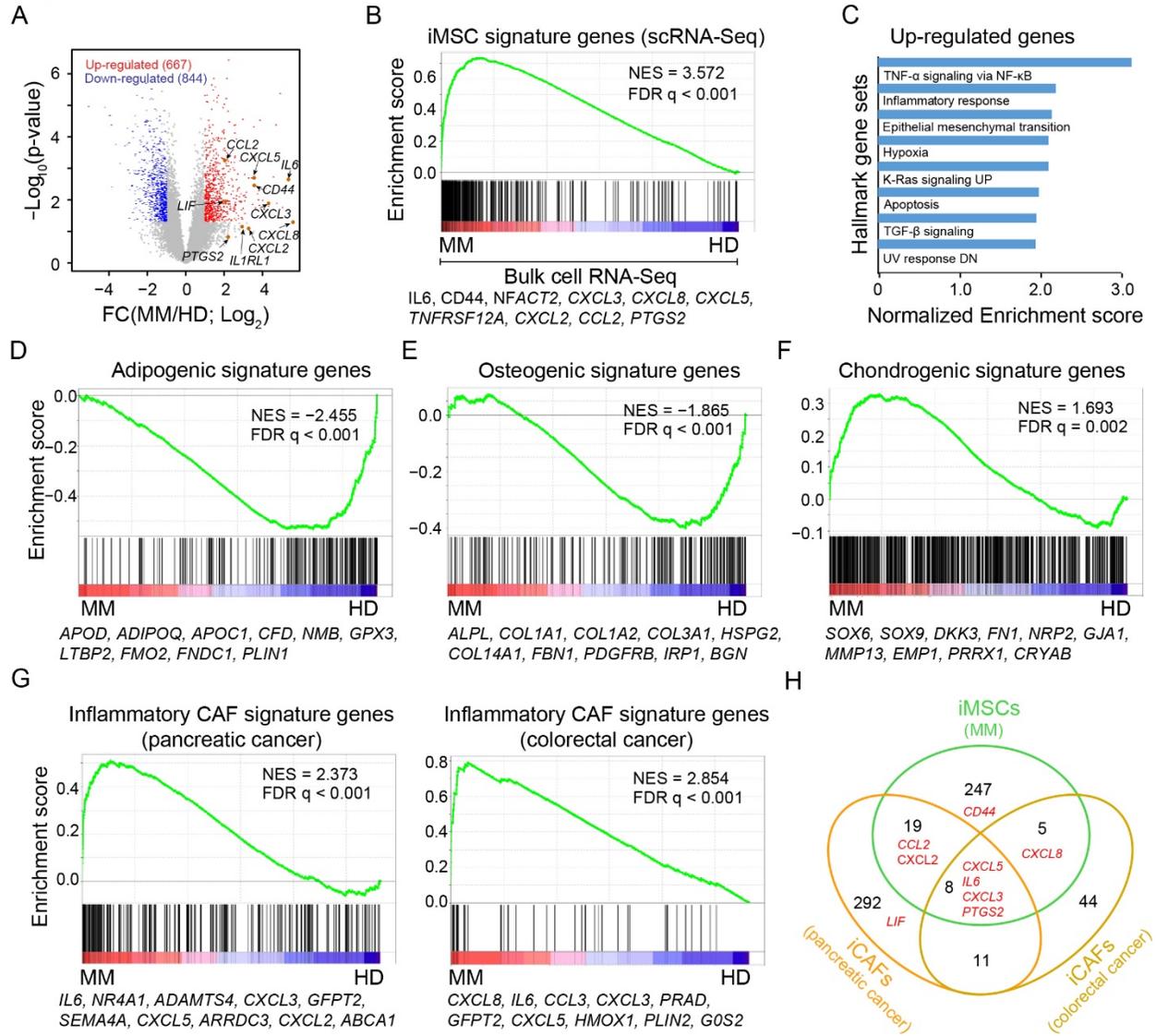


Supplemental Information

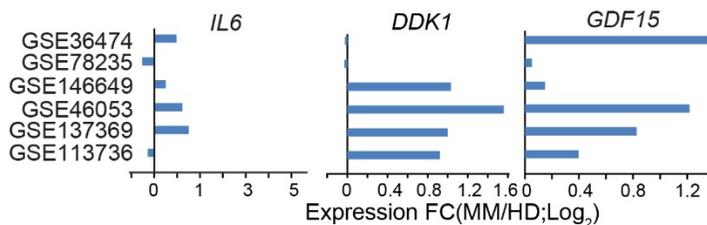
Figure S1



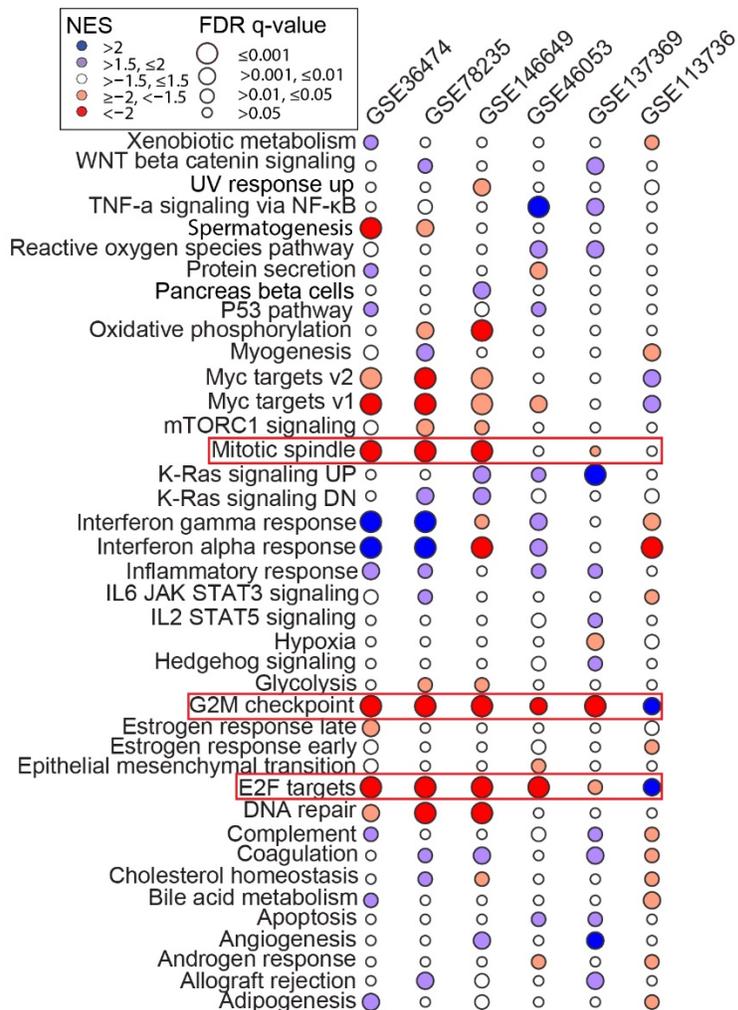
Supplementary Figure S1: Molecular signatures of iMSCs captured by bulk cell RNA-Seq for MM patients. (A) Volcano-plot displaying fold changes of gene expression and p-values from bulk-cell RNA-Seq analysis of BM MSCs to differentiate MM patients (MM) from healthy donors (HD). Red: up-regulated genes in MM. Blue: down-regulated genes. Gray: other expressed genes. Indicated by orange dots and arrow heads are examples of immune-related genes. (B) GSEA of expressed genes sorted by expression changes from high (red in the color spectrum) to low (blue) in BMSCs of MM as relative to HD (calculated from bulk cell RNA-Seq data) against iMSC signature genes defined for MM patients from scRNA-Seq analysis (vertical bars). Highlighted are selected leading genes related to inflammatory response. NES: normalized enrichment score. (C) Top hits of GSEA conducted as in panel B but against MSigDB hallmark gene sets. (D) GSEA like panel B but against adipogenic signature genes. Highlighted are representative leading genes enriched in adipocytes. (E) GSEA like panel B but against osteogenic signature genes. Highlighted are representative leading genes enriched in osteoblasts. (F) GSEA like panel B but against chondrogenic signature genes. Highlighted are representative leading genes enriched in chondrocytes. (G) GSEA like panel B but against iCAF signature genes defined for pancreatic cancer patients (left panel) or colorectal cancer patients (right panel). Highlighted are top ten leading genes. (H) Venn diagram comparing iMSC signature genes defined for MM patients to iCAF signature genes defined for pancreatic cancer patients and colorectal cancer patients. In red are examples of immune-related genes.

Figure S2

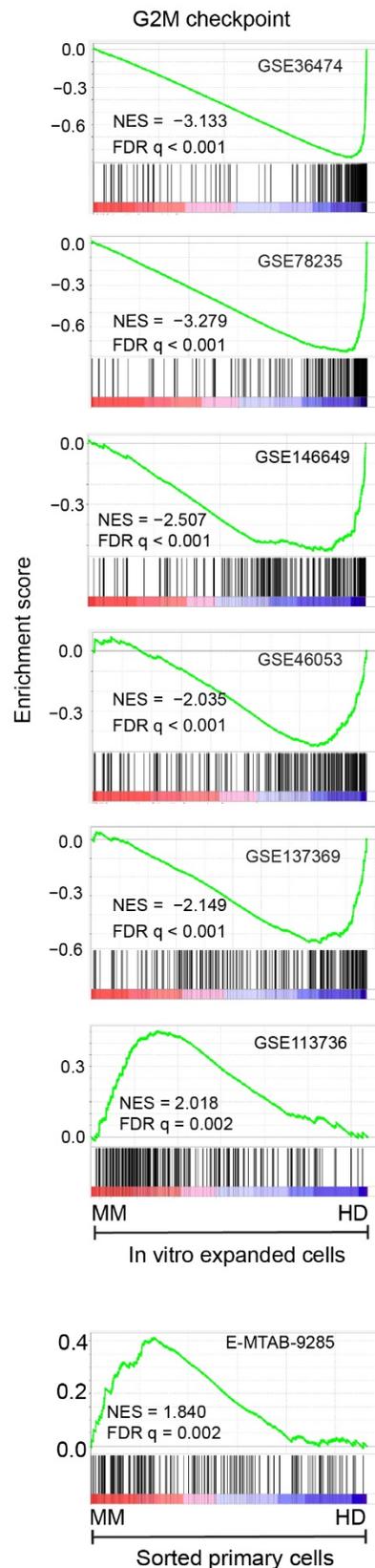
A



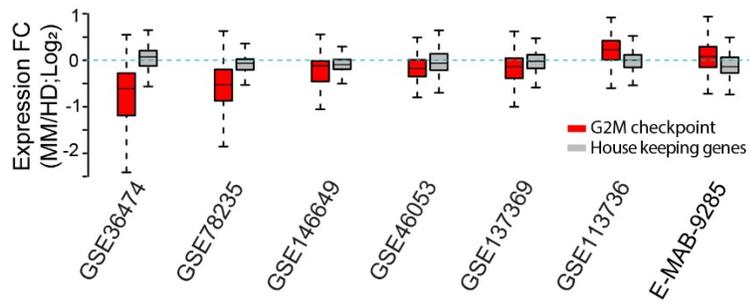
B



C



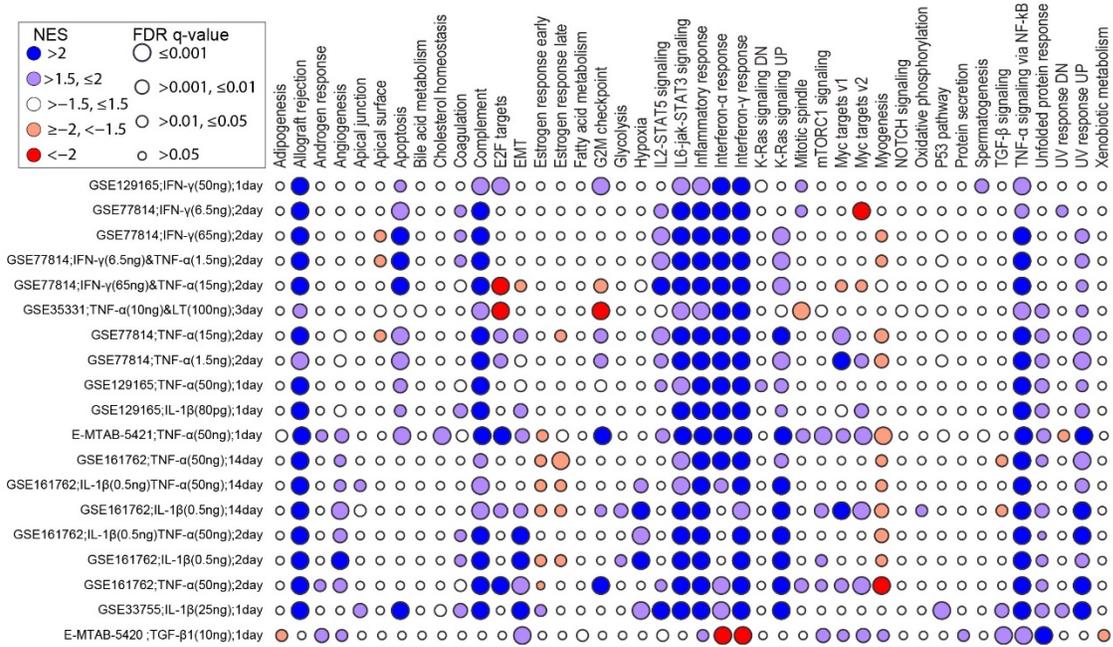
D



Supplementary Figure S2: Down-regulation of proliferation-related pathways in MM MSCs expanded in vitro. (A) Expression fold-change of *IL6*, *DKK1*, and *GDF15* in BM MSCs in vitro expanded from MM patients (MM) as relative to those expanded from healthy donors (HD). Accession number for each study indicated on the left. (B) Bubble plot visualization of results from GSEA of expression changes contrasting MSCs in vitro expanded from MM to HD against MSigDB hallmark gene sets (rows) across different studies (columns). Color indicates an overall upregulation (blue) or downregulation (red) at gene set level. Circle size indicates the significance measured by FDR q-value. In red rectangle are three gene sets linked to cell proliferation. (C) GSEA of expressed genes sorted by expression changes of in vitro expanded MSCs (MM/HD) from high (red) to low (blue) against MSigDB hallmark gene set “G2M checkpoint” (vertical bars). NES: normalized enrichment score. (D) Boxplot visualization of expression fold-change (MM/HD) for genes from gene set “G2M checkpoint” or house-keeping genes across studies (rows).

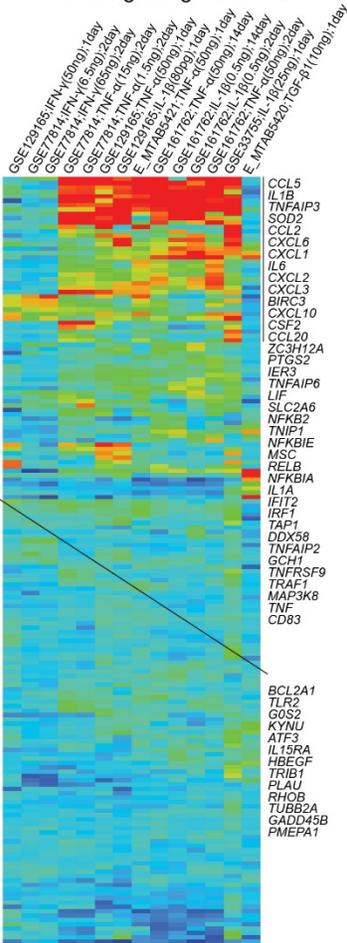
Figure S3

A



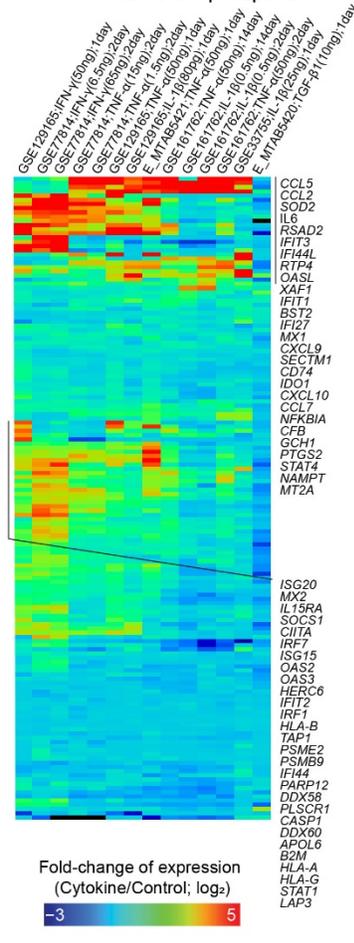
B

TNF-α signaling via NF-κB



C

Interferon-γ response

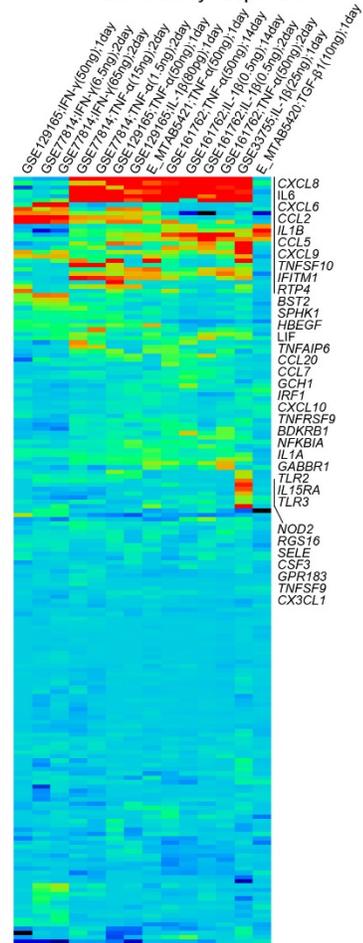


Fold-change of expression
 (Cytokine/Control; log₂)



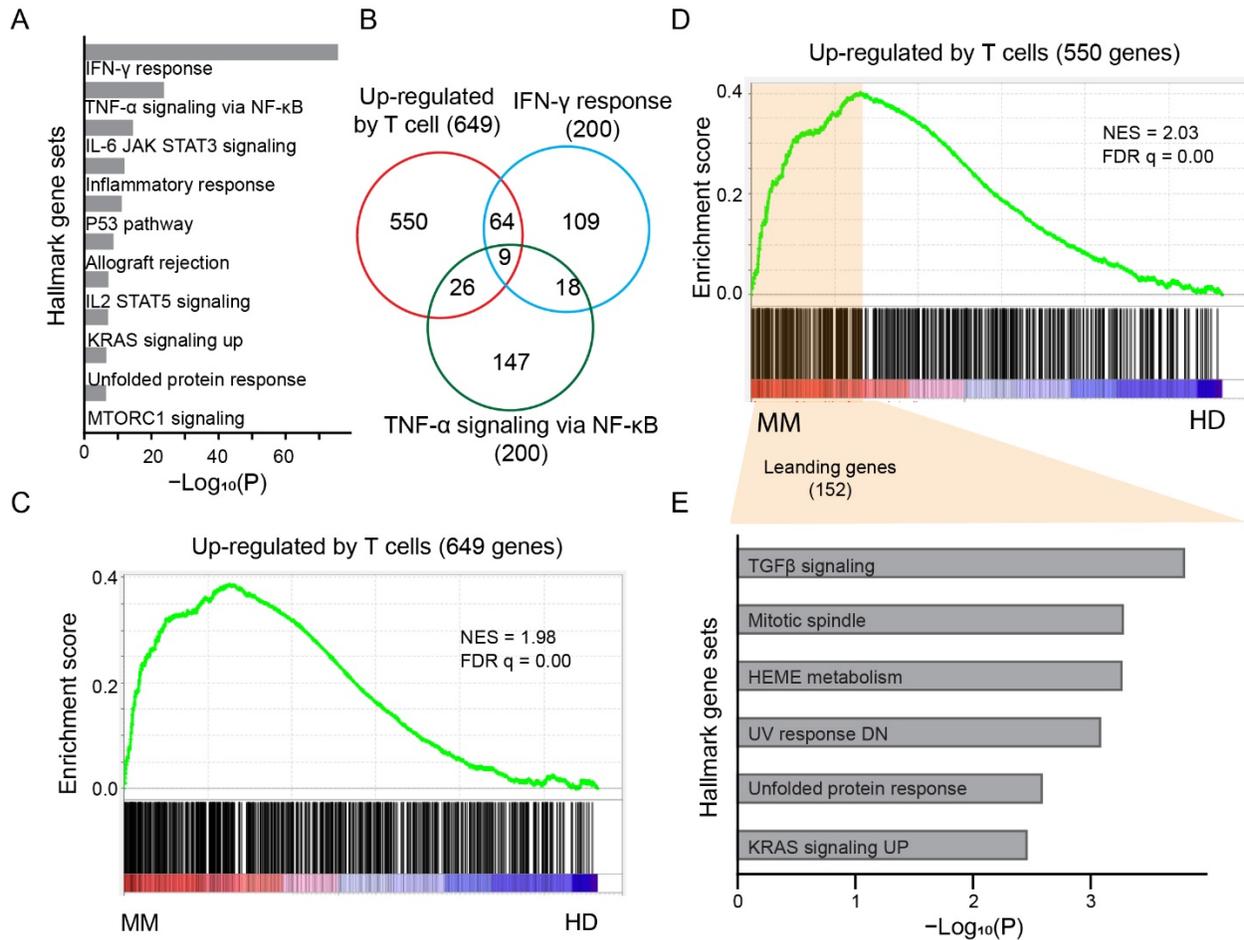
D

Inflammatory response



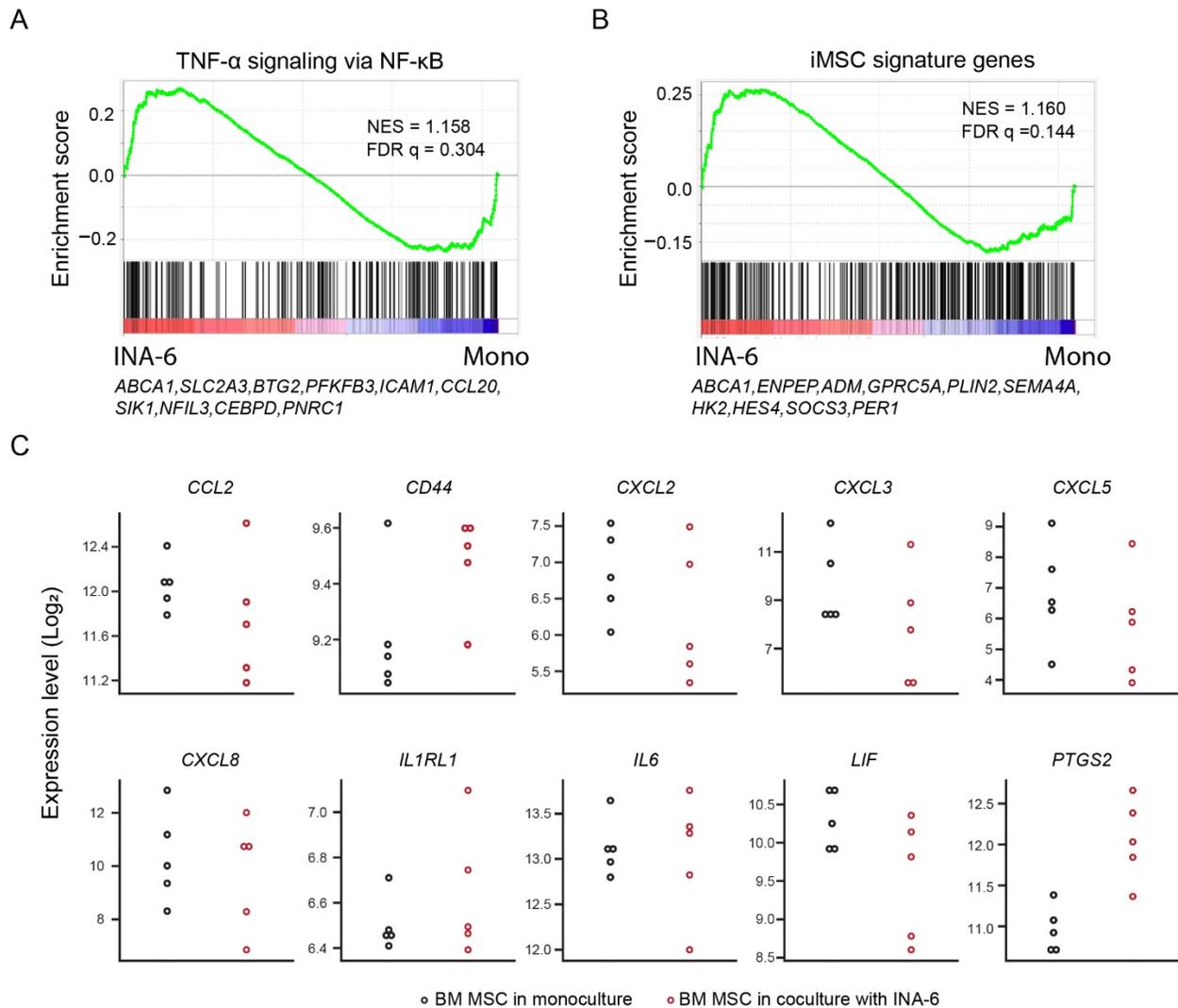
Supplementary Figure S3: Expression activation of TNF- α signaling pathway in MM MSCs by cytokines. (A) Bubble plot visualization of results from GSEA of expression changes induced by cytokine stimulations (rows) in BM MSCs against MSigDB hallmark gene sets (columns). Color indicates upregulation (blue) or downregulation (red) at gene set level. Circle size indicates significance (FDR q-value). (B) Heat map visualization of expression changes induced by mono-treatment of cytokines including IFN- γ , IL1- β , TNA- α , and TGF- β 1 for gene set “TNF- α signaling through NF- κ B”. Top upregulated genes were indicated. (C) Like panel B, but for gene set “IFN- γ response”. (D) Like panel B, but for gene set “inflammatory response”.

Figure S4



Supplementary Figure S4: Expression activation of iMSC signature genes by activated T cells. (A) Metascape enrichment analysis for genes upregulated by activated T cells in BM MSCs against MSigDB hallmark gene sets. (B) Venn diagram for genes upregulated by activated T cells and genes annotated in “IFN- γ response” and “TNF- α signaling via NF- κ B”. (C) GSEA of expressed genes sorted by expression changes from high (red in the color spectrum) to low (blue) in BMSCs of MM as relative to HD (calculated from bulk cell RNA-Seq data) against the 649 genes upregulated by activated T cells (vertical bars). NES: normalized enrichment score. (D) Similar to panel C, but against genes upregulated by activated T cells excluding those from “IFN- γ response” or “TNF- α signaling via NF- κ B”. (E) Metascape enrichment analysis for leading genes defined from panel D against MSigDB hallmark gene sets.

Figure S5



Supplementary Figure S5: INA-6 failed to activate the expression of iMSC signature genes. (A) GSEA of expressed genes sorted by expression changes induced by INA-6 (as compared to monoculture; Mono) in BM MSCs from high (left side) to low (right side) against MSigDB hallmark gene set “TNF- α signaling via NF- κ B”. NES: normalized enrichment score. (B) Like panel A, but against iMSC signature genes. (C) Dot plots for the expression of immune-related genes in BM MSCs cocultured with INA-6 or in monoculture.