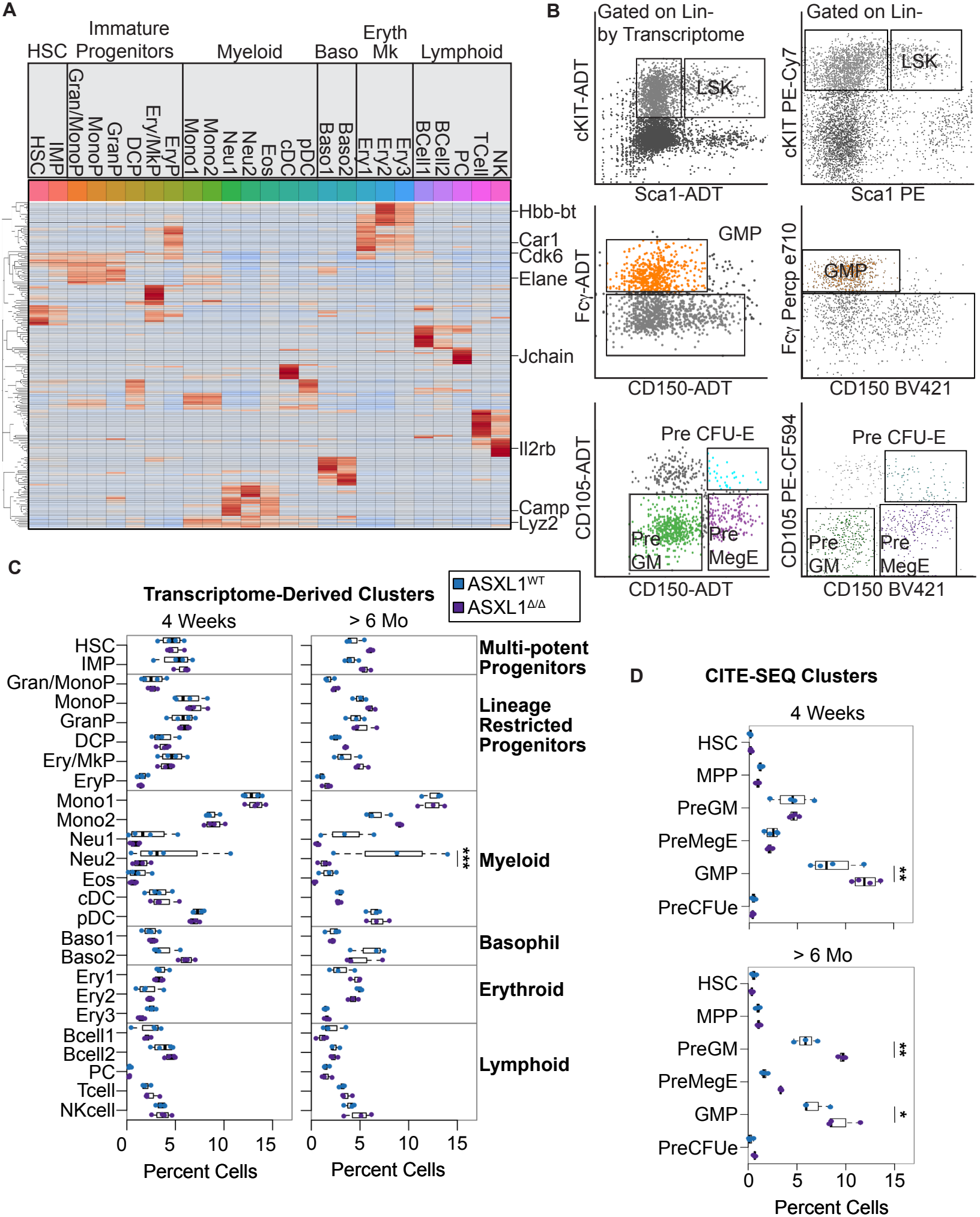

A
HSC
Immature Progenitors
Myeloid
Eryth
Baso
Mk
Lymphoid
HSC
IMP
Gran/MonoP
MonoP
GranP
DCP
Ery/MkP
EryP
Mono1
Mono2
Neu1
Neu2
Eos
cDC
pDC
Baso1
Baso2
Ery1
Ery2
Ery3
BCell1
BCell2
PC
TCell
NK
Hbb-bt
Car1
Cdk6
Elane
Jchain
Il2rb
Camp
Lyz2
B
Gated on Lin- by Transcriptome
cKIT-ADT
Sca1-ADT
LSK
Gated on Lin-
cKIT PE-Cy7
Sca1 PE
LSK
Fcγ-ADT
CD150-ADT
GMP
Fcγ Percp e710
CD150 BV421
GMP
CD105-ADT
CD150-ADT
Pre CFU-E
Pre GM
Pre MegE
CD105 PE-CF594
CD150 BV421
Pre CFU-E
Pre GM
Pre MegE
C
Transcriptome-Derived Clusters
ASXL1WT
ASXL1Δ/Δ
4 Weeks
> 6 Mo
HSC
IMP
Gran/MonoP
MonoP
GranP
DCP
Ery/MkP
EryP
Mono1
Mono2
Neu1
Neu2
Eos
cDC
pDC
Baso1
Baso2
Ery1
Ery2
Ery3
Bcell1
Bcell2
PC
Tcell
NKcell
***
Multi-potent Progenitors
Lineage Restricted Progenitors
Myeloid
Basophil
Erythroid
Lymphoid
0
5
10
15
Percent Cells
Percent Cells
D
CITE-SEQ Clusters
4 Weeks
HSC
MPP
PreGM
PreMegE
GMP
PreCFUe
**
> 6 Mo
HSC
MPP
PreGM
PreMegE
GMP
PreCFUe
**
*
0
5
10
15
Percent Cells

Figure S1

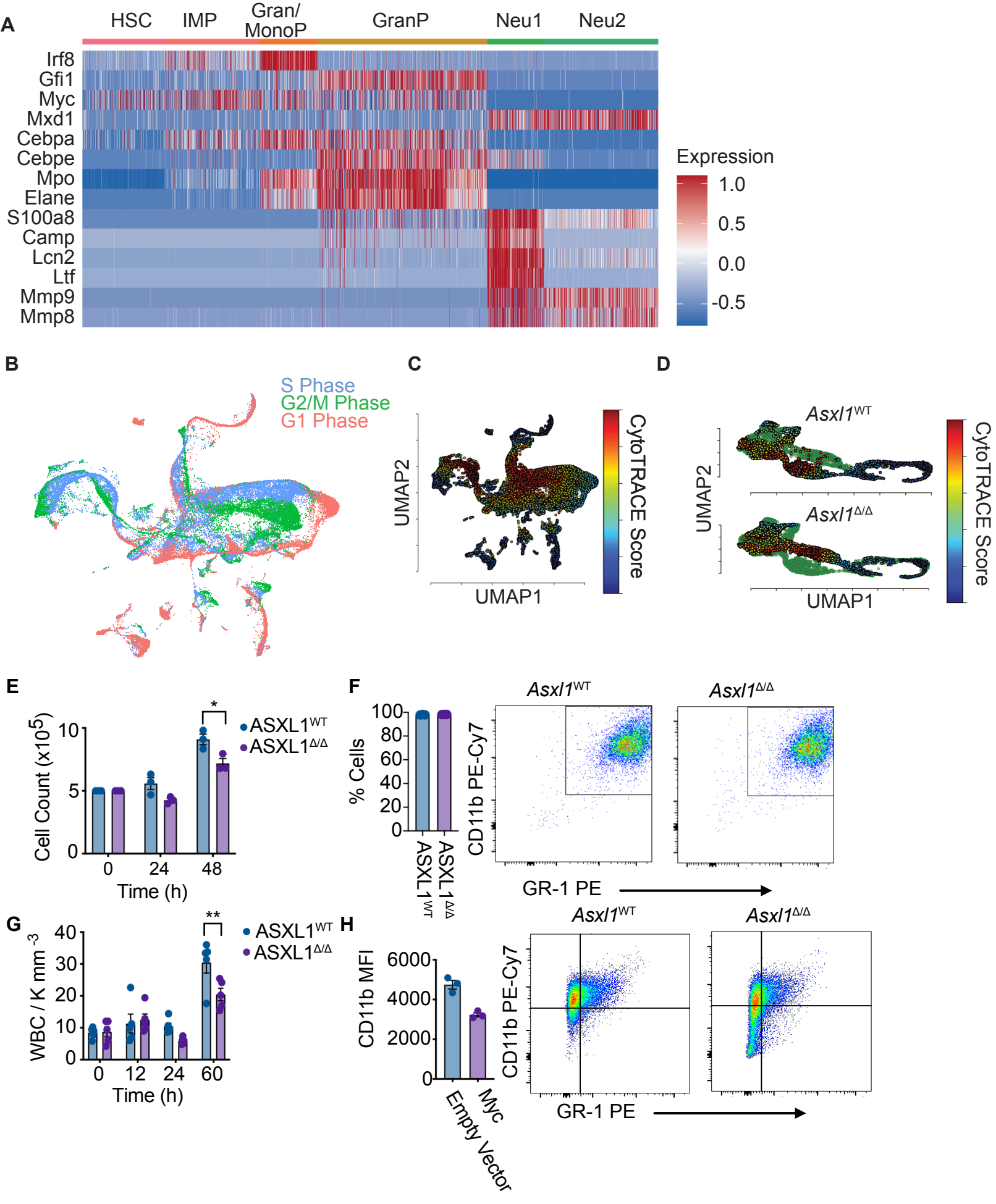
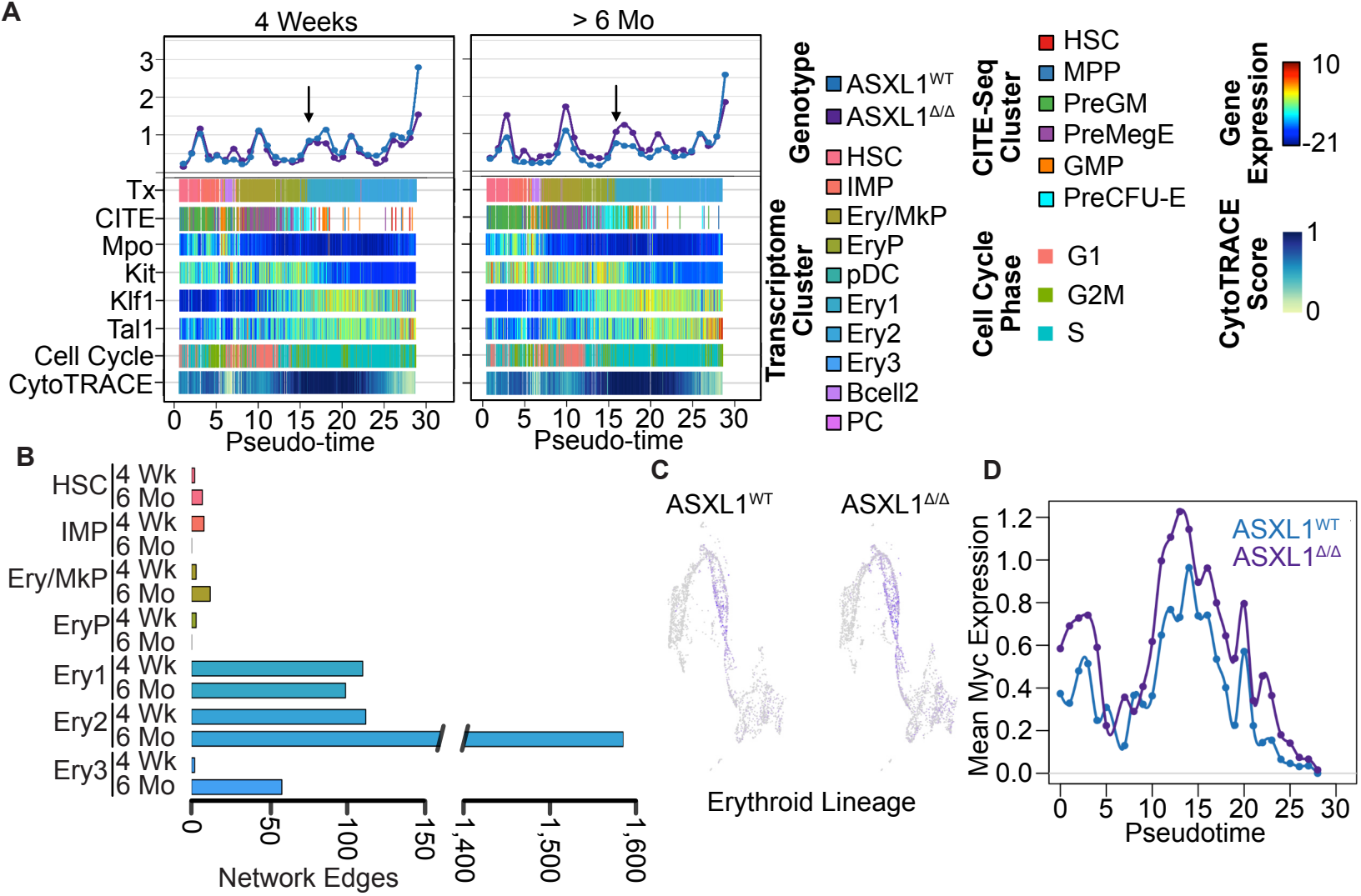

A
HSC
IMP
Gran/
MonoP
GranP
Neu1
Neu2
Irf8
Gfi1
Myc
Mxd1
Cebpa
Cebpe
Mpo
Elane
S100a8
Camp
Lcn2
Ltf
Mmp9
Mmp8
Expression
1.0
0.5
0.0
-0.5
B
S Phase
G2/M Phase
G1 Phase
C
UMAP2
UMAP1
CytoTRACE Score
D
Asxl1WT
Asxl1Δ/Δ
UMAP2
UMAP1
CytoTRACE Score
E
Cell Count (x10^5)
ASXL1WT
ASXL1Δ/Δ
Time (h)
F
% Cells
ASXL1WT
ASXL1Δ/Δ
Asxl1WT
Asxl1Δ/Δ
CD11b PE-Cy7
GR-1 PE
G
WBC / K mm-3
ASXL1WT
ASXL1Δ/Δ
Time (h)
H
CD11b MFI
Empty Vector
Myc
Asxl1WT
Asxl1Δ/Δ
CD11b PE-Cy7
GR-1 PE

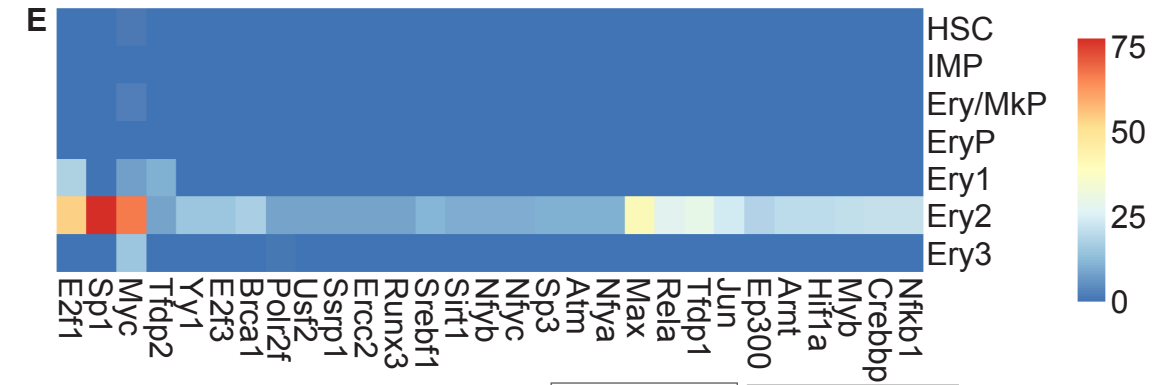
Figure S2


A
4 Weeks
> 6 Mo
Tx
CITE
Mpo
Kit
Klf1
Tal1
Cell Cycle
CytoTRACE
Pseudo-time
Genotype
ASXL1WT
ASXL1Δ/Δ
Transcriptome Cluster
HSC
IMP
Ery/MkP
EryP
pDC
Ery1
Ery2
Ery3
Bcell2
PC
CITE-Seq Cluster
HSC
MPP
PreGM
PreMegE
GMP
PreCFU-E
Cell Cycle Phase
G1
G2M
S
Gene Expression
CytoTRACE Score

B
HSC
IMP
Ery/MkP
EryP
Ery1
Ery2
Ery3
4 Wk
6 Mo
Network Edges

C
ASXL1WT
ASXL1Δ/Δ
Erythroid Lineage

D
Mean Myc Expression
ASXL1WT
ASXL1Δ/Δ
Pseudotime


E
HSC
IMP
Ery/MkP
EryP
Ery1
Ery2
Ery3
E2f1
Sp1
Myc
Tfdp2
Yy1
E2f3
Brca1
Polr2f
Usf2
Ssrp1
Ercc2
Runx3
Srebf1
Sirt1
Nfyb
Nfyc
Sp3
Atm
Nfya
Max
Rela
Tfdp1
Jun
Ep300
Arnt
Hif1a
Myb
Crebbp
Nfkb1

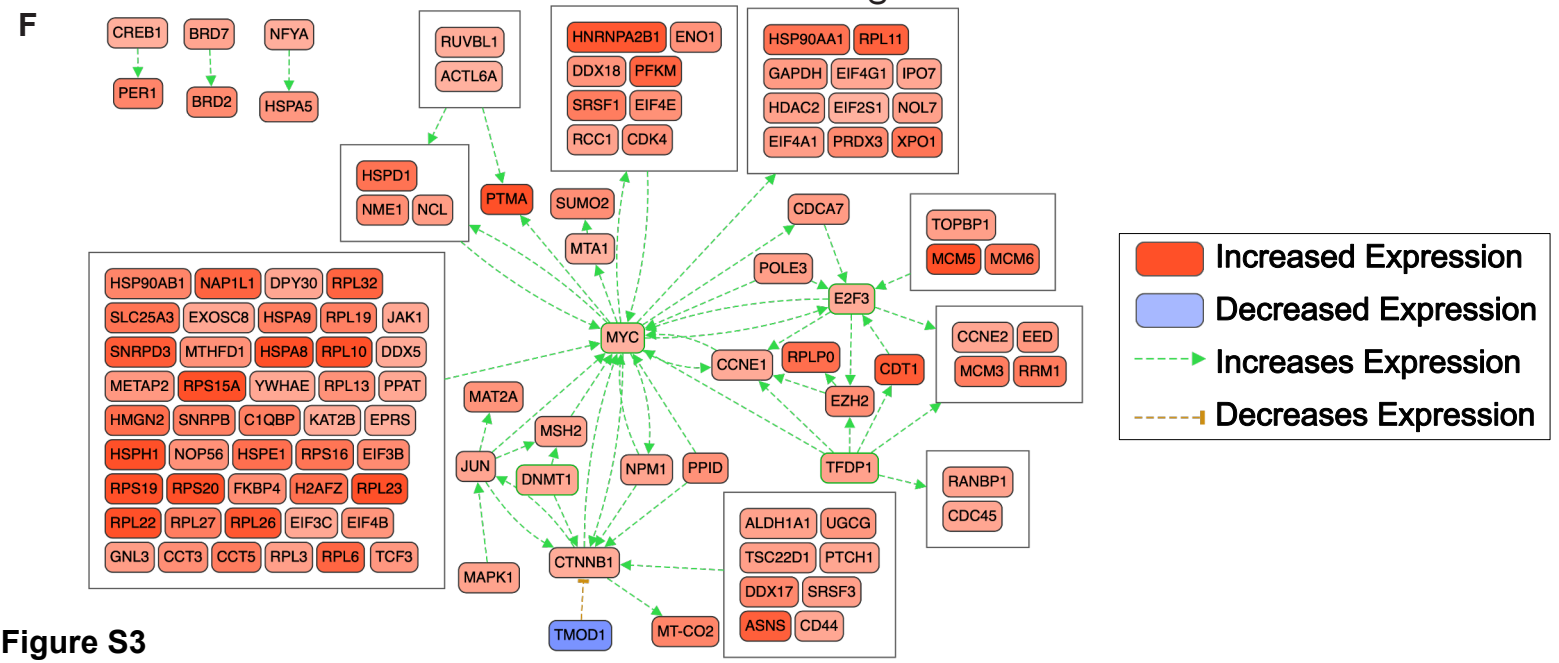

F
CREB1
BRD7
NFYA
PER1
BRD2
HSPA5
RUVBL1
ACTL6A
HNRNPA2B1
ENO1
DDX18
PFKM
SRSF1
EIF4E
RCC1
CDK4
HSP90AA1
RPL11
GAPDH
EIF4G1
IPO7
HDAC2
EIF2S1
NOL7
EIF4A1
PRDX3
XPO1
HSPD1
NME1
NCL
PTMA
SUMO2
MTA1
CDCA7
TOPBP1
MCM5
MCM6
POLE3
E2F3
MYC
CCNE1
RPLP0
CDT1
CCNE2
EED
MCM3
RRM1
EZH2
MAT2A
MSH2
JUN
DNMT1
NPM1
PPID
TFDP1
RANBP1
CDC45
ALDH1A1
UGCG
TSC22D1
PTCH1
DDX17
SRSF3
ASNS
CD44
CTNNB1
MAPK1
TMOD1
MT-CO2
HSP90AB1
NAP1L1
DPY30
RPL32
SLC25A3
EXOSC8
HSPA9
RPL19
JAK1
SNRPD3
MTHFD1
HSPA8
RPL10
DDX5
METAP2
RPS15A
YWHAE
RPL13
PPAT
HMGN2
SNRPB
C1QBP
KAT2B
EPRS
HSPH1
NOP56
HSPE1
RPS16
EIF3B
RPS19
RPS20
FKBP4
H2AFZ
RPL23
RPL22
RPL27
RPL26
EIF3C
EIF4B
GNL3
CCT3
CCT5
RPL3
RPL6
TCF3
Increased Expression
Decreased Expression
Increases Expression
Decreases Expression

Figure S3

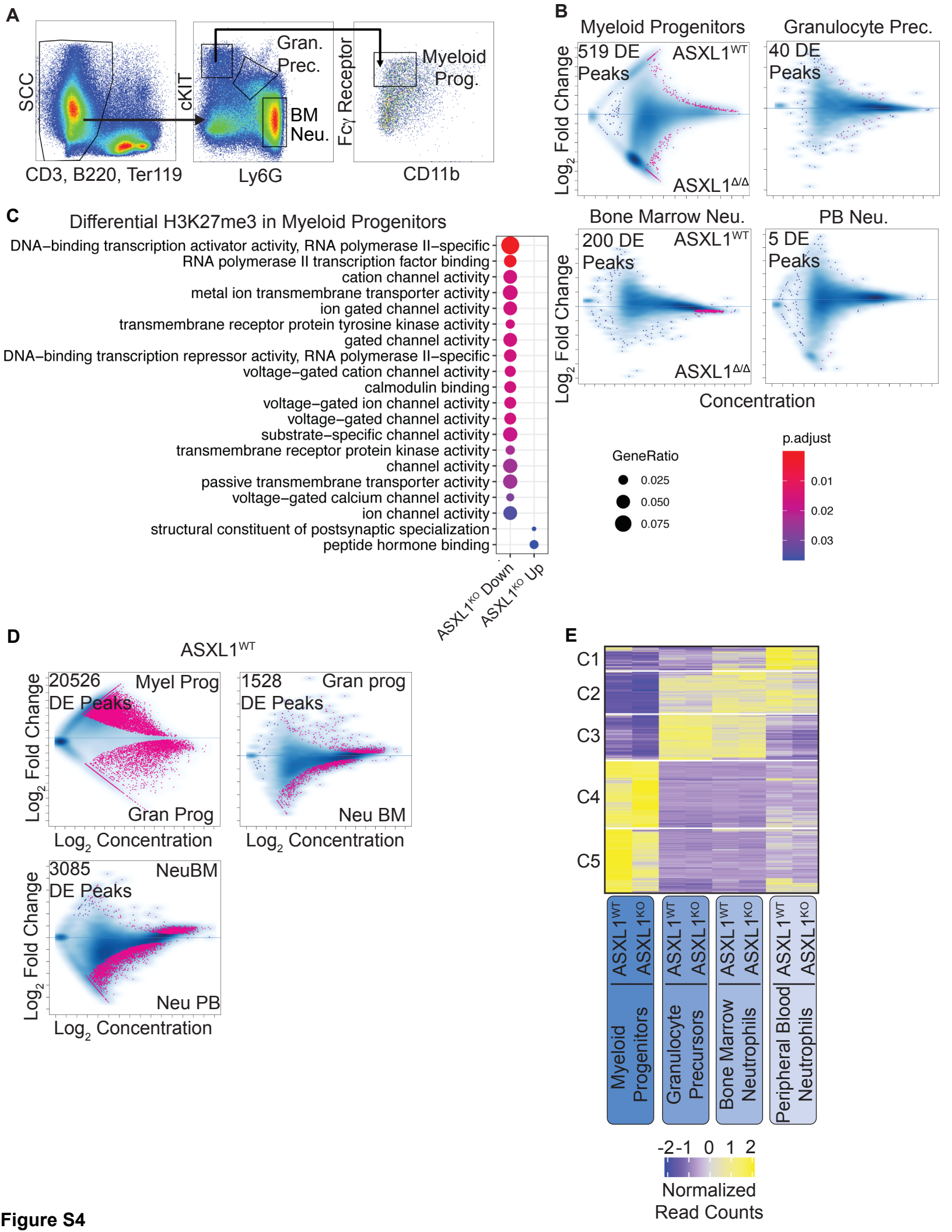

A
SCC
CD3, B220, Ter119
cKIT
Gran.
Prec.
BM
Neu.
Ly6G
Fcγ Receptor
Myeloid
Prog.
CD11b
B
Myeloid Progenitors
519 DE
Peaks
ASXL1WT
ASXL1Δ/Δ
Granulocyte Prec.
40 DE
Peaks
Bone Marrow Neu.
200 DE
Peaks
ASXL1WT
ASXL1Δ/Δ
PB Neu.
5 DE
Peaks
Log2 Fold Change
Concentration
C
Differential H3K27me3 in Myeloid Progenitors
DNA−binding transcription activator activity, RNA polymerase II−specific
RNA polymerase II transcription factor binding
cation channel activity
metal ion transmembrane transporter activity
ion gated channel activity
transmembrane receptor protein tyrosine kinase activity
gated channel activity
DNA−binding transcription repressor activity, RNA polymerase II−specific
voltage−gated cation channel activity
calmodulin binding
voltage−gated ion channel activity
voltage−gated channel activity
substrate−specific channel activity
transmembrane receptor protein kinase activity
channel activity
passive transmembrane transporter activity
voltage−gated calcium channel activity
ion channel activity
structural constituent of postsynaptic specialization
peptide hormone binding
ASXL1KO Down
ASXL1KO Up
GeneRatio
0.025
0.050
0.075
p.adjust
0.01
0.02
0.03
D
ASXL1WT
20526
DE Peaks
Myel Prog
Gran Prog
1528
DE Peaks
Gran prog
Neu BM
3085
DE Peaks
NeuBM
Neu PB
Log2 Fold Change
Log2 Concentration
E
C1
C2
C3
C4
C5
ASXL1WT
ASXL1KO
Myeloid Progenitors
Granulocyte Precursors
Bone Marrow Neutrophils
Peripheral Blood Neutrophils
-2 -1 0 1 2
Normalized Read Counts

Figure S4

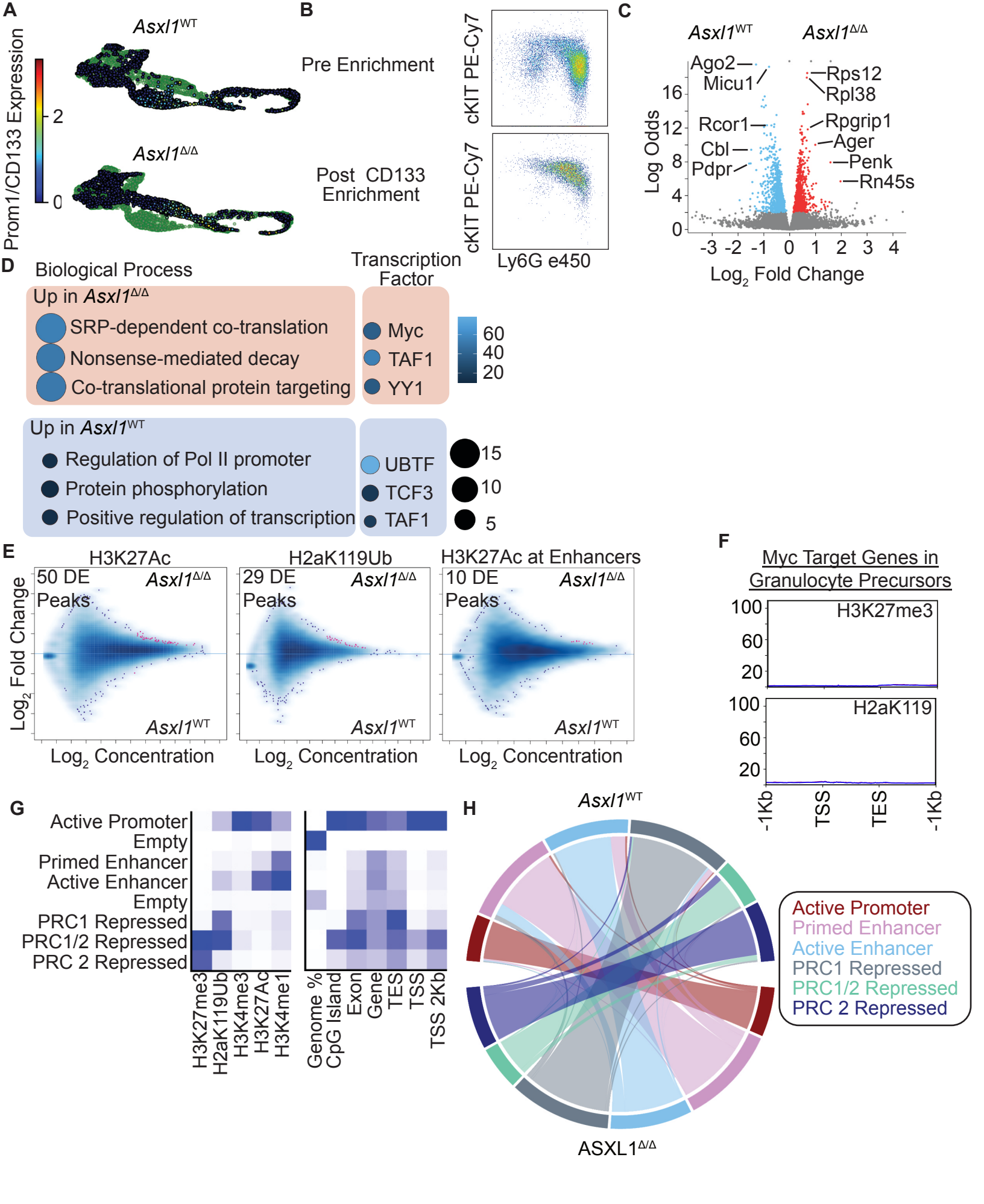

A
Asxl1WT
Asxl1Δ/Δ
Prom1/CD133 Expression
2
0
B
Pre Enrichment
Post CD133 Enrichment
cKIT PE-Cy7
Ly6G e450
C
Asxl1WT
Asxl1Δ/Δ
Ago2
Micu1
Rcor1
Cbl
Pdpr
Rps12
Rpl38
Rpgrip1
Ager
Penk
Rn45s
Log Odds
Log2 Fold Change
D
Biological Process
Transcription Factor
Up in Asxl1Δ/Δ
SRP-dependent co-translation
Nonsense-mediated decay
Co-translational protein targeting
Myc
TAF1
YY1
60
40
20
Up in Asxl1WT
Regulation of Pol II promoter
Protein phosphorylation
Positive regulation of transcription
UBTF
TCF3
TAF1
15
10
5
E
H3K27Ac
H2aK119Ub
H3K27Ac at Enhancers
50 DE Peaks
29 DE Peaks
10 DE Peaks
Asxl1Δ/Δ
Asxl1WT
Log2 Fold Change
Log2 Concentration
F
Myc Target Genes in Granulocyte Precursors
H3K27me3
H2aK119
100
60
20
-1Kb
TSS
TES
-1Kb
G
Active Promoter
Empty
Primed Enhancer
Active Enhancer
Empty
PRC1 Repressed
PRC1/2 Repressed
PRC 2 Repressed
H3K27me3
H2aK119Ub
H3K4me3
H3K27Ac
H3K4me1
Genome %
CpG Island
Exon
Gene
TES
TSS
TSS 2Kb
H
Asxl1WT
ASXL1Δ/Δ
Active Promoter
Primed Enhancer
Active Enhancer
PRC1 Repressed
PRC1/2 Repressed
PRC 2 Repressed

Figure S5