Description of the model "Karen_MoDC_25Jan2021"

Annotation

Sallusto and Lazavecchia (1994) described for the first time a protocol enabling the differentiate human monocytes into dendritic cells (moDC) in vitro, in the presence of granulocyte macrophage colony stimulating factor (CSF2) and interleukin 4 (IL4) [1].

This model integrates current data on the signaling pathways involved in this differentiation process, together with relevant transcription factor and chromatin mark ChIP-seq data

In particular, we consider novel putative regulatory interactions based on the prediction of TF binding sites in regulatory regions delineated with ChromHMM and public epigenomic ChIP-seq data) proximal to target genes, using the tool matrix-scan from the RSAT software suite [2] together with selected transcriptional factor binding profiles from the JASPAR database [3]

https://www.ncbi.nlm.nih.gov/pubmed/8145033

http://rsat.eu

http://jaspar.genereg.net/

Nodes

ID	Val	Logical function
CSF2	Input node	
Granulocyte-macrophage colony-stimulating factor [1] CSF2 stimulates the growth and differentiation of hematopoietic precursor cells from various lineages, including granulocytes, macrophages, eosinophils and erythrocytes. In 1994, Sallusto and Lazavecchia reported an in vitro protocol enabling the differentiation of human monocyte into dendritic cells (moDC), in the presence of granulocyte macrophage colony stimulating factor (CSF2) and interleukin 4 (IL4) [2]. 1. https://www.uniprot.org/uniprot/P04141 https://pubmed.ncbi.nlm.nih.gov/8145033		
IL4	Input node	
Interleukin-4 [1]. IL4 participates in several B cell activation process. It induces the expression of class II MHC molecules in resting B cells. In 1994, Sallusto and Lazavecchia reported an in vitro protocol enabling the differentiation of human monocyte into dendritic cells (moDC), in the presence of granulocyte macrophage colony stimulating factor (CSF2) and interleukin 4 (IL4) [2]. 1. https://www.uniprot.org/uniprot/P05112 https://pubmed.ncbi.nlm.nih.gov/8145033		
CSF2R	1	• CSF2
Granulocyte-macrophage colony-stimulating factor receptor [1]. Low affinity receptor for granulocyte-macrophage colony-stimulating factor.		

Upon CSF2 binding, CSF2R induces the proliferation, differentiation, and functional activation of hematopoietic cells [1]. GM-CSFR contains two distinct subunits, a specific-chain (GM CSFR; CD116) and a common chain, which is shared between the GM CSFR, the IL3 receptor, and the IL5 receptor. Signaling is initiated by the cytoplasmic tyrosine kinasejanus kinase 2 (JAK2), which then acts on various downstream proteins [2]. 1. https://www.uniprot.org/uniprot/P15509 https://pubmed.ncbi.nlm.nih.gov/22323450		
IL4R	1	• IL4
Receptor for both interleukin 4, activating the JAK (1,3)-STAT (3,6) pathway [1]. Upon binding of IL4, the activation of the JAK-STAT pathway, enables the development of immature DCs [2]. 1. https://www.uniprot.org/uniprot/P24394 https://pubmed.ncbi.nlm.nih.gov/25159217		
AhR	1	• (NCOR2 & USF1 & STAT6) | (IRF4 & STAT6 & !ERK)
Aryl hydrocarbon receptor [1]. Ligand-activated transcription factor that enables cells to adapt to changing conditions by sensing compounds from the environment, diet, microbiome and cellular metabolism, and which plays important roles in development, immunity and cancer. ERK inhibition upregulates AhR dependent transcription [2]. 1. https://www.uniprot.org/uniprot/P35869 https://pubmed.ncbi.nlm.nih.gov/23430108/		
AP1	1	• JUN & FOS
Transcription factor AP-1, which recognizes and binds to the enhancer heptamer motif 5'-TGA[CG]TCA-3' [1]. Macrophage specific H3K4me1 regions were characterized by a distinct motif composition, including GT box, an AP1 like motif, an E box element, the consensus PU.1 motif, a composite CEBP_bZIP element, and a NFKB motif [2]. 1. https://www.uniprot.org/uniprot/P05412 https://pubmed.ncbi.nlm.nih.gov/22550342/		
ATF1	1	• STAT6
Cyclic AMP-dependent transcription factor ATF-1 [1]. ATF1 binds the cAMP response element (CRE) present in many viral and cellular promoters. Using matrix-scan, we predicted STAT6 binding sites in the regulatory region of the ATF1 coding gene. 1. https://www.uniprot.org/uniprot/P18846		

BATF3	1	• USF1 | IRF8
Basic leucine zipper transcriptional factor ATF-like 3 [1] AP-1 family transcription factor that controls the differentiation of CD8+ thymic conventional dendritic cells in the immune system. KLF4 and BATF3 serve as critical transcription factors downstream of IRF8 to induce the differentiation of monocytes and DCs, respectively [2] Using matrix-scan, we predicted binding of USF1 and IRF8 in the regulatory region of the BATF3 coding gene. 1. https://www.uniprot.org/uniprot/Q9NR55 https://pubmed.ncbi.nlm.nih.gov/28781277		
CEBPa	1	• PU1 & !FOXO1 & !IRF8 & !STAT5
CCAAT/enhancer-binding protein alpha [1], expressed in myeloid progenetors [2] . IRF8 blocks the activity of CEBPa to suppress the neutrophil differentiation program [3]. CEBP transcription factors, and CEBPb in particular, have long been implicated in the regulation of monocyte macrophage differentiation, whereas CEBPa appears to be more important for the maturation of granulocytes. STAT5-mediated downregulation [4]. Using matrix-scan, we predicted binding sites for CEBBa, FOXO1, and PU.1 in the regulatory region of the CEBPa gene. 1. https://www.uniprot.org/uniprot/P49715 https://pubmed.ncbi.nlm.nih.gov/21558273/ https://pubmed.ncbi.nlm.nih.gov/28781277 https://pubmed.ncbi.nlm.nih.gov/22323450/		
CEBPb	1	• PU1 & (CEBPa | MAFB)
CCAAT/enhancer-binding protein beta [1]. CEBP transcription factors, and CEBPb in particular, have long been implicated in the regulation of monocyte macrophage differentiation, whereas CEBPa appears to be more important for the maturation of granulocytes [1]. Macrophage specific H3K4me1 regions were characterized by a distinct motif composition, including GT box, an AP1 like motif, an E box element, the consensus PU.1 motif, a composite CEBP_bZIP element, and a NFKB motif [2]. C/EBPb almost always binds at C/EBPa binding sites and can rescue the formation of granulocytes in C/EBPalpha deficient mice [3]. There is a consensus ets-binding site at 7.8-kb upstream and a consensus C/EBP-binding site at 86-bp upstream of the transcription		

initiation site of the MafB coding gene [4]. Using matrix-scan, we predicted binding of CEBPa in the regulatory region of the CEBPb coding gene. 1. https://www.uniprot.org/uniprot/P17676 https://pubmed.ncbi.nlm.nih.gov/22550342 https://pubmed.ncbi.nlm.nih.gov/28584084/ https://pubmed.ncbi.nlm.nih.gov/12966068/		
FOS	1	• ERK
Proto-oncogene c-Fos [1]. Nuclear phosphoprotein which together with JUN forms the AP-1 complex. Activated ERK stabilizes c-Fos [2]. 1. https://www.uniprot.org/uniprot/P01100 https://pubmed.ncbi.nlm.nih.gov/21725048/		
cMYC	1	• ERK & !GSK3B
Myc proto-oncogene protein [1]. Transcription factor that binds DNA in a non-specific manner, but also specifically recognizes the core sequence 5'-CAC[GA]TG-3'. Myc ctivates the transcription of growth-related genes. U0126 treatment significantly reduced the expression of wellknown targets of ERK (FOS, MYC, DUSP6) [2]. 1. https://www.uniprot.org/uniprot/P01106 https://pubmed.ncbi.nlm.nih.gov/23430108/		
CREB	1	• AKT | ERK
Cyclic AMP-responsive element-binding protein 1 [1]. Phosphorylation-dependent transcription factor that stimulates transcription upon binding to the DNA cAMP response element (CRE), a sequence present in many viral and cellular promoters. It has been reported that the phosphorylation of CREB is mediated by p38 and by ERK-1/2 [2]. 1. https://www.uniprot.org/uniprot/P16220 https://pubmed.ncbi.nlm.nih.gov/27446931/		
ELK4	1	• ERK
ETS domain-containing protein Elk-4 [1]. Rlk-4 is Involved in both transcriptional activation and repression. Interaction with SIRT7 leads to recruitment and stabilization of SIRT7 at promoters, followed by deacetylation of histone H3 at 'Lys-18' (H3K18Ac) and subsequent transcriptional repression [1]. The expression of ELK4 is upregulated during human monocytic differentiation in vitro [2]. 1. https://www.uniprot.org/uniprot/P28324 https://pubmed.ncbi.nlm.nih.gov/22550342/		

FOXO1	1	• (PU1 | KLF4) & !AKT
Forkhead box protein O1 [1]. Transcription factor that is the main target of insulin signaling and regulates metabolic homeostasis in response to oxidative stress [1]. Activated PKB regulates many targets, including the FOXO transcription factors, the TSC1 TSC2 complex, and the mTOR complex 1 (mTORC1) [2]. Using matrix-scan, we predicted binding sites for KLF4 and PU.1 in the regulatory region of the FOXO1 coding gene. 1. https://www.uniprot.org/uniprot/Q12778 https://pubmed.ncbi.nlm.nih.gov/22323450		
IRF4	1	• AhR | (PU1 & STAT6 & NFKB1_RelA & IRF4)
Interferon regulatory factor 4 [1]. Transcriptional activator. Binds to the interferon-stimulated response element (ISRE) of the MHC class I promoter. Binds the immunoglobulin lambda light chain enhancer, together with PU.1 [1]. DCs were found to express IRF4 mRNA and protein constitutively, and STAT and NFkB transcription factors play an important role inregulating IRF4 expression in DCs [2,3]. The promoter of IRF4 contains several putative NF-kB binding sites [4]. Using matrix-scan, we predicted binding sites for AHR, IRF4, PU1, and STAT6 in the regulatory region of the IRF4 gene. 1. https://www.uniprot.org/uniprot/Q15306 https://pubmed.ncbi.nlm.nih.gov/10453013 https://pubmed.ncbi.nlm.nih.gov/29871928/ https://pubmed.ncbi.nlm.nih.gov/16272311/		
IRF8	1	• (PU1 | KLF4) & !NCOR2
Interferon regulatory factor 8 [1]. Transcription factor that specifically binds to the upstream regulatory region of type I interferon (IFN) and IFN-inducible MHC class I genes [1]. The differentiation of MO in vitro culture systems is multifaceted, integrating time-dependent signals delivered by GM-CSF and IL-4 and orchestrated by NCOR2 [2]. Introduction of KLF4 into an Irf8(-/-) myeloid progenitor cell line induced a subset of IRF8 target genes and caused partial monocyte differentiation [3].		

Using matrix-scan, we predicted binding sites for KLF4 and PU1 in the regulatory region of the IRF8 gene. 1. https://www.uniprot.org/uniprot/Q02556 https://pubmed.ncbi.nlm.nih.gov/29262348 https://pubmed.ncbi.nlm.nih.gov/23319570/		
KLF4	1	• (NR4A1 & IRF8 & AP1) | (PU1:1 & !STAT5)
Krueppel-like factor 4 [1]. PU.1 induced the KLF4 promoter 15 fold [2]. KLF4 and BATF3 serve as critical transcription factors downstream of IRF8 to induce the differentiation of monocytes and DCs, respectively [3,4]. Using matrix-scan, we predicted binding sites for AP1, NR4A1 and STAT5 in the regulatory region of the KLF4 gene. 1. https://www.uniprot.org/uniprot/O43474 https://pubmed.ncbi.nlm.nih.gov/17762869 https://pubmed.ncbi.nlm.nih.gov/28781277 https://pubmed.ncbi.nlm.nih.gov/23319570/		
MAFB	1	• (CEBPb | IRF8) & !AhR & !PU1:2
Transcription factor MafB [1]. Acting as a transcriptional activator or repressor, MAFB plays a pivotal role in regulating lineage-specific hematopoiesis by repressing ETS1-mediated transcription of erythroid-specific genes in myeloid cells [1]. PU1 in monocytes favors DC development at the expense of a macrophage fate by directly inhibiting expression of MAFB, suggesting that PU1 could be an important decision factor between DC and macrophage commitment [2]. MAFB gene silencing improved the differentiation potential of CD14+ cells into mDCs, increasing the percentage of mDCs by >75%. Furthermore, GATA1+ and HLA-DR+ mDCs were increased following MAFB silencing [3]. MAFB have also been implicated in monocyte differentiation [4]. Using matrix-scan, we predicted binding sites for AHR and CEBPb in the regulatory region of the MAFB coding gene. 1. https://www.uniprot.org/uniprot/Q9Y5Q3 https://pubmed.ncbi.nlm.nih.gov/24070385 https://pubmed.ncbi.nlm.nih.gov/22868453 https://pubmed.ncbi.nlm.nih.gov/23319570/		
NFKB1_RelA	1	• IKK

Nuclear factor NF-kappa-B p105 subunit [1]. NFkB complexes are formed by Rel like domain containing proteins RELA/p65, RELB, NFKB1/p105, NFKB1/p50, REL or NFKB2/p52. The heterodimeric p65-p50 complex appears to be most abundant. NFkB activation is achieved through the IKK complex, which phosphorylates IkB [2, 3]. 1. https://www.uniprot.org/uniprot/P19838 https://pubmed.ncbi.nlm.nih.gov/22323450/ https://pubmed.ncbi.nlm.nih.gov/16540365/		
NFKB2	1	• NFKB1_RelA | STAT5
Nuclear factor NF-kappa-B p100 subunit [1]. NFkB is a pleiotropic transcription factor present in almost all cell types and is the endpoint of a series of signal transduction events that are initiated by a vast array of stimuli related to many biological processes such as inflammation, immunity, differentiation, cell growth, tumorigenesis and apoptosis [1]. GM CSF induced activation of STAT5 and canonical NFkB transcription factors increases the intrinsic immunogenicity of the DCs generated. STAT5 activates NFKB2 by phosphorylation [2]. 1. https://www.uniprot.org/uniprot/Q00653 https://pubmed.ncbi.nlm.nih.gov/22323450		
NR4A1	1	• ERK & STAT6
Nuclear receptor subfamily 4 group A member 1 [1,2]. Nr4a1 is required for the differentiation of the Ly6Clo monocyte. In the absence of Nr4a1, this specific population of monocytes is arrested in the bone marrow, as shown in studies of Nr4a1−/− mice [3]. 1. https://www.uniprot.org/uniprot/P22736 https://www.genome.jp/dbget-bin/www_bget?hsa04010 https://pubmed.ncbi.nlm.nih.gov/26580501/		
PRDM1	1	• IRF4 & AhR & !KLF4
PR domain zinc finger protein 1 [1]. Transcription factor that mediates a transcriptional program in various innate and adaptive immune tissue-resident lymphocyte T cell types. PRDM1 silencing significantly decreased moDC differentiation, while increasingthe proportion of moMacs [2]. Using matrix-scan, we predicted binding of IRF4 and KLF4 in the promoter region of PRDM1 coding gene. 1. https://www.uniprot.org/uniprot/O75626 https://pubmed.ncbi.nlm.nih.gov/28930664		

PU1	1	• (ERK | STAT6) & !(ERK & STAT6)
2	• ERK & STAT6	
Transcription factor PU.1 [1]. PU1 is a transcriptional activator involved in the differentiation of lymphoid and myeloid cells [2]. PU1 is necessary for all DC development because Sfpi1 homozygotic mutant neonates were shown to lack thymic DCs and to be unable to generate DCs in vitro in response to GMCSF [3]. An alternative mechanism may involve STAT6 [4]. 1. https://www.uniprot.org/uniprot/P17947 https://pubmed.ncbi.nlm.nih.gov/11594748/ https://pubmed.ncbi.nlm.nih.gov/20510871/ https://pubmed.ncbi.nlm.nih.gov/26758199/		
STAT3	1	• JAK1 & SHP1
2	• JAK1 & !SHP1	
Signal transducer and transcription activator that mediates cellular responses to interleukins, KITLG/SCF, LEP and other growth factors [1]. SOCS proteins are themselves encoded by STAT target genes and thus provide a transcription dependent negative feedback mechanism [3]. lncDC bound directly to STAT3 in the cytoplasm, which promoted STAT3 phosphorylation on tyrosine705 by preventing STAT3 binding to and dephosphorylation by SHP1 [2,4]. 1. https://www.uniprot.org/uniprot/P40763 https://pubmed.ncbi.nlm.nih.gov/24744378 https://pubmed.ncbi.nlm.nih.gov/30578415 https://pubmed.ncbi.nlm.nih.gov/28465674		
STAT5	1	• Src | JAK2
Signal transducer and activator of transcription 5A. STAT5 carries out a dual function: signal transduction and activation of transcription [1]. STAT5 clearly contributes to GM CSF driven DC development [2]. 1. https://www.uniprot.org/uniprot/P42229 https://pubmed.ncbi.nlm.nih.gov/22323450		
STAT6	1	• JAK3
Signal transducer and activator of transcription 6 [1]. STAT6 carries out a dual function: signal transduction and activation of transcription. It is involved in IL4/interleukin-4 and IL3/interleukin-3-mediated signaling [1]. The IL4 receptor (IL4R) signals the activation of the JAK3-STAT6		

pathway through its common gamma chain, which leads to the development of immature DCs [2,3,4]. 1. https://www.uniprot.org/uniprot/P42226 https://pubmed.ncbi.nlm.nih.gov/16540365 https://pubmed.ncbi.nlm.nih.gov/25159217 https://pubmed.ncbi.nlm.nih.gov/10485906		
USF1	1	• PU1 | KLF4
Upstream stimulatory factor [1]1. Transcription factor that binds to a symmetrical DNA sequence (E-boxes) (5'-CACGTG-3') that is found in a variety of viral and cellular promoters [1]. USF is involved in myeloid cell differentiation[2]. Using matrix-scan, we predicted binding sites for KLF4 and PU1 in the regulatory region of the USF1 coding gene. 1. https://www.uniprot.org/uniprot/P22415 https://pubmed.ncbi.nlm.nih.gov/10085160		
NCOR2	1	• IRF4 | AhR | STAT6
Nuclear receptor corepressor 2 [1]. NCOR2 mMediates the transcriptional repression activity of some nuclear receptors by promoting chromatin condensation, thus preventing access of the basal transcription [1]. NCOR2 was identified as a key transcriptional hub linked to IL4 dependent differentiation of MOs [2]. Using matrix-scan, we predicted binding sites for AHR, IRF4 and STAT6 in the regulatory regio of the NCOR2 coding gene. 1. https://www.uniprot.org/uniprot/Q9Y618 https://pubmed.ncbi.nlm.nih.gov/29262348		
JAK2	1	• CSF2R & !PTPN1
Tyrosine-protein kinase JAK2 [1]. Non-receptor tyrosine kinase involved in various processes such as cell growth, development, differentiation or histone modifications. JAK2 mediates signaling events essential for both innate and adaptive immunity [1]. Src kinases are recruited to BetaC by their SH2 domains that interact with phosphorylated Y612, Y695 and Y750 [2]. The STATs are primarily phosphorylated by JAK2. PTP1B recognizes TYK2 on JAK2, but not on JAK1, and can modulate signaling responses to IFNgamma and IFNalfa [3]. 1. https://www.uniprot.org/uniprot/O60674 https://pubmed.ncbi.nlm.nih.gov/22323450 https://pubmed.ncbi.nlm.nih.gov/11694501		
Src	1	• CSF2R:1 | JAK2

Proto-oncogene tyrosine-protein kinase Src [1]. Non-receptor protein tyrosine kinase activated following engagement of many different classes of cellular receptors including immune response receptors, integrins and other adhesion receptors, receptor protein tyrosine kinases, G protein-coupled receptors as well as cytokine receptors [1]. Src kinases are recruited to BetaC by their SH2 domains that interact with phosphorylated Y612, Y695, and Y750. The STATs are primarily phosphorylated by JAK2, but also by Src kinases [2]. 1. https://www.uniprot.org/uniprot/P12931 https://pubmed.ncbi.nlm.nih.gov/22323450		
PI3K	1	• RAS | JAK2
Phosphatidylinositol 4,5-bisphosphate 3-kinase catalytic subunit gamma isoform [1]. PI3K phosphorylates PtdIns(4,5)P2 (Phosphatidylinositol 4,5 bisphosphate) to generate phosphatidylinositol 3,4,5 trisphosphate (PIP3) [1]. Activity of PI3K is promoted by JAK2 mediated phosphorylation of p85 [2]. 1. https://www.uniprot.org/uniprot/P48736 https://pubmed.ncbi.nlm.nih.gov/22323450/		
PIP3	1	• PI3K & !PTEN
Phosphatidylinositol (3,4,5) trisphosphate [1]. PIP3 is the product of the phosphorylation of phosphatidylinositol (4,5) bisphosphate (PIP2) by class I phosphoinositide 3 kinases (PI3K). It is a phospholipid that resides on the plasma membrane [1]. PI3K functions mainly through the generation of PIP3, an activity counteracted by phosphatases PTEN and SHIP [2]. 1. https://en.wikipedia.org/wiki/Phosphatidylinositol_(3,4,5)-trisphosphate https://pubmed.ncbi.nlm.nih.gov/22323450/		
AKT	1	• PIP3 & !NCOR2
RAC-alpha serine/threonine-protein kinase [1]. There are three closely related serine/threonine-protein kinases (AKT1, AKT2 and AKT3), which regulate metabolism, proliferation, cell survival, growth and angiogenesis. PIP3 acts as a second messenger, regulating a large variety of downstream targets, including the protein kinase B (PKB; also called AKT) [2]. 1. https://www.uniprot.org/uniprot/P31749 https://pubmed.ncbi.nlm.nih.gov/22323450/		
PTEN	1	• MAGI1 & MEK1

Phosphatidylinositol 3,4,5 trisphosphate 3 phosphatase and dual-specificity protein phosphatase PTEN [1]. PTEN acts as a dual specificity protein phosphatase, dephosphorylating tyrosine, serine and threonine phosphorylated proteins. It is activated by MEK1 [2] A ternary complex between MEK1, MAGI1 and PTEN mediates the translocation of PTEN to the membrane and thereby regulates the concentration of PIP3 and AKT activation. Both MEK1 and MAGI1 are necessary for complex formation, and PTEN will not bind to one component if the other is missing [3]. 1. https://www.uniprot.org/uniprot/P60484 https://pubmed.ncbi.nlm.nih.gov/23453810/ https://pubmed.ncbi.nlm.nih.gov/22323450/		
MEK1	1	• RAF | (AKT & ERK)
Dual specificity mitogen-activated protein kinase kinase 1 (MAP2K1 or MEK1) [1]. Phosphorylation of MEK1 T292 relays a negative feedback within the ERK pathway and initiates the deactivation of the PIP3 AKT pathway through the membrane localization of MAGI PTEN, acting as a temporal switch for both cascades. ERK regulates the binding of MEK1 to WW domain containing proteins and may negatively affect survival by promoting the membrane recruitment of PTEN in the context of the MEK1/MAGI1/PTEN complex [2]. 1. https://www.uniprot.org/uniprot/Q02750 https://pubmed.ncbi.nlm.nih.gov/23453810/		
MAGI1	1	• MEK1
Membrane associated guanylate kinase, WW and PDZ domain containing protein 1 [1]. MAGI1 presumably plays a role as scaffolding protein at cell-cell junctions and regulates acid-induced ASIC3 currents by modulating its expression at the cell surface [1]. MEK1 is essential for the formation of a complex containing MAGI1 and PTEN and for their membrane translocation upon growth factor stimulation. Mutation of the WW domains of MAGI1, in particular of WW2, strongly reduced MEK1 binding by a WW MAGI1 fragment or by full length MAGI1. A ternary complex involving MEK1, MAGI1, and PTEN, mediates the translocation of PTEN to the membrane and therebye regulates the concentration of PIP3 and AKT activation. Both MEK1 and MAGI1 are necessary for complex formation, and PTEN will not bind to one component if the other is missing. MEK1 ablation prevented MAGI1 membrane translocation [2].		

1. https://www.uniprot.org/uniprot/Q96QZ7 https://pubmed.ncbi.nlm.nih.gov/23453810/		
CLIP1	1	• mTORC1 | PU1
CAP-Gly domain-containing linker protein 1 [1,2]. CLIP1 binds to the plus end of microtubules and regulates the dynamics of the microtubule cytoskeleton, promoting microtubule growth and microtubule bundling. CLIP1 links cytoplasmic vesicles to microtubules and thereby plays an important role in intracellular vesicle trafficking, including macropinocytosis and endosome trafficking [1]. The microtubule plus-end protein CLIP-170 (also known as CLIP1) is a direct AMPK substrate [3]. 1. https://www.uniprot.org/uniprot/P30622 https://www.genome.jp/dbget-bin/www_bget?hsa04150 https://pubmed.ncbi.nlm.nih.gov/21892142/		
mTORC1	1	• AKT
Serine/threonine-protein kinase mTOR [1,2]. The mTOR complex 1 (MTORC1) belongs to a family of phosphatidylinositol kinase-related kinases. These kinases mediate cellular responses to stresses such as DNA damage and nutrient deprivation. MTORC1 acts as the target for the cell-cycle arrest and immunosuppressive effects of the FKBP12-rapamycin complex [1]. Activated PKB regulates mTORC1 [3]. 1. https://www.uniprot.org/uniprot/P42345 https://www.genecards.org/cgi-bin/carddisp.pl?gene=MTOR https://pubmed.ncbi.nlm.nih.gov/22323450/		
SHC_GRB2_mSOS	1	• CSF2R
Complex involving SHC, GRB2 and mSOS. The main MAPK pathway activated by the GM CSF receptor is the MEK/ERK pathway. The recruitment of mSOS to the SHC GRB2 complex enables mSOS to catalyze RAS activation [1]. 1. https://pubmed.ncbi.nlm.nih.gov/22323450/		
RAS	1	• SHC_GRB2_mSOS
GTPase KRas [1]. Ras proteins bind GTP and possess intrinsic GTPase activity) [1]. The main MAPK pathway activated by the GM CSF receptor is the MEK/ERK pathway. The recruitment of mSOS to the SHC GRB2 complex enables mSOS to catalyze RAS activation. Formation of active GTP bound RAS from inactive GDP bound RAS leads to the successive activation of RAF, MEK, and ERK [2].		

1. https://www.uniprot.org/uniprot/P01116 https://pubmed.ncbi.nlm.nih.gov/22323450/		
RAF	1	• RAS
RAF proto-oncogene serine, threonine-protein kinase [1]. RAF acts as a regulatory link between the membrane-associated Ras GTPases and the MAPK ERK cascade, and functions as a switch determining cell fate decisions including proliferation, differentiation, apoptosis, survival and oncogenic transformation [2]. 1. https://www.uniprot.org/uniprot/P04049 https://pubmed.ncbi.nlm.nih.gov/22323450/		
ERK	1	• MEK1
Mitogen-activated protein kinase 3 [1]. ERK is an essential component of the MAP kinase signal transduction pathway. MAPK1/ERK2 and MAPK3/ERK1 are the 2 MAPKs which play an important role in the MAPK/ERK cascade. DUSP6 Inactivates MAP kinases, with a specificity for the ERK family [2,3]. 1. https://www.uniprot.org/uniprot/P27361 https://pubmed.ncbi.nlm.nih.gov/9858808/ https://pubmed.ncbi.nlm.nih.gov/22323450/		
JUN	1	• JNK
Proto-oncogene c-Jun [1]. Nuclear phosphoprotein which together with FOS forms AP-1 complex. In response to growth factors, ERK-1/2, c-Jun NH2-terminal kinase 1 (JNK-1), and p38 are activated [2]. 1. https://www.uniprot.org/uniprot/P05412 https://pubmed.ncbi.nlm.nih.gov/27446931/		
JNK	1	• ERK
Jun N-Terminal Kinase [1]. Extracellular stimuli such as proinflammatory cytokines or physical stress stimulate the stress-activated protein kinase/c-Jun N-terminal kinase (SAP/JNK) signaling pathway [2,3]. 1. https://www.uniprot.org/uniprot/P45983 https://pubmed.ncbi.nlm.nih.gov/17409820/ https://pubmed.ncbi.nlm.nih.gov/27446931/		
TAU	1	• ERK
Microtubule-associated protein tau [1,2]. TAU promotes microtubule assembly and stability. The C-terminus binds axonal microtubules while the N-terminus binds neural plasma membrane components, suggesting that tau functions		

as a linker protein between both [1]. ERK regulated TAU phosphorylation [3]. 1. https://www.uniprot.org/uniprot/P10636 https://www.genome.jp/dbget-bin/www_bget?hsa04010 https://pubmed.ncbi.nlm.nih.gov/31908108/		
CPLA2	1	• ERK
Cytosolic phospholipase A2 [1]. CPLA2 has primarily calcium-dependent phospholipase and lysophospholipase activities, with a major role in membrane lipid remodeling and biosynthesis of lipid mediators of the inflammatory response [1,2]. CPLA2 is downregulated when ERk is inhactive [3]. 1. https://www.uniprot.org/uniprot/P47712 https://www.genome.jp/dbget-bin/www_bget?hsa04010 https://pubmed.ncbi.nlm.nih.gov/23430108/		
FLT3	1	• PU1
Receptor-type tyrosine-protein kinase FLT3 [1]. FLT3 acts as cell-surface receptor for the cytokine FLT3LG and regulates differentiation, proliferation and survival of hematopoietic progenitor cells and of dendritic cells. PU1 directly regulated Flt3 expression in DCs and their precursors in a dose-dependent manner [2]. 1. https://www.uniprot.org/uniprot/P36888 https://pubmed.ncbi.nlm.nih.gov/24070385		
GSK3B	1	• !AKT
Glycogen synthase kinase-3 beta [1]. GSK3B is negatively regulated by AKT dependent phosphorylation and is required to avoid human monocyte to macrophage differentiationin monocyte derived DC differentiation cultures [2]. 1. https://www.uniprot.org/uniprot/P49841 https://pubmed.ncbi.nlm.nih.gov/22323450/		
IKK	1	• CSF2R | AKT
Inhibitor of nuclear factor kappa-B kinase, involving two subunits A and B [1,2]. Serine kinase that plays an essential role in the NF-kappa-B signaling pathway which is activated by multiple stimuli such as inflammatory cytokines, bacterial or viral products, DNA damages or other cellular stresses. IKKA and IKKB act as parts of the canonical IKK complex in the conventional pathway of NF-kappa-B activation and phosphorylates inhibitors of NF-kappa-B on serine residues. GM CSF induced canonical NFkB activation is scrucial to ensure differentiation and survival of DC precursors [1].		

1. https://www.uniprot.org/uniprot/O14920 https://www.uniprot.org/uniprot/O15111 https://pubmed.ncbi.nlm.nih.gov/22323450		
JAK3	1	• IL4R
Tyrosine-protein kinase JAK3 [1]. JAK3 mediates essential signaling events in both innate and adaptive immunity. The IL4 receptor (IL4R) signals the activation of the JAK3-STAT6 pathway through its common gamma chain, which leads to the development of immature DCs [2]. 1. https://www.uniprot.org/uniprot/P52333 https://pubmed.ncbi.nlm.nih.gov/25159217/		
JAK1	1	• IL4R
Tyrosine-protein kinase JAK1 [1] IL4R signal transduction is initiated by receptor-associated kinases, i.e. a member of JAK family, including JAK1 [2]. 1. https://www.uniprot.org/uniprot/P23458 https://pubmed.ncbi.nlm.nih.gov/27165851/		
SHP1	1	• USF1:1 & !LnC_DC
Tyrosine-protein phosphatase non-receptor type 6 [1]. SHP1 modulates signaling by tyrosine phosphorylated cell surface receptors such as KIT and the EGF receptor/EGFR. The SH2 region interacts with other cellular components to modulate its own phosphatase activity against interacting substrates. LncDC promotes STAT3 phosphorylation via inhibiting the action of Src homology region 2 domain containing phosphatase 1 (SHP1) [2]. 1. https://www.uniprot.org/uniprot/P29350 https://pubmed.ncbi.nlm.nih.gov/28465674		
CIITA	1	• STAT5
MHC class II transactivator [1]. CIITA is essential for transcriptional activity of the HLA class II promoter, via the proximal promoter. No DNA binding of in vitro translated CIITA was detected. CIITA may act in a coactivator-like fashion through protein-protein interactions by contacting factors binding to the proximal MHC class II promoter, to elements of the transcription machinery, or both [1]. STAT5 promotes the expression of CIITA [2]. 1. https://www.uniprot.org/uniprot/P33076 https://pubmed.ncbi.nlm.nih.gov/22323450		
ITGAX	1	• IRF4 & PU1 & PRDM1
Integrin alpha-X [1]. ITGAX is a receptor for fibrinogen and a moDC marker [2,3,5,6].		

It mediates cell-cell interaction during inflammatory responses. It is especially important for monocyte adhesion and chemotaxis. PU1 transactivates the Itgax promoter via direct binding to the cis element on the gene in DCs and through gene regulation of a partner molecule, IRF4, which transactivates the Itgax gene in a synergistic manner with PU1 [4]. Using matrix-scan, we predicted binding sites for IRF4, PU.1 and PRDM1 in the regulatory region of the ITGAX coding gene. 1. https://www.uniprot.org/uniprot/P20702 https://pubmed.ncbi.nlm.nih.gov/29448070 https://pubmed.ncbi.nlm.nih.gov/24513968/ https://pubmed.ncbi.nlm.nih.gov/28338898/ https://pubmed.ncbi.nlm.nih.gov/29262348/ https://pubmed.ncbi.nlm.nih.gov/27401672		
LnC_DC	1	• PU1 & IRF4 & STAT5
Long non coding RNA espressed in DCs [1,2]. This lncRNA lncDC regulates differentiation of dendritic cells (DCs), the most potent antigen-presenting cells of the immune system [1]. lncDC binds directly to STAT3 in the cytoplasm, which promoted STAT3 phosphorylation on tyrosine705 by preventing STAT3 binding to and dephosphorylation by SHP1 [3]. PU1 directs lncDC expression in human cDCs [4]. Using matrix-scan, we predicted binding sites for IRF4 and STAT5 in the regulatory region of the LnC-DC gene. 1. https://omim.org/entry/615772 https://www.genenames.org/data/gene-symbol-report/#!/hgnc_id/50357 https://www.ncbi.nlm.nih.gov/pubmed/24744378 https://www.ncbi.nlm.nih.gov/pubmed/28465674		
IL4_gene	1	• STAT6
Gene encoding Interleukin-4 [1]. IL4 gene is regulated by STAT6 [2]. 1. https://www.uniprot.org/uniprot/P05112 https://pubmed.ncbi.nlm.nih.gov/16540365/		
DUOX1	1	• STAT6 & IRF4 & PU1
Dual oxidase 1 [1]. DUOX1 generates hydrogen peroxide which is required for the activity of thyroid peroxidase/TPO and lactoperoxidase/LPO [1]. STAT6 did interacts specifically with DC-specific genes, including DUOX1 and SLAMF1, during DC differentiation [2].		

Using matrix-scan, we predicted binding sites for IRF4 and PU1 in the regulatory region of the DUOX1 coding gene. 1. https://www.uniprot.org/uniprot/Q9NRD9 https://pubmed.ncbi.nlm.nih.gov/26758199		
SLAMF1	1	• STAT6 & IRF4 & ELK4
Signaling lymphocytic activation molecule [1]. SLAM receptors triggered by homo- or heterotypic cell-cell interactions are modulating the activation and differentiation of a wide variety of immune cells and are involved in the regulation and interconnection of both innate and adaptive immune response [1]. STAT6 interacts specifically with DC-specific genes, incluing DUOX1 and SLAMF1, duing DC differentiation [2]. IRF4 and STAT6 bind to SLAMF1 promoter and regulate its activity [3]. Using matrix-scan, we predicted binding sites for IRF4 and ELK4 in the regulatory region of the SLAMF1 coding gene. 1. https://www.uniprot.org/uniprot/Q13291 https://pubmed.ncbi.nlm.nih.gov/26758199 https://pubmed.ncbi.nlm.nih.gov/29284783/		
MAOA	1	• STAT6 & NCOR2 & PU1
Amine oxidase [flavin-containing] A [1]. MAOA catalyzes the oxidative deamination of biogenic and xenobiotic amines and has important functions in the metabolism of neuroactive and vasoactive amines in the central nervous system and peripheral tissues [1]. The IL4/,Jak1/Stat3/Stat6 cascade regulates the expression of critical inflammatory genes, including ALOX15, monoamine oxidase A (MAOA), and the scavenger receptor CD36 [2]. Using matrix-scan, we predicted binding sites for STAT6 and PU1 in the regulatory region of the MAOA coding gene. 1. https://www.uniprot.org/uniprot/P21397 https://pubmed.ncbi.nlm.nih.gov/23124025		
HLA_DR	1	• STAT3 | (STAT6 & CIITA)
HLA class II histocompatibility antigen, DRB1 beta chain [1], expressed by DCs [2,3] STAT5 promotes the expression of MHC class II transactivatorprotein (CIITA), which is essential for proper transcripiton of the MHC class II promoter [4]. 1. https://www.uniprot.org/uniprot/P01911 https://pubmed.ncbi.nlm.nih.gov/29448070 https://pubmed.ncbi.nlm.nih.gov/29262348		

https://pubmed.ncbi.nlm.nih.gov/22323450/		
ALOX15	1	• CREB & STAT6 & STAT3
Polyunsaturated fatty acid lipoxygenase ALOX15 [1]. Non-heme iron-containing dioxygenase that catalyzes the stereo-specific peroxidation of free and esterified polyunsaturated fatty acids generating a spectrum of bioactive lipid mediators [1]. The IL4-Jak1-Stat3-Stat6 cascade regulates the expression of critical inflammatory genes, including ALOX15 [2]. Using matrix-scan, we predicted binding sites for STAT3 in the regulatory region of the ALOX15 coding gene. 1. https://www.uniprot.org/uniprot/P16050 https://pubmed.ncbi.nlm.nih.gov/16540365/		
TIMP3	1	• STAT6 & AP1 & IRF4
Metalloproteinase inhibitor 3 [1]. IL-4 specifically stimulates the expression of TIMP3 mRNA [2]. Using matrix-scan, we predicted binding sites for AP1 and IRF4 in the regulatory region of the TIMP3 coding gene. 1. https://www.uniprot.org/uniprot/P48032 https://pubmed.ncbi.nlm.nih.gov/23124025		
DUSP6	1	• ERK
Dual specificity protein phosphatase 6 [1]. DUSP6 inactivates MAP kinases and has a specificity for the ERK family. MEK1/2 inhibitor U0126 treatment significantly reduces the expression of wellknown targets of ERK (FOS, MYC, DUSP6) [2]. 1. https://www.uniprot.org/uniprot/Q16828 https://pubmed.ncbi.nlm.nih.gov/23430108/		
CCL2	1	• ERK & STAT5 & STAT3 & FOXO1
C-C motif chemokine 2 [1]. CCL2 is a chemokine constitutively produced by immature MDDCs, acting as a ligand for C-C chemokine receptor CCR2 [1]. The CCL2 chemokine directs monocyte/macrophage recruitmentinto tissues under resting and inflamed conditions [2]. ERK upregulated CCL2 expression while impairing the expression of DC maturation markers (RUNX3, ITGB7, IDO1) [3]. Using matrix-scan, we predicted binding sites for FOXO1, STAT3 and STAT5 in the regulatory regio of the CCL2 coding gene. 1. https://www.uniprot.org/uniprot/P13500 https://pubmed.ncbi.nlm.nih.govd/23430108 https://pubmed.ncbi.nlm.nih.gov/22328945		

CCL22	1	• (AhR & NCOR2 & FOXO1) | (KLF4 & MAFB)
C-C motif chemokine 22 [1], moDC marker [2]. May play a role in the trafficking of activated/effector T-lymphocytes to inflammatory sites and other aspects of activated T-lymphocyte physiology. Chemotactic for monocytes, dendritic cells and natural killer cells [1]. Using Matrix-scan , we predicted binding sites for AHR, NCOR2, FOXO1, KLF4, and MAFB in the regulatory region, annotated with chromHMM in this study, of the CCL22 gene. 1. https://www.uniprot.org/uniprot/O00626 https://pubmed.ncbi.nlm.nih.gov/29262348		
TLR3	1	• IRF4 | PRDM1
Toll-like receptor 3 [1], moDC marker[2]. TLRs control host immune response against pathogens through recognition of molecular patterns specific to microorganisms [1]. Using matrix-scan, we predicted binding sites for IRF4 and PRDM1 in the regulatory region of the TLR3 coding gene. 1. https://www.uniprot.org/uniprot/O15455 https://pubmed.ncbi.nlm.nih.gov/24513968		
TLR4	1	• AP1 | IRF4 | PRDM1 | PU1
Toll-like receptor 4 [1], moDC marker [2,3]. TLR4 cooperates with LY96 and CD14 to mediate the innate immune response to bacterial lipopolysaccharide (LPS) [1]). Using matrix-scan, we predicted binding sites for AP1, IRF4, PRDM1 and PU1 in the regulatory region of the TLR4 coding gene. 1. https://www.uniprot.org/uniprot/O00206 https://pubmed.ncbi.nlm.nih.gov/24513968 https://pubmed.ncbi.nlm.nih.gov/27022195/		
TLR6	1	• CEBPa | CEBPb | STAT6
Toll-like receptor 6 [1], moDC marker [2,3,4]. TLR6 participates in the innate immune response to Gram-positive bacteria and fungi. TLR6 specifically recognizes diacylated and, to a lesser extent, triacylated lipopeptides [1]. Using matrix-scan, we predicted binding sites for CEBPa, CEBPb and STAT6 in the regulatory region of the TLR6 coding gene. 1. https://www.uniprot.org/uniprot/Q9Y2C9 https://pubmed.ncbi.nlm.nih.gov/24513968 https://pubmed.ncbi.nlm.nih.gov/20037584/		

https://pubmed.ncbi.nlm.nih.gov/29593736/		
TLR7	1	• CEBPa | CEBPb | IRF4
Toll-like receptor 7 [1], moDC marker [2]. Endosomal receptor that plays a key role in innate and adaptive immunity. ILR7 controls host immune response against pathogens through recognition of uridine containing single strand RNAs (ssRNAs) of viral origin or guanosine analogs [1]. Using matrix-scan, we predicted binding sites for CEBPa, CEBPb and IRF4 in the regulatory region of the TLR7 coding gene. 1. https://www.uniprot.org/uniprot/Q9NYK1 https://pubmed.ncbi.nlm.nih.gov/24513968		
TLR8	1	• KLF4 | CEBPa | STAT6 | BATF3
Toll-like receptor 8 [1], moDC marker [2]. Endosomal receptor that plays a key role in innate and adaptive immunity. TLR8 controls host immune response against pathogens through recognition of RNA degradation products specific to microorganisms that are initially processed by RNASET2 [3] Using matrix-scan, we predicted binding sites for CEBPA, KLF4 and STAT6 in the regulatory region of TLR8 coding gene. 1. https://www.uniprot.org/uniprot/Q9NR97 https://pubmed.ncbi.nlm.nih.gov/24513968 https://pubmed.ncbi.nlm.nih.gov/31778653/		
CD48	1	• PU1 & IRF4
CD48 antigen [1], expressed in moDC [2], ligand for CD2 and presumably involved in regulating T-cell activation [1]. Using matrix-scan, we predicted binding sites for IRF4 and PU1 in the regulatory region of the CD48 coding gene. 1. https://www.uniprot.org/uniprot/P09326 https://pubmed.ncbi.nlm.nih.gov/29262348		
CD1A	1	• (BATF3 | CEBPa | CEBPb | CREB) & IRF4 & PU1 & PRDM1 & NCOR2
T-cell surface glycoprotein CD1a [1]. Antigen-presenting protein that binds self and non-self lipid and glycolipid antigens and presents them to T-cell receptors on natural killer T-cells [1]. IL4 signaling upregulates CD1a on cell surface of DC cells [2]. NCOR2 silencing repressed CD1A, that is one of the IL-4 signature		

genes [3]. Using matrix-scan, we predicted binding sites for BATF3, CEBPA, CEBPB, CREB1, IRF4, PRDM1, PU1 and NCOR2 in the regulatory region of the CD1A coding gene. 1. https://www.uniprot.org/uniprot/P06126 https://pubmed.ncbi.nlm.nih.gov/10629465/ https://pubmed.ncbi.nlm.nih.gov/29262348		
CD1B	1	• (CEBPa | CEBPb | IRF4) & PRDM1
T-cell surface glycoprotein CD1b [1]. During protein synthesis and maturation, CD1 family members bind endogenous lipids that are replaced by lipid or glycolipid antigens when the proteins are internalized and pass through endosomes or lysosomes, before trafficking back to the cell surface [1]. Human inflammatory moDC are HLADR CD11c cells that express markers found on classical DC such as CD1c, CD1a, CD1b [2]. Using matrix-scan, we predicted binding sites for CEBPA, CEBPB, IRF4 and PRDM1 in the regulatory region of the CD1B coding gene. 1. https://www.uniprot.org/uniprot/P29016 https://pubmed.ncbi.nlm.nih.gov/29448070		
CD1C	1	• FOXO1 & IRF4 & NR4A1 & PU1 & STAT6
T-cell surface glycoprotein CD1c [1], expressed in DC [2]. Antigen-presenting protein that binds self and non-self lipid and glycolipid antigens and presents them to T-cell receptors on natural killer T-cells. Using matrix-scan, we predicted binding sites for FOXO1, IRF4, NR4A1, PU1 and STAT6 in the regulatory region of the CD1C coding gene. 1. https://www.uniprot.org/uniprot/P29017 https://pubmed.ncbi.nlm.nih.gov/29448070		
CD40	1	• AP1
Tumor necrosis factor receptor superfamily member 5 [1], moDC marker [2]. Receptor for TNFSF5/CD40LG [3]. CD40 transduces TRAF6- and MAP3K8-mediated signals that activate ERK in macrophages and B cells, leading to induction of immunoglobulin secretion [1]. Using matrix-scan, we predicted binding sites for AP1 in the regulatory region of the CD40 coding gene. 1. https://www.uniprot.org/uniprot/P25942 https://pubmed.ncbi.nlm.nih.gov/24513968		

https://pubmed.ncbi.nlm.nih.gov/31331973/		
CD86	1	• AP1
T-lymphocyte activation antigen CD86 [1], moDC marker [2,3]. Receptor involved in the costimulatory signal essential for T-lymphocyte proliferation and interleukin-2 production, by binding CD28 or CTLA-4. CD86 presumably plays a critical role in the early events of T-cell activation and costimulation of naive T-cells. Using matrix-scan, we predicted binding sites for AP1 in the regulatory region of the CD86 coding gene. 1. https://www.uniprot.org/uniprot/P42081 https://pubmed.ncbi.nlm.nih.gov/27401672 https://pubmed.ncbi.nlm.nih.gov/29262348		
CD83	1	• STAT6 & NFKB2 & IRF4
CD83 antigen [1], moDC marker [2,3]. CD83 presumably plays a significant role in antigen presentation or the cellular interactions that follow lymphocyte activation. Using matrix-scan, we predicted binding sites for IRF4, NFKB2 and STAT6 in the regulatory regio of the CD83 coding gene. 1. https://www.uniprot.org/uniprot/Q01151 https://pubmed.ncbi.nlm.nih.gov/27401672 https://pubmed.ncbi.nlm.nih.gov/26758199/		
CD209	1	• AP1 & CREB & ELK4 & IRF4 & PU1 & STAT6
CD209 antigen [1], moDC marker [2]. Pathogen-recognition receptor expressed on the surface of immature dendritic cells (DCs) and involved in initiation of primary immune response. CD209 mediates the endocytosis of pathogen,s which are subsequently degraded in lysosomal compartments. CD209 was found exclusively expressed by MOs GMCS IL4 (0 tp 72h) [3]. Treatment with a STAT6 inhibitor affected the presence of the surface markers CD209 and CD83 during GM-CSF/IL-4-mediated differentiation to DCs [4]. Using matrix-scan, we predicted binding sites for AP1, CREB1, ELK4, IRF4, PU1 and STAT6 in the regulatory region of the CD209 coding gene. 1. https://www.uniprot.org/uniprot/Q9NNX6 https://pubmed.ncbi.nlm.nih.gov/24513968 https://pubmed.ncbi.nlm.nih.gov/29262348		

https://pubmed.ncbi.nlm.nih.gov/26758199/		
CD141	1	• (CEBPa | CREB) & USF1 & ATF1 & IRF4
Thrombomodulin [1,2], marker for moDC [3]. CD141 is a specific endothelial cell receptor that forms a 1:1 stoichiometric complex with thrombin. This complex is responsible for the conversion of protein C to the activated protein Ca [1]. Using matrix-scan, we predicted binding sites for ATF1, CEBPa, CREB1, IRF4 and USF1 in the regulatory region of the CD141 coding gene. 1. https://www.uniprot.org/uniprot/P07204 https://www.genecards.org/cgi-bin/carddisp.pl?gene=THBD&keywords=CD141 https://pubmed.ncbi.nlm.nih.gov/29448070		
CD226	1	• (BATF3 | CEBPa) & FOXO1 & IRF4 & PRDM1 & PU1 & STAT3 & STAT5 & STAT6 & USF1
CD226 antigen [1], expressed in moDCs [2]. Involved in intercellular adhesion, stimulates T-cell proliferation and cytokine production [1]. Using matrix-scan, we predicted binding sites for BATF3, CEBPa, FOXO1, IRF4, PRDM1, PU1, STAT3, STAT5, STAT6 and USF1 in the regulatory region of the CD226 coding gene. 1. https://www.uniprot.org/uniprot/Q15762 https://www.ncbi.nlm.nih.gov/pubmed/29262348		
DEC205	1	• FOXO1 & AP1 & PRDM1
Lymphocyte antigen 75 [1], moDC marker [2]. Acts as an endocytic receptor to direct captured antigens from the extracellular space to a specialized antigen-processing compartment (By similarity). Using matrix-scan, we predicted binding sites for FOXO1, AP1 and PRDM1 in the regulatory region of the DEC205 gene. 1. https://www.uniprot.org/uniprot/O60449 https://pubmed.ncbi.nlm.nih.gov/24513968		
DCIR	1	• STAT6 & PU1
C-type lectin domain family 4 member A [1,2], moDC marker [3]. Using matrix-scan, we predicted binding sites for STAT6 and PU1 in the regulatory region of the DCIR coding gene.		

1. https://www.uniprot.org/uniprot/Q9UMR7 https://www.genecards.org/cgi-bin/carddisp.pl?gene=CLEC4A&keywords=DCIR https://pubmed.ncbi.nlm.nih.gov/24513968		
Tet2	1	• PU1
Methylcytosine dioxygenase Tet2 [1]. Tet2 catalyzes the conversion of the modified genomic base 5-methylcytosine (5mC) into 5-hydroxymethylcytosine (5hmC) and plays a key role in active DNA demethylation. Tet2 has a preference for 5-hydroxymethylcytosine in CpG motifs [1]. TET2 downregulation partially impaired demethylation of both common and DC/ MAC-specific genes. PU1 has been shown to recruit TET2 [2]. 1. https://www.uniprot.org/uniprot/Q6N021 https://pubmed.ncbi.nlm.nih.gov/26758199		
PTPN1	1	• AhR
Tyrosine-protein phosphatase non-receptor type 1 [1]. PTPN1 acts as a regulator of endoplasmic reticulum unfolded protein response. It mediates the dephosphorylation of EIF2AK3 and PERK and thereby inactivates their protein kinase [2]. 1. https://www.uniprot.org/uniprot/P18031 https://pubmed.ncbi.nlm.nih.gov/11694501		
SOCS	1	• STAT3
Suppressor of cytokine signaling 1 [1]. SOCS family proteins form part of a classical negative feedback system that regulates cytokine signal transduction. SOCS1 is involved in negative regulation of cytokines that signal through the JAK/STAT3 pathway [1]. SOCS proteins are themselves encoded by STAT target genes and thus provide a transcription dependent negative feedback mechanism [2]. 1. https://www.uniprot.org/uniprot/O15524 https://pubmed.ncbi.nlm.nih.gov/30578415		
CD14	1	• STAT3 & FOXO1 & KLF4 & !STAT5
Monocyte differentiation antigen CD14 [1]. Coreceptor for bacterial lipopolysaccharide [1]. In concert with LBP, CD14 binds to monomeric lipopolysaccharide and delivers it to the LY96/TLR4 complex, thereby mediating the innate immune response to bacterial lipopolysaccharide [2]. The CD14 promoter is induced by KLF4 [3]. Using matrix-scan, we predict binding sites for FOXO1, KLF4, STAT3 and STAT5 in the regulatory region of CD14 coding gene.		

1. https://www.uniprot.org/uniprot/P08571 https://pubmed.ncbi.nlm.nih.gov/20133493/ https://pubmed.ncbi.nlm.nih.gov/17762869		
SELL	1	• STAT6 & FOXO1 & !PRDM1
L-selectin, monocyte associated [1], expressed in monocytes [2]. Calcium-dependent lectin that mediates cell adhesion by binding to glycoproteins on neighboring cells [1]. Using matrix-scan, we predicted binding sites for STAT6, FOXO1 and PRDM1 in the regulatory region of the SELL coding gene. 1. https://www.uniprot.org/uniprot/P14151 https://pubmed.ncbi.nlm.nih.gov/29262348		
CD163	1	• MAFB & IRF8 & !PRDM1:1
Scavenger receptor cysteine-rich type 1 protein M130 [1], expressed in macrophages [2]. Acute phase-regulated receptor involved in clearance and endocytosis of hemoglobin/haptoglobin complexes by macrophages, presumably thereby protecting tissues from free hemoglobin-mediated oxidative damage [1]. Using matrix-scan, we predicted binding sites for PRDM1, IRF8 and MAF8 in the regulatory region of the CD163 coding gene. 1. https://www.uniprot.org/uniprot/Q86VB7 https://pubmed.ncbi.nlm.nih.gov/29262348		
CD206	1	• MAFB & IRF8 & USF1 & !PRDM1
Macrophage mannose receptor 1 [1], expressed in macrophage [2]. CD206 mediates the endocytosis of glycoproteins by macrophages. CD206 binds both sulfated and non-sulfated polysaccharide chains [1]. Using matrix-scan, we predicted binding sites for MAFB, IRF8, USF1, and PRDM1 in the regulatory region of the CD206 coding gene. 1. https://www.uniprot.org/uniprot/P22897 https://pubmed.ncbi.nlm.nih.gov/29262348		
MERTK	1	• IRF8 & MAFB
Tyrosine-protein kinase Mer [1], expressed in macrophages [2]. MERTK transduces signals from the extracellular matrix into the cytoplasm by binding to several ligands including LGALS3, TUB, TULP1 or GAS6. MERTK regulates many physiological processes including cell survival, migration, differentiation, and phagocytosis of apoptotic cells [1]. Using matrix-scan, we predicted binding sites for IRF8 and MAFB in the regulatory region of the MERTK coding gene.		

1. https://www.uniprot.org/uniprot/Q12866 https://pubmed.ncbi.nlm.nih.gov/29262348		
CCDC151	1	• PU1:1 & AP1 & CEBPb
Coiled-coil domain-containing protein 115 [1], expressed in macrophages [2]. Ciliary protein involved in outer dynein arm assembly and required for motile cilia function [1]. Using matrix-scan, we predicted TFBS for PU1, CEBPB and AP1 in the regulatory region of the CCDC151 coding gene. 1. https://www.uniprot.org/uniprot/A5D8V7 https://pubmed.ncbi.nlm.nih.gov/28093525		
BCL2	1	• !JNK & STAT3:2
Apoptosis regulator Bcl-2 [1]. Bcl-2 suppresses apoptosis in a variety of cell systems including factor-dependent lymphohematopoietic and neural cells. Bcl-2 regulates cell death by controlling the mitochondrial membrane permeability. BCL2 is involved in a feedback loop system with caspases. STAT3 blocks the formation of autophagosomes by driving increased expression of antiautophagic genes Bcl2, Bcl2l1 and Mcl1 and suppression of the proautophagic gene Becn1, which encodes BCL1 [2,3]. 1. https://www.uniprot.org/uniprot/P10415 https://pubmed.ncbi.nlm.nih.gov/30578415 https://pubmed.ncbi.nlm.nih.gov/22323450		
BECN1	1	• !STAT3 & !BCL2 & JNK
Beclin-1 [1]. Plays a central role in autophagy and acts as core subunit of the PI3K complex that mediates formation of phosphatidylinositol 3-phosphate. GM CSF presumably induces autophagy by activating JNK, leading to the release of Beclin1 during monocyte differentiation. STAT3 blocks the formation of autophagosomes by driving increased expression of antiautophagic genes Bcl2, Bcl2l1 and Mcl1 and suppressing the proautophagic gene Becn1, which encodes BECN1 [2,3]. 1. https://www.uniprot.org/uniprot/Q14457 https://pubmed.ncbi.nlm.nih.gov/22323450 https://pubmed.ncbi.nlm.nih.gov/30578415		