gene	avg_log2FC	pct.1	pct.2	p_val_adj	cluster
USF2...	0.04452958	1	1	4.79981024711174e-47	FABP4hi AM
NR1H3...	0.03164061	1	1	1.25294875005036e-39	FABP4hi AM
HES2...	0.03762867	1	1	8.3155975584224e-31	FABP4hi AM
PPARG...	0.16312055	1	0.994	6.35980225234383e-27	FABP4hi AM
SOX4...	0.02671431	1	0.993	2.21079906361224e-24	FABP4hi AM
DDIT3...	0.03033194	1	1	4.5322960137874e-22	FABP4hi AM
H2AFY...	0.11335242	1	1	2.40876367137582e-15	FABP4hi AM
JDP2...	0.03182379	0.974	0.861	7.64004232950183e-11	FABP4hi AM
CEBPZ...	0.06438393	1	0.995	1.79793179078302e-09	FABP4hi AM
HOXB7...	0.04020791	0.924	0.642	3.86176534576863e-09	FABP4hi AM
MYB...	0.0522305	1	1	1.93214935752076e-49	IGF1+ AM
TCF7L2...	0.14242319	1	0.978	5.14893355182825e-35	IGF1+ AM
NR3C1...	0.08735016	0.968	0.707	4.72087552571353e-30	IGF1+ AM
AR...	0.03160895	0.995	0.903	1.49273982038412e-29	IGF1+ AM
PPARG...	0.1580657	1	0.995	5.03127221825548e-27	IGF1+ AM
RARA...	0.03174471	1	1	1.04087085840752e-22	IGF1+ AM
H2AFY...	0.10046219	1	1	6.2128352498231e-15	IGF1+ AM
HOXB7...	0.03829909	0.922	0.662	4.34217078380606e-11	IGF1+ AM
SMAD7...	0.03886045	0.944	0.837	1.45692397196735e-06	IGF1+ AM
HOXB6...	0.03029254	0.66	0.366	1.71441229684706e-05	IGF1+ AM
SREBF2...	0.0407982	1	1	4.62419460551769e-33	CD206hi FN1l
NFE2...	0.03740231	1	1	2.15978087746013e-29	CD206hi FN1l
TCF7L2...	0.12068453	1	0.979	8.33224014696877e-26	CD206hi FN1l
MYB...	0.03576173	1	1	2.59237497313704e-22	CD206hi FN1l
CEBPA...	0.02832639	1	1	3.41790750738598e-21	CD206hi FN1l
RARA...	0.02915534	1	1	7.79626775017224e-21	CD206hi FN1l
IKZF2...	0.02783788	0.997	0.932	2.28952084222987e-19	CD206hi FN1l
PPARG...	0.09641751	1	0.995	6.02781647383412e-12	CD206hi FN1l
MYC...	0.02668437	1	1	7.57445994243513e-10	CD206hi FN1l
H2AFY...	0.06596164	1	1	1.35924661958344e-06	CD206hi FN1l
BCL3...	0.10250241	1	0.948	1.10326222620696e-51	CXCL10+ AM
HIVEP1...	0.05525507	1	1	7.54501634212353e-40	CXCL10+ AM
ATF5...	0.04182584	1	0.996	1.19435151364362e-32	CXCL10+ AM
BCL6...	0.04614229	0.998	0.904	4.6265805449594e-28	CXCL10+ AM
NFKB2...	0.04090099	1	1	3.73056258544313e-25	CXCL10+ AM
ETV7...	0.04715321	1	1	3.96783072070525e-25	CXCL10+ AM
ZNF267...	0.07716277	0.847	0.484	9.11728771687721e-14	CXCL10+ AM
H2AFY...	0.09529093	1	1	2.56234096901642e-13	CXCL10+ AM
HIF1A...	0.04445686	0.819	0.558	1.11433826282697e-06	CXCL10+ AM
PPARG...	0.0703568	1	0.996	4.16865984660279e-06	CXCL10+ AM
MEF2C...	0.04590784	1	1	7.30862189360295e-52	mono-SPP1+ A
ATF5...	0.05133811	1	0.995	1.09518817865746e-47	mono-SPP1+ A
MYC...	0.07880119	1	1	5.12764152988185e-46	mono-SPP1+ A

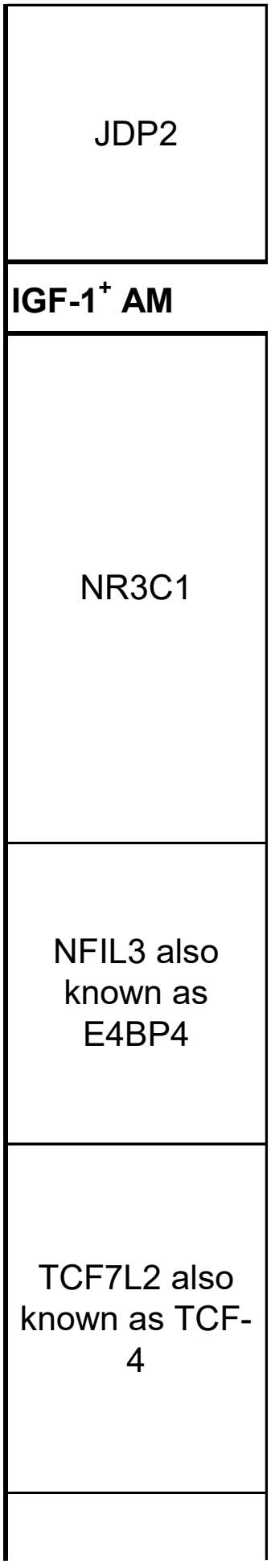
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FOSL2...	0	04572333	1		1	2.02563702395829e-39	mono-SPP1+ A
ARID3A...	0	04714999	0 997	0	963	1.69081228020653e-28	mono-SPP1+ A
MEF2A...	0	03875991	1	0	999	1.06148610990517e-23	mono-SPP1+ A
EGR1...	0	05771439	0 7	0	383	4.97818529865365e-09	mono-SPP1+ A
HIF1A...	0	07320324	0 723	0	544	5.79750800124858e-08	mono-SPP1+ A
SMAD7...	0	04213915	0 932	0	848	3.53778623305223e-05	mono-SPP1+ A
E2F1...	0	02532774	1		1	5.06038546754949e-56	Cycling AM1
BRCA1...	0	02196068	1		1	5.5500793518561e-43	Cycling AM1
POLE4...	0	03310046	1		1	4.83642641917727e-42	Cycling AM1
POLE3...	0	02653675	1		1	5.83761973235858e-41	Cycling AM1
MYBL2...	0	02299048	1		1	6.61880947976282e-38	Cycling AM1
TCF7L2...	0	06709782	0 995	0	982	7.40527376779655e-09	Cycling AM1
H2AFY...	0	07004393	1		1	1.13616516506536e-08	Cycling AM1
PPARG...	0	07851256	0 998	0	996	5.06731943361298e-08	Cycling AM1
CEBPZ...	0	0253841	1	0	996	2.19433572018786e-06	Cycling AM1
SMAD7...	0	0331535	0 945	0	855	0 000127277	Cycling AM1
FOXM1...	0	318173	0 994	0	292	5.67173829909988e-103	Cycling AM2
MYBL2...	0	07604906	1		1	6.43450795756264e-100	Cycling AM2
HMGB3...	0	11912249	1	0	999	6.40680579355029e-95	Cycling AM2
E2F7...	0	06836095	1		1	3.01569713576088e-94	Cycling AM2
EZH2...	0	07099917	1		1	4.05669698639092e-93	Cycling AM2
MAZ...	0	08446491	1		1	2.10285166347547e-92	Cycling AM2
E2F2...	0	06478127	1		1	1.10684947820855e-83	Cycling AM2
NFYC...	0	10313278	1	0	988	4.26282193228674e-71	Cycling AM2
CTCF...	0	06634199	1		1	6.91871338786468e-62	Cycling AM2
YEATS4...	0	10539058	0 611	0	053	1.09419583671401e-37	Cycling AM2

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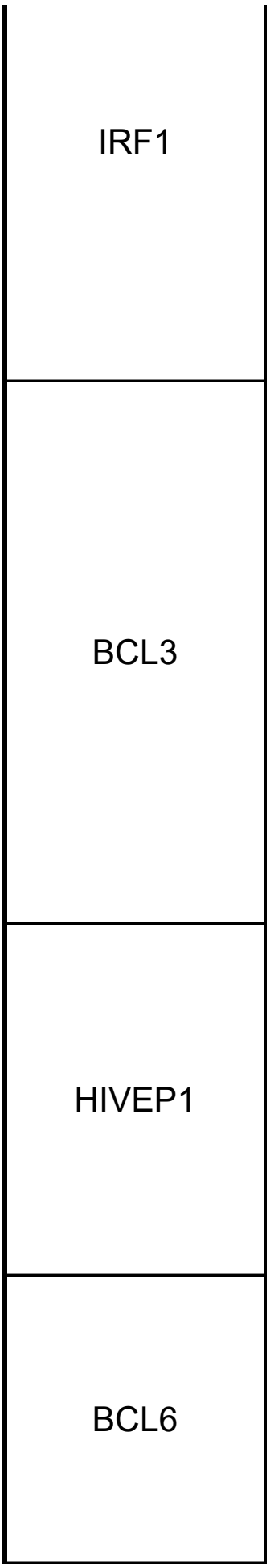
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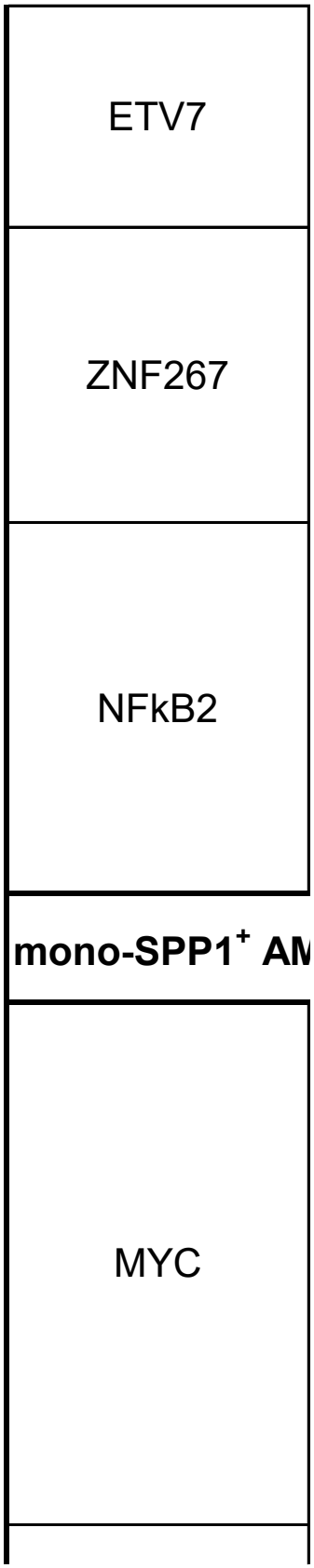
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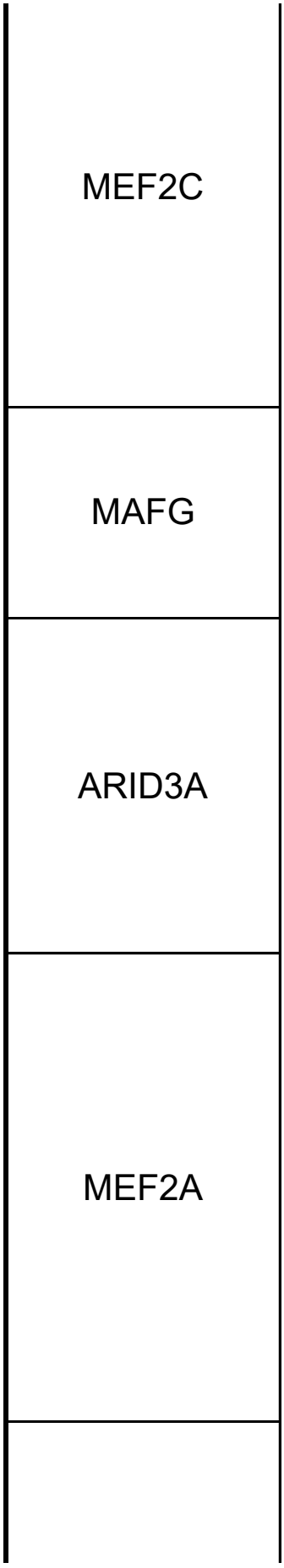
AM Subset / Transcription Factor
FABP4^{+} AM
USF3
HES2 - paralog HES1
PPARG
NR1H3...
SOX4
CEBPZ


JDP2
IGF-1+ AM
NR3C1
NFIL3 also known as E4BP4
TCF7L2 also known as TCF-4


AR
CD206hi FN1hi AI
SREBF2
NFE2 also known as NRF-2
EGR2
CXCL10+ AM


IRF1
BCL3
HIVEP1
BCL6


ETV7
ZNF267
NFkB2
mono-SPP1+ AM
MYC


MEF2C
MAFG
ARID3A
MEF2A


EGR1

Overview Transcription Factor function, mechanisms of action and effects across all cell types

Upstream transcription factor 3 (USF3) - limited data on function. Recognised to play a role in the negative regulation EMT in epithelial cells.
Hes family bHLH transcription factor 2 (HES- 2) is an co-transcription factor augmenting NOTCH signalling. Is a paralog of HES-1.
Peroxisome proliferator activated receptor gamma (PPARG) Regulates expression of genes involved in lipid transport and metabolism expressed in adipose tissue and macrophages. In adipose tissue central role in adipocyte erdifferentiation, fatty acid storage, adipogenesis and metabolism. In macrophages supresses immune responses including response to LPS and inhibits HIF1A transcription. PPARG is upregulated following IL-4 stimulation in vitro. Considered a crucial regulator of Tissue resident homeostatic alveolar macrophage populations.
Also known as Liver X receptor alpha. Is inducible in macrophages, lung, liver, adipose tissue, kidney and gut. (Whilst LXR-beta is ubiquitously expressed). Play a central role in lipid metabolism including cholesterol uptake, efflux from cells, transport and excretion via the bile. In immune cells act as cholesterol sensors and can regulate inflammatory responses. Also can influence lipid and fatty acid metabolism via activating additional TFs including SREBP1c (the aster regulator of lipid metabolism and transport) and several other TFs including ABCA1 and fatty acid synthase (FAS). (10)
SRY-box transcription factor 4 (SOX4) interacts with multiple other transcription factors - Its impacts on gene expression however effect is variable and context and tissue-specific. Recognised as a pro-oncogene - SOX4 hyperactivity involved in the promotion of cell survival, stemness, epithelial to mesenchymal transition, cell migration and metastasis.
CCAAT/enhancer-binding protein z (CEBPZ) Part of the CCAAT enhancer binding protein family which are crucial TFs that influence cellular response to environmental cues.

Jun dimerization proetin 2 (JDP2) belongs to a family of the stress response group of TFs, has multiple functions however primarily behaves as a repressor and counteracts the effects of AP-1 via repressing transcription of c-Jun and ATF-2 (14). Many effects including i) promoting the differentiation of multiple cell types including (adipocytes, cardiomyocytes, myoblasts, osteoclast, neutrophils, megakaryocytes and embryonic stem cells), ii) is a negative regulator of apoptosis and senescence, iii) acts as an anti-oxidant supressing the generation of reactive oxygen species (ROS) in response to stress (LDL oxidation, ER stress and DNA oxidation) (15) iv) has been reported as both a pro-oncogene and tumour suppressor

Nuclear receptor subfamily 3 group C member 1 (NR3C1) encodes the glucocorticoid receptor. Upon glucocorticoid binding NR3C1 is translocated acting as a TF for glucocorticoid response elements thereby mediating a range of effects including i) upregulation of genes related to metabolism PCK1, TAT and G6PC, ii) trans repression via tethering of pro-inflammatory TF including NFkB, AP-1 and STATs, resulting in repression of pro-inflammatory genes and pathways and iii) upregulation of immune regulators including IL-10. The effects and transcription programme of NR3C1 can be highly divergent dependent on differing isoforms and post translational modification, exposure duration, context and cell type although a degree of immune suppression via tethering of NFkB is consistently and widely reported (16,17).

Nuclear Factor IL3 regulated protein is a crucial TF in development and maturation of NK Cells, Innate Lymphoid cells, CD8+ DCs and supresses T and B Cell self-reactivity.

Transcription factor 7 like 2 has a wide range of functions with distinct organ and cell type effects including i) enhancer of WNT signalling and behaves as a co-activator of beta-catenin and WNT signalling, ii) glucose metabolism iii) lipid homeostasis and iv) neuronal development.

Androgen receptor (AR) effects principally studied in prostate cancer. AR has a wide range of functions and modulates several physiological responses including male sexual organ

development, masculisation and spermiogenesis. AR interacts with a significant number of co-activators and co-repressors exerting a diverse range of activities. Investigated for a role in the development of prostate cancer where AR confers a pro-oncogene effect mediated by a range of mechanisms.

M

Sterol Regulatory element binding factor 2 (SREBF2) - an important regulator of sterols (including cholesterol), fatty acid biosynthesis and brain development. Involved in cholesterol homeostasis balancing luminal cholesterol intake with sterol synthesis and induced in context of sterol deficiency. (30)

Nrf2 (NF-E2-related factor-2) transcription factor regulates expression of >250 oxidative/xenobiotic stress response genes expressing the anti-oxidant response element (ARE) binding site responsible for anti-oxidant homeostasis. Principal functions include i) protection against oxidative damage via ROS, ii) supress inflammation including via repression of the NLRP3 inflammasome, iii) promotes mitochondrial autophagy and degradation. Additionally, NRF2 promoted erythroid and megakaryocyte poesis and differentiation.

Early growth response 2 (EGR2) was initially identified as a crucial TF in hindbarin formation and formation of the myelin sheath with mutations associated with Charcot Marie tooth disease. Also implicated in lymphocyte maturation and Th17 tissue homing and promoting T Cell anergy. It is upregulated in repsonse to PPARG and implicated in the polarisation of M2 like phenotype.

Inteferon Regulatory Factor (IRF-1) promote an interferon response via several mechanisms. i) IRF-1 is an ISG and IRF1 transcription can be upregulated by type 1 and type 2 IFNs signalling. ii) as a TF can subsequently further promote transcription of a subset of ISGs by binding to ISRE like promoters. IRF1 may also amplify T1 IFN signalling in a feed forward mechanism upstream and

promotors. IRF1 may also amplify T1 IFN signalling in a feed forward mechanism upstream and downstream of IFNAR signalling; i) can induce the expression of type 1 and type 3 IFNs in an IRF3/7 dependent and independent manner ii) promotes the expression of STAT1 transcription, enhances STAT1 phosphorylation and dimerisation enhancing IFN signalling downstream of IFNAR (37) . IRF1 can additionally promote the expression of several pro-inflammatory cytokines and cellular states i) is a critical inducer of IL-12 in DCs macrophages and Th1 CD4 T Cells, ii) is required to facilitate T-bet mediated Th1 polarisation and Th1 mediated immune responses (385), iii) IRF -/- KO mice are protected against LPS mediated mortality, production of inflammatory cytokines INFy, TNF-a, IL1b in addition to IFNb and reduction in iNOS and ROS production (39), iv) IRF1 is also a key factor in the regulation of canonical and non canonical inflammasomes following viral / bacterial infection and sterile inflammation. (40-31)

B-Cell lymphoma 3 (BCL-3) promotes cell proliferation and survival. It is a member of the inhibitor of NFkB family (ikB) and supress NFkB signalling via a number of mechanisms. However, may also act as a co-activator and promote transcription of NFkB target genes. Action as either (or both) an inhibitor or co-activator of NFkB signalling BCL3 has been shown to exert either pro-inflammatory and anti-inflammatory effects in varying immune cells and disease models (45). The effects of BCL3 are thought to be context and cell type specific and its function as a inhibitor or co-activator of NFkB signalling is dependent in part on it phosphorylation state and intracellular location. BCL-3 expression can be induced by other TFs including STAT3, NFkB and AP-1 and inflammatory stimuli.

HIV type 1 enhancer binding protein 1 (HIVE-P1) binds to the DNA motif 5'-TGGGGATTCCCA-3, which has been identified in promoting regions including IL-2, IFNB1, and viral promotes including HIV and CMV. Results in upregulated HIV-LTR (long terminal repeat) gene transcription.

B Cell Lymphoma 6 (BCL-6) is a critical transcription factor in regulating and promoting T follicular cell identify and function. In addition, promotes B cell proliferation in B Cells. Also plays a critical role in the initiation and maintenance in the formation of germinal centres.

ETS Variant Transcription factor 7 (ETV7) is an ISG with expression upregulated by exposure to type 1 and type 2 IFNs and viral infection in line with IRF-1, STAT1 and NFkB (54). ETV7 confers an immune regulatory effect supressing the expression of a subset of ISGs following T1 IFN (55) where overexpression of ETV7 in vitro in HEK293 or lung epithelial cells resulted in repression of ISGs whilst functional ETV7 loss enhances anti-viral ISG expression and reduced IFN mediated control of several strains of influenza virus.
Undertsanding of Zinc Finger family transcription factor 267 (ZNF267) function is limited. In one study of hepatic stellate cells ZN267 expression increased in human tissue of hepatic steatosis and non alcoholic steatohepatitis (NASH). ZNF267 expression increased on exposure to intracellular lipids, and reactive oxygen species (56). Overexpressed ZNF267 in HEK 293 cells resulted in decrease in proteins associated with extracellular matrix (ECM) degradation including MMP-1, MMP10 and ADAM family proteases (57). Taken with increased expression in NASH the authors speculate a potential profibrotic role through repression of ECM degrading proteases.
Nuclear Factor kappa b (NFkB2) or NFkB modulates multiple aspects of both innate and adaptive immune signalling and mediates the cellular response to stress, injury/damage and invading pathogens. Activation of NFkB2 occurs in response to a wide range of stimuli including a range of pattern recognition receptors, cytokines, TNF superfamily members and T/B cell receptor signalling through degradation of regulatory IkBa which maintains NFkB2 in its inactive form. Following activation NFkB undergoes nuclear translocation and able to initiate transcription. NFkB is considered the master regulator mediating induction of pro-inflammatory responses and inflammasome activation. Additionally modulates several physiological functions in cells including anti-apoptosis, proliferation. In oncology implicated in promoting angiogenesis, tumour adhesion, invasion and metastasis. (58)

M

Pro-oncogene c-myc (MYC) belongs to the pro-oncogene family of MYC genes. Also known as c-myc. Regulates a diverse range of cellular physiological process including promoting cell cycling, proliferation, metabolism, differentiation and apoptosis. Amplifies gene transcription. Extensively studied in oncology and considered a pro-oncogene.
Myocyte enhancer factor 2 c (MEF2C) belong to the MADS transcriptional factor family. Initially

identified are involved in muscle cel regulation MEF2C is widely expressed in various cell types including skeletal and smooth muscle, neuronal, chondrocytes, endothelial and immune cells. MEF2C promoted the expression of a wide range of genes with a broad range of cell specific functions involved in cell / tissue morphogenesis (64)
MAF BZIP transcription factor g (MAFG) belongs to the MAF family of transcription factors. Distinct from large MAF TF's (inc MAFA/B). MAFG is a small MAF TFs (including MAFG and its paralog MAFK). Limited data investigating the function of MAFG
AT rich interaction domain 3A (ARI3a) belongs to the AT rich interaction domain (ARID) family of transcription factors. The specific function of ARI3A poorly understood but known to upregulate gene expression via direct binding to AT rich motifs and through recruiting histone deacetylases and acetly transferases. AIR3A has been studied in B cell development and in the expansion of autoreactive B cells and autoantibody production and implicated in the pathology of SLE. (67)
Myocyte enhancer factor 2a. Similar to MEF2c a member of the MEF TF family involved in the development of cardiac, skeletal and smooth muscle cell and tissue development and neuronal and endothelial cell development and function. MEF2a function has been extensively investigated in cardiac myocytes where MEF2a deficiency results in ventricular myocardial dilatation and disordered muscle fibre organisation. (69) In addition MEF2a has been shown to mediate a range of cellular physiological processes including proliferation, differentiation, apoptosis and senescence.
Early growth response 1 (ERG1) is an immediate early response transcription factor family member and promotes transcription of hundreds of genes and is implicated a wide range of physiological and pathological processes including cell proliferation, neurotransmission, tissue responses to injury, inflammation, wounds healing and fibrosis and tumorigenesis. ERG1 is well recognised to act as a profibrotic TF in epithelial cells and fibroblasts. ERG1 expression is

recognised to act as a profibrotic TF in epithelial cells and fibroblasts. ERG1 expression is upregulated in response to TGF-b and involved in promoting epithelial to mesenchymal transition in epithelial cells and expression of COL1A2 and increased expression of transcripts associated with TGFb signalling, wound healing and ECM protein production and is upregulated in pulmonary and skin fibrosis whilst EGR1-/- protects against BLM induced fibrosis (72, 73).

Glossary Of Abbreviations

AM

ANAX1

AP-1

AR

Arg1

BLM

BMDM

CCL

CCR

Chil3

COVID

COX

CSF1

CXCL

CXCL

CXCR

DUSP

ECM

EMT

ER

G6PC

HIF1a

IFN

IFNAR

IL

IncRNA

IFN-b

IFN-g

iNOS
IRF
ISG
ISRE
JUN
Keap1
KO
LDL
LPS
MERTK
MMP9
mTB
NADPH
NASH
NFkB
NK
NOS
OAS1
PBC
PCK1
PDL1
PI3K
PRR
RIP1
ROS
SLE
SphK1
STAT
STING
TAM
TAT
TF
TGF-b
Th

TLR

TNF

UV

VEGF

WT

Known or proposed function in monocyes, macrophages or related myeloid cells reported in literature

Limited data regarding function in macrophages however implicated in modulating osteoporosis by promoting osteoblast differentiation
HES-2 - limited data regarding function in Macrophages. HES-1 is a known paralog of HES-2. i) HES1-/- LPS induced Bone marrow derived macrophages (BMDM) resulted in increased induction of 25 transcripts vs WT BMDM including IL*12b* , IL*6* and CXCL*1 in vitro. HES1-/- restricts neutrophil recruitment in vivo via inhibiting CXCL1 production in peritoneal macrophages and attenuates development of inflammatory arthritis (1).*
PPARG i) influences differentiation of fetal monocytes to Alveolar Macrophages (2), ii) supress pro-inflammatory responses to LPS inc TNF-a, IL1b, IL-6 (3-4), iii) promote anti-inflammatory genes expression Arg1 and Mgl1 (5), iii) promotes FC gamma mediated phagocytosis and efferocytosis (6-7), iv) protect against collagen deposition post influenza injury (8) v) promotes surfactant metabolism and maintenence of surfactant homeostasis (9). Described as having a critical role in promoting lung alveolar macrophage function in particular surfactant homeostasis and lipid handling. PPAR-y deficient mice have reduced alveolar macrophage populations and develop pulmonary alveolar proteinosis.
Considered a key regulator of macrophage homeostatic function in particular in relation to the phagocytosis of oxidized lipoprotein but also controlling transcriptional programs involved in lipid metabolism and inflammation . LXRs are critical in macrophage cholesterol efflux and regulating intracellular cholesterol levels and counteract the development of foam cells - this is via activating the TF ABCA1 after LXR ligands and LXR receptor complexes and reverse cholesterol transport receptors APOE/APOC (11). LXRs will also repress pro-inflammatory gene expression on murine BMDM and RAW 2after stimulation with TNF and LPS and bacterial infection including iNOS, IL-6, IL1b and CCL2 and antagonises NFkB signalling (12) in vitro and in vivo.
Limited information on function in macrophages.
Limited data on specific function in macrophage however CEBPZ known to promote expression of HSP 70. Heat shock proteins being chaperones involved in maintaining homeostasis in protein folding. Endogenous HSP 70 is constitutively expressed however intracellular concentration increases by various insults (raised temperature, oxidative stress, nutritional deficiencies, UV radiation, chemicals ethanol infection) that induce protein unfolding, misfolding or aggregation. May play a role in retaining AM homeostasis and function in context of multiple external insults encountered in alveolar space (13)

Limited data on specific function in macrophages. Function of JDP2 in ROS homeostasis described in embryonic fibroblasts. May in alveolar macrophages regulate/repress ROS responses to environmental stressors and insults.

Endogenous glucocorticosteroids induce predominately anti-inflammatory / immuno-regulatory programmes via NR3C1 in macrophages with a negative relationship between NR3C1 and TLR4, NFkB and IFN receptor pathways. Upregulation of NR3C1 causes cells to be more sensitive to the effects of endogenous gluococorticosetroids. Ligand activated NR3C1 in Monocytes-Macrophage results in a range of effects including i) repression of activities of pro-inflammatory TFs including NfkB, AP-1 and IRF-3 via trans repression and tethering, ii) enhancing transcription of anti-inflammatory genes Dusp1, Anax1 and in myeloid cells Sphk1 (18, 19), and ii) in COVID19 myeloid NR3C1 expression negatively correlates with CXCL8 expression and neutrophil infiltration (20). However in certain contexts iv) NR3C1 have been reported to induce proinflammatory effects including induction of NLRP3 transcription in monocyte like THP-1 cells (21), whilst chronic NR3C1 activation, with exogenous glucocorticoids in macrophages results in downregulation of adaptive immune system activation but upregulation of innate immune pathways including chemokine expression and leucocyte recruitment (22). Finally, v) NR3C1 promoted macrophage phagocytosis, efferocytosis and promotes wound healing and tissue repair (23)
Limited data on NFIL3 in lung / alveolar macrophages, in other macrophage populations confers an anti-inflammatory / immune regulatory role. i) in BMDM IL10 is required for NFIL3 induction and expression (24, 25), ii) NFIL3 represses IL-12b (and IL-6) expression at basal state and post LPS stimulation (24), iii) upregulation of NR3C1 in gut macrophages and RAW264.7 cells promotes IL-4ra expression, repression of pro-inflammatory cytokine production and protects from chemical colitis (26).
2 studies report on TCF7L2 functioning macrophages. i) TCF7L2 prevents HIF1a-beta catenin mediated inflammation; In AMs beta catenin couples with HIF1a after exposure to Wnt3a / viral infection to promote pro-inflammatory cytokine release, reduced AM self-renewal and inhibits lung recovery. In the absence on Wnt3A beta catenin couples with TCF7L2. At steady state TCFL2 acts as a competitive inhibitor preventing HIF1a coupling and supressing beta-catenin-HIF1a mediated pro-inflammatory activity (27). ii) THP-1 Monocyte to M2 macrophage polarisation via IL-4 stimulation is mediated via lncRNA XIST. Downregulation of lncRNA XIST can be rescued by TCF7L2 over expression - highlighting a role of TCF7L2 in regulating lncRNA Xist mediated M2 polarisation (28)
AR expression negatively correlates with IL-1b expression in prostate cancer TAM and is thought to repress IL1b expression (29). Androgens are known to limit inflammatory responses although

In this study macrophages from AR-/- mice had lower TNF-a i.e. suggesting AR promoted TNF-a expression

SREP2 function in macrophages investigated In one study (31). SREBP2 signalling and cholesterol biosynthesis supresses Type 1 Inteferon signalling. Scap -/- mice with attenuated SREBP1 and 2 and specific SREBP2 depletion in BMDM or THP-1 monocytes in vitro resulted in i) reduction of genes related to cholesterol synthesis and ii) spontaneous IFN signalling via a STING - IRF3 - IFN-b mechanism with upregulation of ISGs and iii) resistance to viral infection. Whilst restoring cholesterol homeostasis repressed INF signalling. Overall SREBP2, by maintaining cholesterol homeostasis appears to repress a Type 1 IFN phenotype.

NRF2 confers a anti-inflammatory phenotype in macrophages; macrophages from NRF2 -/- mice have increased ROS, activation of TLR, IRF-3 and NFkB signalling following LPS and increased pro-inflammatory cytokine production (32) via NADPH oxidase. The anti-inflammatory effects of NRF2 are mediated by both a redox (antioxidant) dependent and independent mechanisms (32). In a latter study NRF2 was also shown to directly bind to sites in the proximity of several pro-inflammatory genes IL1a, IL1β and IL-6 and repress RNA pol mediated transcription (33). Specific increased NRF2 activity (by depletion of its repressor Keap-1) in myeloid cells protects against caecal puncture induced sepsis, with lower mortality and lower pro-inflammatory marker expression compared to wild type and NRF2-/- models (34).

Early Growth response 2 (EGR2) is a distinct feature of murine AMs and appears to promote typical AM related function and phenotype. i) EGR2-/- murine AMs express lower levels of the mature AM marker SiglecF and transcriptionally resemble interstitial macrophages than AMs therefore thought to be an important TF in the development and differentiation of macrophages towards an AM phenotype. Although indispensable in AM function relating to lipid handling and metabolism (35). ii) EGR2 is implicated in promoting the differentiation of infiltrating monocytes toward an AM phenotype (35) and in this model EGR2 -/- was associated with impaired repopulation of the alveolar niche following bleomycin injury and improper healing suggesting EGR2 promoted an AM poplation / phenotype crucial to restoring homeostasis in a single dose model of injury-fibrosis and repair (35). iii) On the other hand EGR-2 overexpression in liver steato-hepatitis has been implicated in the differentiation of monocytes to fibrogenic macrophages and ablation of EGR-2 protects from liver fibrosis (36)

IRF 1 is a transcriptional activator in macrophages, promoting expression of pro-inflammatory genes and conferring resistance to infection. IRF1-/- macrophages have impaired iNOS production, IL-12 and Cox-2 expression in response to stimulating conditions including IFNb, IFNg and LPS (42,43). Macrophages from IRF1 -/- mice have impaired IL-12 production and

IFNg and LPS (42,43) . Macrophages from IRF1 -/- mice have impaired IL-12 production and impaired susceptibility to bacterial, viral and parasitic stimuli or infection in vivo and in vitro (43). In addition to the known effects of IRF-1 as a promotor of ISGs evidence from transcriptomic and atac-seq data reveals IRF-1 a critical TF in the induction of ISGs following TLR4 stimulation in monocyte derived macrophages and TLR7/8 stimulation in primary monocytes (44). Whilst myeloid cells from IRF1 deficient patients demonstrated reduction in ISG expression and IL-12 transcripts following IFN-g reduced reactive oxidative species production and impaired resistance to intracellular pathogens (44).

AMs from BCL3-/- mice have increased production of IL-10 (compared to WT AM), but no difference in TNFa expression upon exposure to Klebsiella Pneumoniae or LPS in vitro. Whilst BCL3-/- mice have increased lung damage, impaired bacterial clearance, reduced IFN-g and increased IL-10 following Klebsiella lung infection. In this model BCL3 promotes inflammation, supress IL-10 production in AMs and confer protection to bacterial infection. (46). On the other hand peritoneal murine macrophages from BCL3 KO mice have reduced IL-10 expression and increased TNF-a upon LPS stimulation suggesting in this population BCL3 may supresses TNF-a mediated inflammation via IL-10. (47) Similarly, RAW264.7 and primary BMDM BCL3-/- cells demonstrated increased TNF-a and reduced IL-10 following LPS stimulation (48). In a liver injury, steatohepatitis and fibrosis murine model BCL3-/- protected against hepatic inflammation and fibrosis, whilst overexpression resulted in increased IL-6 production and accelerated steatohepatitis. In patients with non-alcoholic steatohepatitis BCL3 expression was increased. In this disease model BCL3 appears to promote inflammation and accelerate steatohepatitis although the contribution of BCL3 in liver macrophage populations was not examined (49). Overall, the effects of BCL3 appear to vary depending on the macrophage subset and disease context and may confer either pro or anti-inflammatory effects

Macrophage function described in a single study. HIVEP1 expression is upregulated in human monocytes of patients with sepsis and following stimulation with TLR 2 agonists and LPS in an NFkB dependent manner. Overexpression of HIVE-P1 inhibits NFkB activity following TLR stimulation in THP-1 monocyte. Similarly HIVE-P1 deletion results in increased NFkB activity following TLR stimulation or bacterial infection with increased IL1b, TNF-a, IL-6, IL-8 mRNA expression in both THP-1 HIVE-P1 deficient cells and BMDM macrophages from HIVEP1-/- mice. Suggesting HIVE-P1 exerts and immune regulatory effect by repression of NFkB signalling (47). In this same study HIVEP-1 deficient THP-1 cells also demonstrate *reduced* expression of key genes of IFN signalling (IRF1/9, OAS1, STAT1, STAT2, TLR7, TLR9) with downregulation of IFN signalling pathways suggesting HIVE-P1 may promote INF signalling although this was not further explored. (50)

BMDM from BCL6-/- mice had increased expression of specific chemokines CCL2/CCL7 and IL1a although no difference in CCL3 or IL-12 expression following stimulation with LPS. BCL6 -/- mice are prone to a fatal Th2 mediated inflammation (51) with eosinophilic/ Th2 and monocytic infiltration in the lung and spleen. Additional studies demonstrate that BCL6 represses expression of approximately 1/3 of genes upregulated by LPS and opposes the activity of NFkB (52). Taken together BCL6 oppose NFkB signalling and represses expression of several chemokines and increased proliferation. The effects of BCL6 on macrophages is mediated through DNA of the TF to its DNA motif which overlaps with STAT binding and exerts in anti-inflammatory effects by preventing STAT binding. (53)

No specific studies of effect in macrophages
No specific studies of effect in macrophages
NFkB activation and transcription occurs in response to a wide range of PRRs which share common downstream signalling pathways including activation of NFkB2 where signalling promotes expression of a range of pro-inflammatory cytokines and chemokines including IL-1, IL-5, IL-12, TNFa and COX-2. NFkB is a key transcription factor in promoting an M1 like macrophage phenotype. NFkB activation also occurs via IRF3 via RIP1 resulting in NFkB signalling in conjunction with type 1 IFN responses. (58)

C-Myc is required for the polarisation of macrophages to an alternative activation (M2) phenotype. C-Myc expression was upregulated in monocytes following exposure to M2 promoting stimuli including IL-4, IL-13, IL-10, TGF and upregulated in M2 macs with a 'wound healing' phenotype where C-Myc inhibition reduced expression of a number of genes implicated in wound healing including VEGF, MMP9, TGF-b and HIF1a (59). Similarly pro-inflammatory stimuli resulted in down regulation of C-Myc (60). Whilst C-Myc metabolic reprogramming supresses inflammatory cytokine expression in an IRF-4 mediated mechanism and suppression of C-Myc results in overexpression of inflammatory cytokines IL-6, IL-1b and TNFa (61). In fibrotic murine models C-Myc is upregulated in pro-fibrotic macrophages implicated in regulating and promoting fibroblast activation (62) and directly implicated in promoting renal fibrosis via upregulation of integrin AV and TGF-b signalling whilst blockade of C-Myc ameliorated fibrosis. (63)
MEF2c may mediate both pro-inflammatory and anti-inflammatory responses. in BMDM - MEF2c

promotes M1 like phenotypes; transcriptome in MEF2cflox/flox Lyz2 cre murine BMDM following LPS revealed downregulation of M1 genes iNOs, IL-12, CD83, CD40 and upregulation of M2 like gene Arg1, Chil3, IL-10 compared to WT counterparts. Furthermore, MEF2c macrophage specific deletion resulted in reduced macrophage killing of listeria, with reduced expression of IL-12, IL-6, TNF-a in vivo and MEF2c deletion reduced inflammatory colitis with reduction in inflammatory macrophages and Th1 responses (65). Alternatively in microglia specific MEF2c deficiency resulted in exaggerated inflammatory responses in a TNF-a induced brain inflammation model with upregulation of TNFa, IL1b, CCL2/5 expression in vivo and ex vivo. Suggesting MEF2c in microglial may confer an immune suppressive effect following stimulation (66).
Limited data exploring the function of MAFG in macrophages
AR1D3a function has been studied in hepatic macrophages in primary biliary cirrhosis (PBC). ARID3a expression was increased in PBC, whilst myeloid specific deletion of ARID3a, resulted in a reduced accumulation of macrophages and reduced cholestatic liver injury and hepatic fibrosis tissue accumulation. ARID3a -/- macrophages in vitro displayed a reparative phenotype with increased Arg1 and CD206 expression following LPS. ARID3a-/- macrophages functionally displayed enhanced efferocytosis of apoptotic biliary cells demonstrated to be due to increased MERTK expression (where inhibition of MERTK in ARID3a mice abrogated the protective effects observed in ARID3a deficiency. The authors concluded ARID3a promotes an inflammatory, less reparative phenotype in macrophages with reduced efferocytosis (68).
MEF2a in macrophages has been implicated in both supressing (in basal non stimulated setting) *and* promoting (following stimulation) inflammatory and type 1 IFN signalling. MEF2a knock down in THP-1 cells (and cardiac myocytes) results in spontaneous production of IFNb and CXCL10 expression. Spontaneous type 1 IFN inflammation in MEF2a cardiac myocytes (not investigated in THP-1 cells) was mediated by STING signalling with evidence of genomic instability. The authors concluded MFE2a promoted genomic stability thereby supressing aberrant STING dependent T1 IFN activation (70). On the other hand in murine BMDM MEF2a has been shown to be critical in inducing LPS mediated IFNb production and inflammatory signalling. In iMACs (macrophages generated from immortalised haematopoietic stem cell line Hoxb8-FL cultured with CSF1) with MEF2a silencing displayed IFN-b deficiency and downregulation of ISGs following LPS stimulation or viral or mTb infection. Additional pro-inflammatory markers including IL12 were similarly downregulated. Overall MEF2a was in this study implicated in promoting pro-inflammatory signalling and type 1 IFN mediated inflammation in macrophages following LPS stimulation. (71)
ERG1 in haematopoietic stem cells is required to promote the maturation to monocytic colonies though non redundant in monocyte to macrophage differenation (74). ERG1 has both enhancer and repressive activities. In monocytes and mature differentiated macrophages ERG1 overexpression limits inflammatory responses in unstimulated and LPS stimulated human monocyte derived macrophages by associating with an additional TF NuRD to limit pro-

monocyte derived macrophages by associating with an additional TF NuRD to limit pro-inflammatory gene expression including IL-6, IL-12 and TNFa in addition downregulation of CD86 and increased expression of PDL1. (75), whilst ERG2 was identified as a critical TF in M0 to M2 polarisation (76). Although described extensively in structural cells a profibrotic role of EGR1 in macrophages has not been investigated in the literature.

Alveolar Macrophage

Annexin 1

Activator Protein 1

Androgen Receptor

Arginase 1

Bleomycin

Bone Marrow Derived Macrophage

CC Motif Chemokine Ligand

CC Motif Chemokine Receptor

Chitinase like 3

Coronavirus Disease 2019

Cyclooxygenase

Colony Stimulating Factor 1

CXC Motif Chemokine Ligand

CXC motif chemokine ligand

CXC Motif Chemokine Receptor

Dual Specificity Phosphatase 1

Extra Cellular Matrix

Epithelial Mesenchymal Transition

Endoplasmic Reticulum

Glucose-6-Phosphatase Catalytic

Hypoxia Inducible Factor 1

Interferon

Interferon alpha receptor

Interleukin

Inclusion RNA

Interferon beta

Interferon gamma

inducible Nitric Oxide Synthase

Inteferon Regulatory Factor

Inteferon Stimulated Gene

Inteferon Sensitive Response Element

JUN Proto-Oncogene

Kelch Like ECH Associated Protein 1

Konckout

Low Density Lipoprotein

Lipopolysacchiride

MER Proto-Oncogene, Tyrosine Kinase

Matrix Metalloproteinase 9

mycobacterium Tuberculosis

Nicotinamide adenine dinucleotide phosphate

Non Alcoholic Steratohepatitis

Nuclear Factor kappa B

Natural Killer

Nitric Oxide Synthase

Ornithine Acid Synthase 1

Primary Billiary Cirrhosis

Phosphoenolpyruvate carboxykinase 1

Programmed Death Ligand 1

Phosphoinositide-3-Kinase

Pattern Recognition Receptor

Receptor interacting serine/threonine kinase 1

Reactive Oxygen Species

Systelic Lupus Erythromatosis

SPHK1 Interactor, AKAP Domain Containing

Signal Transducer and Activator

Stimulator of Interferon Genes

Tumour Associated Macrophage

Tyrosine Aminotransferase

Trancription Factor

Trancription Factor

T helper

Toll Like Receptor

Tumor Necrosis Factor

Ultraviolet

Vascular Endothelial Growth Facotr

Wild Type

Summary of transcription factor function in macrophages

Limited data regarding function in macrophages in the literature
Anti-Inflammatory function
Master AM TF promotes multiple AM related functions including immune regulatory, phagocytosis/efferocytosis and surfactant metabolism
Important in cholesterol efflux, is induced by efferocytosis and has a immune repressive effect esp. if activated following stim with pro inflammatory cytokines
Limited data regarding function in literature
Regulatory function protecting and restraining responses to external stimuli

Regulator of ROS responses to external stimuli
Conflicting evidence in the literature with some differential effects of steroids on Tissue resident vs monocyte derived macs. However, in tissue resident populations substantial body of evidence highlight glucocorticoids promoting anti-inflammatory anbd homeostatic tissue repair .
Is upregulated in response to IL-10 and promoted and immune regulatory function
Inhibits the pro-inflammatory effects of HIF-1a and exerts immune regulatory effect
Limited data on function in alveolar macrophages, mixed

effects on macrophage inflammatory responses.
Critical regulator in cholesterol and homeostasis. Through regulation of cholesterol may represses IFN signalling
Promotes redox of oxidative elements and confers an anti-inflammatory effect
Critical in the terminal differentiation of monocytes to mature AMs and acts downstream of TGF-b signalling. May play a role in restoring homeostasis following acute injury though also implicated in promoting a profibrotic phenotype
Promotes pro-inflammatory effectors functions. Promotes type 1 and type 2 IFN mediated inflammation

inflammation
Is upregulated in response to infection and inflammatory stimuli where it can confer either pro and anti-inflammatory effects depending on context.
Also induced in response in line with NFkB signalling but confers a regulatory role in limiting the NFkB response
Confers an immunoregulatory response opposing the effects of NFkB mediated inflammation

Confers an Immunoregulatory effect based on known effects across all cell types
Master transcription factor in mediating pro-inflammatory effects in response to innate immune and PRR pathway signalling
Promotes polarisation to M2 wound healing phenotype of macrophages. A feature of profibrotic macrophages and induced in response to TGF-b signalling
Can promote either pro and anti-

inflammatory effects in a context dependent manner
Limited information of function outside of liver macrophage populations where promotes a pro-inflammatory effect with reduced efferocytosis
In a basal / non stimulated state induces genomic stability and protects against IFN mediated inflammation. Upon stimulation however appears to promote inflammatory responses.
EGR1 is associated with fibrosis and wonund healing in non immune cell types. Studies of function in macrophage highlight an anti-inflammatory effect

an anti-inflammatory effect associated with abrogating the inflammatory responses associated with LPS

Cluster	Anti-Oxidant / regulation of Oxidative stress	Phagocytosis / Efferocytosis	Surfactant / Lipid Metabolism
FABP4Hi AM	CEPBZ	PPARG	NR1H3
IGF-1+ AM		PPARG	
CD206Hi FN1+ AM	NRF2		SREBF2
CXCL10+ AM			
Mono-SPP1+ Macs			

* Downstream effect between imm

Stem Cell / Renewal	Immune Regulatory	Pro-Inflamm	Inteferon Signalling	Repiar, Fibrogenic / ECM Orgnisation
SOX4	PPARG			
	PPARG, NR3C1, NFIL3, TCF4			
				EGR2
	BCL3*, HIVEP1*, BCL6	NFkB2, HIF1a BCL3*, HIVEP1*	IRF1, ETV7	
	MEF2A	NFkB2, HIF1a MEF2C,		MYC, EGR1

ıue regulatory and pro-inflammation can be conext sepecific