CRISPR screens with single-cell transcriptome readout reveal potential mechanisms of response to natural killer cell treatment in multiple myeloma

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COI disclosure

- *No COI to declare*

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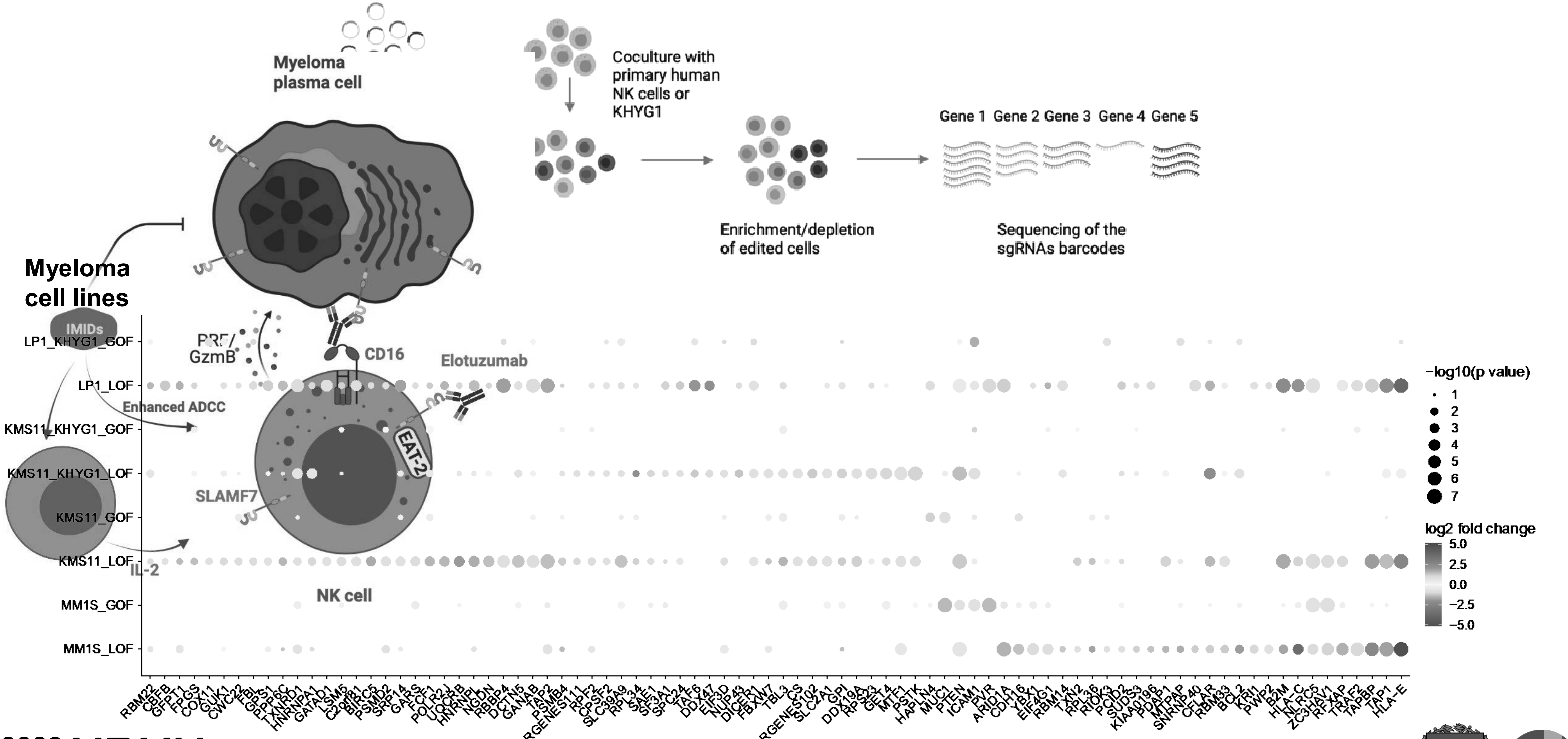
Background



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CRISPR with single cell readout

CRISPR hits

IFNg signaling pathway

JAK1
JAK2
STAT1
IFNGR2
NLRC5
RFXAP

Death receptor/NF-kB signaling

TRAF2
NFKBIA
NFKBIB
TNFRSF10A
CASP8

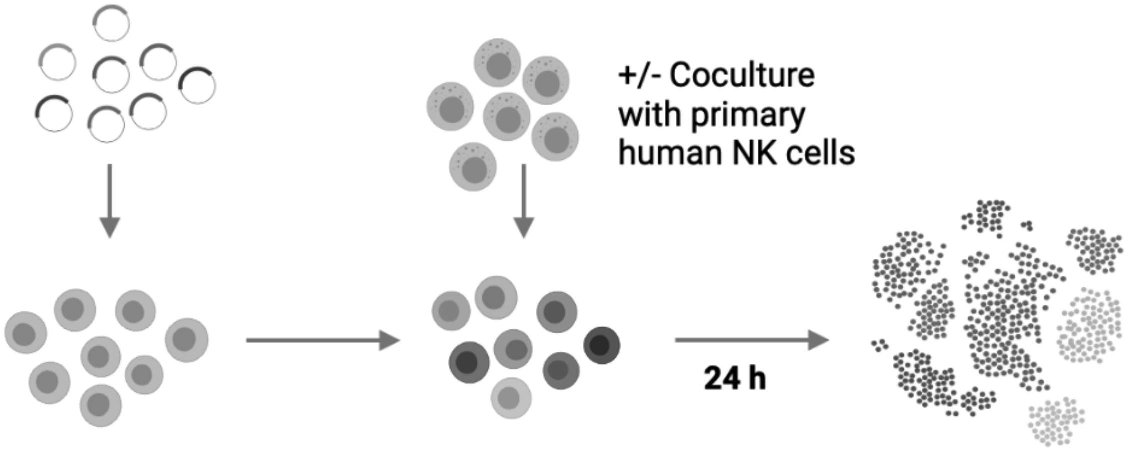
Transcription factors/others

GNA13
PCGF5
AEBP2
ARHGAP1
RNF31
PTEN

+ non-targeting controls

Gandolfi S et al, ASH 2018

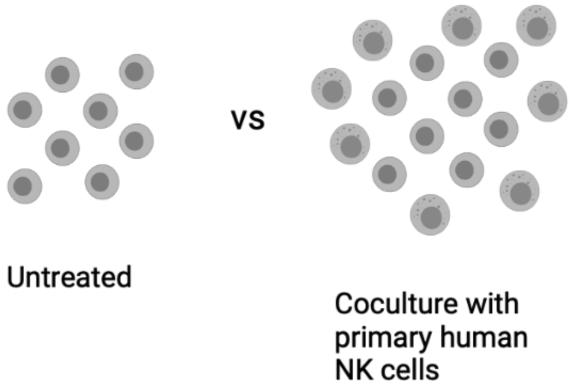
CROPseq



CROPseq - ***Datlinger P et al., Nat Methods 2017***

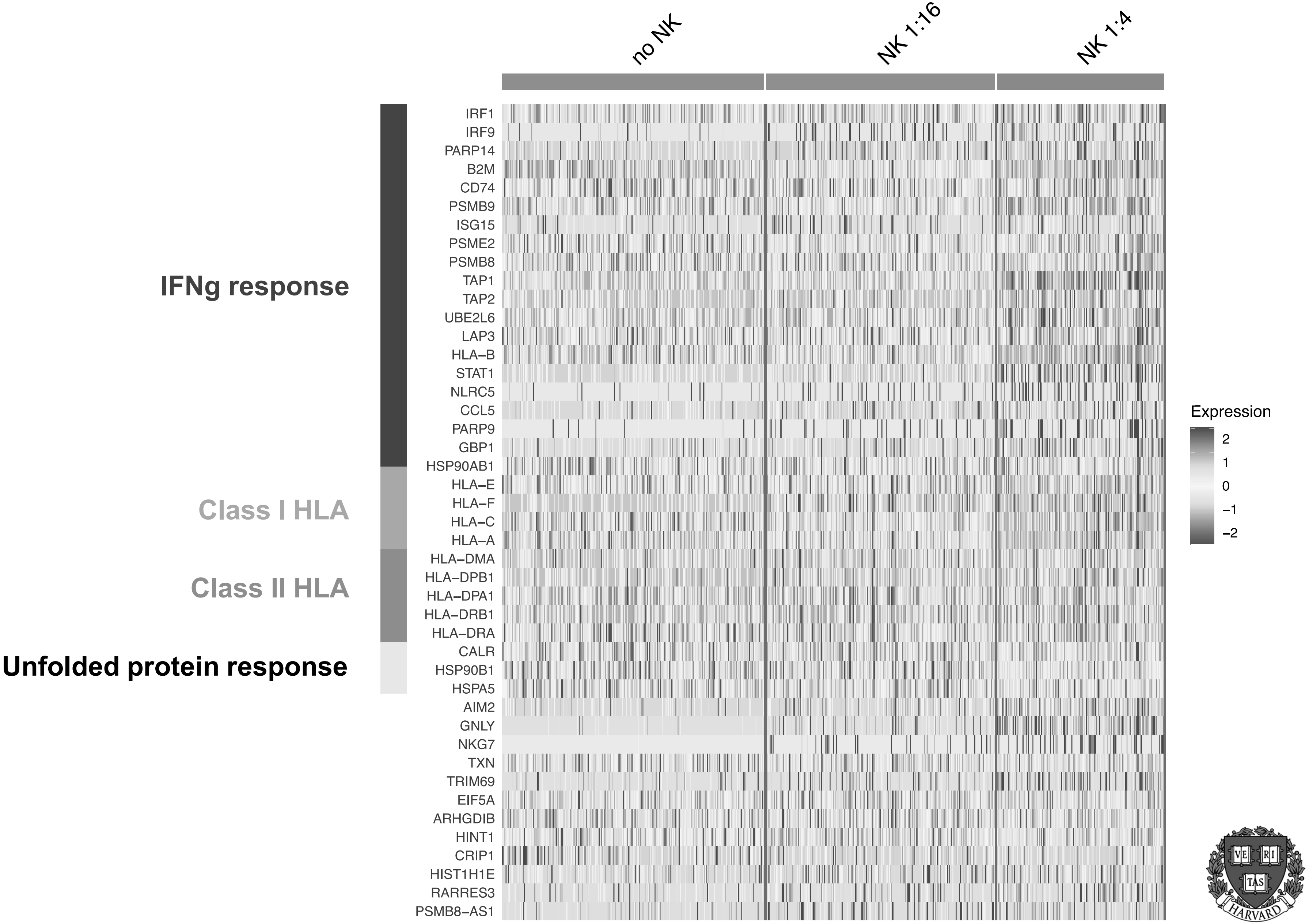
Transcriptional changes upon engagement with NK cells

MM1.S carrying non – targeting guides



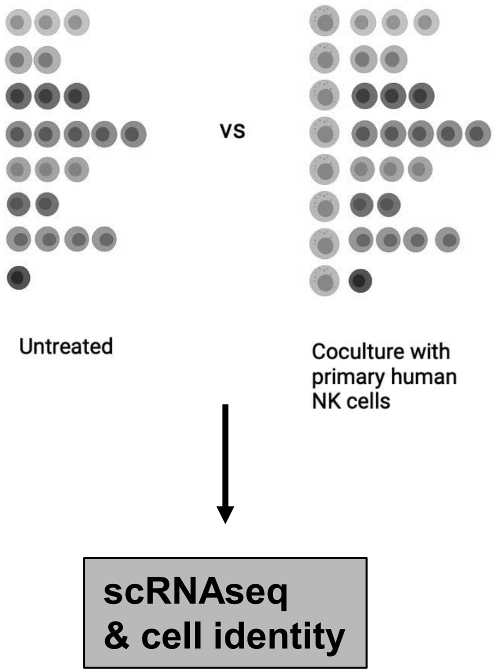
Untreated

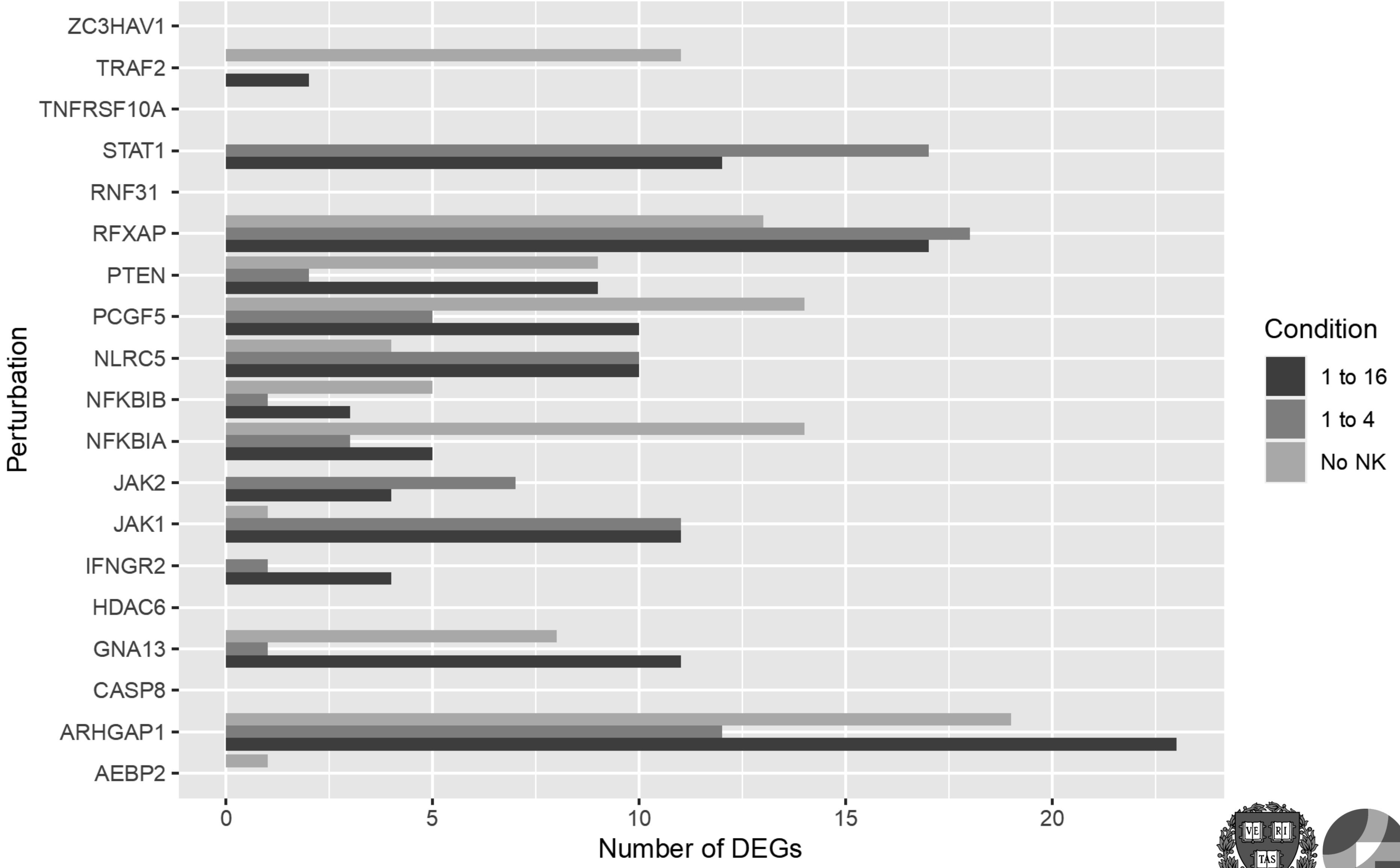
Coculture with primary human NK cells



Not all the perturbations are associated with a transcriptomic phenotype

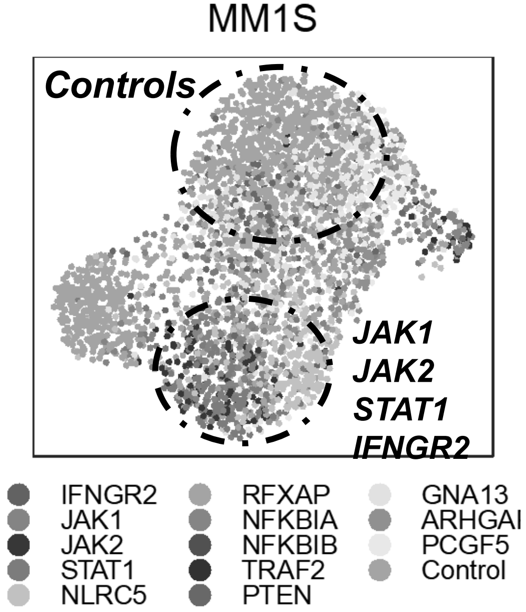
MM1.S with KO guides

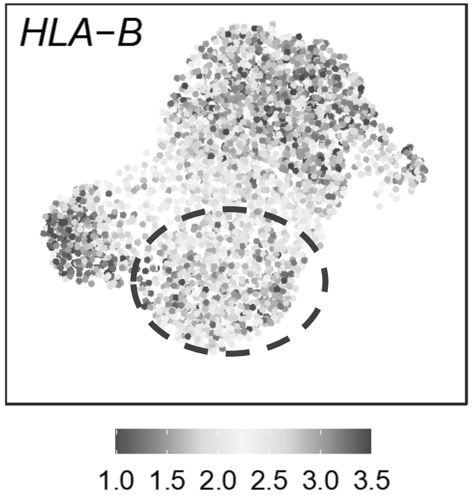


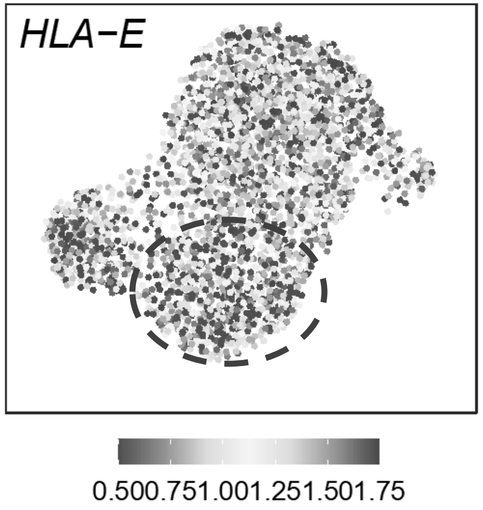


Differentially expressed genes with CRISPR perturbations upon NK cell engagement

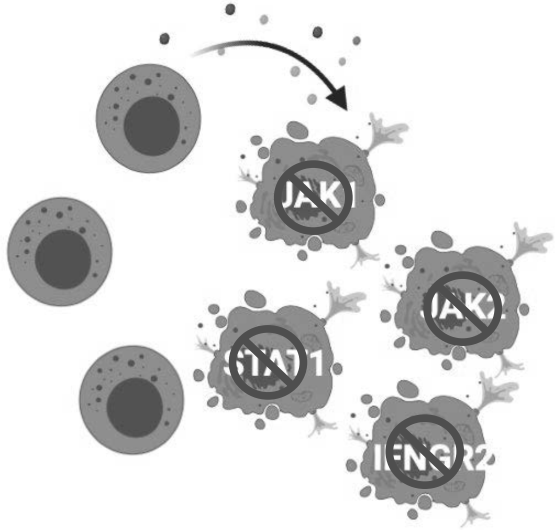
CROPseq

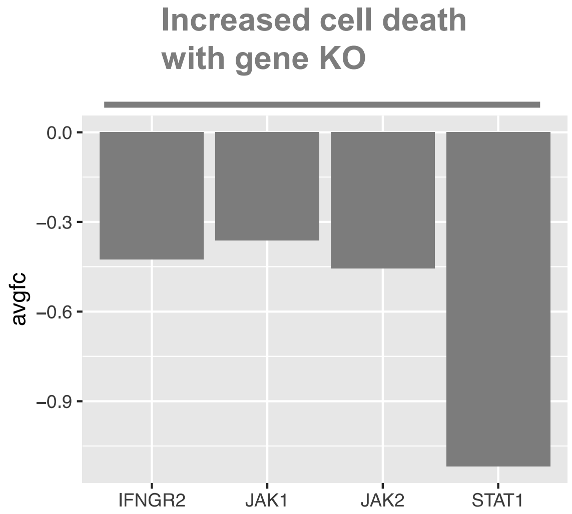






CRISPR





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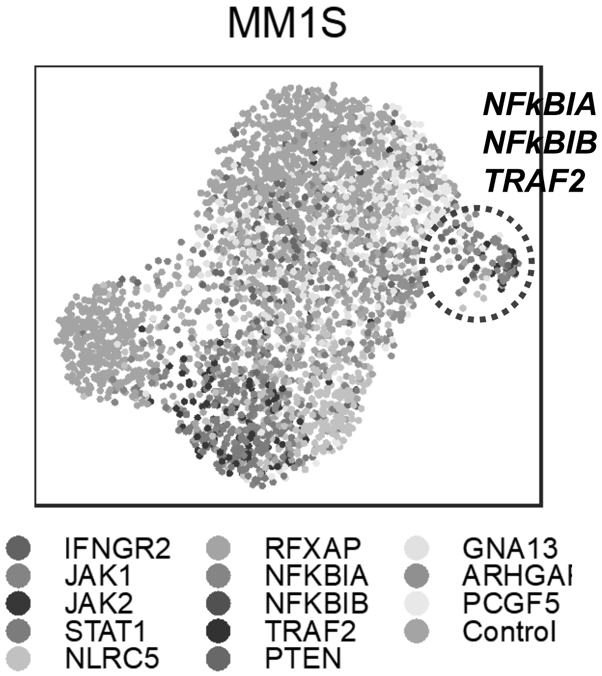
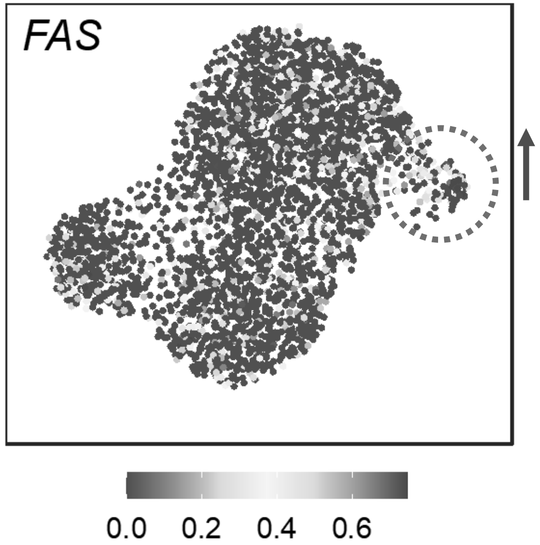
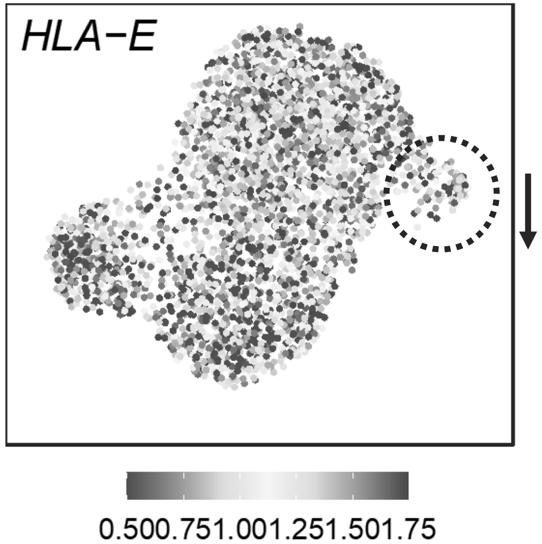
Disruption of negative regulators of NFkB is associated with *HLA-E* downregulation and *FAS* upregulation

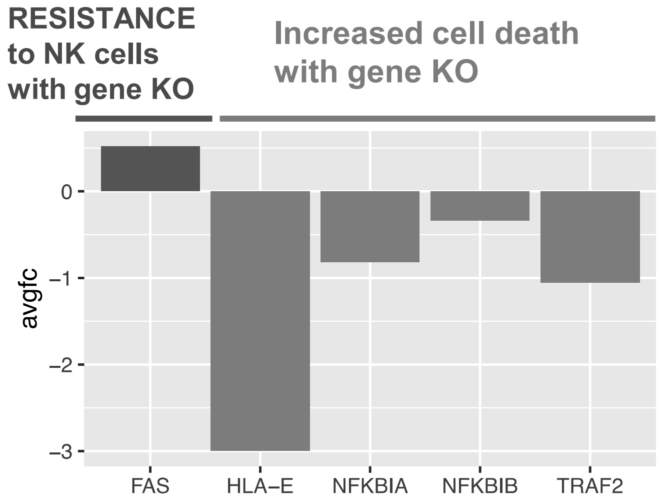


Gene expression levels

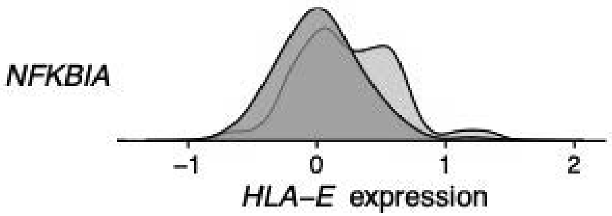




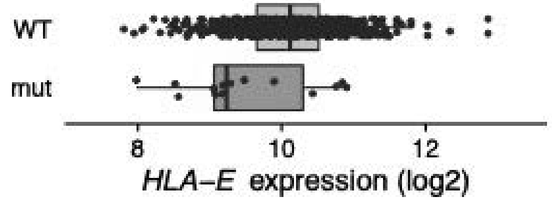
Concordance with CRISPR LOF data



CROPseq



CoMMpass



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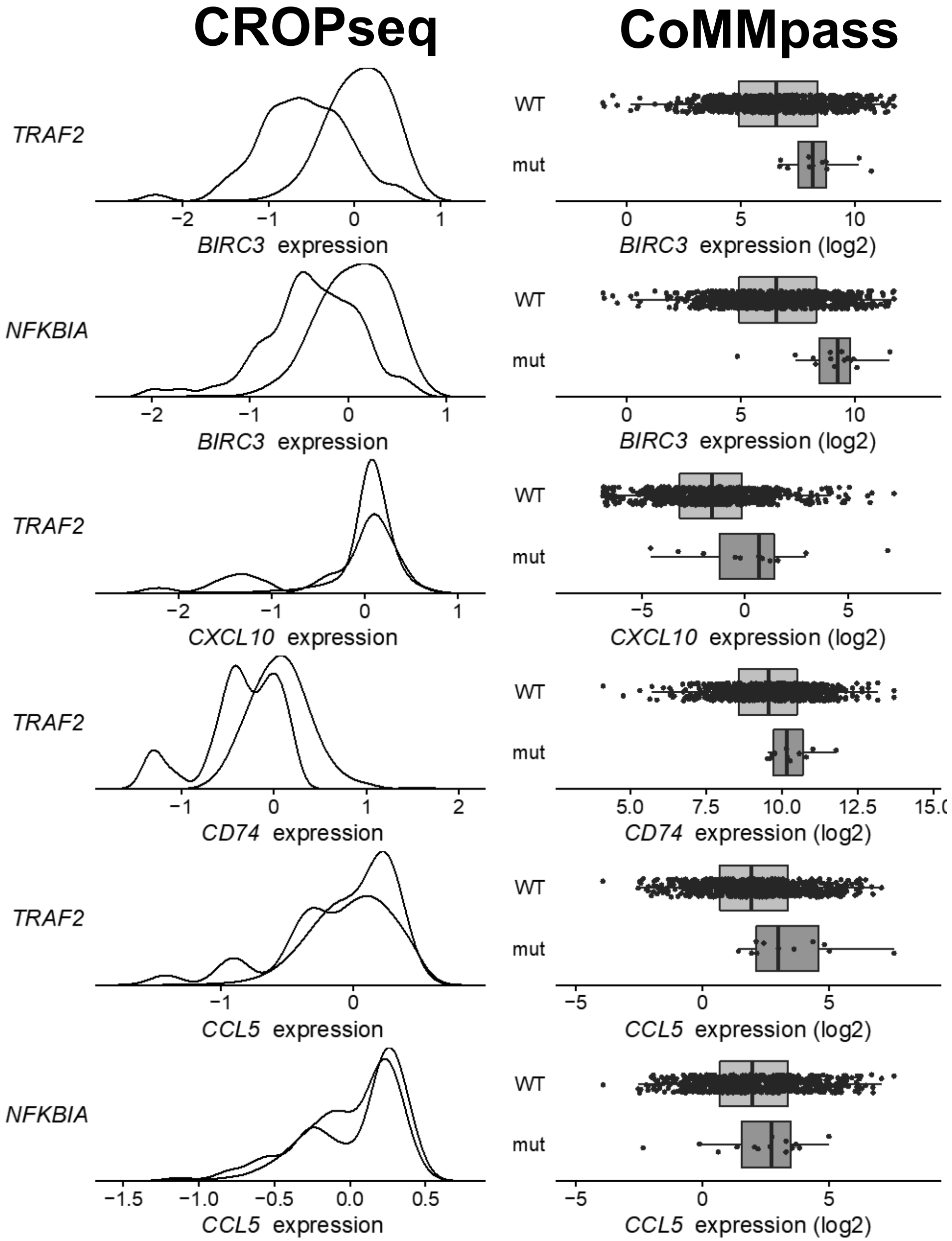
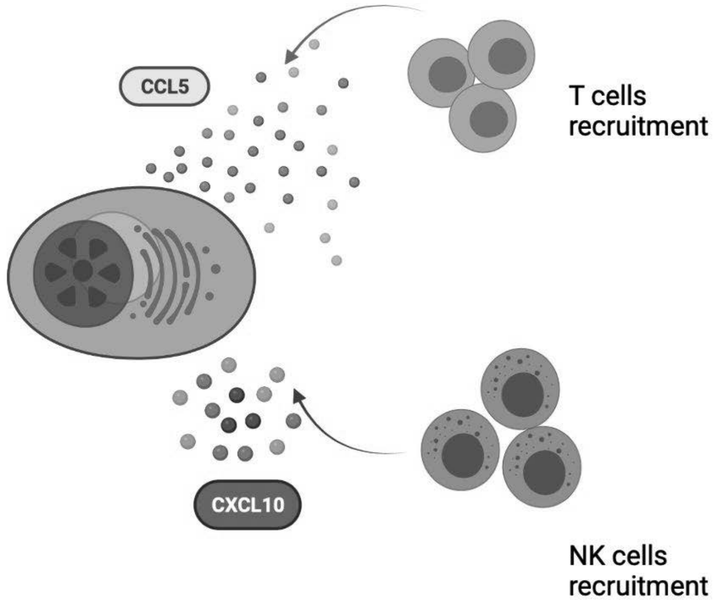
Disruption of *NFkB* negative regulators increases NFkB signature in MM patients


CROPseq

CoMMpass



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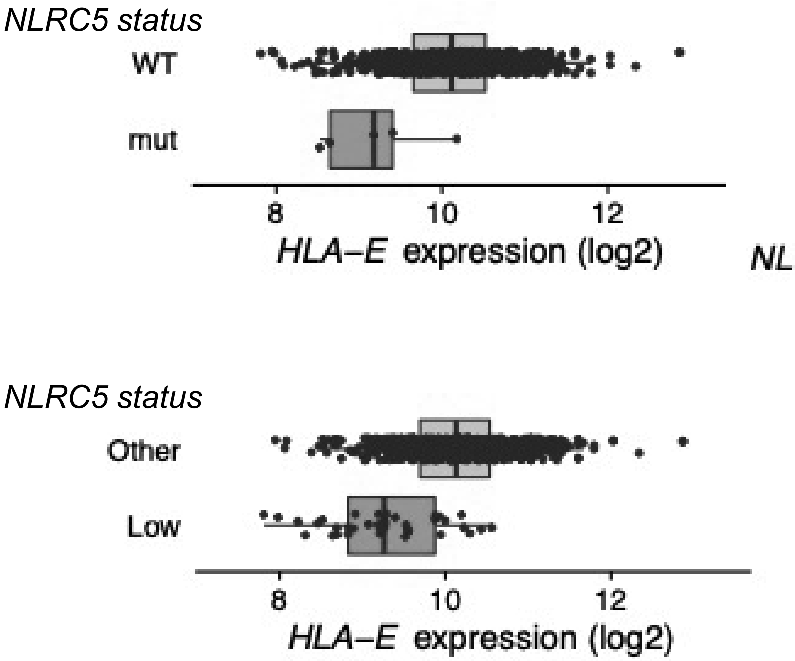
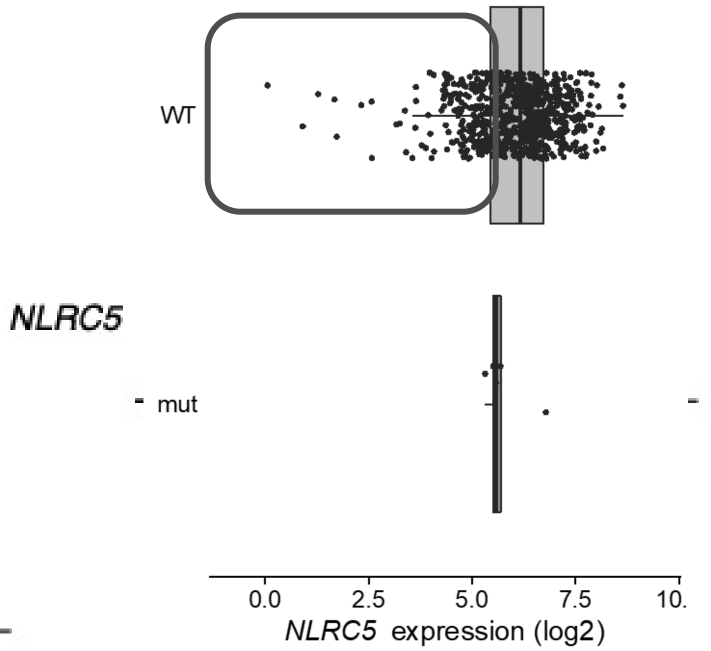
Identification of a potential subset of MM patient with low *NLRC5* expression and a more NK cell sensitive phenotype

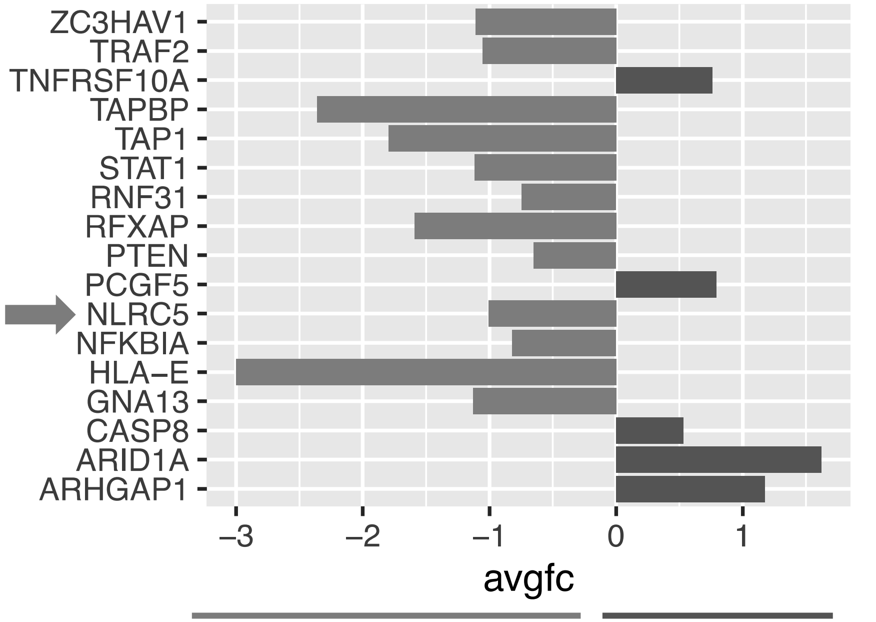
CoMMpass



NLRC5 expression in CoMMpass



CRISPR loss of function



Gene LOF causes increased response to NK cells

Gene LOF causes resistance to NK cells

Conclusions

- Our study sheds light in some of the mechanisms driving NK cell response in MM
- Data from large molecular profiling studies of patient samples are concordant with our *in vitro* observations, supporting their translational relevance
- Studies on NK cell transcriptional changes upon MM cells engagement are underway

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