
Supplements

Supplementary Resource 1

Genes marked in blue represent genes documented to be related in aging.

Below is a complete list (included found gene-specific information about the genes we looked up online that were implicated in our analyses).

(1) 3 cell types pseudo-bulk top DEGs

Downregulated in LR dataset:

Mrc1: The recognition of complex carbohydrate structures on glycoproteins is an important part of several biological processes, including cell-cell recognition, serum glycoprotein turnover, and neutralization of pathogens. The protein encoded by this gene is a type I membrane receptor that mediates the endocytosis of glycoproteins by macrophages.

Cbr2: Enables carbonyl reductase (NADPH) activity; identical protein binding activity; and protein self-association. Predicted to be involved in glucose metabolic process and xylulose metabolic process. Predicted to act upstream of or within NADH oxidation. Located in mitochondrion.

Dab2: This gene encodes a mitogen-responsive phosphoprotein. It is expressed in normal ovarian epithelial cells, but is down-regulated or absent from ovarian carcinoma cell lines, suggesting its role as a tumor suppressor.

Mgl2: macrophage galactose N-acetyl-galactosamine specific lectin 2

Lye1: This gene encodes a type I integral membrane glycoprotein. The encoded protein acts as a receptor and binds to both soluble and immobilized hyaluronan. This protein may function in lymphatic hyaluronan transport and have a role in tumor metastasis.

Pf4: This gene encodes a member of the CXC chemokine family. This chemokine is released from the alpha granules of activated platelets in the form of a homotetramer which has high affinity for heparin and is involved in platelet aggregation. This protein is chemotactic for numerous other cell type and also functions as an inhibitor of hematopoiesis, angiogenesis and T-cell function.

Ms4a7: This gene encodes a member of the membrane-spanning 4A gene family, members of which are characterized by common structural features and similar intron/exon splice boundaries and display unique expression patterns in hematopoietic cells and nonlymphoid tissues. This family member is associated with mature cellular function in the monocytic lineage, and it may be a component of a receptor complex involved in signal transduction.

Folr2: The protein encoded by this gene is a member of the folate receptor (FOLR) family, and these genes exist in a cluster on chromosome 11. Members of this gene family have a high affinity for folic acid and for several reduced folic acid derivatives, and they mediate delivery of 5-methyltetrahydrofolate to the interior of cells.

Ccl7: This gene encodes monocyte chemotactic protein 3, a secreted chemokine which attracts macrophages during inflammation and metastasis. It is a member of the C-C subfamily of chemokines which are characterized by having two adjacent cysteine residues.

Ifi47: Predicted to enable GTPase activity. Acts upstream of or within defense response. Predicted to be located in endoplasmic reticulum.

Upregulated in LR dataset:

Bloc1s1: BLOC1S1 is a component of the ubiquitously expressed BLOC1 multisubunit protein complex. BLOC1 is required for normal biogenesis of specialized organelles of the endosomal-lysosomal system

Tnfsf8: The protein encoded by this gene is a cytokine that belongs to the tumor necrosis factor (TNF) ligand family. This cytokine is a ligand for TNFRSF8/CD30, which is a cell surface antigen and a marker for Hodgkin lymphoma and related hematologic malignancies. The engagement of this cytokine expressed on B cell surface plays an inhibitory role in modulating Ig class switch.

Tnfaip2: This gene was identified as a gene whose expression can be induced by the tumor necrosis factor alpha (TNF) in umbilical vein endothelial cells. The expression of this gene was shown to be induced by retinoic acid in a cell line expressing a oncogenic version of the retinoic acid receptor alpha fusion protein

Rbpms: This gene encodes a member of the RNA recognition motif family of RNA-binding proteins. The RNA recognition motif is between 80-100 amino acids in length and family members contain one to four copies of the motif. The RNA recognition motif consists of two short stretches of conserved sequence, as well as a few highly conserved hydrophobic residues.

Zcchc7: Enables RNA binding activity. Located in cytosol and nucleolus.

Ttc1: This gene encodes a protein that belongs to the tetratrico peptide repeat superfamily of proteins. The encoded protein plays a role in protein-protein interactions, and binds to the Galpha subunit of G protein-coupled receptors to activate the Ras signaling pathway.

Gnl3: The protein encoded by this gene may interact with p53 and may be involved in tumorigenesis. The encoded protein also appears to be important for stem cell proliferation. This protein is found in both the nucleus and nucleolus.

Cox6a2: Cytochrome c oxidase (COX), the terminal enzyme of the mitochondrial respiratory chain, catalyzes the electron transfer from reduced cytochrome c to oxygen. It is a heteromeric complex consisting of 3 catalytic subunits encoded by mitochondrial genes and multiple structural subunits encoded by nuclear genes.

Itgax: This gene encodes the integrin alpha X chain protein. Integrins are heterodimeric integral membrane proteins composed of an alpha chain and a beta chain. This protein combines with the beta 2 chain (ITGB2) to form a leukocyte-specific integrin referred to as inactivated-C3b (iC3b) receptor 4 (CR4).

Tnf: This gene encodes a multifunctional proinflammatory cytokine that belongs to the tumor necrosis factor (TNF) superfamily. This cytokine is mainly secreted by macrophages. It can bind to, and thus functions through its receptors TNFRSF1A/TNFR1 and TNFRSF1B/TNFBR. This cytokine is involved in the regulation of a wide spectrum of biological processes including cell proliferation, differentiation, apoptosis, lipid metabolism, and coagulation.

Downregulated in the TMS dataset:

Zzz3: Predicted to enable DNA binding activity and zinc ion binding activity. Predicted to be involved in histone H4 acetylation. Located in nucleolus and nucleoplasm.

Phf20l1: Predicted to enable metal ion binding activity. Predicted to be involved in histone acetylation and regulation of transcription by RNA polymerase II. Predicted to be located in nucleus. Predicted to be part of NSL complex.

Pde6d: This gene encodes the delta subunit of rod-specific photoreceptor phosphodiesterase (PDE), a key enzyme in the phototransduction cascade.

Pdk1l: Predicted to enable protein serine/threonine kinase activity. Predicted to be involved in meiotic cell cycle.

Pdk2: This gene encodes a member of the pyruvate dehydrogenase kinase family. The encoded protein phosphorylates pyruvate dehydrogenase, down-regulating the activity of the mitochondrial pyruvate dehydrogenase complex.

Pea15a: This gene encodes a death effector domain-containing protein that functions as a negative regulator of apoptosis. The encoded protein is an endogenous substrate for protein kinase C.

Peo1: This gene encodes a hexameric DNA helicase which unwinds short stretches of double-stranded DNA in the 5' to 3' direction and, along with mitochondrial single-stranded DNA binding protein and mtDNA polymerase gamma, is thought to play a key role in mtDNA replication.

Pex5: The product of this gene binds to the C-terminal PTS1-type tripeptide peroxisomal targeting signal (SKL-type) and plays an essential role in peroxisomal protein import. Peroxins (PEXs) are proteins that are essential for the assembly of functional peroxisomes

Pfdn1: This gene encodes a member of the prefoldin beta subunit family. The encoded protein is one of six subunits of prefoldin, a molecular chaperone complex that binds and stabilizes newly synthesized polypeptides, thereby allowing them to fold correctly.

Upregulated in the TMS dataset:

Cst7: The cystatin superfamily encompasses proteins that contain multiple cystatin-like sequences. Some of the members are active cysteine protease inhibitors, while others have lost or perhaps never acquired this inhibitory activity.

Wdr89: WDR89 (WD Repeat Domain 89) is a Protein Coding gene. Diseases associated with WDR89 include Adamantinous Craniopharyngioma

Ch25h: This is an intronless gene that is involved in cholesterol and lipid metabolism. The encoded protein is a membrane protein and contains clusters of histidine residues essential for catalytic activity. Unlike most other sterol hydroxylases, this enzyme is a member of a small family of enzymes that utilize diiron cofactors to catalyze the hydroxylation of hydrophobic substrates.

Sfn1: This gene encodes a cell cycle checkpoint protein. The encoded protein binds to translation and initiation factors and functions as a regulator of mitotic translation. In response to DNA damage this protein plays a role in preventing DNA errors during mitosis.

Nrgn: Neurogranin (NRGN) is the human homolog of the neuron-specific rat RC3/neurogranin gene. This gene encodes a postsynaptic protein kinase substrate that binds calmodulin in the absence of calcium.
Slamf9: This gene encodes a member of the signaling lymphocytic activation molecule family. The encoded protein is a cell surface molecule that consists of two extracellular immunoglobulin domains, a transmembrane domain and a short cytoplasmic tail that lacks the signal transduction motifs found in other family members.
Pou3f1: Enables sequence-specific double-stranded DNA binding activity. Predicted to be involved in negative regulation of transcription by RNA polymerase II; positive regulation of gene expression; and positive regulation of transcription, DNA-templated.

Crlf2: This gene encodes a member of the type I cytokine receptor family.

AW112010: lncRNA AW112010 expression is increased in proinflammatory T cells, AW112010 associates with histone demethylase KDM5A, AW112010 suppresses IL-10 expression through histone demethylation.

(2) Microglia top DEGs

Upregulated in the TMS dataset

Dlg5: This gene encodes a member of the family of discs large (DLG) homologs, a subset of the membrane-associated guanylate kinase (MAGUK) superfamily. The MAGUK proteins are composed of a catalytically inactive guanylate kinase domain, in addition to PDZ and SH3 domains, and are thought to function as scaffolding molecules at sites of cell-cell contact.

Pdzrn4: Predicted to enable metal ion binding activity.

Il8bp: The protein encoded by this gene functions as an inhibitor of the proinflammatory cytokine, IL18. It binds IL18, prevents the binding of IL18 to its receptor, and thus inhibits IL18-induced IFN-gamma production, resulting in reduced T-helper type 1 immune responses.

Lsp1: This gene encodes an intracellular F-actin binding protein. The protein is expressed in lymphocytes, neutrophils, macrophages, and endothelium and may regulate neutrophil motility, adhesion to fibrinogen matrix proteins, and transendothelial migration.

Cst7: The cystatin superfamily encompasses proteins that contain multiple cystatin-like sequences. Some of the members are active cysteine protease inhibitors, while others have lost or perhaps never acquired this inhibitory activity.

Tnfsf8: The protein encoded by this gene is a cytokine that belongs to the tumor necrosis factor (TNF) ligand family. This cytokine is a ligand for TNFRSF8/CD30, which is a cell surface antigen and a marker for Hodgkin lymphoma and related hematologic malignancies.

Tnfsf13b: The protein encoded by this gene is a cytokine that belongs to the tumor necrosis factor (TNF) ligand family.

Mit4: Predicted to enable metal ion binding activity. Predicted to be involved in cellular response to metal ion; cellular zinc ion homeostasis; and detoxification of copper ion.

Idr2: Predicted to act upstream of or within several processes, including homeostasis of number of cells within a tissue; insulin secretion; and response to glucose. Predicted to be located in endoplasmic reticulum membrane.

Iifitm3: Interferon-induced transmembrane (IFITM) proteins are a family of interferon induced antiviral proteins.

Downregulated in the TMS dataset

Zzz3: Predicted to enable DNA binding activity and zinc ion binding activity. Predicted to be involved in histone H4 acetylation.

Nudcd3: The product of this gene functions to maintain the stability of dynein intermediate chain. Depletion of this gene product results in aggregation and degradation of dynein intermediate chain, mislocalization of the dynein complex from kinetochores, spindle microtubules, and spindle poles, and loss of gamma-tubulin from spindle poles.

Nup155: Nucleoporins are proteins that play an important role in the assembly and functioning of the nuclear pore complex (NPC) which regulates the movement of macromolecules across the nuclear envelope (NE). The protein encoded by this gene plays a role in the fusion of NE vesicles and formation of the double membrane NE.

Nup160: NUP160 is 1 of up to 60 proteins that make up the 120-MD nuclear pore complex, which mediates nucleoplasmic transport.

Nup11: This gene encodes a member of the nucleoporin family that shares 87% sequence identity with rat nucleoporin p58. The protein is localized to the nuclear rim and is a component of the nuclear pore complex (NPC).

Nxt2: The protein encoded by this gene contains a nuclear transport factor 2 (NTF2) domain, which plays an important role in the trafficking of macromolecules, ions, and small molecules between the cytoplasm and nucleus. This protein may also have a role in mRNA nuclear export.

Odf2l: Involved in negative regulation of cilium assembly. Located in centriolar satellite and ciliary basal body.

Odf1: OFD1 protein is located at the base of cilia, which are finger-like projections that stick out from the surface of cells. Cilia are involved in cell movement and in many different chemical signaling pathways.

Ogfod1: Enables peptidyl-proline 3-dioxygenase activity. Involved in several processes, including peptidyl-proline hydroxylation; regulation of translational termination; and stress granule assembly.

Opa1: OPA1 protein is active in the inner membrane of cell structures called mitochondria, which are the energy-producing centers in cells.

Upregulated in the LR dataset

Idr2: Predicted to act upstream of or within several processes, including homeostasis of number of cells within a tissue; insulin secretion; and response to glucose

Fcgr4: is a mouse IgE receptor that resembles macrophage MS4A2 protein in humans

Mtpn: The transcript produced from this gene is bi-cistronic and can encode both myotrophin and leucine zipper protein 6.

Bag4: The protein encoded by this gene is a member of the BAG1-related protein family. BAG1 is an anti-apoptotic protein that functions through interactions with a variety of cell apoptosis and growth related proteins including BCL-2, Raf-protein kinase, steroid hormone receptors, growth factor receptors and members of the heat shock protein 70 kDa family. This protein contains a BAG domain near the C-terminus, which could bind and inhibit the chaperone activity of Hsc70/Hsp70.

Capg: This gene encodes a member of the gelsolin/villin family of actin-regulatory proteins. The encoded protein reversibly blocks the barbed ends of F-actin filaments in a Ca²⁺ and phosphoinositide-regulated manner, but does not sever preformed actin filaments.

Nrd1: This gene encodes a zinc-dependent endopeptidase that cleaves peptide substrates at the N-terminus of arginine residues in dibasic moieties and is a member of the peptidase M16 family. This protein interacts with heparin-binding EGF-like growth factor and plays a role in cell migration and proliferation.

Atg5: The protein encoded by this gene, in combination with autophagy protein 12, functions as an E1-like activating enzyme in a ubiquitin-like conjugating system. The encoded protein is involved in several cellular processes, including autophagic vesicle formation, mitochondrial quality control after oxidative damage, negative regulation of the innate antiviral immune response, lymphocyte development and proliferation, MHC II antigen presentation, adipocyte differentiation, and apoptosis.

Fam172a: Predicted to contribute to siRNA binding activity. Predicted to be involved in heterochromatin assembly by small RNA; neural crest cell development; and regulation of alternative mRNA splicing, via spliceosome. Located in endoplasmic reticulum.

Ttc1: This gene encodes a protein that belongs to the tetratrico peptide repeat superfamily of proteins. The encoded protein plays a role in protein-protein interactions, and binds to the Galpha subunit of G protein-coupled receptors to activate the Ras signaling pathway.

Dock9: Enables cadherin binding activity. Predicted to be involved in positive regulation of GTPase activity. Located in membrane.

Downregulated in the LR dataset:

Tmem229b: Predicted to act upstream of or within response to bacterium. Predicted to be integral component of membrane.

St8sia4: The protein encoded by this gene catalyzes the polycondensation of alpha-2,8-linked sialic acid required for the synthesis of polysialic acid, a modulator of the adhesive properties of neural cell adhesion molecule (NCAM1).

Ccr1: This gene encodes a member of the beta chemokine receptor family, which is predicted to be a seven transmembrane protein similar to G protein-coupled receptors.

Pld1: This gene encodes a phosphatidylcholine-specific phospholipase which catalyzes the hydrolysis of phosphatidylcholine in order to yield phosphatidic acid and choline. The enzyme may play a role in signal transduction and subcellular trafficking.

Luzp1: This gene encodes a protein that contains a leucine zipper motif. The exact function of the encoded protein is not known. In mice this gene affects neural tube closure.

Rundc3a: Predicted to enable GTPase regulator activity. Predicted to be involved in positive regulation of cGMP-mediated signaling. Located in intracellular membrane-bounded organelle.

Metrn: Meteorin regulates glial cell differentiation and promotes the formation of axonal networks during neurogenesis

Micall1: Enables identical protein binding activity; phosphatidic acid binding activity; and small GTPase binding activity. Involved in several processes, including plasma membrane tubulation; protein localization to endosome; and slow endocytic recycling.

S1pr2: This gene encodes a member of the G protein-coupled receptors, as well as the EDG family of proteins. The encoded protein is a receptor for sphingosine 1-phosphate, which participates in cell proliferation, survival, and transcriptional activation.

Arhgdig: The GDP-dissociation inhibitors (GDIs) play a primary role in modulating the activation of GTPases by inhibiting the exchange of GDP for GTP.

(3) Neurons top DEGs

Upregulated in the TMS dataset:

Fhad1: FHAD1 (Forkhead Associated Phosphopeptide Binding Domain 1) is a Protein Coding gene.

Chst1: This locus encodes a member of the keratin sulfotransferase family of proteins. The encoded enzyme catalyzes the sulfation of the proteoglycan keratin.

Camk2a: The product of this gene belongs to the serine/threonine protein kinases family, and to the Ca(2+)/calmodulin-dependent protein kinases subfamily. Calcium signaling is crucial for several aspects of plasticity at glutamatergic synapses.

Etv1: This gene encodes a member of the ETS (E twenty-six) family of transcription factors. The ETS proteins regulate many target genes that modulate biological processes like cell growth, angiogenesis, migration, proliferation and differentiation.

Prkce: Protein kinase C (PKC) is a family of serine- and threonine-specific protein kinases that can be activated by calcium and the second messenger diacylglycerol. PKC family members phosphorylate a wide variety of protein targets and are known to be involved in diverse cellular signaling pathways.

Wfdc2: This gene encodes a protein that is a member of the WFDC domain family. The WFDC domain, or WAP Signature motif, contains eight cysteines forming four disulfide bonds at the core of the protein, and functions as a protease inhibitor in many family members.

Hmox1: Heme oxygenase, an essential enzyme in heme catabolism, cleaves heme to form biliverdin, which is subsequently converted to bilirubin by biliverdin reductase, and carbon monoxide, a putative neurotransmitter.

Nbn: *NBN* gene provides instructions for making a protein called nibrin. This protein is involved in several critical cellular functions, including the repair of damaged DNA.

Acot1: Enables acyl-CoA hydrolase activity. Involved in acyl-CoA metabolic process; long-chain fatty acid metabolic process; and very long-chain fatty acid metabolic process. Located in cytosol.

Nbl1: This gene product is the founding member of the evolutionarily conserved CAN (Cerberus and DAN) family of proteins, which contain a domain resembling the CTCK (C-terminal cystine knot-like) motif found in a number of signaling molecules. These proteins are secreted, and act as BMP (bone morphogenetic protein) antagonists by binding to BMPs and preventing them from interacting with their receptors. They may thus play an important role during growth and development.

Downregulated in the TMS dataset:

Rnf146: Enables poly-ADP-D-ribose binding activity and ubiquitin-protein transferase activity. Involved in positive regulation of canonical Wnt signaling pathway; protein ubiquitination; and ubiquitin-dependent protein catabolic process.

Txn2: This nuclear gene encodes a mitochondrial member of the thioredoxin family, a group of small multifunctional redox-active proteins. The encoded protein may play important roles in the regulation of the mitochondrial membrane potential and in protection against oxidant-induced apoptosis.

Uba6: Modification of proteins with ubiquitin (UBB; MIM 191339) or ubiquitin-like proteins controls many signaling networks and requires a ubiquitin-activating enzyme (E1), a ubiquitin conjugating enzyme (E2), and a ubiquitin protein ligase (E3). UBE1L2 is an E1 enzyme that initiates the activation and conjugation of ubiquitin-like proteins

Uba3: The modification of proteins with ubiquitin is an important cellular mechanism for targeting abnormal or short-lived proteins for degradation. Ubiquitination involves at least three classes of enzymes: ubiquitin-activating enzymes, or E1s, ubiquitin-conjugating enzymes, or E2s, and ubiquitin-protein ligases, or E3s.

Osgin2: Predicted to enable growth factor activity. Predicted to be involved in negative regulation of cell growth.

Usp1: This gene encodes a member of the ubiquitin-specific processing (UBP) family of proteases that is a deubiquitinating enzyme (DUB) with His and Cys domains. This protein is located in the cytoplasm and cleaves the ubiquitin moiety from ubiquitin-fused precursors and ubiquitinylated proteins.

Dnajc6: DNAJC6 belongs to the evolutionarily conserved DNAJ/HSP40 family of proteins, which regulate molecular chaperone activity by stimulating ATPase activity. DNAJ proteins may have up to 3 distinct domains: a conserved 70-amino acid J domain, usually at the N terminus, a glycine/phenylalanine (G/F)-rich region, and a cysteine-rich domain containing 4 motifs resembling a zinc finger domain

Dnajc9: Enables chaperone binding activity; heat shock protein binding activity; and histone binding activity. Involved in nucleosome assembly and positive regulation of ATPase activity. Located in several cellular components, including cytosol; extracellular space; and nucleoplasm. Part of chaperone complex.

Dner: Predicted to enable Notch binding activity. Involved in central nervous system development. Located in dendrite; early endosome; and plasma membrane.

Csbpl6: This gene encodes a member of the oxysterol-binding protein (OSBP) family, a group of intracellular lipid receptors. Most members contain an N-terminal pleckstrin homology domain and a highly conserved C-terminal OSBP-like sterol-binding domain.

Upregulated in the LR dataset:

Tbc1d12: Predicted to enable GTPase activator activity. Predicted to be involved in activation of GTPase activity; intracellular protein transport; and regulation of autophagosome assembly. Predicted to be active in autophagosome and recycling endosome.

Dpp3: This gene encodes a protein that is a member of the M49 family of metallopeptidases. This cytoplasmic protein binds a single zinc ion with its zinc-binding motif (HELLGH) and has post-proline dipeptidyl aminopeptidase activity, cleaving Xaa-Pro dipeptides from the N-termini of proteins.

Atg2a: Predicted to enable phosphatidylinositol-3-phosphate binding activity. Involved in autophagosome assembly. Predicted to be located in endoplasmic reticulum membrane; lipid droplet; and phagophore assembly site membrane. Predicted to be active in phagophore assembly site.

Gpx7: Enables catalase activity. Predicted to be involved in cellular response to oxidative stress. Located in endoplasmic reticulum.

Cul7: UL7 gene provides instructions for making a protein called cullin-7. This protein plays a role in the ubiquitin-proteasome system, which is the cell machinery that breaks down (degrades) unwanted proteins

Pp4r1: This gene encodes one of several alternate regulatory subunits of serine/threonine protein phosphatase 4 (PP4). The protein features multiple HEAT repeats. This protein forms a complex with PP4RC.

Bcl2l11: The protein encoded by this gene belongs to the BCL-2 protein family. BCL-2 family members form hetero- or homodimers and act as anti- or pro-apoptotic regulators that are involved in a wide variety of cellular activities.

Downregulated in the LR dataset:

Tpm4: This gene encodes a member of the tropomyosin family of actin-binding proteins involved in the contractile system of striated and smooth muscles and the cytoskeleton of non-muscle cells. Tropomyosins are dimers of coiled-coil proteins that polymerize end-to-end along the major groove in most actin filaments. They provide stability to the filaments and regulate access of other actin-binding proteins.

Sms: MS gene provides instructions for making an enzyme called spermine synthase. This enzyme is involved in the production of spermine, which is a type of small molecule called a polyamine. Specifically, the enzyme carries out the reaction that creates spermine from a related polyamine, spermidine. Polyamines have many critical functions within cells. Studies suggest that these molecules play roles in cell growth and division, the production of new proteins, the repair of damaged tissues, and the controlled self-destruction of cells (apoptosis).

Gnl3: The protein encoded by this gene may interact with p53 and may be involved in tumorigenesis. The encoded protein also appears to be important for stem cell proliferation. This protein is found in both the nucleus and nucleolus.

Bloc1s1: BLOC1S1 is a component of the ubiquitously expressed BLOC1 multisubunit protein complex. BLOC1 is required for normal biogenesis of specialized organelles of the endosomal-lysosomal system, such as melanosomes and platelet dense granules

Mast4: This gene encodes a member of the microtubule-associated serine/threonine protein kinases. The proteins in this family contain a domain that gives the kinase the ability to determine its own scaffold to control the effects of their kinase activities. Alternative splicing results in multiple transcript variants encoding different isoforms.

Ahi1: This gene is apparently required for both cerebellar and cortical development in humans. This gene mutations cause specific forms of Joubert syndrome-related disorders. Joubert syndrome (JS) is a recessively inherited developmental brain disorder with several identified causative chromosomal loci.

Nolc1: Enables protein heterodimerization activity and protein-macromolecule adaptor activity. Involved in neural crest cell development; neural crest formation; and regulation of translation.

Zfp385b: zinc finger protein 385B

Lrp1b: This gene encodes a member of the low density lipoprotein (LDL) receptor family. These receptors play a wide variety of roles in normal cell function and development due to their interactions with multiple ligands.

(4) Macrophage top DEGs

Upregulated in the TMS dataset:

Ephx1: Epoxide hydrolase is a critical biotransformation enzyme that converts epoxides from the degradation of aromatic compounds to trans-dihydrodiols which can be conjugated and excreted from the body.

Dcdc28a

Oasl1: Enables DNA binding activity and double-stranded RNA binding activity. Involved in several processes, including interleukin-27-mediated signaling pathway; negative regulation of viral genome replication; and positive regulation of RIG-I signaling pathway.

Zbtb25: Predicted to enable DNA-binding transcription repressor activity, RNA polymerase II-specific and RNA polymerase II cis-regulatory region sequence-specific DNA binding activity. Predicted to be involved in regulation of transcription by RNA polymerase II. Located

Cbr4: Enables several functions, including 3-oxoacyl-[acyl-carrier-protein] reductase (NADPH) activity; NADPH binding activity; and NADPH dehydrogenase (quinone) activity. Involved in fatty acid biosynthetic process; glycoside metabolic process; and protein tetramerization. Located in mitochondrial matrix. Part of oxidoreductase complex.

Kat5: The protein encoded by this gene belongs to the MYST family of histone acetyl transferases (HATs) and was originally isolated as an HIV-1 TAT-interactive protein. HATs play important roles in regulating chromatin remodeling, transcription and other nuclear processes by acetylating histone and nonhistone proteins. This protein is a histone acetylase that has a role in DNA repair and apoptosis and is thought to play an important role in signal transduction. Alternative splicing of this gene results in multiple transcript variants.

Zbtb17: This gene encodes a zinc finger protein involved in the regulation of c-myc. The symbol MIZ1 has also been associated with PIAS2 which is a different gene located on chromosome 18.

Cpt2: The protein encoded by this gene is a nuclear protein which is transported to the mitochondrial inner membrane. Together with carnitine palmitoyltransferase I, the encoded protein oxidizes long-chain fatty acids in the mitochondria. Defects in this gene are associated with mitochondrial long-chain fatty-acid (LCFA) oxidation disorders.

Immp2l: This gene encodes a protein involved in processing the signal peptide sequences used to direct mitochondrial proteins to the mitochondria. The encoded protein resides in the mitochondria and is one of the necessary proteins for the catalytic activity of the mitochondrial inner membrane peptidase (IMP) complex.

Il7r: The protein encoded by this gene is a receptor for interleukin 7 (IL7). The function of this receptor requires the interleukin 2 receptor, gamma chain (IL2RG), which is a common gamma chain shared by the receptors of various cytokines, including interleukins 2, 4, 7, 9, and 15. This protein has been shown to play a critical role in V(D)J recombination during lymphocyte development.

Downregulated in the TMS dataset:

Impact: Predicted to enable actin binding activity and ribosome binding activity. Predicted to be involved in several processes, including GCN2-mediated signaling; cellular response to starvation; and negative regulation of nitrogen compound metabolic process.

Arnt: This gene encodes a protein containing a basic helix-loop-helix domain and two characteristic PAS domains along with a PAC domain. The encoded protein binds to ligand-bound aryl hydrocarbon receptor and aids in the movement of this complex to the nucleus, where it promotes the expression of genes involved in xenobiotic metabolism.

Dab2: This gene encodes a mitogen-responsive phosphoprotein. It is expressed in normal ovarian epithelial cells, but is down-regulated or absent from ovarian carcinoma cell lines, suggesting its role as a tumor suppressor.

Wdr3: This gene encodes a nuclear protein containing 10 WD repeats. WD repeats are approximately 30- to 40-amino acid domains containing several conserved residues, which usually include a trp-asp at the C-terminal end. Proteins belonging to the WD repeat family are involved in a variety of cellular processes, including cell cycle progression, signal transduction, apoptosis, and gene regulation.

Ncbp2: The product of this gene is a component of the nuclear cap-binding protein complex (CBC), which binds to the monomethylated 5' cap of nascent pre-mRNA in the nucleoplasm. The encoded protein has an RNP domain commonly found in RNA binding proteins, and contains the cap-binding activity.

Ube2q2: Enables ubiquitin-protein transferase activity. Involved in protein K48-linked ubiquitination. Predicted to be located in cytosol. Predicted to be active in nucleus.

Map2k1: MAP2K1 gene provides instructions for making a protein known as MEK1 protein kinase. This protein is part of a signaling pathway called the RAS/MAPK pathway, which transmits chemical signals from outside the cell to the cell's nucleus.

Maged1: This gene is a member of the melanoma antigen gene (MAGE) family. Most of the genes of this family encode tumor specific antigens that are not expressed in normal adult tissues except testis

Zfp87: zinc finger protein 87

Dse: The protein encoded by this gene is a tumor-rejection antigen. It is localized to the endoplasmic reticulum and functions to convert D-glucuronic acid to L-iduronic acid during the biosynthesis of dermatan sulfate.

Upregulated in the LR dataset:

Ap3d1: The protein encoded by this gene is a subunit of the AP3 adaptor-like complex, which is not clathrin-associated, but is associated with the golgi region, as well as more peripheral structures. The AP-3 complex facilitates the budding of vesicles from the golgi membrane, and may be directly involved in trafficking to lysosomes.

Herc2: This gene belongs to the HERC gene family that encodes a group of unusually large proteins, which contain multiple structural domains. All members have at least 1 copy of an N-terminal region showing homology to the cell cycle regulator RCC1 and a C-terminal HECT (homologous to E6-AP C terminus) domain found in a number of E3 ubiquitin protein ligases.

Mhas1: MLH1 gene provides instructions for making a protein that plays an essential role in repairing DNA.

Tmcc1: Enables identical protein binding activity. Involved in several processes, including endosome fission; endosome membrane tubulation; and membrane fission. Located in cytosol; endoplasmic reticulum-endosome membrane contact site; and rough endoplasmic reticulum.

Zfp260: Predicted to enable DNA-binding transcription factor activity, RNA polymerase II-specific and RNA polymerase II cis-regulatory region sequence-specific DNA binding activity. Predicted to be involved in regulation of transcription by RNA polymerase II. Located in cytosol and nucleoplasm.

Trip10: Enables identical protein binding activity. Predicted to be involved in actin cytoskeleton organization; endocytosis; and signal transduction. Located in nucleoplasm. Biomarker of Huntington's disease.

Prp8: Pre-mRNA splicing occurs in 2 sequential transesterification steps. The protein encoded by this gene is a component of both U2- and U12-dependent spliceosomes, and found to be essential for the catalytic step II in pre-mRNA splicing process.

Phf12: Enables phosphatidylinositol binding activity and transcription corepressor activity. Involved in negative regulation of transcription, DNA-templated. Acts upstream of or within negative regulation of transcription by RNA polymerase II.

Tnfaip2: This gene was identified as a gene whose expression can be induced by the tumor necrosis factor alpha (TNF) in umbilical vein endothelial cells. The expression of this gene was shown to be induced by retinoic acid in a cell line expressing a oncogenic version of the retinoic acid receptor alpha fusion protein, which suggested that this gene may be a retinoic acid target gene in acute promyelocytic leukemia.

Downregulated in the LR dataset:

Mt2: is gene is a member of the metallothionein family of genes. Proteins encoded by this gene family are low in molecular weight, are cysteine-rich, lack aromatic residues, and bind divalent heavy metal ions, altering the intracellular concentration of heavy metals in the cell. These proteins act as anti-oxidants, protect against hydroxyl free radicals, are important in homeostatic control of metal in the cell, and play a role in detoxification of heavy metals.

Vegfb: This gene encodes a member of the PDGF (platelet-derived growth factor)/VEGF (vascular endothelial growth factor) family. The VEGF family members regulate the formation of blood vessels and are involved in endothelial cell physiology. This member is a ligand for VEGFR-1 (vascular endothelial growth factor receptor 1) and NRP-1 (neuropilin-1). Studies in mice showed that this gene was co-expressed with nuclear-encoded mitochondrial genes and the encoded protein specifically controlled endothelial uptake of fatty acids.

Ctdsp2: Enables RNA polymerase II CTD heptapeptide repeat phosphatase activity. Involved in protein dephosphorylation. Predicted to be located in nucleoplasm.

Ccdc107: This gene encodes a membrane protein which contains a coiled-coil domain in the central region. Multiple alternatively spliced transcript variants encoding different isoforms have been found for this gene.

Mapk8ip1: This gene encodes a regulator of the pancreatic beta-cell function. It is highly similar to JIP-1, a mouse protein known to be a regulator of c-Jun amino-terminal kinase (Mapk8). This protein has been shown to prevent MAPK8 mediated activation of transcription factors, and to decrease IL-1 beta and MAP kinase kinase 1 (MEKK1) induced apoptosis in pancreatic beta cells. This protein also functions as a DNA-binding transactivator of the glucose transporter GLUT2.

Sec23b: SEC23B gene provides instructions for making one component of a large group of interacting proteins called coat protein complex II (COPII). COPII is involved in the formation of vesicles, which are small sac-like structures that transport proteins and other materials within cells. Specifically, COPII triggers the formation of vesicles in a cellular structure called the endoplasmic reticulum (ER)

Smad5: The protein encoded by this gene is involved in the transforming growth factor beta signaling pathway that results in an inhibition of the proliferation of hematopoietic progenitor cells. The encoded protein is activated by bone morphogenetic proteins type 1 receptor kinase, and may be involved in cancer. Alternative splicing results in multiple transcript variants.

(5) Intersection of the two datasets, mean top DEGs

Downregulated in the intersection:

Gsn: a protein that binds to the plus ends of actin monomers, to prevent the exchange of monomers

Dcn: Dcn plays a role in collagen fibril assembly, crucial to the extracellular matrix, and is a stromal-associated gene

Jun: c-Jun is a protein that in humans is encoded by the JUN gene. c-Jun, in combination with c-Fos, forms the AP-1 early response transcription factor.

Fos: c-Jun, in combination with c-Fos, forms the AP-1 early response transcription factor.

Dusp1: The protein encoded by this gene is a phosphatase with dual specificity for tyrosine and threonine. The encoded protein can dephosphorylate MAP kinase MAPK1/ERK2, which results in its involvement in several cellular processes. This protein appears to play an important role in the human cellular response to environmental stress as well as in the negative regulation of cellular proliferation.

Egr1: The protein encoded by this gene belongs to the EGR family of C2H2-type zinc-finger proteins. It is a nuclear protein and functions as a transcriptional regulator. The products of target genes it activates are required for differentiation and mitogenesis.

Ins2: Insulin

Serpingle1: SERPING1 gene provides instructions for making a protein called C1 inhibitor, which is a type of serine protease inhibitor (serpin). Serpins help control several types of chemical reactions by blocking the activity of certain proteins. C1 inhibitor is important for controlling a range of processes involved in maintaining blood vessels, including inflammation.

S100a9: The protein encoded by this gene is a member of the S100 family of proteins containing 2 EF-hand calcium-binding motifs. S100 proteins are localized in the cytoplasm and/or nucleus of a wide range of cells, and involved in the regulation of a number of cellular processes such as cell cycle progression and differentiation.

Ccdc80: Predicted to enable glycosaminoglycan binding activity. Predicted to act upstream of or within extracellular matrix organization; positive regulation of cell-substrate adhesion; and response to bacterium. Predicted to be located in extracellular matrix.

Upregulated in the intersection:

Crlf2: This gene encodes a member of the type I cytokine receptor family. The encoded protein is a receptor for thymic stromal lymphopoietin (TSLP). Together with the interleukin 7 receptor (IL7R), the encoded protein and TSLP activate STAT3, STAT5, and JAK2 pathways, which control processes such as cell proliferation and development of the hematopoietic system.

Tnfsf13b: The protein encoded by this gene is a cytokine that belongs to the tumor necrosis factor (TNF) ligand family. This cytokine is a ligand for receptors TNFRSF13B/TACI, TNFRSF17/BCMA, and TNFRSF13C/BAFFR. This cytokine is expressed in B cell lineage cells, and acts as a potent B cell activator. It has been also shown to play an important role in the proliferation and differentiation of B cells.

H2-Q6: Predicted to enable several functions, including 14-3-3 protein binding activity; TAP binding activity; and signaling receptor binding activity. Predicted to be involved in several processes, including antigen processing and presentation of endogenous peptide antigen via MHC class I via ER pathway

Cst7: The cystatin superfamily encompasses proteins that contain multiple cystatin-like sequences. Some of the members are active cysteine protease inhibitors, while others have lost or perhaps never acquired this inhibitory activity.

Pcdl1: Programmed cell death protein 1 (PDCD1) is an immune-inhibitory receptor expressed in activated T cells; it is involved in the regulation of T-cell functions, including those of effector CD8+ T cells. In addition, this protein can also promote the differentiation of CD4+ T cells into T regulatory cells.

Rxrg: This gene encodes a member of the retinoid X receptor (RXR) family of nuclear receptors which are involved in mediating the antiproliferative effects of retinoic acid (RA). This receptor forms dimers with the retinoic acid, thyroid hormone, and vitamin D receptors, increasing both DNA binding and transcriptional function on their respective response elements.

Kcnj12: This gene encodes an inwardly rectifying K+ channel which may be blocked by divalent cations. This protein is thought to be one of multiple inwardly rectifying channels which contribute to the cardiac inward rectifier current (IK1).

Tnfsf8: The protein encoded by this gene is a cytokine that belongs to the tumor necrosis factor (TNF) ligand family. This cytokine is a ligand for TNFRSF8/CD30, which is a cell surface antigen and a marker for Hodgkin lymphoma and related hematologic malignancies.

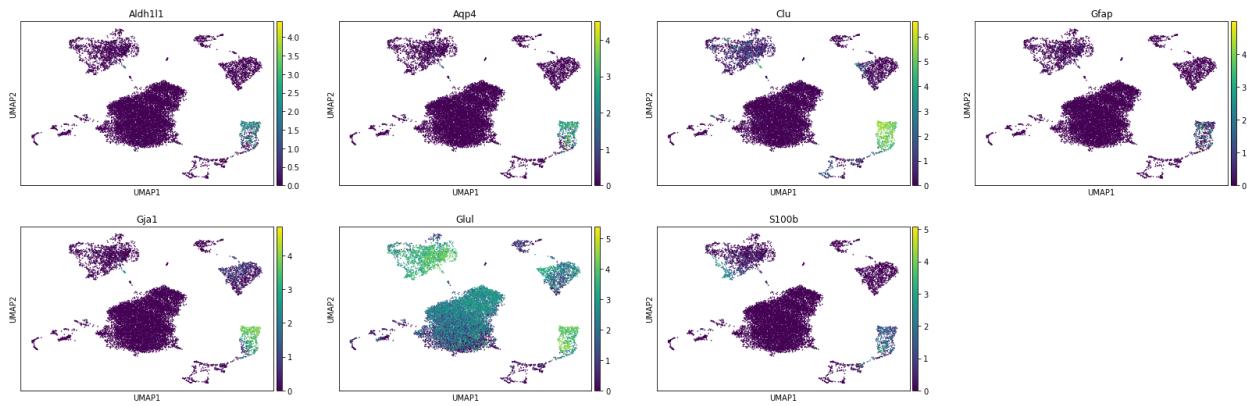
Cox6a2: Cytochrome c oxidase (COX), the terminal enzyme of the mitochondrial respiratory chain, catalyzes the electron transfer from reduced cytochrome c to oxygen. It is a heteromeric complex consisting of 3 catalytic subunits encoded by mitochondrial genes and multiple structural subunits encoded by nuclear genes.

Itgax: This gene encodes the integrin alpha X chain protein. Integrins are heterodimeric integral membrane proteins composed of an alpha chain and a beta chain. This protein combines with the beta 2 chain (ITGB2) to form a leukocyte-specific integrin referred to as inactivated-C3b (iC3b) receptor 4 (CR4).

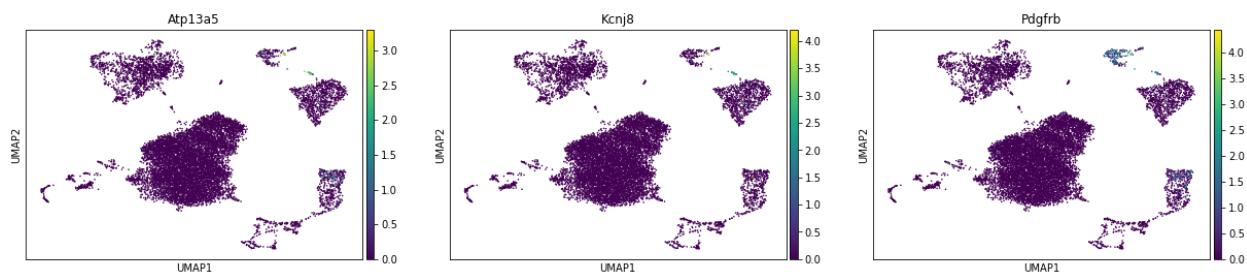
Supplementary Resource 2

Additionally cell-type specific figures corresponding to Figure 1 & 2 [7 cell type and 3 cell type overlap)

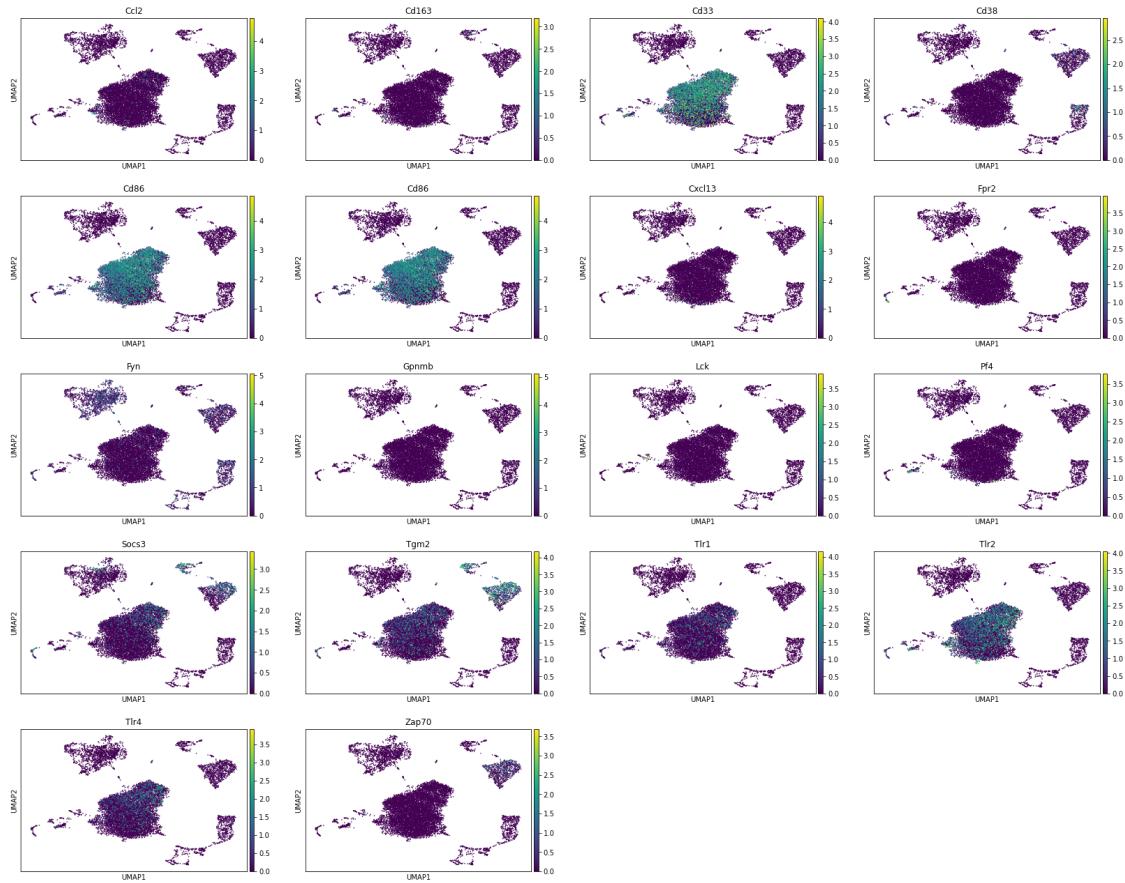
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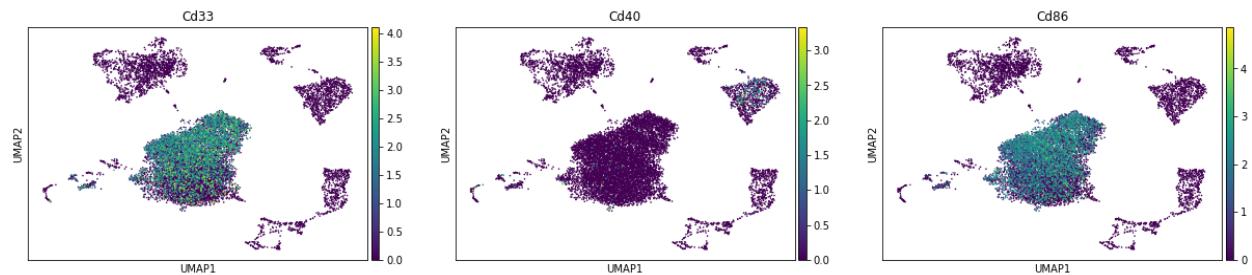
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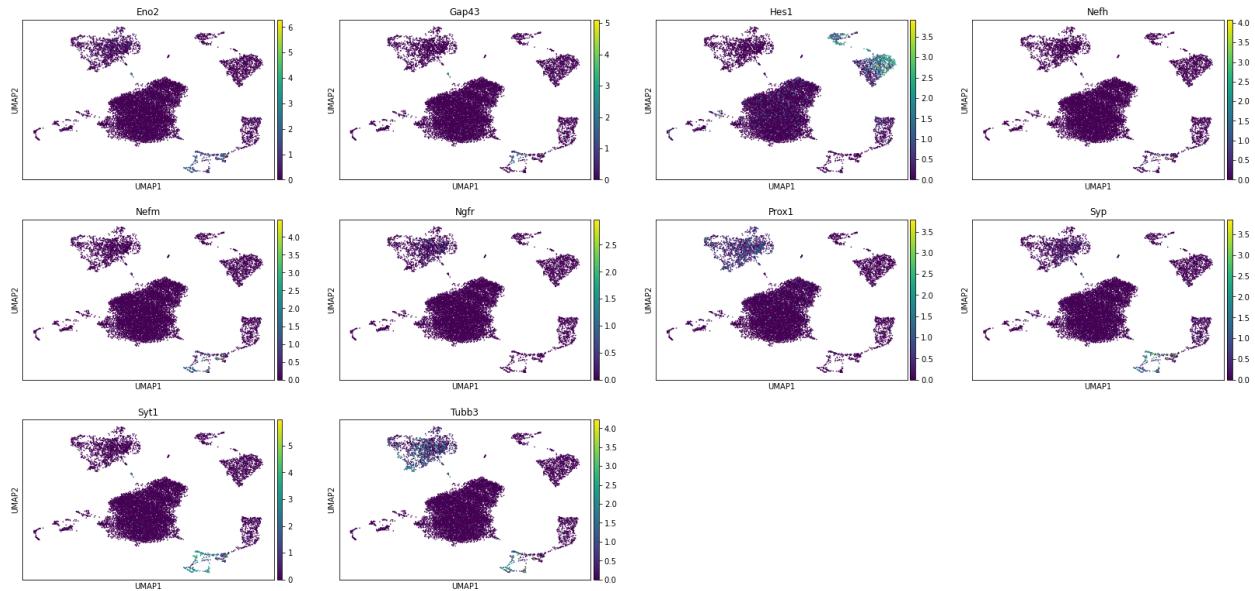
Macrophage TMS:



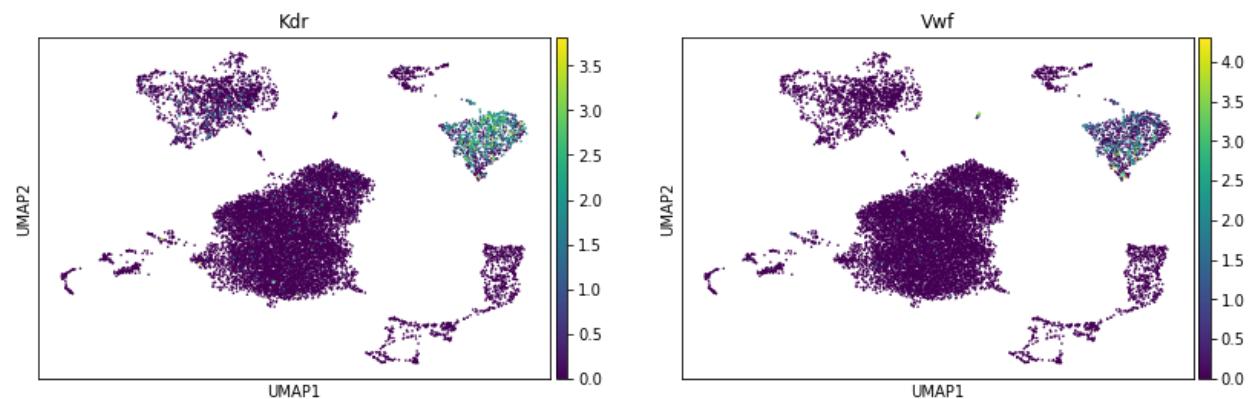
Microglia TMS:



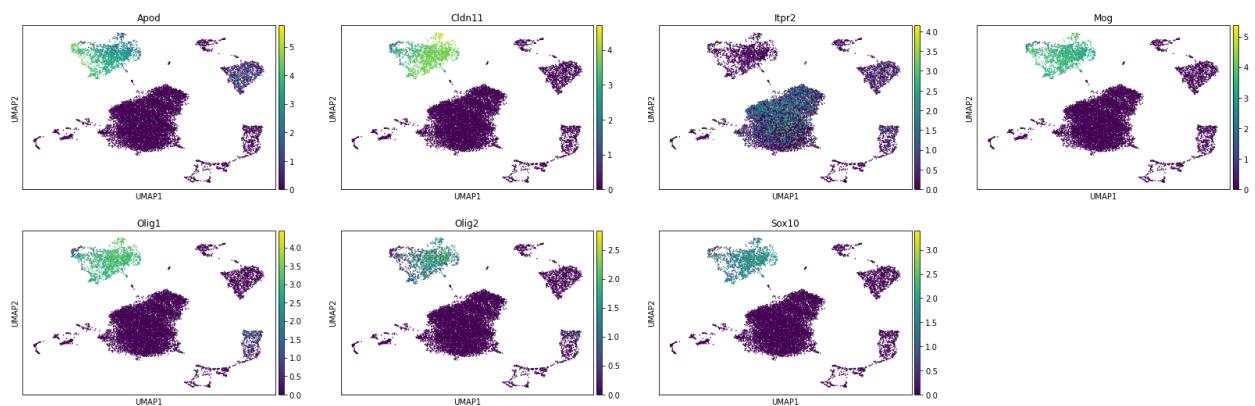
Neuron TMS:



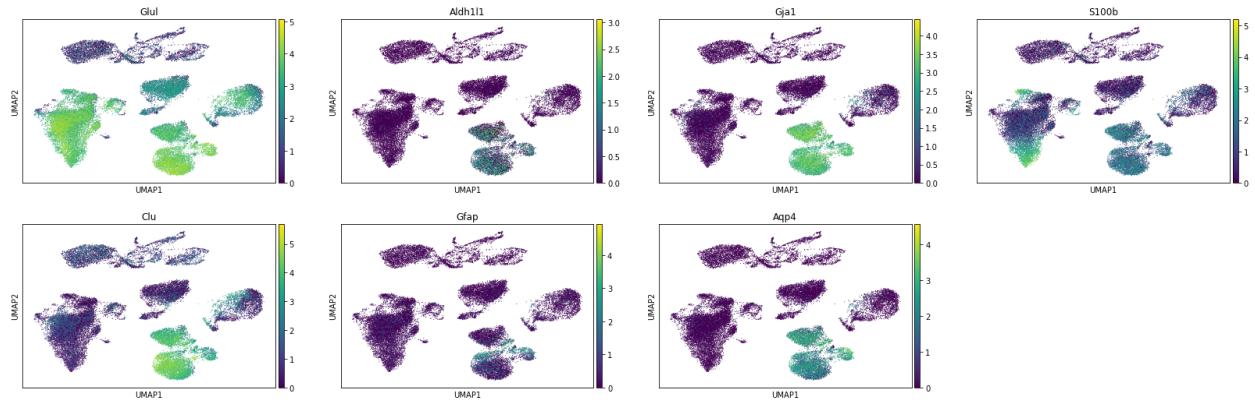
Endothelial TMS:



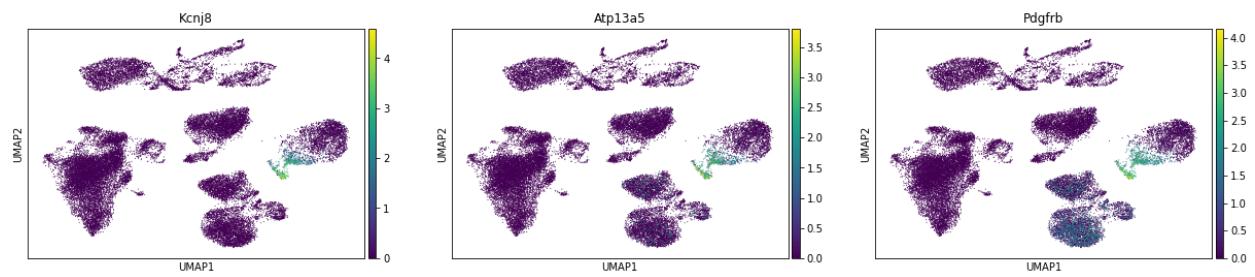
Oligodendrocyte TMS:



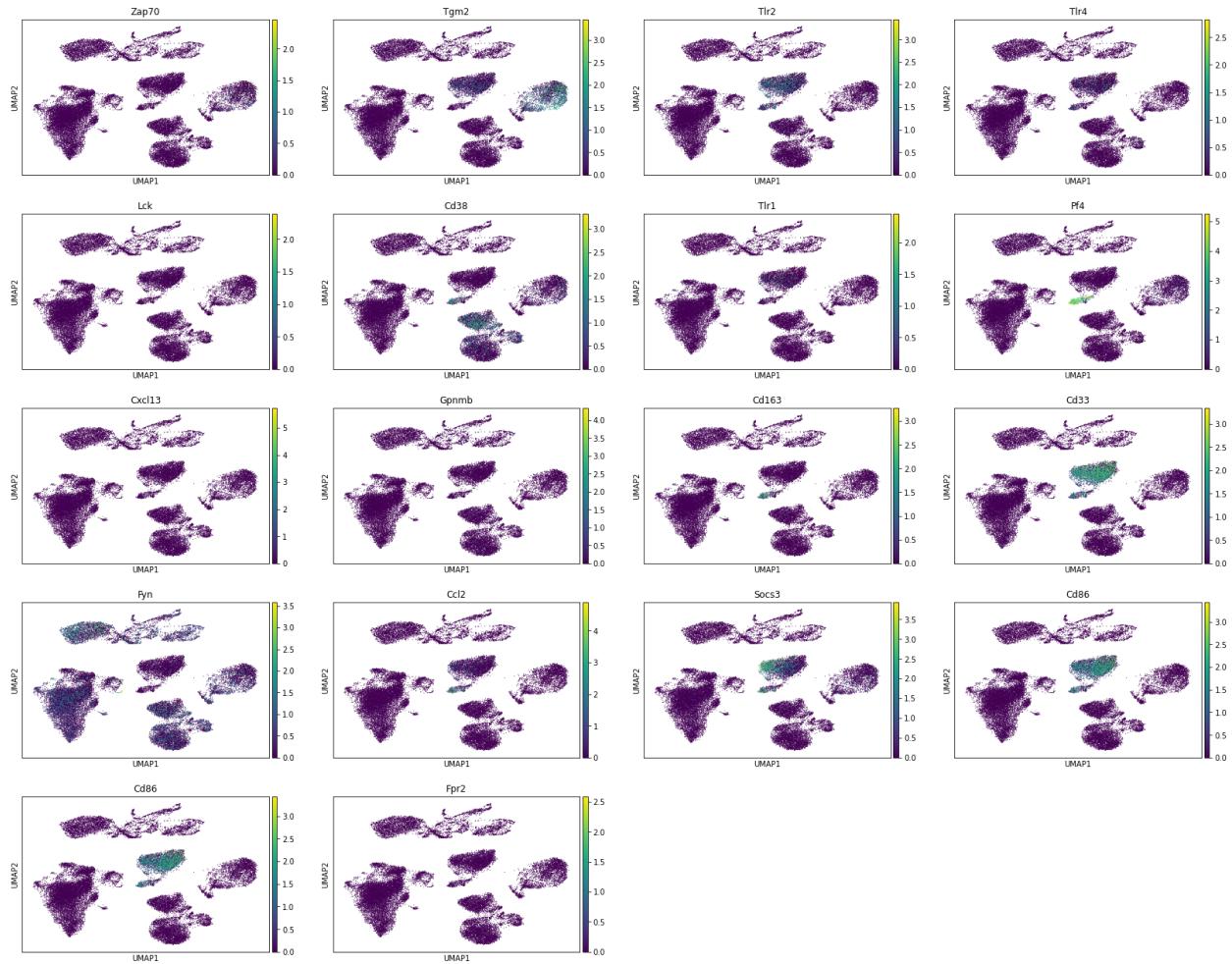
Astrocyte LR:



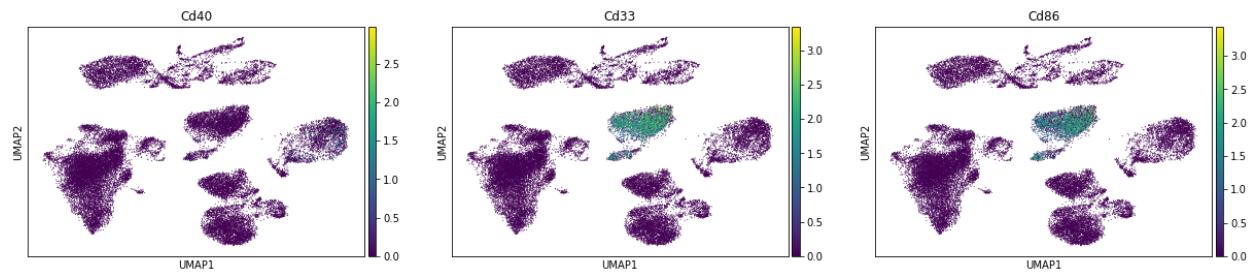
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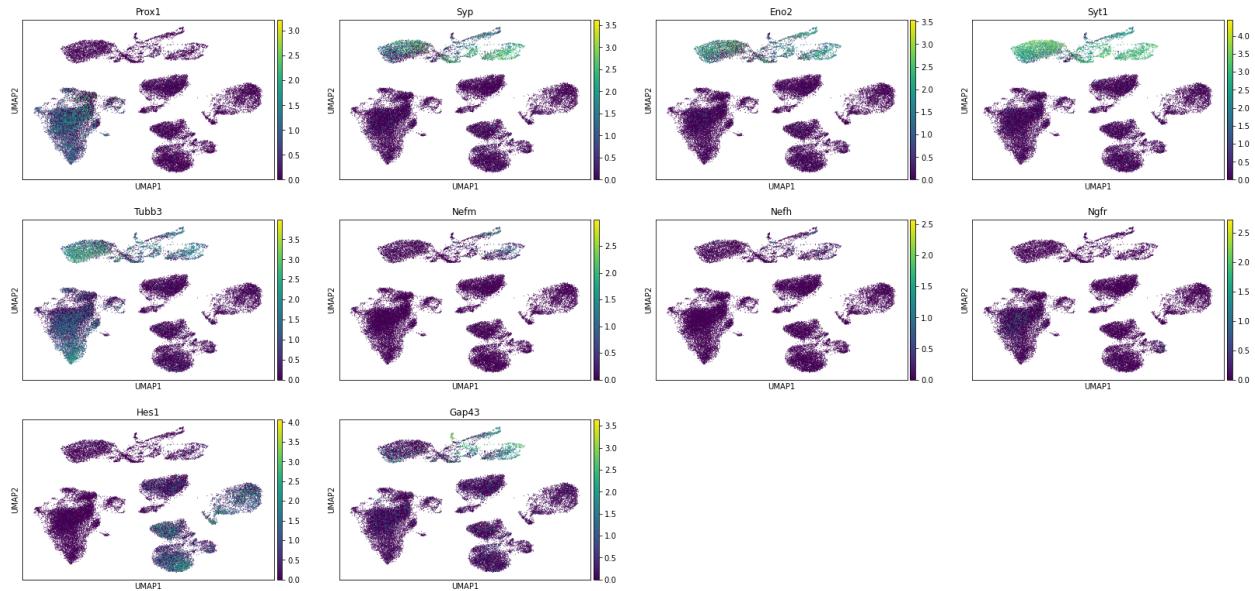
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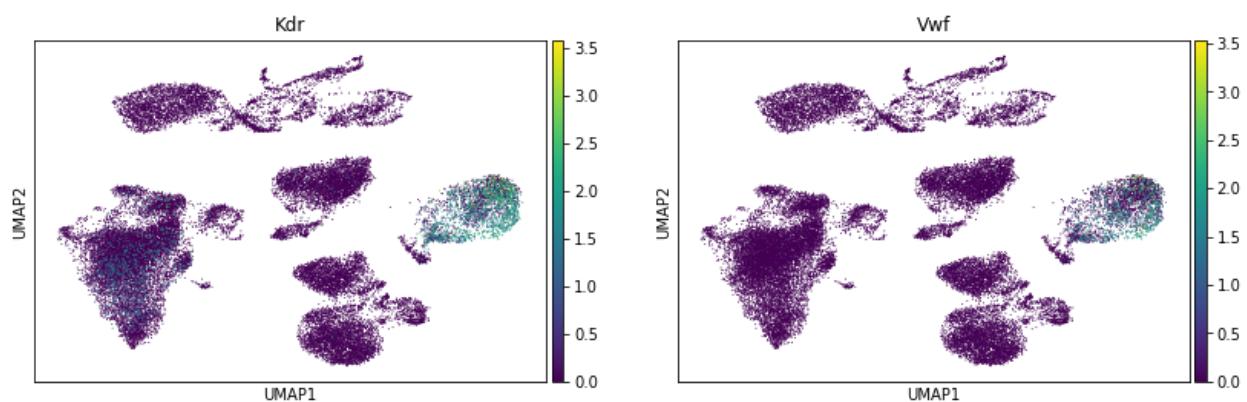
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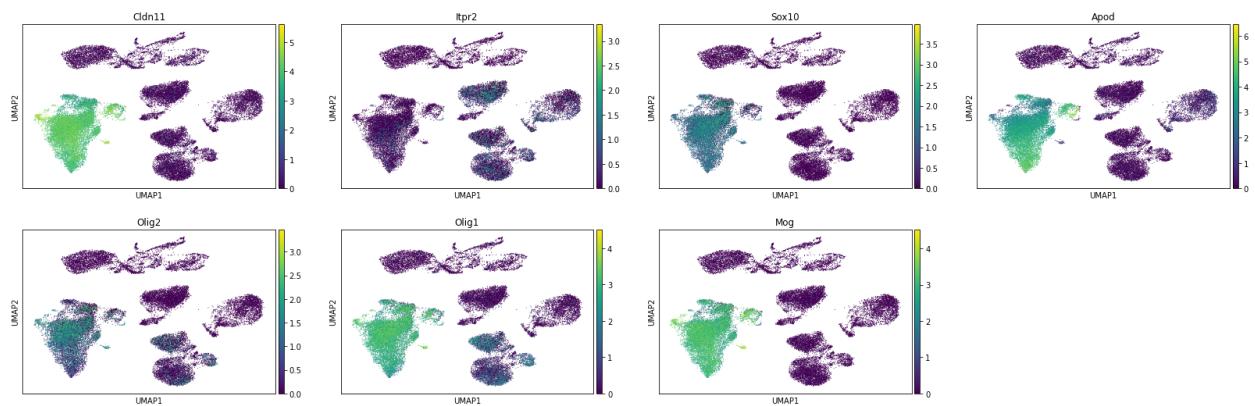
Neuron LR:



Endothelial LR:

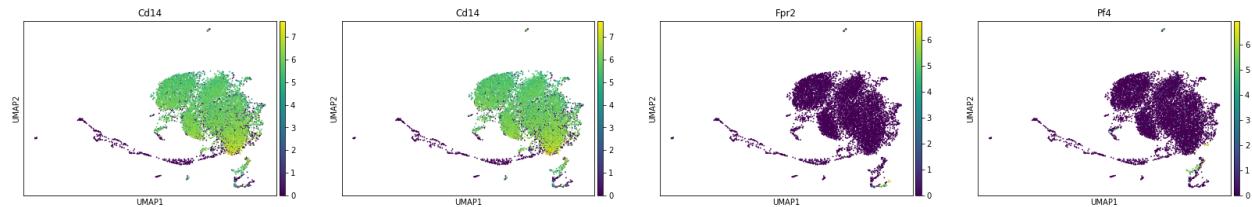


Oligodendrocyte LR:

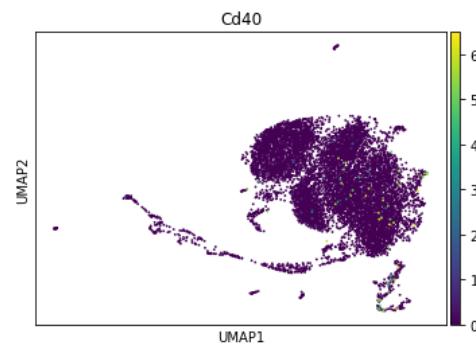


Cell type marker overlaps:

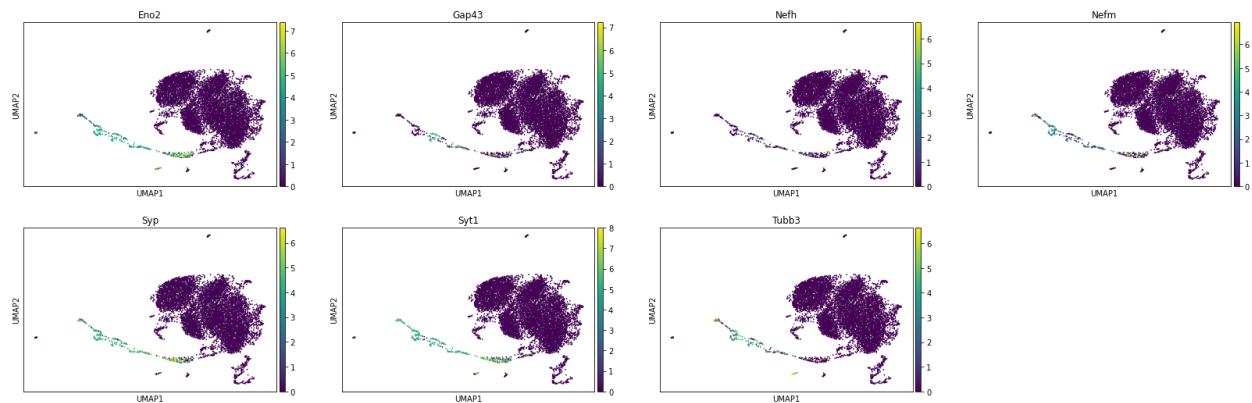
Macrophage:



Microglia:

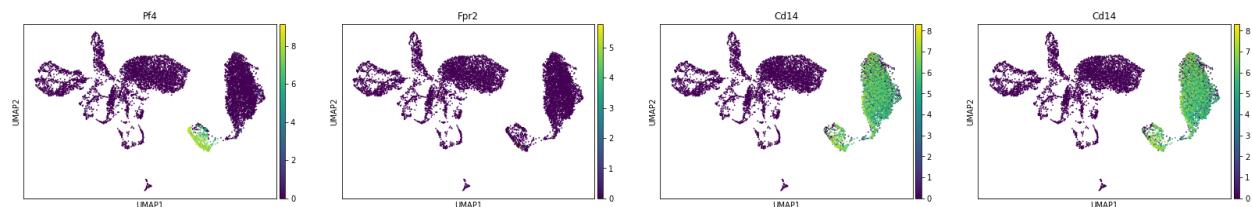


Neuron:

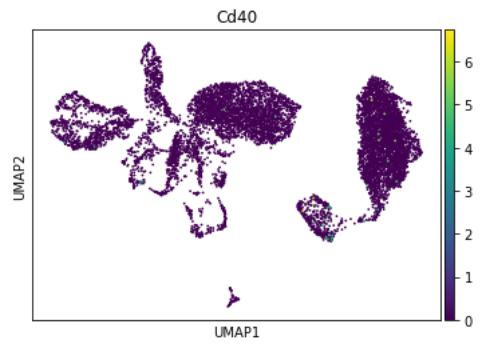


Lee Rubin:

Macrophage:



Microglial:



Neuron:

