.12E-08	1.37E-06	C3AR1,ADORA3,ADORA1,AWAT2,APLN,MYO7A,SDC4,PPBP,SDC1,OXGR1,GAL,CNR2,PRKCQ,ADCY2,ADCY8,P2RY4,SAA1,GPSM3,RBP4,FPR1,FPR3,FPR2,GPR17,ABCA4,GPR18,GPR37,CXCL13,CXCL10,CXCL11,CCL5,CCL4,CCR1,PPP1R1B,CCR8,CCR7,CCR5,CCR4,CCR2,GPC1,GPC2,RGS4,RGS1,RGS6,TAS1R3,GPR183,PNOC,PLCB2,CCL23,CCL20,CNGB1,AKR1B10,NMU,CXCR4,CXCR6,CXCR1,CXCR3,CXCR2,CAMK4,NPY1R,RGS9BP,APLNR,C5AR1,CXCL6,CXCL9,CXCL8,CXCL1,CXCL3,CXCL2,CXCL5,NPY5R,RGS18,CAMK2B,RGS16,S1PR1,RGS20,PDE6A,S1PR5,S1PR4,PDE6G
Beta1 integrin cell surface interactions(N)	2.79E-07	1.17E-05	FN1,SPP1,COL3A1,ITGA4,ITGA1,ITGA5,TGM2,VCAM1,FBN1,TNC,PLAUR,COL6A2,COL6A1,COL

			6A3,THBS1,COL1A1,COL1A2,F13A1,CD14,COL5A1,COL5A2,COL4A1,COL4A4,COL4A6,NID1
Malaria(K)	4.89E-07	2.00E-05	ITGB2,ITGAL,ICAM1,SDC1,IL10,IL1B,VCAM1,CSF3,CR1,PECAM1,TLR4,TLR2,CD40LG,SELE,SELP,THBS1,CCL2,IL6,KLRB1,TGFB1,CXCL8
Beta3 integrin cell surface interactions(N)	8.08E-07	3.15E-05	FN1,SPHK1,SPP1,ITGB3,SDC4,SDC1,FBN1,TNC,PECAM1,PLAUR,THBS1,THY1,COL1A1,COL1A2,CCN1,PDGFRB,COL4A1,COL4A4,COL4A6
Fc epsilon receptor (FCERI) signaling(R)	1.18E-06	4.36E-05	IGHV3-23,IGHV3-7,IGHV3-30,IGHV3-33,IGHV3-11,LCP2,IGHV3-48,IGHV3-53,BTK,FCER1G,IGKC,IGKV1-5,CARD11,IGLV3-1,IGKV1-16,IGKV1-17,IGKV1-12,PRKCQ,IGHV4-59,IGLV1-40,IGLV1-47,IGLV1-44,IGHV4-34,IGHV4-39,VAV1,IGHV1-69,LYN,IGHV1-46,IGLV2-11,IGLV2-14,IGLV2-23,IGHV1-2,LAT2,IGLV6-57,IGKV3-15,IGKV3-11,IGKV3-20,IGLC3,IGLC2,ITK,IGLV3-19,IGLV3-25,IGLV3-21,IGKV3D-20,IGHV2-70,IGHV2-5,IGLV2-8,IGKV4-1,IGLV7-43,IGKV2-30
TCR signaling in naïve CD4+ T cells(N)	1.60E-06	5.77E-05	SLA2,MAP3K8,LCP2,CD247,CARD11,CD4,PRKCQ,LCK,VAV1,TRPV6,ZAP70,FYB1,PTPRC,CD28,CD3G,CD3E,CD3D,CD86,CD80,RASGRP2,ITK,INPP5D,MAP4K1,WAS
Amoebiasis(K)	3.35E-06	1.14E-04	FN1,COL3A1,ITGAM,ITGB2,IL10,IL1B,TLR4,TLR2,COL1A1,COL1A2,ARG1,PIK3CD,CD1D,CD1A,CD14,IL6,LAMB4,SERPINB3,SERPINB4,SERPINB9,PLCB2,COL4A2,COL4A1,COL4A4,COL4A6,TGFB1,CXCL8,CXCL1,CXCL3,CXCL2
IL12-mediated signaling events(N)	3.93E-06	1.30E-04	IL12RB1,IL2RG,GZMA,GZMB,IL2RA,CD247,IL1B,TBX21,CD4,LCK,STAT4,FASLG,CCL4,CCL3,CD3G,CD3E,CD3D,CCR5,EOMES,CD8B,CD8A,IL18RAP
Costimulation by the CD28 family(R)	5.04E-06	1.61E-04	MAP3K8,CD274,PDCD1,CD247,TRAV19,CD4,ICOS,HLA-DQB2,TRBV7-9,BTLA,LCK,PDCD1LG2,VAV1,TRBC1,LYN,CTLA4,CD28,CD3G,CD3E,CD3D,CD86,CD80
TCR signaling in naïve CD8+ T cells(N)	7.49E-06	2.20E-04	MAP3K8,LCP2,CD247,CARD11,PRKCQ,LCK,VAV1,TRPV6,ZAP70,PTPRC,PRF1,CD28,CD3G,CD3E,CD3D,CD86,CD80,CD8B,CD8A,RASGRP2
Phagosome(K)	7.59E-06	2.20E-04	OLR1,CORO1A,ITGAM,ITGB3,ITGB2,ITGA5,C1R,MSR1,CD209,SFTPD,ATP6V1B1,TUBB4A,TCIRG1,FCAR,ATP6V0D2,ATP6V0A4,TLR4,TLR2,N

			OS1,THBS1,HLA-DMA,NCF1,NCF2,NCF4,FCGR3A,FCGR3B,FCGR1A,FCGR2A,FCGR2B,CD14,CTSS,CTSL,MPO,CYBB,CYBA,MRC1,CLEC7A,MARCO
Leukocyte transendothelial migration(K)	7.59E-06	2.20E-04	ITGAM,ITGB2,ITGAL,ITGA4,ICAM1,RAC2,VCAM1,PECAM1,VAV1,CLDN10,CLDN19,CLDN16,CLDN1,CLDN3,CLDN8,THY1,NCF1,NCF2,NCF4,PIK3CD,CYBB,CYBA,MMP2,MMP9,MAPK12,ITK,CDH5,ESAM,OCLN,RHOH,CXCR4
Urokinase-type plasminogen activator (uPA) and uPAR-mediated signaling(N)	9.27E-06	2.59E-04	FN1,MMP12,MMP13,ITGAM,ITGB3,ITGB2,ITGA5,PLAUR,FPR1,FPR3,FPR2,PDGFRB,MMP3,MMP9,SERPINE1,GPLD1,TGFB1
Pertussis(K)	9.99E-06	2.70E-04	LY96,ITGAM,ITGB2,ITGA5,C1S,C1R,C4B,IL10,IL1A,IL1B,CALML5,TLR4,C1QB,C1QA,C1QC,NLRP3,C2,CD14,IL6,IRF8,MAPK12,CXCL6,CXCL8,CXCL5
Primary immunodeficiency (K)	1.04E-05	2.72E-04	JAK3,IL2RG,BTK,IL7R,CD4,ICOS,LCK,CD79A,CD40LG,ZAP70,PTPRC,CD19,CD3E,CD3D,CD8B,CD8A
ErbB receptor signaling network(N)	1.10E-05	2.85E-04	NRG2,NRG3,NRG4,BTC,AREG,EREG,EGF,HBEGF,ERBB3,ERBB4
IL-17 signaling pathway(K)	1.52E-05	3.80E-04	MMP13,IL1B,FOSL1,CSF3,MAPK4,PTGS2,S100A9,S100A8,S100A7,CXCL10,CCL2,IL17D,IL6,MMP1,MMP3,MMP9,MAPK15,MAPK12,CCL11,CCL20,IL17RE,CXCL6,CXCL8,CXCL1,CXCL3,CXCL2,CXCL5
PI3K-Akt signaling pathway(K)	2.22E-05	5.32E-04	FN1,JAK3,SPP1,ITGB3,ITGA4,ITGA1,ITGA5,IL2RG,NTRK1,NTRK2,IL2RA,PIK3AP1,LPAR4,PCK1,IGF2,OSM,FGF22,FGF18,IL7R,CSF3,TNC,IFNAR2,PGF,ANGPT2,TLR4,TLR2,EFNA4,EFNA3,FGFR3,FGFR2,COL6A2,COL6A1,COL6A3,COL6A6,THBS1,NOS3,PPP2R2C,COL1A1,COL1A2,AREG,NTF4,FLT1,PIK3CD,FASLG,TCL1A,EREG,PIK3R5,CD19,GNGT2,CCND1,PDGFRB,PDGFRA,CHAD,IL6,EGF,LAMB4,CREB3L1,CHRM1,CSF3R,VWF,IL3RA,SGK2,COL4A2,COL4A1,COL4A4,COL4A6,ERBB3,ERBB4

IL12 signaling mediated by STAT4(N)	2.42E-05	5.81E-04	IL2RA,CD247,TBX21,CD4,STAT4,PRF1,CD28,CD3G,CD3E,CD3D,CD86,CD80,IL18RAP,TGFB1
B cell receptor signaling pathway(K)	3.30E-05	7.60E-04	PIK3AP1,BTK,RAC2,CARD11,IFITM1,CD79B,CD79A,VAV1,LYN,PIK3CD,FCGR2B,CD19,CD22,CD72,INPP5D,LILRA6,LILRA1,LILRA2,LILRA5,LILRB1,LILRB2,LILRB3,LILRB4,LILRB5
Beta2 integrin cell surface interactions(N)	3.65E-05	8.09E-04	ITGAM,ITGB2,ITGAL,ITGAX,ITGAD,ICAM2,ICAM1,VCAM1,CD40LG,PLAUR,THY1,FCGR2A,CCN1
Post-translational modification: synthesis of GPI-anchored proteins(R)	3.68E-05	8.09E-04	LYPD1,LYPD3,LY6K,LY6D,LY6H,ALPL,CNTN4,CPM,VNN1,VNN2,VNN3,PLAUR,THY1,LYPD6B,FCGR3B,MDGA2,CD52,PRND,GPLD1,PSCA,RTN4RL1,FOLR2,CEACAM5,LY6G6C,ULBP2
AGE-RAGE signaling pathway in diabetic complications(K)	4.31E-05	9.04E-04	FN1,COL3A1,ICAM1,IL1A,IL1B,VCAM1,EDN1,SELE,NOS3,COL1A1,COL1A2,NOX4,PIK3CD,CCL2,CCND1,CYBB,IL6,MMP2,MAPK12,SERPINE1,PLCB2,COL4A2,COL4A1,COL4A4,COL4A6,TGFB1,CXCL8
ROS and RNS production in phagocytes(R)	4.61E-05	9.52E-04	RAC2,ATP6V1B1,TCIRG1,ATP6V0D2,ATP6V0A4,NOS1,NOS3,NCF1,NCF2,NCF4,MPO,CYBB,CYBA,SLC11A1
Protein digestion and absorption(K)	4.76E-05	9.52E-04	SLC7A7,COL22A1,COL3A1,COL17A1,PRSS3,COL10A1,COL6A2,COL6A1,COL6A3,COL6A6,ATP1A2,COL1A1,COL1A2,CPA3,COL28A1,COL15A1,MME,COL5A1,COL5A2,COL12A1,KCNJ13,COL4A2,COL4A1,COL4A4,COL4A6,DPP4
Complement and coagulation cascades(K)	5.72E-05	1.14E-03	C3AR1,ITGAM,ITGB2,ITGAX,C1S,C1R,C4B,CFD,CFI,CR1,C1QB,C1QA,F2RL2,F2RL3,C1QC,PLAUR,C2,F13A1,A2M,MASP1,SERPINE1,SERPINA1,VWF,C5AR1
IL4-mediated signaling events(N)	6.08E-05	1.22E-03	SPI1,JAK3,ITGB3,IL2RG,IL10,ETS1,IGHG3,IGHG1,CD40LG,SELP,THY1,COL1A1,COL1A2,PIGR,ARG1,SOCS3,DOK2,CCL11,INPP5D,PARP14
ECM-receptor interaction(K)	9.61E-05	1.83E-03	FN1,SPP1,ITGB3,ITGA4,ITGA1,ITGA5,SDC4,SDC1,FREM2,TNC,COL6A2,COL6A1,COL6A3,COL6A6,THBS1,COL1A1,COL1A2,CHAD,LAMB4,VWF,COL4A2,COL4A1,COL4A4,COL4A6
Leishmaniasis(K)	9.67E-05	1.84E-03	ITGAM,ITGB2,ITGA4,IL10,IL1A,IL1B,CR1,TLR4,TLR2,PTGS2,HLA-DMA,NCF1,NCF2,NCF4,FCGR3A,FCGR3B,FCGR1A,FCGR2A,CYBB,CYBA,MAPK12,TGFB1

IL23-mediated signaling events(N)	1.11E-04	2.00E-03	IL12RB1,IL24,IL19,IL1B,CD4,STAT4,SOCS3,CCL2,CD3E,MPO,IL6,IL18RAP,CXCL9,CXCL1
Downstream signaling in naïve CD8+ T cells(N)	2.12E-04	3.81E-03	TNFRSF4,TNFRSF9,IL2RG,GZMB,IL2RA,CD247,PRKCQ,FOSL1,IFNAR2,STAT4,FASLG,PTPN7,PRF1,CD3G,CD3E,CD3D,EOMES,CD8B,CD8A
TNF signaling pathway(K)	2.61E-04	4.63E-03	MAP3K8,TNFRSF1B,ICAM1,IL15,IL1B,VCAM1,EDN1,MLKL,SELE,PTGS2,SOCS3,CXCL10,PIK3CD,BIRC3,CCL5,CCL2,IL6,MMP3,MMP9,MAPK12,CREB3L1,CCL20,CXCL6,CXCL1,CXCL3,CXCL2,CXCL5
amb2 Integrin signaling(N)	2.73E-04	4.63E-03	ITGAM,ITGB2,ICAM1,SELPLG,HCK,SELP,THY1,CCN2,MST1R,IL6,MMP2,MMP9
Melanin biosynthesis(R)	2.93E-04	4.98E-03	SLC45A2,TYR,DCT,OCA2,TYRP1
NF-kappa B signaling pathway(K)	3.41E-04	5.80E-03	LY96,TNFSF13B,ICAM1,BTK,TNFSF14,IL1B,CARD11,VCAM1,PRKCQ,LBP,LCK,TLR4,CD40LG,ZAP70,LTB,LYN,PTGS2,BIRC3,CCL4,CD14,BCL2A1,CXCL8,CXCL1,CXCL3,CXCL2
T cell receptor signaling pathway(K)	4.50E-04	7.20E-03	MAP3K8,LCP2,PDCD1,CD247,IL10,CARD11,CD4,PRKCQ,ICOS,LCK,VAV1,CD40LG,ZAP70,CTLA4,PTPRC,PIK3CD,CD28,CD3G,CD3E,CD3D,PAK6,CD8B,CD8A,MAPK12,ITK
Alzheimer disease-presenilin pathway(P)	5.11E-04	8.18E-03	JUP,MMP25,MMP12,MMP13,MMP19,WNT7B,ACTBL2,NECTIN1,WNT5A,WNT3A,WNT2B,WNT16,LRP4,PCSK2,PCSK1,PCSK5,WNT2,WNT4,MMP1,MMP2,MMP8,MMP9,WNT10B,FZD2,CDH1,ERBB4
Thromboxane A2 receptor signaling(N)	5.59E-04	8.88E-03	BLK,ICAM1,TGM2,VCAM1,PRKCQ,LCK,HCK,SELE,NOS3,LYN,ARRB2,EGF,PLCB2,TBXA2R,PTGIR,FGR
Chemical carcinogenesis(K)	5.68E-04	8.88E-03	GSTM2,GSTO2,CYP2C19,CYP2C18,UGT2A1,UGT2B7,ADH7,ADH6,ADH4,UGT1A1,CYP3A4,CYP3A5,UGT1A4,UGT1A6,ADH1C,GSTA3,HSD11B1,PTGS2,MGST1,ALDH3A1,ALDH3B2
Intestinal immune network for IgA production(K)	5.92E-04	8.88E-03	TNFRSF17,TNFSF13B,ITGA4,IL10,IL15,ICOS,CD40LG,PIGR,HLA-DMA,CD28,CD86,CD80,IL6,CXCR4,TGFB1
Estrogen signaling pathway(K)	6.60E-04	9.79E-03	KCNJ6,ADCY2,ADCY8,CALML5,KRT9,KRT33B,KRT33A,NOS3,PIK3CD,MMP2,MMP9,CREB3L1,PLCB2,HBEGF,KRT28,KRT27,KRT26,KRT25,KR

			T35,KRT34,KRT32,KRT31,KRT39,KRT38,KRT36,KRT10,KRT19,KRT18,KRT15,KRT40
Alpha9 beta1 integrin signaling events(N)	6.70E-04	9.79E-03	FN1,SPP1,TGM2,ADAM12,VCAM1,TNC,F13A1,SAT1,ADAM8,CSF2RA
Proteoglycans in cancer(K)	6.99E-04	9.79E-03	FN1,SHH,WNT7B,ITGB3,ITGA5,SDC4,IGF2,SDC1,VAV1,TLR4,TLR2,WNT5A,WNT3A,WNT2B,PLAUR,WNT16,THBS1,LUM,COL1A1,COL1A2,PIK3CD,FASLG,CTSL,GPC1,CCND1,WNT2,WNT4,MMP2,MMP9,MAPK12,WNT10B,FZD2,HCLS1,HBEGF,HOXD10,HPSE2,TGFB1,CAMK2B,ERBB3,ERBB4
Fluid shear stress and atherosclerosis(K)	7.38E-04	0.0103	GSTM2,GSTO2,ITGB3,ICAM1,SDC4,SDC1,RAC2,IL1A,IL1B,VCAM1,HMOX1,PECAM1,CALML5,EDN1,GSTA3,SELE,NOS3,NCF1,NCF2,PIK3CD,CCL2,CTSL,GPC1,CYBA,MMP2,MMP9,MAPK12,CDH5,KLF2,MGST1
Chagas disease (American trypanosomiasis) (K)	7.73E-04	0.0108	CD247,IL10,IL1B,TLR4,TLR2,C1QB,C1QA,C1QC,PPP2R2C,PIK3CD,FASLG,CCL5,CCL3,CCL2,CD3G,CD3E,CD3D,IL6,MAPK12,SERPINE1,ACE,PLCB2,TGFB1,CXCL8
Interleukin-2 family signaling(R)	7.84E-04	0.011	JAK3,IL2RG,IL2RA,LGALS9,IL15,IL21R,STAT4,PIK3CD,HAVCR2,IL3RA,INPP5D,CSF2RB,CSF2RA
Calcineurin-regulated NFAT-dependent transcription in lymphocytes(N)	9.36E-04	0.0126	GATA3,IL2RA,IKZF1,TBX21,PRKCQ,FOSL1,CD40LG,CTLA4,PTGS2,FOXP3,FASLG,RNF128,BATF3,CXCL8
EPHA forward signaling(N)	9.71E-04	0.0126	BLK,LCK,HCK,EFNA3,NGEF,LYN,EPHA5,EPHA7,EPHA1,ARHGEF15,FGR
Toll-like receptor signaling pathway(K)	1.00E-03	0.013	SPP1,MAP3K8,LY96,IL1B,IFNAR2,LBP,TLR8,TLR7,TLR4,TLR2,CXCL10,CXCL11,PIK3CD,CCL5,CCL4,CCL3,CD14,CTSK,CD86,CD80,IL6,MAPK12,CXCL9,CXCL8
G alpha (q) signaling events(R)	1.04E-03	0.0136	PTAFR,HTR2A,BTK,LPAR4,PROK2,PROK1,PRKCQ,TRPC3,XCL2,P2RY6,EDN1,SAA1,F2RL2,F2RL3,FPR2,GPR17,P2RY10,GPR65,RGS4,RGS1,RASGRP2,MMP3,GPR132,PLCB2,HBEGF,CCL23,GPR4,GPR143,CHRM3,CHRM1,TBXA2R,OXTR,NMU,FFAR2,AVPR1A,CCKBR,RGS18,RGS16

Platelet activation(K)	1.16E-03	0.0145	COL3A1,TBXAS1,ITGB3,LCP2,BTK,FCER1G,APBB1IP,ADCY2,ADCY8,F2RL3,NOS3,LYN,COL1A1,COL1A2,FERMT3,PIK3CD,FCGR2A,PIK3R5,RASGRP2,PLA2G4F,PLA2G4E,PLA2G4B,MAPK12,PLCB2,TBXA2R,VWF,PTGIR
Fc gamma R-mediated phagocytosis(K)	1.17E-03	0.0145	SPHK1,RAC2,ARPC1B,VAV1,HCK,LYN,NCF1,PTPRC,PIK3CD,FCGR3A,FCGR3B,FCGR1A,FCGR2A,FCGR2B,PLA2G4F,PLA2G4E,PLA2G4B,PLPP2,INPP5D,WAS,SCIN,DOCK2
activation of csk by camp-dependent protein kinase inhibits signaling through the t cell receptor(B)	1.21E-03	0.0145	CD247,LCK,EDN1,FPR1,PTPRC,CCL4,CD3G,CD3E,CD3D,CCR5,CCL11,CHRM1,CXCR4
Validated transcriptional targets of AP1 family members Fra1 and Fra2(N)	1.25E-03	0.015	HMOX1,FOSL1,PLAUR,NOS3,COL1A2,CCL2,CCND1,IL6,MMP1,MMP2,MMP9,CXCL8
Natural killer cell mediated cytotoxicity(K)	1.25E-03	0.015	HCST,ITGB2,ITGAL,LCP2,GZMB,CD247,CD244,ICAM2,ICAM1,RAC2,FCER1G,TYROBP,IFNAR2,LCK,SH2D1A,SH2D1B,VAV1,ZAP70,PIK3CD,FASLG,FCGR3A,FCGR3B,PRF1,CD48,MICB,KLRC1,KLRD1,ULBP2
Integrin signaling pathway(P)	1.38E-03	0.0166	FN1,COL3A1,COL17A1,ITGAM,ITGB3,ITGB2,ITGAL,ITGAX,ITGA4,ITGA1,ITGAD,ITGA5,GRAP,RAC2,RND2,ARPC1B,COL10A1,ACTBL2,COL6A2,COL6A1,COL6A3,COL1A1,COL1A2,PIK3CD,COL15A1,COL5A1,COL5A2,COL12A1,COL4A2,COL4A1,COL4A4,COL4A6
Th17 cell differentiation(K)	1.45E-03	0.0166	GATA3,JAK3,IL12RB1,IL2RG,IL2RA,CD247,IL1B,TBX21,CD4,PRKCQ,LCK,IL21R,ZAP70,HLA-DMA,RORC,FOXP3,CD3G,CD3E,CD3D,RXRG,IL17D,IL6,MAPK12,TGFB1
Inflammatory bowel disease (IBD)(K)	1.46E-03	0.0166	GATA3,IL12RB1,IL2RG,IL10,IL1A,IL1B,TBX21,IL21R,TLR4,TLR2,HLA-DMA,STAT4,RORC,FOXP3,IL6,IL18RAP,TGFB1
Drug metabolism - cytochrome P450(K)	1.51E-03	0.0166	GSTM2,GSTO2,CYP2C19,UGT2A1,UGT2B7,ADH7,ADH6,ADH4,UGT1A1,CYP3A4,CYP3A5,UGT1A4,UGT1A6,ADH1C,GSTA3,MGST1,ALDH3A1,ALDH3B2

JAK-STAT signaling pathway(K)	2.02E-03	0.0223	JAK3,IL12RB1,CRLF2,IL2RG,IL2RA,IL24,IL10,IL15,IL19,OSM,IL7R,IL10RA,CSF3,IFNAR2,IL21R,LEP,IL20RA,IL20RB,STAT4,SOCS3,PIK3CD,IL17D,CCND1,PDGFRB,PDGFRA,IL6,EGF,CNTFR,CSF3R,IL3RA,CSF2RB,CSF2RA
Endogenous TLR signaling(N)	2.47E-03	0.0272	BGN,LY96,TLR4,TLR2,SAA2,S100A9,S100A8,CD14,VCAN
Metabolism of xenobiotics by cytochrome P450(K)	2.69E-03	0.0296	GSTM2,GSTO2,UGT2A1,UGT2B7,ADH7,ADH6,ADH4,UGT1A1,CYP3A4,CYP3A5,UGT1A4,UGT1A6,ADH1C,GSTA3,HSD11B1,MGST1,ALDH3A1,ALDH3B2
Graft-versus-host disease(K)	2.87E-03	0.0302	GZMB,IL1A,IL1B,HLA-DMA,FASLG,PRF1,CD28,CD86,CD80,IL6,KLRC1,KLRD1
Tuberculosis(K)	3.00E-03	0.0302	SPHK1,CORO1A,ITGAM,ITGB2,ITGAX,CD209,IL10,FCER1G,IL1A,IL1B,IL10RA,TCIRG1,LBP,CR1,CALML5,ATP6V0D2,ATP6V0A4,TLR4,TLR2,HLA-DMA,FCGR3A,FCGR3B,FCGR1A,FCGR2A,FCGR2B,CD14,CTSS,IL6,MAPK12,MRC1,CLEC4E,CLEC7A,TGFB1,CAMK2B
the co-stimulatory signal during t-cell activation(B)	3.01E-03	0.0302	CD247,ICOS,CTLA4,CD28,CD3G,CD3E,CD3D,CD80
Glycosaminoglycan metabolism(R)	3.02E-03	0.0302	CHST9,BGN,CHST1,SDC4,SDC1,HS3ST6,HS3ST2,BCAN,PAPSS2,CHSY3,LUM,ARSB,GPC1,GPC2,HS3ST3B1,VCAN,CHST11,CHST13,CEMIP,HPSE2,B3GNT4,B3GNT3,ACAN
PPAR signaling pathway(K)	3.08E-03	0.0308	OLR1,ACSBG1,FADS2,ADIPOQ,SLC27A2,PCK1,ACOX2,PLIN1,PLIN5,PLTP,HMGCS2,HMGCS1,AQP7,FABP3,FABP7,ACADL,RXRG,MMP1
Metabolism of water-soluble vitamins and cofactors(R)	3.08E-03	0.0308	FASN,GSTO2,ALDH1L1,ALDH1L2,ACP5,NNMT,NAMPT,PRSS3,TCN2,TCN1,VNN1,VNN2,SLC5A8,PTGS2,CD38,NMNAT3,AMN,FOLR2
Beta5 beta6 beta7 and beta8 integrin cell surface interactions(N)	3.54E-03	0.0354	FN1,ITGA4,SDC1,VCAM1,FBN1,PLAUR,CCN1
Metabolism of Angiotensinogen	3.92E-03	0.0392	ANPEP,CPA3,CTSZ,MME,ENPEP,ACE

to Angiotensins(R)			
DAP12 interactions(R)	4.96E-03	0.0496	LCP2,BTK,TYROBP,CD300LB,LCK,SIRPB1,TREM2,TREM1,SIGLEC16,SIGLEC14,CD300E,KLRD1
(R): Reactome, (K): Kyoto Encyclopedia of Genes and Genomes, (N): National Cancer Institute Pathways Interactions Database, (C): CellMap, (P): Panther, (B) BioCarta.			

Table S1: List of cytokines previously implicated in PG pathogenesis

We included genes for both cytokines/chemokines and associated receptors. 59 genes were entered and 55 were used (4 were not present in our dataset, including IL2, IL17A, IL23R, and IFNG). These genes were *a priori* selected genes known to be important in PG pathogenesis and treatment.

TNF	**IL17RE**	**JAK1**
TNFRSF1A	**IL23A**	**JAK2**
IL1B	**IL23R**	**JAK3**
IL1R1	**IL18**	**TYK2**
IL1RAP	**IL18R1**	**STAT1**
IL2	**IL36G**	**STAT2**
IL2RA	**IL1RL1**	**STAT3**
IL2RB	**NCAM1**	**STAT4**
IL2RG	**CD163**	**STAT5A**
IL6	**MPO**	**STAT5B**
IL6R	**MMP2**	**STAT6**
CXCL8	**MMP9**	**C5AR1**
CXCR1	**MMP10**	**STAT5B**
CXCR2	**CXCL9**	**STAT6**
IL15	**CXCL10**	**C5AR1**
IL15RA	**CXCL11**	**CXCR3**
IL17A	**IFNG**	**CD40**
IL17RA	**IFNGR1**	**CD40LG**
IL17RB	**IFNGR2**	**FAS**
IL17RC	**VEGFA**	**FASLG**
IL17RD	**CSF3**	

Table S2: PG patient characteristics

PG	Perilesional	Non-affected site	Age	Gender	Comorbidities	Treatment
1	Left arm	Left arm	59	F	None	None
2	Left lower leg	Left lower leg	52	F	GPA	None
3	Right lower leg	Right forearm	63	M	Factor V Leiden deficiency	5 days of high- dose prednisone
4	Right lower leg	Right forearm	60	F	PVD	1 day of high- dose prednisone
5	Right face	Right forearm	18	F	None	Lenalidomide, oral methotrexate, high-dose prednisone
6	Left lower leg	Right forearm	52	F	None	None
7	Right lower leg	Right forearm	63	F	Psoriasis, venous stasis dermatitis	Topical steroids
8	Back	Left arm	55	M	Cystic acne, hidradenitis suppurativa	Infliximab, oral dapsone, low- dose prednisone
GPA=granulomatosis with polyangiitis, PVD=peripheral vascular disease. Healthy control patients did not have associated comorbidities; their samples were collected from the forearms.						

Table S4: Pathways associated with differentially expressed genes in the dermis of perilesional PG vs dermis of non-lesional PG

Significant genes were defined as having an FC >4 and an FDR p-value of <0.05. 405 differentially expressed genes were identified and entered into Cytoscape. 25 pathways were significantly enriched (FDR <0.05).

Table S4: Dermis of perilesional PG vs dermis of non-lesional PG pathways			
Pathway	P-value	FDR	Nodes
Extracellular matrix organization(R)	1.10E-06	5.83E-04	ICAM5,FN1,COL1A2,CTSB,MMP12,PXDN,COL3A1,COMP,COL4A1,COL4A4,COL4A5,TGFB3,BMP7,COL5A1,ITGAX,ITGA4,ITGA1,LUM
Beta1 integrin cell surface interactions(N)	3.15E-06	8.36E-04	FN1,COL1A2,COL3A1,COL4A1,COL4A4,COL4A5,COL5A1,ITGA4,ITGA1
Integrin signaling pathway(P)	5.49E-06	9.66E-04	FN1,COL1A2,GRAP,ARPC1B,COL3A1,COL4A1,COL4A4,COL4A5,COL5A1,PIK3CG,ITGAX,ITGA4,ITGA1
Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell(R)	1.23E-05	1.20E-03	ICAM5,CXADR,SH2D1A,PILRA,RAET1E,SIGLEC9,CD33,SIGLEC7,CD300LB,SELL,TREM2,FCGR3A,ITGA4,KLRG1
AGE-RAGE signaling pathway in diabetic complications(K)	1.32E-05	1.20E-03	FN1,COL1A2,IL1A,COL3A1,COL4A1,COL4A4,COL4A5,TGFB3,SELE,MAPK12
Cell adhesion molecules (CAMs)(K)	1.37E-05	1.20E-03	ICOS,CD28,CTLA4,CLDN19,NRCAM,SELE,IGSF11,PTPRC,SELL,ITGA4,CDH15,PDCD1
Human papillomavirus infection(K)	2.48E-05	1.86E-03	ATP6V0A4,FN1,COL1A2,WNT7B,CRB3,COMP,COL4A1,MFNG,COL4A4,COL4A5,WNT2,WNT3A,ISG15,ITGA4,ITGA1,WNT16,PARD6G,LAMB4
ECM-receptor interaction(K)	3.02E-05	1.99E-03	FN1,COL1A2,COMP,COL4A1,COL4A4,COL4A5,ITGA4,ITGA1,LAMB4
Primary immunodeficiency (K)	6.46E-05	3.75E-03	CD79A,ICOS,JAK3,PTPRC,IL7R,ZAP70
Amoebiasis(K)	9.26E-05	4.91E-03	FN1,COL1A2,COL3A1,COL4A1,COL4A4,COL4A5,TGFB3,CXCL2,LAMB4

Beta3 integrin cell surface interactions(N)	1.26E-04	6.06E-03	THY1,FN1,COL1A2,COL4A1,COL4A4,COL4A5
Rheumatoid arthritis(K)	2.68E-04	0.0118	ATP6V0A4,CD28,CTLA4,IL1A,CCL20,TGFB3,CXCL2,LTB
Tuberculosis(K)	3.83E-04	0.0143	CALML5,CALML3,ATP6V0A4,TLR1,IL1A,TGFB3,FCGR3A,ITGAX,LBP,CR1,MAPK12
Platelet activation(K)	3.87E-04	0.0143	COL1A2,ADCY4,COL3A1,GUCY1B1,GUCY1A1,PIK3CG,PLA2G4F,PLA2G4E,MAPK12
Neutrophil degranulation(R)	4.96E-04	0.0174	CALML5,GMFG,BST2,SIGLEC9,CTSZ,CD33,CTSB,RHOF,ALOX5,RAB31,PKP1,GPR84,PTPRC,SELL,ITGAX,CR1,PTX3,MNDA
PI3K-Akt signaling pathway(K)	5.69E-04	0.0188	FN1,COL1A2,JAK3,CSF3R,CHRM1,COMP,COL4A1,COL4A4,COL4A5,IL7R,PIK3CG,ITGA4,ITGA1,ERBB4,NTRK2,LAMB4
Cytokine-cytokine receptor interaction(K)	7.65E-04	0.0237	TNFSF18,IL31RA,CD27,IL1A,CCL20,CSF3R,IL18RAP,TGFB3,BMP7,IL7R,CXCL2,LTB,IL1RL1,IL1RL2
Signaling pathways regulating pluripotency of stem cells(K)	9.09E-04	0.0264	ISL1,JAK3,WNT7B,DLX5,OTX1,WNT2,WNT3A,WNT16,MAPK12
VEGFR3 signaling in lymphatic endothelium(N)	1.06E-03	0.0285	FN1,COL1A2,ITGA4,ITGA1
WNT ligand biogenesis and trafficking(R)	1.22E-03	0.0317	WNT7B,WNT2,WNT3A,WNT16
Protein digestion and absorption(K)	1.57E-03	0.0392	COL1A2,COL3A1,COL4A1,COL4A4,COL4A5,COL5A1,KCNJ13
Hematopoietic cell lineage(K)	1.97E-03	0.0474	CD33,IL1A,CSF3R,IL7R,CR1,ITGA4,ITGA1
Ovarian steroidogenesis(K)	2.20E-03	0.0485	ADCY4,ALOX5,CYP11A1,PLA2G4F,PLA2G4E
Melanogenesis(K)	2.21E-03	0.0485	CALML5,CALML3,ADCY4,WNT7B,WNT2,WNT3A,WNT16
(R): Reactome, (K): Kyoto Encyclopedia of Genes and Genomes, (N): National Cancer Institute Pathways Interactions Database, (C): CellMap, (P): Panther, (B) BioCarta.			

Table S5: Pathways associated with differentially expressed genes in the epidermis of perilesional PG vs epidermis of HC

Significant genes were defined as having an FC >4 or < -4 and an FDR p-value of <0.05. 1780 differentially expressed genes were identified and entered into Cytoscape. 16 pathways were significantly enriched with an (FDR <0.05).

Table S5: Epidermis of perilesional PG vs Epidermis of HC pathways			
Pathway	P value	FDR	Nodes
NCAM signaling for neurite out-growth(R)	1.10E-06	5.33E-04	SPTB,FYN,COL9A2,CACNA1H,CACNA1G,CACNA1S,CNTN2,CACNB1,SPTBN4,SPTBN5,GFRA1,COL4A3,FGFR1,COL6A2
Hematopoietic cell lineage(K)	1.29E-06	5.33E-04	HLA-DMB,HLA-DPB1,HLA-DOA,HLA-DOB,FLT3,ITGA6,CD1E,CD1C,CD1B,CD1A,CD38,CD37,CD33,IL4R,CD4,HLA-DQA1,TNF,CSF1R,IL1R2
Calcium signaling pathway(K)	1.01E-05	2.65E-03	HTR7,GRIN2A,GRIN2C,MCU,CD38,CACNA1H,CACNA1G,CACNA1S,ATP2B2,PRKCB,TNNC1,TNNC2,ADCY2,PLCD3,CHRM1,SLC8A1,CYSLTR1,DRD1,CALML6,PDE1B,CCKBR,ADRB1,HRH2,CASQ1,CAMK2B,ERBB4
Dilated cardiomyopathy (DCM)(K)	1.28E-05	2.65E-03	CACNA2D2,MYBPC3,ITGB7,ITGB6,ITGA8,ITGA7,ITGA6,CACNA1S,TNNC1,ADCY2,TNF,SLC8A1,CACNB1,ITGA11,SGCG,TNNT2,ADRB1
Cell adhesion molecules (CAMs)(K)	3.09E-05	5.14E-03	CLDN3,CLDN8,LRRC4,HLA-DMB,HLA-DPB1,HLA-DOA,HLA-DOB,CD274,SPN,ITGB7,ITGA8,ITGA6,CD226,CD86,VCAM1,CNTN2,CD4,ALCAM,HLA-DQA1,CDH3,CLDN16
ECM-receptor interaction(K)	6.22E-05	8.19E-03	ITGB7,ITGB6,ITGA8,ITGA7,ITGA6,COL9A2,CHAD,LAMA3,FREM1,GP6,TNC,ITGA11,COL4A3,COL6A2,THBS2
Potassium Channels(R)	7.95E-05	8.19E-03	KCNMB1,KCNMB4,KCNA2,KCNH8,KCNJ1,KCNJ4,KCNQ1,KCNQ3,KCNN4,GABBR2,GABBR1,GNB3,KCNJ11,KCNJ12,ABCC8
Hypertrophic cardiomyopathy (HCM)(K)	7.95E-05	8.19E-03	CACNA2D2,MYBPC3,ITGB7,ITGB6,ITGA8,ITGA7,ITGA6,CACNA1S,TNNC1,TNF,SLC8A1,CACNB1,ITGA11,SGCG,TNNT2
Cardiac conduction(R)	1.59E-04	0.0147	CACNA2D2,FXYD6,KCNJ4,KCNQ1,NPR2,CACNA1S,FGF13,ATP2B2,SLC8A1,CACNB1,KCNJ11,KCNIP2,KCNJ12,CORIN,CAMK2B,ATP1A1
Class A/1 (Rhodopsin-like receptors)(R)	2.58E-04	0.0214	HTR7,FPR3,GPR35,P2RY13,GPR68,OXER1,MC2R,GNRHR,GAL,MC5R,CCRL2,MCHR1,ACKR2,CCL19,CCL17,CCL22,CHRM1,CYSLTR1,MT

			NR1B,DRD1,DRD4,CX3CR1,P2RY6,P2RY2,FFAR4,EDN2,CCKBR,MT-RNR2,SUCNR1,ADRB1,HRH2,NPY5R
Neuroactive ligand-receptor interaction(K)	3.89E-04	0.0292	HTR7,FPR3,GRIN2A,GRIN2C,GPR35,P2RY13,LEPR,GIPR,MC2R,GRIK3,GNRHR,GAL,GABBR2,GABBR1,GCGR,MC5R,MCHR1,GRM2,CHRM1,CYSLTR1,MTNR1B,CALCRL,DRD1,DRD4,P2RY6,P2RY2,EDN2,CCKBR,GABRD,ADRB1,HRH2,UCN,NPY5R
Extracellular matrix organization(R)	5.37E-04	0.0365	COL24A1,MMP13,MMP16,ITGB7,ITGB6,DST,ITGA8,ITGA7,ITGA6,COL9A2,CTSV,CTSL,TMPRSS6,ADAM12,FBN2,VCAM1,COL5A2,LAMA3,SERPINE1,COL12A1,FMOD,TNC,ITGA11,ADAMTS4,MATN4,COL4A3,COL6A2
Keratinization(R)	5.91E-04	0.0365	DSC2,DSG3,KLK13,LCE1A,PI3,KRT2,KRT7,SPRR2A,KRT16,KRT6A,KRT79,KRT77,KRT73,LOR,KRT72
Heterotrimeric G-protein signaling pathway-Gi alpha and Gs alpha mediated pathway(P)	6.81E-04	0.0365	HTR7,PRKAR2B,GNRHR,RGS9,GRM2,PYGM,PYGL,ADCY2,CHRM1,MTNR1B,DRD1,DRD4,ADRB1,HRH2,GPSM1,GPSM2,RGS17,RGS11
Beta1 integrin cell surface interactions(N)	6.88E-04	0.0365	ITGA8,ITGA7,ITGA6,VCAM1,COL5A2,LAMA3,TNC,ITGA11,COL4A3,COL6A2,THBS2
Arrhythmogenic right ventricular cardiomyopathy (ARVC)(K)	7.15E-04	0.0365	CACNA2D2,DSC2,ITGB7,ITGB6,ITGA8,ITGA7,ITGA6,CACNA1S,SLC8A1,CACNB1,ITGA11,SGCG
(R): Reactome, (K): Kyoto Encylopedia of Genes and Genomes, (N): National Cancer Institute Pathways Interactions Database, (C): CellMap, (P): Panther, (B) BioCarta.			

Table S6: Pathways associated with differentially expressed genes in the epidermis of perilesional PG vs epidermis of nonlesional PG

Significant genes were defined as having a FC >4 and an FDR p-value of <0.05. 1917 differentially expressed genes were identified and entered into Cytoscape. 11 pathways were significantly enriched with an (FDR <0.05).

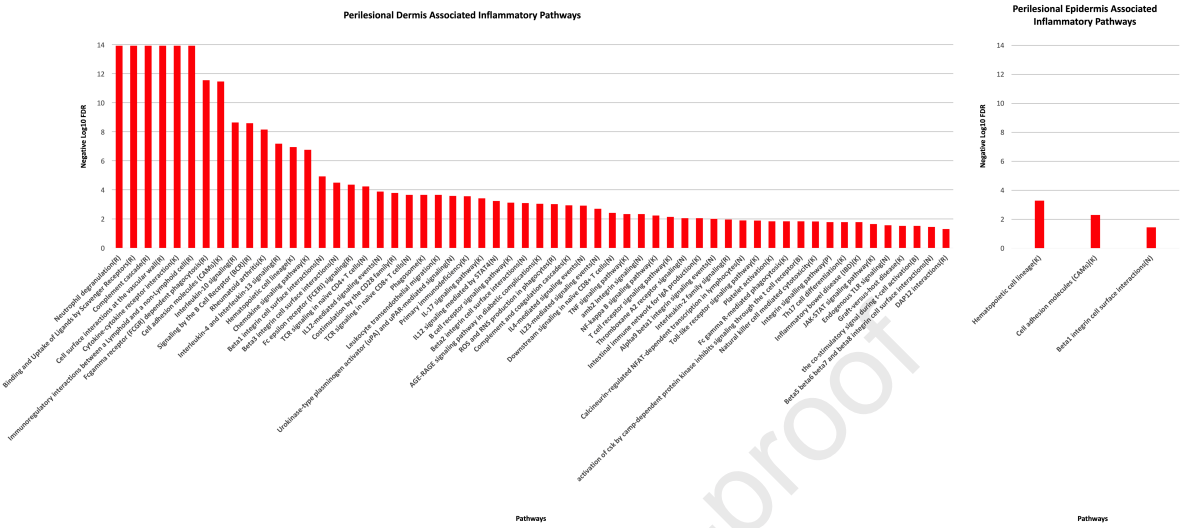
Table S6: Epidermis of perilesional PG vs epidermis of nonlesional PG pathways			
Pathway	P value	FDR	Nodes
Interleukin-4 and Interleukin-13 signaling(R)	1.70E-06	1.51E-03	GATA3,FSCN1,SOCS3,LCN2,CCL2,ICAM1,IL12A,CD36,IL4R,MMP1,HIF1A,ANXA1,CCL22,IL13RA2,IL13RA1,BCL2,LIF,RHOU,SAA1,CXCL8,MUC1,POMC
Class A/1 (Rhodopsin-like receptors)(R)	1.34E-05	5.93E-03	HTR7,C3AR1,GPR35,GPR68,CCL7,CCL5,CCL2,GNRHR,CCR3,MCHR1,HCAR1,TAC1,GPER1,ACKR2,GPR183,ANXA1,CCL22,CHRM1,CHRM4,DRD4,P2RY6,P2RY2,EDNRA,PTGDR,NMB,XCR1,CCKBR,PTGER3,CXCR4,KISS1R,SAA1,NPY1R,APLNR,HRH2,CXCL9,CXCL8,CXCL1,NPY5R,TSHR,POMC
Calcium signaling pathway(K)	6.15E-05	0.0181	MYLK,HTR7,GRIN2A,MCU,CD38,CACNA1F,CACNA1H,CACNA1S,ATP2B2,PRKCB,TNNC1,TNNC2,PLCB2,ADCY2,PLCD3,PLCD4,CHRM1,SLC8A1,CALML6,EDNRA,CCKBR,PTGER3,CXCR4,HRH2,NOS1,CAMK2B,ERBB4
Cytokine-cytokine receptor interaction(K)	1.32E-04	0.0235	NGFR,IL12RB2,TNFRSF4,TNFRSF21,CCL7,CCL5,CCL2,TNFSF10,IL12A,IL1F10,IL20,CCR3,IL16,IL33,IL37,IL34,IL17B,IL4R,INHBA,BMP7,IL7R,TNFSF9,CCL22,IL13RA2,IL13RA1,NGF,IL1R2,XCR1,LIF,GDF7,CXCR4,CXCL9,CXCL8,CXCL1,TGFBR1
Striated Muscle Contraction(R)	1.33E-04	0.0235	MYBPC3,MYBPC2,TMOD1,TNNC1,TNNC2,TNNI2,TNNT1,TNNT2,TNNT3
Extracellular matrix organization(R)	1.62E-04	0.0238	COL13A1,ADAMTS14,MMP10,MMP13,PXDN,COL28A1,ITGB6,ITGA7,ITGA6,ITGA9,NTN4,ICAM1,ACTN1,CTSV,CTSL,TMPRSS6,BMP7,MMP1,COL12A1,SERPINE1,TIMP2,TNC,ADAMTS4,MFAP2,TLL1,CEACAM1,MATN4,LOX,COL4A3,NID1,LTBP1,THBS1
ErbB receptor signaling network(N)	3.34E-04	0.0294	NRG1,EREG,BTC,EGF,HBEGF,ERBB4

Interferon alpha/beta signaling(R)	3.05E-04	0.0294	SOCS3,RSAD2,BST2,MX1,XAF1,IFITM3,IFITM1,IFITM2,IFIT1,IFIT3,IFI6,OASL,OAS2
Malaria(K)	2.75E-04	0.0294	CCL2,ICAM1,IL12A,CD36,HBA1,TLR4,TLR2,KLRB1,CXCL8,THBS2,THBS1
Pertussis(K)	2.64E-04	0.0294	LY96,C1S,C1R,IL12A,CD14,SERPING1,SFTPA1,CALML6,TLR4,C1QB,C1QA,C1QC,NLRP3,CXCL8
Keratinization(R)	4.16E-04	0.0333	DSC2,DSG3,KLK13,LCE1A,PI3,KRT2,SPRR2A,KRT23,KRT13,KRT16,KRT6C,KRT6B,KRT6A,KRT77,LOR,KRT73,KRT72
(R): Reactome, (K): Kyoto Encylopedia of Genes and Genomes, (N): National Cancer Institute Pathways Interactions Database, (C): CellMap, (P): Panther, (B) BioCarta.			

a

Differentially Expressed Genes with a Fold Change >2 and False Discovery Rate p<0.05			
	Up	No Change	Down
8 DPPG vs 8 HC dermis*	2826	13836	2936
8 DPPG vs 7 DNPG*	2460	16359	2099
4 DNPG vs 4 HC dermis	3	20910	5
4 EPPG vs 3 HC epidermis*	928	17964	2355
4 EPPG vs 4 ENPG*	1589	16964	2365
4 ENPG vs 3 HC epidermis	7	20798	113

b



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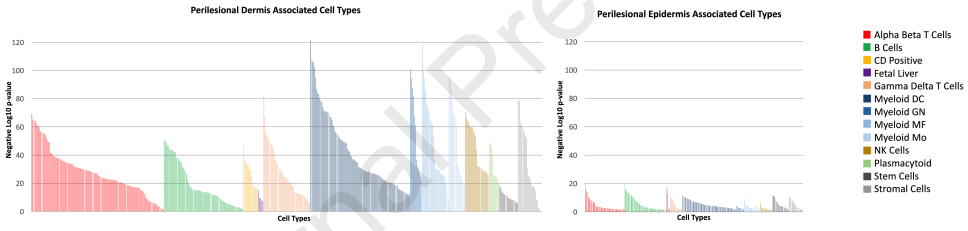
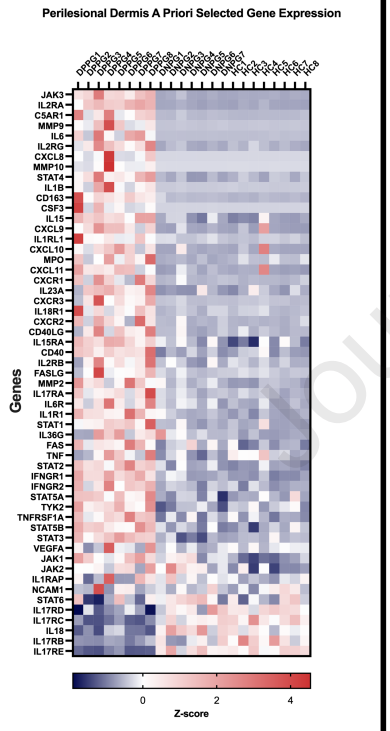


a

Cell Types Associated with A Priori Selected Genes	
Cell	**Genes**
α/β T cells	IL1R1, IL2, IL2RA, IL2RB, IL6R, IL18R1, IL1RL1, MMP9, CXCL10, IFNGR1, JAK3, STAT1, STAT4, CXCR3, CD40LG, FASLG
B cells	IL1B, IL1R1, IL2, IL2RA, CXCR2, IL15, IL18R1, IL36G, MMP9, C5AR1, CD40
CD-Positive	IL2RA, IL2RB, IL18R1, STAT1, STAT4, CXCR3, CD40, CD40LG, FASLG
Fetal Liver	IL15, MPO
γ/δ T cells	IL1R1, IL2, IL2RA, IL2RB, IL18R1, CD163, IFNGR1, JAK3, STAT4, CXCR3, CD40LG, FASLG
NK cells	IL2RA, IL2RB, IL18R1, CXCL10, JAK3, STAT4, CXCR3, FASLG
Plasmacytoid	STAT2, CXCR3
Stem cells	IL1B, IL1R1, CXCR2, IL15, IL36G, IL1RL1, CD163, MPO, MMP9
Stromal cells	IL1B, IL2RA, IL6, IL18R1, MMP2, MMP9, CXCL9, CXCL10, CD40
Myeloid	
Dendritic Cell	IL1B, IL1R1, IL2RA, IL6, IL6R, CXCL8, CXCR2, IL15, IL15RA, IL1RL1, CD163, MMP2, MMP9, CXCL9, CXCL10, CXCL11, IFNGR1, STAT2, STAT4, C5AR1, CXCR3, CD40
Granulocyte	IL1B, IL6R, CXCR1, CXCR2, IL15, IL36G, IL1RL1, MMP2, MMP9, CXCL10, C5AR1
Macrophage	IL1B, IL1R1, IL2RA, IL2RB, IL6R, CXCR2, IL15, IL18R1, IL1RL1, CD163, MPO, CXCL9, CXCL10, C5AR1, CXCR3, CD40, FASLG
Monocyte	IL1B, IL6R, CXCR2, IL15, IL17RA, IL36G, CD163, MPO, MMP9, CXCL9, CXCL10, IFNGR1, C5AR1, CD40

b



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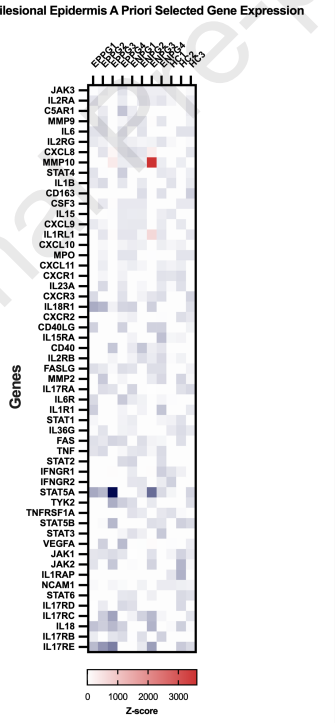

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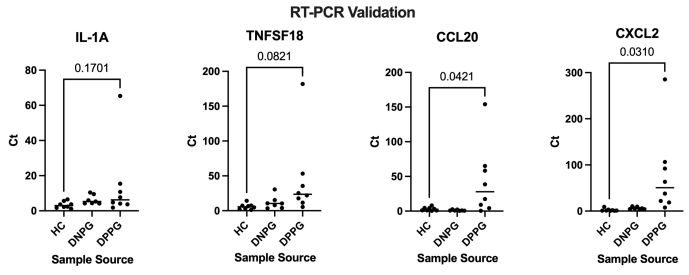


Figure S1: Patient characteristics

Representative clinical picture and histopathology of patient with PG.

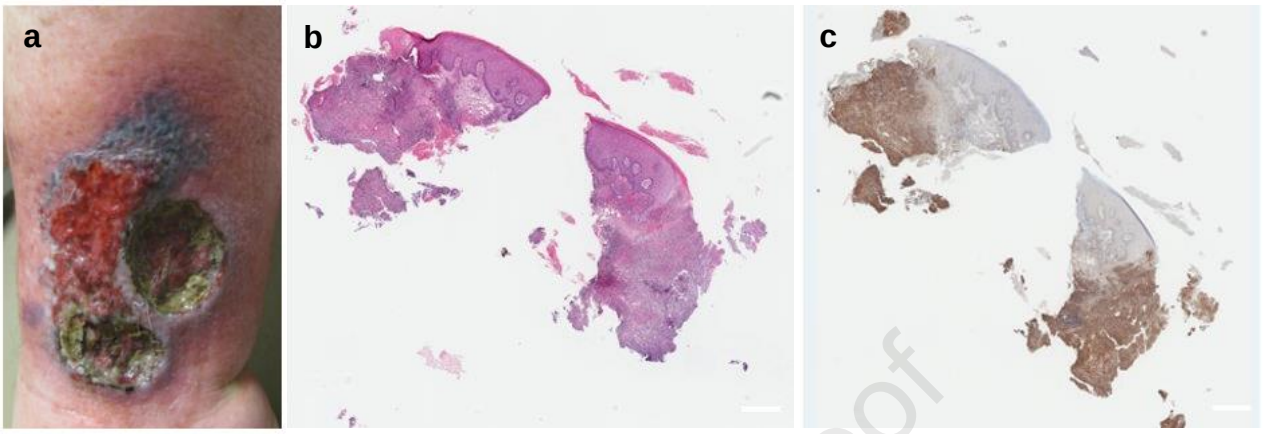
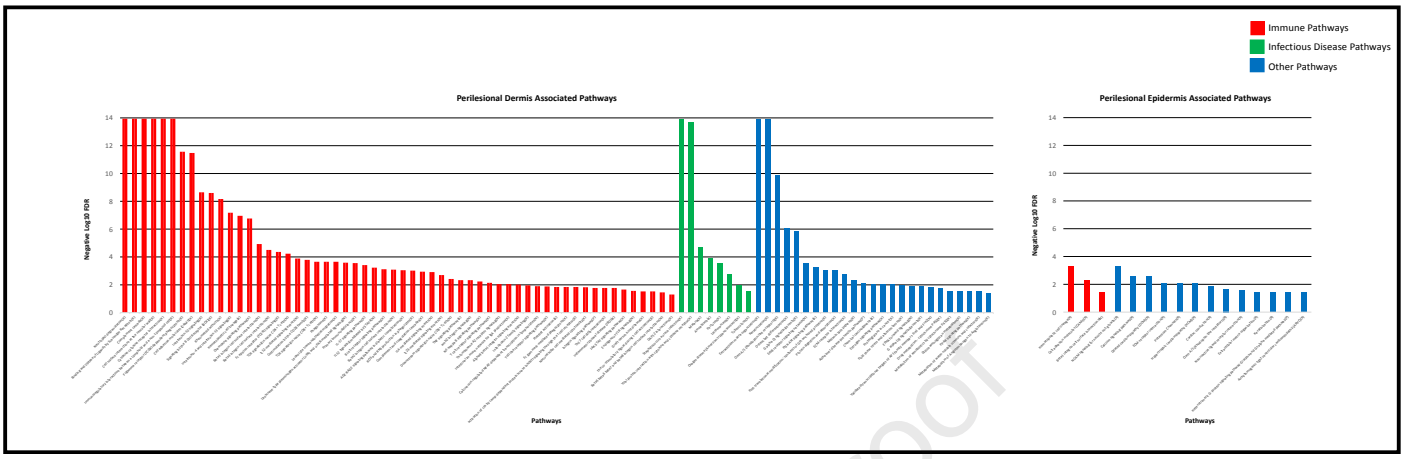


Figure S1a: Patient with PG with a classic ulcer on the left ankle showing with undermining and violaceous erythema. **Figure S1b:** Hematoxylin and eosin staining (20x) of the perilesional area showing diffuse neutrophilic infiltrate. Scale bar= 29um. **Figure S1c:** MPO staining (20x) confirmed the presence of abundant neutrophils. Scale bar= 29um.

Figure S2: Pathway analysis in the dermis and epidermis of perilesional PG samples versus healthy controls



This figure shows the different pathways associated with differentially expressed genes in perilesional dermis and epidermis of PG compared to healthy dermis and healthy epidermis respectively. Most of the overexpressed pathways are in the perilesional dermis of PG lesions. The predominance of immune and inflammatory pathways is evident (in red).

Supplemental Methods:

Patient selection:

Pyoderma Gangrenosum (PG): Eight patients with ulcerative pyoderma gangrenosum were selected. The diagnosis was based on the Su criteria (2004) and was confirmed by a second dermatologist to avoid possible misdiagnosis. Two skin biopsies were obtained from each patient; one from non-affected skin and one from the perilesional area. All samples were separated into epidermis and dermis before further processing. Thus, each patient provided four samples for the study. All skin biopsies of the perilesional area from PG patients showed mixed inflammatory infiltrate with neutrophils. Immunohistochemistry using myeloperoxidase (MPO) stain highlighted the presence of neutrophils. Additionally, skin biopsies were obtained from healthy controls (HC).

Sample collection, RNA isolation and quantitative real-time PCR methods:

Two 4mm biopsy samples were collected from perilesional and non-lesional skin from the same patient with active PG and HC. As the epidermis constitutes an entirely different cellular compartment than the underlying dermis, these two layers were separated prior to RNA extraction using ammonium thiocyanate. Following the separation of the epidermis from dermis, RNA was extracted from each layer using the Trizol protocol (Life Technologies) according to the manufacturer's recommendations in the Leachman/Cassidy Lab in the Dermatology Research Division. Following RNA purification, sample quality was assessed by gel electrophoresis using a Bioanalyzer® (Agilent Technologies) in the OHSU Gene Profiling Shared Resource.

RNA sequencing, differential gene expression analysis methods:

The skin was processed at the Massively Parallel Sequencing Shared Resource (MSSPR) at Oregon Health and Science University (OHSU). Based on our previous experiments, the RNA concentration from skin samples was adequate to prepare the RNA-seq libraries using an Illumina TruSeq total RNA-seq Library protocol. For DE analysis, gene-level differential expression analysis was performed in open-source software R (R Core Team). Gene-level raw counts were filtered to remove genes with extremely low counts in many samples following the published guidelines (Chen et al., 2016), normalized using the trimmed mean of M-values method (TMM) (Robinson and Oshlack, 2010), and transformed to log-counts per million with associated sample wise quality weight and observational precision weights using voom (Law et al., 2014) method. Gene-wise linear models containing design factors and adjusting for sequencing batch and within-subject correlation (when comparing dermis perilesional of PG (DPPG) to dermis non-lesional of PG (DNPG), were employed for differential expression analyses using limma with empirical Bayes moderation and false discovery rate (FDR) adjustment (Benjamini et al., 1995). Using this approach, discovery tests comparing epidermis and dermis from PG and HC were performed.

Quantitative RT-PCR methods:

Total RNA was extracted from epidermis and dermis from skin biopsies with RNeasy Kit (Qiagen). RNA was reverse transcribed with High-Capacity RNA-to-cDNA™ Kit (ThermoFisher). All experiments were done in duplicate using SYBR Green PCR Master Mix (ThermoFisher). Human *IL-1A, TNFSF-18, CCL-20 and CXCL-2* mRNA were measured by qRT-PCR using the following primers: CXCL2-H-F: CTCAAGAATGGGCAGAAAGC; CXCL2-H-R: AAACACATTAGGCGCAATCC; CCL20-H-F:

ATGTGCTGTACCAAGAGTTTGC; CCL20-H-R: CCAATTCCATTCCAGAAAAGCC; IL-1A-H-F: CATTGGCGTTTGAGTCAGCA; IL-1A-H-R: CATGGAGTGGGCCATAGCTT; TNFSF18-H-F: GGAGCCCTGTATGGCTAAGT; TNFSF18-H-R: CAGCTTCCAGTCAGACACCTT. Gene expression data were collected using a 7900HT thermocycler (Applied Biosystems). The levels of these cytokine mRNAs were normalized to *GAPDH.*

Pathway analysis methods:
Cytoscape with 2019 Reactome FI Plugin was used for this analysis (Shannon et al., 2003; Fabregat et al., 2018; ReactomeFIViz, 2018). Significantly differentially expressed genes were defined as genes with fold change (FC) >4 or <-4 and FDR p<0.05. Differentially expressed genes were entered into Cytoscape. Linker genes were used to construct the initial network and pathway analysis was performed without using linker genes (to avoid biasing of results). Differentially expressed pathways were defined as having FDR <0.05.

Immgen analysis methods:
We compared the 8 DPPG samples versus 8 dermis of HC samples. All genes with a FC > 2 and FDR p< 0.05 were included. This included 2826 genes, of which 2588 matched genes in the Immgen database. Immgen data were accessed using the ToppGene Suite (https://toppgene.cchmc.org/).

Supplement references

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SUPPLEMENTARY FIGURE TITLES & LEGENDS

Figure S1: Patient characteristics
Representative clinical picture and histopathology of patient with PG. **Figure S1a**: Patient with PG with a classic ulcer on the left ankle showing with undermining and violaceous erythema. **Figure S1b:** Hematoxylin and eosin staining (20x) of the perilesional area showing diffuse neutrophilic infiltrate. Scale bar= 29um. **Figure S1c:** MPO staining (20x) confirmed the presence of abundant neutrophils. Scale bar= 29um.

Figure S2: Pathway analysis in the dermis and epidermis of perilesional PG samples versus healthy controls
This figure shows the different pathways associated with differentially expressed genes in perilesional dermis and epidermis of PG compared to healthy dermis and healthy epidermis respectively. Most of the overexpressed pathways are in the perilesional dermis of PG lesions. The predominance of immune and inflammatory pathways is evident (in red).

SUPPLEMENTARY TABLE TITLES & LEGENDS

Table S1: List of cytokines previously implicated in PG pathogenesis
We included genes for both cytokines/chemokines and associated receptors. 59 genes were entered and 55 were used (4 were not present in our dataset, including IL2, IL17A, IL23R, and IFNG). These genes were *a priori* selected genes known to be important in PG pathogenesis and treatment.

Table S2: PG patient characteristics

Table S3: Pathways associated with differentially expressed genes in the dermis of perilesional PG vs dermis of HC
Significant genes were defined as having an FC >4 and an FDR p-value of <0.05. 2907 differentially expressed genes were identified and entered into Cytoscape. 92 pathways were significantly enriched (FDR <0.05).

Table S4: Pathways associated with differentially expressed genes in the dermis of perilesional PG vs dermis of non-lesional PG
Significant genes were defined as having an FC >4 and an FDR p-value of <0.05. 405 differentially expressed genes were identified and entered into Cytoscape. 25 pathways were significantly enriched (FDR <0.05).

Table S5: Pathways associated with differentially expressed genes in the epidermis of perilesional PG vs epidermis of HC
Significant genes were defined as having an FC >4 or < -4 and an FDR p-value of <0.05. 1780 differentially expressed genes were identified and entered into Cytoscape. 16 pathways were significantly enriched with an (FDR <0.05).

Table S6: Pathways associated with differentially expressed genes in the epidermis of perilesional PG vs epidermis of nonlesional PG

Significant genes were defined as having a FC >4 and an FDR p-value of <0.05. 1917 differentially expressed genes were identified and entered into Cytoscape. 11 pathways were significantly enriched with an (FDR <0.05).

Molecular and cellular characterization of pyoderma gangrenosum: Implications for the use of gene expression

Alex G Ortega-Loayza (0000-0001-5028-9269),[1] **Marcia A Friedman** (0000-0001-6722-2159),[2] **Ashley M Reese** (0000-0003-0528-0622),[1] **Yuangang Liu** (0000-0002-4179-6629),[1] **Teri M Greiling** (0000-0002-0028-8986),[1] **Pamela B Cassidy** (0000-002-4310-9554),[1] **Angelo V Marzano** (0000-0002-8160-4169),[3] **Lina Gao (**0000-0001-9382-0419),[4] **Suzanne S Fei (**0000-0002-9688-2890),[4] **James T Rosenbaum** (0000-0002-8452-2441)[2]

[1]Department of Dermatology, Oregon Health & Science University; [2]Department of Medicine, Division of Arthritis and Rheumatic Disease, Oregon Health & Science University; [3]Dermatology Unit, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico; [4]Oregon National Primate Research Center Bioinformatics & Biostatistics Core

CITY, STATE, COUNTRY WHERE WORK WAS DONE: Portland, Oregon, USA

CORRESPONDING AUTHOR:

Alex G Ortega-Loayza, M.D., M.C.R.

3303 SW Bond Ave, CH 16D

Portland, OR 97239

Phone: 503-494-3376

Email: ortegalo@ohsu.edu; Twitter: @ThePGguy

SHORT TITLE: "Molecular and cellular characterization of pyoderma gangrenosum"

Abbreviations Used: PG: pyoderma gangrenosum, EPPG: epidermis perilesional pyoderma gangrenosum, ENPG: epidermis non-lesional pyoderma gangrenosum, DPPG: dermis perilesional pyoderma gangrenosum, DNPG: dermis non-lesional pyoderma gangrenosum, HC: healthy control, FDR: false discovery rate, FC: fold change, JAK: Janus kinase, IFN: interferon, DC: dendritic cells, GN: granulocytes, MF: macrophages, Mo: monocytes.

To the Editor

Pyoderma gangrenosum (PG) is characterized by painful ulcers typically affecting the lower extremities. PG pathogenesis and triggers are poorly understood (Ortega-Loayza AG et al., 2018). Treatments target systemic inflammation, but clinical response and outcomes remain unpredictable. Further investigations are necessary to understand PG pathobiology; however, little is known about gene expression in PG, including whether important changes localize to the dermis or epidermis and whether non-lesional skin from PG patients shows subclinical signs of disease. Thus, we analyzed gene expression signatures of perilesional and non-lesional skin biopsies from patients with PG to characterize the immunologic and cellular response. This study was approved by Oregon Health and Science University's Institutional Review Board.

We collected paired biopsies of perilesional and non-lesional skin from eight patients with PG and eight healthy controls (HC) (**Supplementary methods**); all patients provided written informed consent. Skin samples were collected while ulcers were clinically active (**Supplementary Figure S1**). Each biopsy specimen was incubated in a solution of aqueous 3.8% ammonium thiocyanate to separate epidermis from dermis. RNA was prepared from each tissue for RNA-sequencing (RNA-Seq) (Clemmensen A et al., 2009) (GenBank: PRJNA590986). After generating alignments and gene counts using STAR (Dobin A et al., 2013), gene-wise linear models were employed for differential expression analyses using limma with empirical Bayes moderation (Ritchie ME et al., 2015) and false discovery rate (FDR) adjustment (Benjamin Y et al., 1995). Discovery tests compared perilesional and non-lesional dermis and epidermis from PG to HC. Pathway analysis (Cytoscape using the Reactome F1 plugin) was performed using genes with a four-fold expression difference and FDR $p<0.05$ (**Supplementary Tables S3, S4, S5, and S6**) (Shannon P et al., 2003). Unregulated genes with

fold change (FC) >2 and FDR p<0.05 were analyzed with Immgen software to correlate gene expression with likely cell types present in perilesional dermis of PG (DPPG) (Heng TSP et al, 2008).

5,762 genes were significantly differentially expressed in DPPG compared to HC, and 5,235 genes were differentially expressed in DPPG compared to dermis of non-lesional PG (DNPG) (FC >2, FDR p<0.05) (**Figure 1a**). Perilesional epidermis also had significantly differentially expressed genes, most of which were downregulated. DNPG and epidermis of non-lesional PG (ENPG) had few differentially expressed genes. Our pathway analysis revealed that differentially expressed genes in DPPG compared to dermis of HC were associated with signaling of neutrophil degranulation, cytokine-cytokine receptor interactions, the expression of complement cascade, and cell adhesion pathways. Pathway analysis comparing DPPG and DNPG revealed signaling within similar pathways**.** Pathways associated with perilesional dermis revealed more clinically meaningful inflammatory pathways than pathways associated with perilesional epidermis, although epidermal gene expression was also associated with interferon (IFN) alpha/beta, cytokine receptors, and adhesion molecule pathways (**Figure 1b and Supplementary Figure S2**). Immgen analysis showed that differentially expressed genes in PG were associated predominantly with myeloid cells; mainly dendritic cells (DC), but also granulocytes (GN), macrophages (MF), and monocytes (Mo) (**Figure 1c**).

This was followed by targeted analyses of an *a priori* list of selected genes previously implicated in PG pathogenesis (**Supplementary Table S1**). **Figure 2a** displays cell types associated with these genes. Targeted analysis of cytokine gene expression revealed that DPPG had a cytokine gene expression signature that distinguished it from dermis of HC, while DNPG did not (**Figure 2b**). Interestingly, the cytokine signature of epidermis of perilesional of PG

(EPPG) and ENPG were not significantly different from epidermis of HC (**Figure 2c**). Based on pathway analysis results, select genes were validated using qPCR (**Figure 2d**) with statistically significant differences for CCL-20 and CXCL-2 (Th17 pathway downstream cytokines).

Based on the results of our study, we corroborate the role of Th17 inflammatory cytokines in the pathogenesis of PG (Ortega-Loayza AG et al., 2018; Wang EA et al., 2018). The relevance of these cytokines is confirmed by successful treatments with biologics; however, not all patients respond to these medications, which suggests other pathways might be involved. Our analysis also revealed differential expression of Janus kinase (JAK) and IFN signaling genes (e.g., JAK3, STAT4), which is consistent with the described therapeutic effectiveness of JAK inhibitors in PG (Orfaly VE et al., 2021). JAK inhibitors effectively treat inflammatory bowel disease and inflammatory arthritis suggesting that these agents can also target PG-associated diseases.

Formed PG ulcers show nonspecific epidermal and superficial necrosis with mixed inflammatory infiltrate. However, early lesions in PG localize to the dermis with intradermal abscess formation (Weedon D, 2010). Our results show that inflammatory gene expression changes occur primarily in the dermis of PG, supporting this pathogenic model of PG. Thus, identifying the cellular profile within this dermal inflammatory response in patients with PG is of utmost importance; single cell RNA sequencing is the next logical step to deepen our understanding of PG pathogenesis. While PG is a neutrophilic dermatosis, our results reveal a strong association between differentially expressed genes and dendritic cell signatures, suggesting that the interactions of neutrophils and dendritic cells may be key drivers of this disease. Interestingly, biologic therapeutic interventions in PG are also proven to interfere with dendritic cell activation (Chung-Chung C et al., 2011).

Overall, we report herein the following observations: 1) Perilesional dermis of PG shows a cytokine gene expression signature consistent with the disease, while perilesional epidermis shows few inflammatory genes/pathways, and non-lesional skin of PG is similar to HC (**Figure 1**). This finding confirms that most inflammatory events occur within the dermis rather than the epidermis. 2) Our pathway analysis implicates several pathways, including complement cascade and trafficking pathways (integrin, cell adhesion molecules), which suggest alternative therapies for PG. 3) Myeloid cells are the predominant cell type in PG and are responsible for the changes of gene expression in perilesional skin of PG.

Limitations of this study include the small sample size and, thus, the inability to control for variables such as age, sex, associated diseases, medications, or disease duration. Future directions will include comparing neutrophil-rich dermatoses to demonstrate that the differences in gene expression are not solely due to the presence of certain immune cell types in PG.

DATA AVAILABILITY STATEMENT: Datasets related to this article can be found at https://www.ncbi.nlm.nih.gov/sra/PRJNA590986, Pyoderma Gangrenosum Study (PyGaS) hosted at Oregon Health and Science University

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ORCiD:

Alex G Ortega-Loayza (0000-0001-5028-9269)

Marcia A Friedman (0000-0001-6722-2159)

Ashley M Reese (0000-0003-0528-0622)

Yuangang Liu (0000-0002-4179-6629)

Teri M Greiling (0000-0002-0028-8986)

Pamela B Cassidy (0000-002-4310-9554)

Angelo V Marzano (0000-0002-8160-4169)

Lina Gao (0000-0001-9382-0419)

Suzanne S Fei (0000-0002-9688-2890)

James T Rosenbaum (0000-0002-8452-2441)

AUTHOR CONTRIBUTIONS: Conceptualization: AGOL and JTR. Methodology: AGOL, MAF, JTR. Investigation: AGOL and MAF. Formal analysis: AGOL, MAF, LG, SF. Data curation: AGOL, MAF, TMG, AVM, JTR. Funding acquisition: AGOL. Writing: AGOL, MAF, TMG, PBC, AVM, JTR, AMR, YL. Supervision: JTR.

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FIGURE LEGENDS

Figure 1: Pathway analysis and cell types associated with differentially expressed genes in the DPPG and EPPG versus HC.

Figure 1a: Number of differentially expressed transcripts with a fold change > 2 and false discovery rate p<0.05. *Comparisons were selected for pathway analysis. **Figure 1b:** Inflammatory pathways associated with differentially expressed genes in perilesional dermis and epidermis compared to healthy dermis and healthy epidermis. Note the increased number of immune pathways found in the perilesional dermis in comparison to the perilesional epidermis suggesting most of the inflammatory events occur in the dermis. **Figure 1c:** Cell types associated with differentially upregulated genes (FC >2, FDR p <0.05) in the perilesional dermis and epidermis of PG compared to HC (Heng TSP et al., 2008); myeloid cells are the most commonly represented (dendritic cells, granulocytes, macrophages, and monocytes). (PG= pyoderma gangrenosum, EPPG= epidermis perilesional pyoderma gangrenosum, ENPG= epidermis non-lesional pyoderma gangrenosum, DPPG=dermis perilesional pyoderma gangrenosum, DNPG=dermis non-lesional pyoderma gangrenosum, HC= healthy controls, DC= dendritic cell, GN= granulocyte, MF=macrophage, Mo=monocyte).

Figure 2: Cytokine gene expression comparison of DPPG and EPPG versus HC using 55 *a priori* selected genes.

Figure 2a: This table shows the cell types associated with *a priori* selected genes implicated in the pathogenesis of PG (GeneCards). **Figure 2b:** Heatmap of selected cytokine, chemokine, and cytokine signaling genes in the perilesional dermis of eight patients with PG. Overexpressed transcripts include genes implicated in Th17 induction/regulation (IL2RA, IL2RB, C5AR1,

CXCL8, CSF3, CD40LG), differentiation (IL1B, IL6, IL23A) and biological effects (JAK, STAT, TYK2, IFN, TNF, IL17RA, IL36G, MMPs). Non-lesional dermis of PG and dermis of HC are indistinguishable. **Figure 2c:** Heatmap of selected cytokine, chemokine, and cytokine signaling in the perilesional and non-lesional epidermis of four patients with PG compared to epidermis of HC. Gene expression Z-scores were calculated using the overall mean and standard deviation of each gene. Expression values used were normalized expression values on the log2 scale with batch effect removed. **Figure 2d:** RT-PCR validation of the main chemokine genes found in the RNA-Seq analyses. These graphs show statistically significant overexpression of CCL-20 and CXCL-2 in perilesional dermis of PG in comparison to non-lesional dermis of PG and healthy controls by one-way analysis of variance (ANOVA). (PG= pyoderma gangrenosum, EPPG= epidermis perilesional pyoderma gangrenosum, ENPG= epidermis non-lesional pyoderma gangrenosum, DPPG=dermis perilesional pyoderma gangrenosum, DNPG= dermis non-lesional pyoderma gangrenosum, HC= dermis of healthy controls (Figure 1b) or epidermis of healthy controls (Figure 1c- 3 subjects); four subjects per group except where noted).