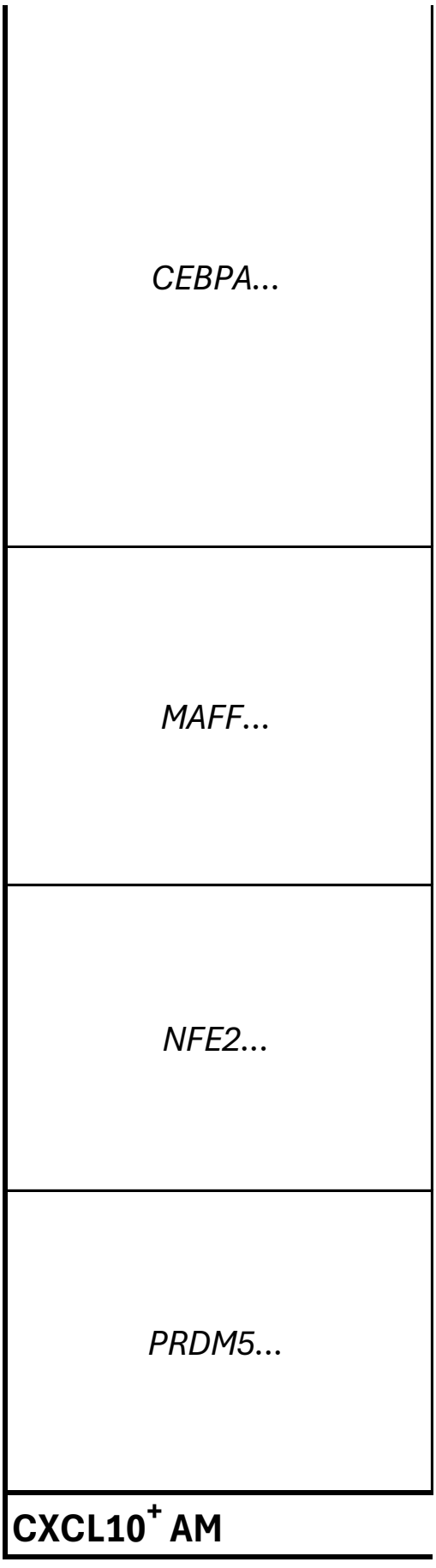
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CREM...	*0 0208016*	*3 44E-14*	IGF1^{+} AM
E2F4...	*0 0275111*	*0 0030386*	IGF1^{+} AM
ELF1...	*0 0243909*	*1 08E-55*	IGF1^{+} AM
ETS2...	*0 0236389*	*8 86E-45*	IGF1^{+} AM
FOS...	*0 0316203*	*1 42E-71*	IGF1^{+} AM
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HIF1A...	*0 0247566*	*0 0080714*	IGF1^{+} AM
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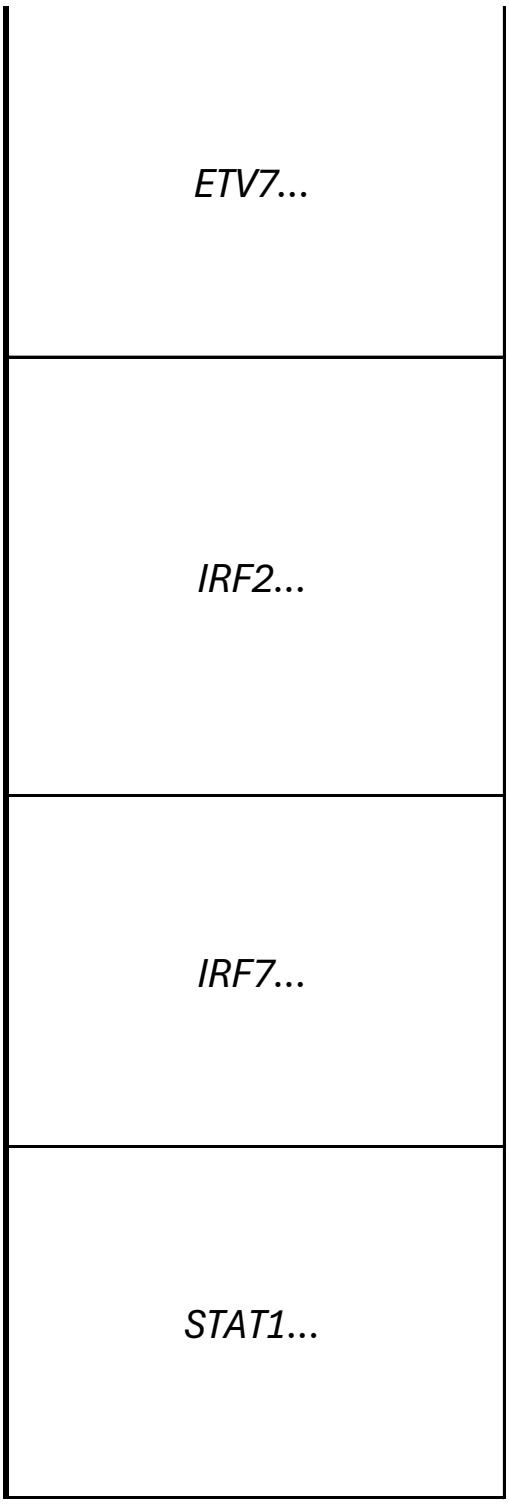
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CREM...	*0*	*0191793*	*1*	*69E-13*	$CD206^{hi}$ $FN1^{hi}$ AM
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FOSB...	*0*	*0206795*	*3*	*27E-33*	$CD206^{hi}$ $FN1^{hi}$ AM
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JUN...	*0*	*018431*	*2*	*50E-24*	$CD206^{hi}$ $FN1^{hi}$ AM
JUNB...	*0*	*0239128*	*9*	*57E-51*	$CD206^{hi}$ $FN1^{hi}$ AM
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ELF1...	*0*	*0308626*	*7*	*18E-31*	$CXCL10^{+}$ AM
ETV7...	*0*	*0440854*	*6*	*12E-11*	$CXCL10^{+}$ AM
FOS...	*0*	*0217756*	*4*	*81E-15*	$CXCL10^{+}$ AM
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IRF7...	*0*	*0315435*	*1*	*02E-18*	$CXCL10^{+}$ AM
JUN...	*0*	*021245*	*1*	*60E-15*	$CXCL10^{+}$ AM
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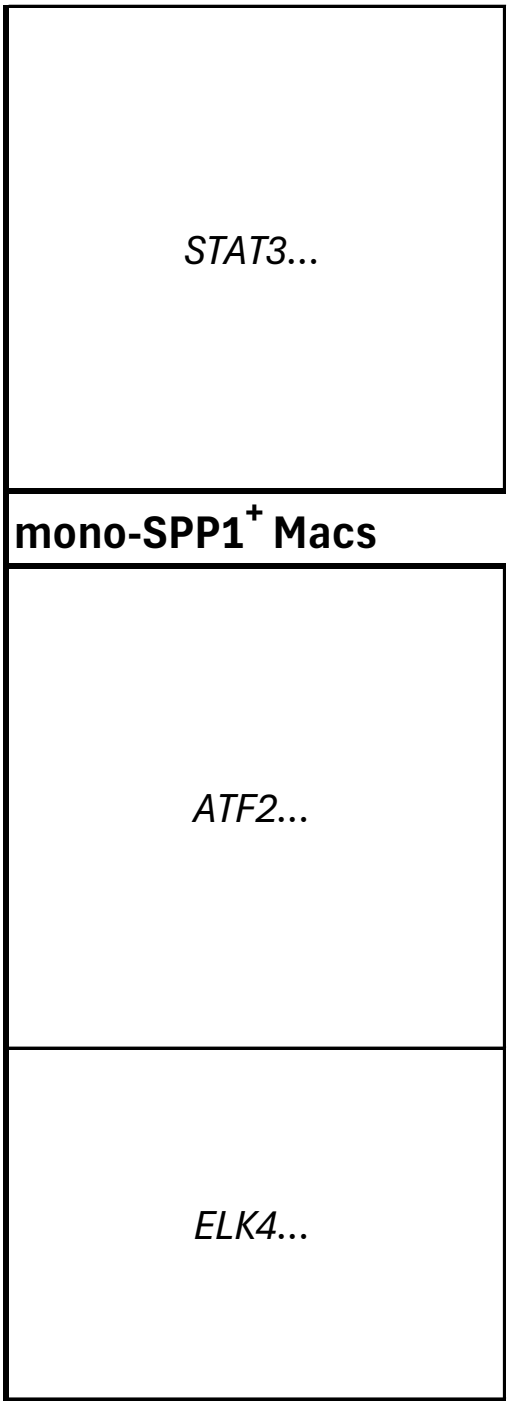
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STAT1...	*0*	*0226409*	*2*	*26E-24*	CXCL10^{+} AM
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BHLHE40...	*0*	*0373962*	*3*	*94E-16*	mono-SPP1^{+}
CBFB...	*0*	*0737403*	*1*	*03E-10*	mono-SPP1^{+}
CREM...	*0*	*0223569*	*4*	*49E-06*	mono-SPP1^{+}
ELF1...	*0*	*025254*	*1*	*44E-42*	mono-SPP1^{+}
ELK4...	*0*	*0212454*	*2*	*84E-10*	mono-SPP1^{+}
EP300...	*0*	*0198735*	*6*	*61E-16*	mono-SPP1^{+}
ETS2...	*0*	*0190212*	*2*	*04E-10*	mono-SPP1^{+}
FOS...	*0*	*0258436*	*3*	*05E-18*	mono-SPP1^{+}
FOSB...	*0*	*0221227*	*2*	*04E-08*	mono-SPP1^{+}
FOXP1...	*0*	*0187244*	*3*	*67E-20*	mono-SPP1^{+}
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MAF...	*0*	*0228582*	*2*	*58E-12*	mono-SPP1^{+}
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RREB1...	*0*	*0242393*	*8*	*31E-18*	mono-SPP1^{+}
SMAD7...	*0*	*059225*	*1*	*85E-10*	mono-SPP1^{+}
SREBF2...	*0*	*0226092*	*2*	*77E-19*	mono-SPP1^{+}
STAT5A...	*0*	*0235122*	*0*	*0036351*	mono-SPP1^{+}
TCF7L2...	*0*	*0620837*	*0*	*0009388*	mono-SPP1^{+}


Transcription Factor
FABP4hi
ATF3...
GTF2F1...
NR1H3...


NR3C1...
SOX4...
IGF1+ AM
E2F4...
LEF1...
CD206hi FN1hi AM

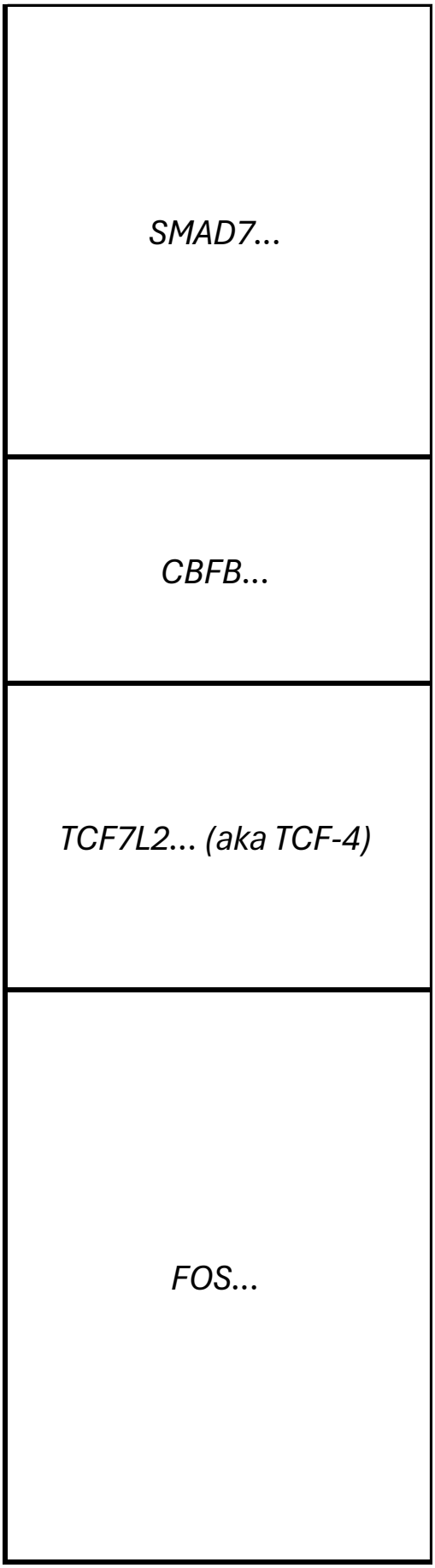

CEBPA...
MAFF...
NFE2...
PRDM5...
CXCL10+ AM


ETV7...
IRF2...
IRF7...
STAT1...


STAT3...
mono-SPP1+ Macs
ATF2...
ELK4...


EP300...
FOXP1...
MAF...


RREB1...
STAT5A...
Pan AM
BHLHE40...


SMAD7...
CBFB...
TCF7L2... (aka TCF-4)
FOS...

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

Activating transcription factor 3 (ATF3) acts as a hub of the cellular adaptive-response network. Multiple extracellular signals, such as endoplasmic reticulum (ER) stress, cytokines, chemokines, and LPS, are connected to ATF3 induction. Can modulate a wide range of effects including metabolism, glucose and adipose homeostasis. In immune response acts as transcriptional repressor downregulating pro-inflammatory responses. (1)
General transcription factor IIf subunit 1 (GTF2F1) is one of 3 subunits that makes up the TF II F. TF II F is a general transcription factor that along with others can stabilise RNA Pol II to enable gene transcription. Therefore behaves not a specific TF with a distinct function instead thought to upregulate global transcription of genes
Nuclear receptor subfamily 1 group H member 3 (NR1H3) also known as Liver X receptor alpha (LXR 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 LXRs act as cholesterol sensors and can regulate inflammatory responses. Also can influence lipid and fatty acid metabolism via activating additional TFs including SREBP1c (the master regulator of lipid metabolism and transport) and several other TFs including ABCA1 and fatty acid synthase (FAS) (6).

Nuclear receptor subfamily 3 group C member 1 (NR3C1) encodes the glucocorticoid receptor (GR) , which 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 (10-11)

SRY-box transcription factor 4 (SOX4) is an essential developmental transcription factor that regulates stemness, differentiation, progenitor development, and multiple developmental pathways including PI3K, Wnt, and TGFβ signalling. Its expression is upregulated in response to TGF-b. Principally in epithelial and cancer cells promotes EMT

E2F Transcription factor 4 (E2F4) belong to the family of E2F transcription factors involved in cell cycling and DNA replication. E2F4 is predominantly considered a transcriptional repressor whose activity is critical to engage and maintain cell cycle arrest in G0/G1. However in rapidly proliferating cells (including Intestinal epithelial cells and tumour cells) can promote cell cycling and proliferation in a non canonical manner.

Lymphoid Enhancing Factor 1 (LEF1) plays a crucial role in mediating WNT/bCatenin signalling. It forms a complex with beta catenin to promote transcription of genes downstream of WNT/bCatenin signalling. Expression of LEF1 is induced by ERG expression (in turn upregulated by TGF-b). Central component of organogenesis, tissue remodelling and specifically EMT. Associated with cancer where it is overexpressed. Also important In B cells important in differentiation of B progenitors to mature cells and proliferation (implicated in induction of AML). (18)

CCAAT Enhancer Binding Protein binding alpha (CEPBPA) is CCAAT enhancers family member with a wide range of functions. Involved in the differentiation and maturation of common myeloid progenitors to granulocyte / monocyte progenitors. Important in neutrophil maturation and terminal differentiation of neutrophils. CEBPA inhibits cell proliferation. CEBPA is downregulated in AML and mutations in CEBPA are thought to promote AML via several mechanisms (19). CEBPA can promote the transdifferentiating of lymphocytic cell types towards a myeloid state by upregulating the activity of PU.1 and CEPBb and upregulation of myeloid gene expression (20)
MAF BZIP Transcription Factor F (MAFF) belongs to the MAF family of transcription factors comprised of large MAF members and small MAF members including MAFF, MAFG and MAFK. Small MAFs can form homodimers with one another and exert a transcriptional repressive function or heterodimers with several other TFs including NFE2, NRF1, NRF2, NRF3. Thus MAFF proteins may have a wide range of effects depending on the TF they form dimers with. Global MAFF KO mice do not have any specific phenotypic differences compared to wild type littermates(22, 23).
Nuclear Factor Erythroid 2 (NFE2) 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 (24).
PR Set Domain 5 (PRDM5) is part of the zinc zipper PRDM family of TFs. PRDM5 like several members of the PRDM family known to play a role in cell cycle and growth arrest and thought to confer a tumour suppressive function with overexpression promoting cell cycle arrest (29). Several tumour suppressive mechanisms have been suggested including antagonising bcatenin signalling. PRDM5 may also interact with GFI1 (growth factor independent 1) which is crucial in haematopoiesis with PDRM5 and GLI1 activating transcription (30).

ETS Variant Transcription factor 7 (ETV7) is an ISG with expression upregulated by exposure to T1 and T2 IFNs and viral infection in line with IRF-1, STAT1 and NFkB (32). ETV7 confers an immune regulatory effect supressing the expression of a subset of ISGs following T1 IFN (33) 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.
Interferon Regulatory Factor 2 (IRF2) considered to function as a transcriptional repressor and expressed in most immune and non immune cells. Expression is induced in response to T1 and T2 IFN signalling where it primarily opposes the activity of IRF1 via several described mechanisms including competing with IRF1 promotor regions and inhibiting IRF1 nuclear translocation. May also interfere with NFkB, STAT1 and IRF9 signalling (34-35). However T1 IFNs may restrict IRF2 promotor sequence binding. Finally in unstimulated cells IRF2 is involved in maintaining TLR3 gene expression and maintains access to TLR3 genes (36).
Interferon Regulatory Factor 7 (IRF7) Considered the 'master regulator of T1 IFN induction' along with IRF3. Both IRF3/7 capable of promoting IFNa/b production following activation of a range of pattern recognition receptors. IRF7 Is highly expressed in pDCs snf whilst IRF3 is responsible for IFNa/b transcription in most cell types. IRF7 at low levels 'prime' IFNa/b production and is (unlike IRF3) upregulated following IFNa/b production resulting in a feed forward of IFN signalling. Is considered a positive regulator of T1 IFN signalling (39).
Signal Transducer And Activator Of Transcription 1 (STAT1) transduces signals from type 1, II and III IFNs from the cell surface to the nucleus. Phosphorylated STAT1 homo and heterodimers (with STAT2) binds to gamma activated sequences (GAS) and Interferon stimulated response element (ISRE) motifs in promotor regions of both pro-inflammatory and anti viral ISGs mediating a wide range of effects including cell activation, differentiation and innate immunity. Also transduces signals of IL-12 and IL-12 associated cytokines IL-23, 27 and 35.

Signal Transducer And Activator Of Transcription 3 (STAT3) transduces signals from the cell surface to nucleus of a wide range of cytokines and growth factors including type 1 and type 2 IFNs, IL-5, IL-6, IL-10, IL-12, IL-23 and growth factors including G-CSF, GM-CSF, EGF, FGF and PDGF exerting a wide range of effects depending on the cytokine and environmental context.

Activating Transcription Factor 2 (ATF2) Is a member of the AP1 family of TFs. It can interact with and form heterodimers with many AP1 family TFs (including AP1, cJun, cFos, CREB1) and consequently implicated in modulating a diverse range of cellular functions. The AT2 protein can also exist as a number of splice variants each interacting with different AP1 family TFs and along with different post translational modifications contributing to this TF functional diversity. ATF2 has been implicated in inducing and repressing cellular activities relating to cell cycling, cell death and immune mediated and inflammatory effects in response to a range of different stimuli (47).

ETS Transcription Factor 4 (ELK4(is a member of the ETS TF family and binds to the c-fos promoter region and a critical regulator of c-fos transcriptional expression so is a recognised proto-oncogene that promotes cell proliferation, malignant cell transformation and tumour progression. Additionally ELK4 has been implicated as an oncogene via c-fos independent mechanisms (51).

E1A Binding Protein P300 (EP300) Is a transcriptional coactivator protein. It binds to activated CREB protein and promotes transcription of genes related to cell proliferation and differentiation and has been implicated in the development of leukaemia and is tumorigenic. Additionally functions as a acetyltransferase and is recognised to acetylate nucleosome histones enabling it influence transcription at an epigenetic level. Finally can acetylate and act as a coactivator of a number of transcription factors resulting in a broad range of actions including response to heat shock (via heat shock transcription factor 1) and cellular stress as a co-activator of p53 signalling. (54, 55) and hypoxia as a co-activator to HIF1a (56). There is growing evidence of EP300 contributing to the development of fibrosis in multiple organs via a number of proposed mechanisms and promoting the expression of profibrotic mediators amongst fibroblasts and epithelial - mesenchymal transformation of epithelial cells and through promoting the effects of TGF-b signalling (57).
Forkhead Box p1 (FOXP1) is a member of the fork head box transcription factor family. Acts primarily as a transcriptional repressor though modulates wide range of tissue and cell specific effects, i) is involved in the development and organogenesis of a range of tissues (including cardiac, muscle, neurological and lung airway development) and angiogenesis. ii) is involved in the maturation of both T and B cells and in regulatory T cels function, iii) can promote proliferation and pluripotency amongst embryonic stem cells and iv) modulate macrophage activity and range of principle macrophage functions.
MAF BZIP Transcription Factor (MAF) is a member of the large MAF transcription factor family. Also known as c-MAF. Acts as a transcriptional activator and repressor and confers a wide range of cell specific effects notably in tissue development and considered a pro-oncogene. Has a wide range of effects on many immune cell types including T cells where it may partner with additional transcription factors and modulate the effects of different T cell subsets (notably Th2, TFH and Th17 subsets although broadly promotes IL-10 production amongst T cells (60).

Ras responsive element binding protein 1 (RREB1) is a transcription factor downstream of RAS-MAPK signalling and can act as a transcriptional activator and repressor. RREB1 is involved in several cellular processes including DNA damage and repair, cell growth and proliferation, differentiation, adipogenesis, fasting glucose balance, insulin production and calcium homeostasis and calcitonin and zinc uptake. It has been shown to promote p53 expression in response to UV radiation. Expression has been associated with the development of several cancers as downregulation is associated with the development of type 2 diabetes (64). RREB1 induced by RAS has been observed as a cofactor of SMAD transcription factors downstream of TGF-b signalling and inhibition of RREB1 prevented EMT in pancreatic epithelial cells and cancer models. Additionally RREB1 silencing downregulated ECM components (collagen, laminin and proteases) and genes associated with fibrosis (Wisp1, Ctgf, IL-11 and PDGFB) in both epithelial cells and fibroblasts. (65)

Signal Transducer And Activator Of Transcription 5A (STAT5A) and STAT5B proteins are 90% homologous with shared effectors function and both impact a range of cellular processes with compensatory redundant function. In non hematopoietic lineages respond to prolactin during mammary gland formation and lactation. In haematopoietic cells involved in myelopoiesis, lymphoid development, megakaryopoiesis and myeloid and granulocyte function. STAT5a/b are key signalling molecules downstream of a range of cytokines and GF's (IL-2, -3, -4, -5, -7, -9, -13, -15, -21, EPO, thrombopoietin (TPO), GH, prolactin, stem cell factor (SCF), Flt3, CSF2 and CSF3. Therefore have a wide range of effects that are context dependent (66).

Basic helix-loop-helix family member E40 (BHLHE40) is generally a transcriptional repressor with a broad range of context dependent effects. Best described for its involvement in regulating circadian rhythms and mitochondrial metabolism. In addition has a wide range of effects on the immune system, typically promoting inflammatory responses but also type 2 immunity. Its effects have been well studies in T lymphocyte populations. It is required for normal innate and adaptive TH1 response to infection including Mycobacterium tuberculosis but also BHLHE40-/- mice are protected from experimental models of experimental autoimmune encephalomyelitis and intestinal colitis (69).

A member of the SMAD family of transcription factors, associated with propagating TGFb signalling from the cell surface to gene expression. SMAD 7 is a negative regulator of TGFb signalling via several mechanisms including restricting TGFb1R signalling, R-SMAD activation, competing for SMAD4 and competing with activatory SMAD-DNA complexes required transcriptional activation (72). Thereby limiting the downstream effects of TGFb and linked to limiting tissue growth and development but also tissue fibrosis. In addition regulates alternative signalling pathways including restricting wnt/b-catenin and NFkB signalling. SMAD7 expression is induced by TGFb signalling with increased expression in regions of high TGFb activity including organ fibrosis, chronic inflammation and cancer.

Core binding factor beta (CBFB) stabilises the transcription factor proteins RUNX 1,2,3 preventing their degradation. Effects of CBFB relate to each RUNX protein. RUNX1 is involved in haematopoietic cell development whilst RUNX3 related to neuronal cell development. Rearrangements of CBFB associated with development of AML (76).

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.

FOS is also known as cFos Protooncogene. FOS family of transcription factors which along with JUN family members form the Immediate early gene (IEG) response group of transcription factors. FOS and JUN members heterodimerise to form the activator protein 1 (AP-1) complex which can bind to a wide range of gene promoting regions and participates in a number of cellular activities including proliferation, differentiation and transformation. FOS/JUN activation can be initiated by a range of extracellular environmental stressors, cytokines and growth factors and are implicated in both physiological process of tissue / organ development and have been extensively studied and implicated in influencing tumour development (80).

Abbreviations

ABCA1

AML

AML
APOC
APOE
Arg1
aSMA
BMDM
CCL
COVID
COX
CREB
CSF2
CSF3
CXCL
ECM
EGF
EMT
ER
FAS
FGF
Fizz-1
FLt3
G-CSF
G0
G1
G6PC
GAS
GM-CSF
HIF1a
IFNg
IL
INF
INFb
iNOS
IRF
ISG
ISRE
JUN
KO
LPS
LXR
NFkB
NK
PCK1
PDGF

PDGFB
PI3K
SCF
SphK1
TAT
TF
TGF-b
Th
TNF
VEGF
WISP
WT

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

The role of ATF3 in host defence is through the regulation of immune responses. In immune cells, such as macrophages, NK, Th2 lymphocyte and neutrophil cells, ATF3 is expressed at low levels. After activation of these immune cells by different signalling pathways initiated by TLRs, LPS, IFNα/β/γ, pneumolysin, IL-12, anti-CD28 antibody and ovalbumin ATF3 is upregulated (1-2). Subsequently, ATF3 downregulates the expression of target genes, including cytokines (IL-1β, IL-4, IL-5, IL-6, IL-12p40, IL-12b, IL-13, TNF, IFNβ/γ) and pro-apoptotic gene (Bak and Bax) by binding to the promoters (4). Mouse AFT3-/- BMDM display significantly higher basal and PRR-inducible IFN-β expression. AFT3 acts a transcriptional repressor with ATF3 binding to a regulatory region in the distal IFN-β promoter region that to control the magnitude of IFN-β promoter activity. ATF3 is also an ISG induced by T1 IFNs however modulates the expression of inflammatory ISGs thereby regulating the T1 IFN Inflammatory ISG response. (5)
No additional studies in myeloid cells
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. The latter effect is via activating the TF ABCA1 after LXR ligands bind to and form LXR receptor complexes (7) and reverse cholesterol transport receptors APOE/APOC (8). LXRs will also repress pro-inflammatory gene expression on murine BMDM and RAW26.7 macrophages after stimulation with TNFa and LPS and bacterial infection including iNOS, IL-6, IL1b and CCL2 and antagonises NFkB signalling (9) in vitro and in vivo.

Endogenous glucocorticosteroids induce predominately anti-inflammatory / immuno-regulatory programmes via NR3C1 in macrophages with a negative relationship between NR3C1 and TLR4, NF-kB and IFN receptor pathways. Upregulation of NR3C1 may result in cells to be more sensitive to the effects of endogenous gluococorticosteroids. Ligand activated NR3C1 TF in mono-macrophage effects include 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 (12, 13), and ii) in COVID19 myeloid NR3C1 expression negatively correlates with CXCL8 expression and neutrophil infiltration (14). However in certain contexts GC-NR3C1 have been reported to induce proinflammatory effects including induction of NLRP3 transcription in monocyte like THP-1 cells (15), whilst chronic NR3C1 activation in macrophages with exogenous glucocorticoids results in downregulation of adaptive immune system activation but upregulation of innate immune pathways including chemokine expression and leucocyte recruitment (16). Finally iv)GC-NR3C1 promoted macrophage phagocytosis, efferocytosis and promotes wound healing and tissue repair (17)
Limited information on function in macrophages.

Limited information on function in macrophages.
Multiple studies investigating LEF1 in AML / leukaemia and development of solid tumours but limited studies on function in macrophages

Limited information on the function of CEBPA in mature macrophages. Upregulation of CEBPa resulted in downregulation of NFkB, ISG15, CCR3, CCL4 and integrin ITGB1 amongst circulating mononuclear cells. Amongst tumour associated macrophages upregulation of CEFBA was associated with downregulation of genes associated with NFkB, Type 1 interferon signalling, IL1b and STAT4 signalling. Additionally Arg1 and NOS2 upregulation of genes associated with PGE2 signalling was observed suggesting CEFBA promoted a broad anti-inflammatory effect amongst tumour associated macrophages (21).
Limited information on function in macrophages. MAFF known to form heterodimers with NFE2 and promote NFE2 transcriptional activity (NFE2 below)
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 (25) via NADPH oxidase. The anti-inflammatory effects of NRF2 are mediated by both a redox (anti-oxidant) dependent (26) and independent mechanism (25). In a further study NRF2 was also shown to directly bind to sites in the proximity of several pro-inflammatory genes IL1a, IL1b and IL-6 and repress RNA pol mediated transcription (27). 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 (28).
No specific studies investigating PDRM5 function in macrophages however in osteoblasts PRDM5 is recognised to play a central role in promoting the transcription and expression of Collagen 1. PRDM5-/- osteoblastic cell lines and primary osteoblasts from PRDM5-/- mice have reduced Col1A (and Decron) mRNA expression whilst murine CHIPseq analysis revealed PRDM5 motifs upstream of 42 of 43 collagen genes with increased enrichment of PRDM5 targets in COL1A1 and COL1A2. Whilst genes targeted by PRDM5 are enriched for signalling pathways related to collagen fibril organisation and ECM organisation (31).

ETV7 is an ISG upregulated in response to T1 IFNs and serves to regulate the Interferon / ISG repones although this has not been specifically studied in macrophages
Whilst considered a negative regulator of T1 IFN signalling by antagonising IRF1 signalling following exposure to IFNb, IRF2 appears to exert a complex role on pro-inflammatory signalling following responses to LPS and TNFa; LPS / TNFa stimulated BMDM from IRF2-/- mice has reduced IL-1b, IL12, IL6 and IFNg mRNA expression and protein secretion (37). Likewise in response to bacterial ligands IRF2 is upregulated and promotes IFNa expression, whilst IFNa and proinflammatory cytokine production was reduced in IRF2 silenced murine macrophages (38). These results suggest the effects of IRF2 is heterogenous and may vary according to the type and duration of stimulation.
IRF7 promotes T1 IFN production and can amplify the T1 IFN response however may modulate and repress other pro-inflammatory pathways following PRR signalling. In BMDM IRF7 was required to induce T1 IFN production and inhibit viral replication. Additionally induction of an IRF7 protein lacking transcriptional activity resulted in reduced NFkB signalling suggesting an anti-inflammatory effect of IRF7 not related to its transcriptional role (40). Similarly IRF7 may polarise monocytes and BMDM macrophages towards an anti-inflammatory phenotype with increase in pro-inflammatory signalling in IRF7 silenced BMDM. This study also highlight upregulated RF7 expression in response to TGF-b. (41).
Transduces and promotes T1 and T2 Interferon signalling and promotes proinflammatory cytokine expression following both IFNg and LPS. Promotes an M1 like macrophage phenotype and antimicrobial and antiviral functions (42, 43).

STAT3 mediates both pro-inflammatory signalling and gene transcription. For example promotes pro-inflammatory response to IL6 and anti-inflammatory effects of IL-10. By transducing a wife range of signalling pathways with >40 ligands activating STAT3 signalling the effects on macrophage function has resulted in many wide ranging and contradictory conclusions. STAT3 activation and signalling is associated with promoting both pro and anti-inflammatory effects. In addition associated with promoting and mediating fibrotic process in cancer and both pulmonary and renal fibrosis. The effect of STAT3 on influencing macrophage phenotypes can be variable and is in part dependent on the stimuli, macrophage population studied and the interplay of several interacting signalling pathways (44). Specifically following T1/T2 IFN signalling of viral infection STAT3 activation and nuclear translocation results in expression of IL-10 and restraining the IFN response via an number of mechanisms (45, 46).

In one study ATF2 function on THP-1 cells reveal ATF2 targets the PPM1A promotor which is upregulated in monocyte to macrophage differentiation, whilst overexpression of ATF2 in THP-1 cells results in M1 like rounded circular inflammatory monocytes. ATF2 overexpression in monocytes sensitised to IFNg and LPS stimulation results in upregulation of HLADR expression, enhanced antibacterial function and enhanced IL-1b and CCL2 expression post Mtb infection compared to control or ATF2 -/- THP-1 cells. Additionally ATF2 overexpression promoted increased glycolytic metabolism associated with pro-inflammatory macrophage states. Overall ATF2 promotes monocyte to macrophage differentiation and enhances pro-inflammatory macrophage responses (48). ATF2 is also known to bind to the TNF-a promoter with impaired TNF-a production in ATF2 -/- THP-1 cells following Mtb infection via a p38 MAPK dependent mechanism (49) and increased TNFa following LPS (50).

Single study has investigated function of ELK 4 in tumour associated macrophages. In TAMs ELK4 knockdown increased expression of proinflammatory cytokines IL-1b and TNFa and NOS whilst Arg1, Fizz1 and Ym1 and IL-10 were reduced indicating ELK4 promotes an M2 macrophage phenotype (52). The effects of ELK4 on macrophage function may also be context dependent. A separate study using murine peritoneal macrophages with ELK4 knockdown treated with zymosan from yeast resulted in transcription of genes relating to stress responses suggesting ELK4 may have a different function in macrophages following response to infection (53).

No specific studies investigating the role of EP300 in monocyte or macrophage subsets
FOXP1 is upregulated in monocytes and becomes downregulated during monocyte to macrophage differentiation FOXP1 regulates CSF1R expression where overexpression of FOXP1 reduces CSF1R cell surface levels. FOXP1 monocyte/macrophage overexpression reduces peritoneal macrophage cytokine (Il1b, IL-12, IFNg, CSF1, CCL1) expression in response to LPS, and reduced phagocytosis in vitro and reduced bacterial clearance in vivo compared to WT (58). Similarly hypoxia induces increased pro-inflammatory cytokine expression in RAW 264.7 cells with downregulation of HMGB1 and increased FOXP1 expression. Whilst knockdown of HMGB1 which reduces FOXP1 expression is associated with reduced pro-inflammatory cytokine expression post hypoxia stimulation. (59). Overall increased FOXP1 in SPP1-Mono cells in PF may reflect i) monocyte abundance in this population or ii) an anti-inflammatory phenotype of macrophages in this cluster
cMAF promotes an M2 like anti-inflammatory phenotype with MAF -/- resulting in increased pro-inflammatory cytokine expression, IL-12, IL1b, IL-6 and reduced expression of IL-10 but also significant impairment of factors involved in wound healing and repair including TGF-b, VEGF and Arginase. cMAF also induces CSF1R expression and cMAF blockade impairs CSF1R expression in murine BMDMs. cMAF expression is induced by IL-10 but not IL-4 or IL-13.(61,62). cMAF expression was increased in hypertrophic scar tissue whilst cMAF overexpression in RAW 264.7 cells cocultured with fibroblasts resulted in increased fibroblast proliferation, migration and ECM protein (COl1,3 and aSMA) compared to WT RAW 264.7 cells (63).

No studies investigating function in monocytes or macrophages

CSF2 mediated STAT5a activity and function has been studied and STAT5 regulation of monocyte / macrophage proliferation, differentiation and activation is recognised. In human BMDM STAT5A silencing resulted in reduced pro-inflammatory cytokine expression (IL-6, TNF-a and IL-8) following LPS and increased phagocytosis and reduced cholesterol uptake (the latter change associated with reduced PPARg transcription). STAT5A silencing also resulted in increased expression of apoptosis markers and macrophage proliferation compared to WT BMDM in keeping with the known effects of CSF2 signalling on macrophage proliferation and survival. These findings suggest STAT5A (as (observed in CSF2 inhibition) increases pro-inflammatory cytokines secretion, and macrophage survival proliferation in addition promotes cholesterol and lipid uptake whilst supressing phagocytic activity (67). Similar findings are observed in murine BMDM where STAT5A KO resulted in reduced pro-inflammatory signalling with upregulation of anti-inflammatory gene sets as well as genes associated with fibrosis including Col1a1m Col5a2 and Vegfa (68). Suggesting STAT5a supresses genes associated with fibrosis.

BHLHE40 is expressed in a number of tissue resident macrophage populations including alveolar macrophages (AMs). Investigation of AMs in global BHLHE40 -/- mice strains compared to WT littermates was associated with impaired proliferation due to a reduction in the repressive activity of MAF and MAFB. Secondly impaired intracellular lipid metabolism with accumulation of and clearance and loss of expression of AM marker genes with de-differentiation into alternative tissue macrophage identities including red pulp macrophages and microglia, in addition to lacking mature AM transcriptional and cell surface markers including SiglecF (70). In myeloid specific conditional BHLHE40-/- lung inflammation following zymosan is reduced with reduced macrophage and neutrophil infiltration, reduced proinflammatory cytokine expression in AMs including Nos2, IFNg, TN, CXCL9 and downregulation of proinflammatory gene sets including IFNa, IFNg, ROS, complement and IL6 signalling pathways, with a global reduction in HIF1a signalling. Overall suggesting BHLHE40 promotes macrophage, granulocyte infiltration and pro-inflammatory signalling specifically via HIF1a mediated mechanisms (71).

SMAD7 over expression protects against bleomycin induced pulmonary fibrosis by mitigating the restricting the effects of TGFb signalling on both epithelial to mesenchymal transition (EMT) and fibroblast activation. (73). The effects of SMAD 7 have not been explored in lung macrophages however in cardiac macrophages SMAD 7 expression increases following coronary occlusion and infarction. SMAD 7 deficiency did not confer benefit in inflammation, scar area or extent of fibrosis or TGFb responses although was associated with a reduction in myofibroblast infiltration (74).Alternatively SMAD7 over expression in leucocytes may promote tissue inflammation by restricting the immunosuppressive activity of TGFb (75).

CBFB was identified as a crucial transcription factor differentially expressed between AM from young and old murine mice with falling expression in AMs with age. CBFB was identified as upregulated in AMs from younger mice. RUNX1 inhibition or adoptive transfer of CBFB -/- macrophages into irradiated mice was associated with reduced proliferation and self renewal. Whilst CBFB -/- macrophages was associated with a senescent more aged phenotype seen in older AMs compared to WT control AMs (77).

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 a supressing beta-catenin-HIF1a mediated pro-inflammatory activity(78). ii) THP-1 Mono 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 (79).

Monocyte and macrophage AP-1 expression has been implicated in the development of pro-inflammatory responses, cytokine expression and inflammatory conditions however the transcriptional effects of AP-1 vary depending on the heterodimer JUN/FOS composition. No specific studies on blockade of cFOS in lung macrophage populations are reported. However generalised cFOS blockade using the small molecule inhibitor T-5224 was associated with reduced cFOS expression on lung tissue sections, reduced ventilatory associated lung injury in rats, reduced inflammatory cell infiltrate and reduced TNFa, IL-6 compared to untreated mice (81). Although these effects may not be attributed to cFOS activity in macrophages. Separately lung macrophages in obesity associated pulmonary hypertension compared to controls were associated with increased pro-inflammatory signalling, elevated pyroptosis and elevated cFos expression. The authors suggesting cFos may be associated with inflammatory AM responses in this condition (82). However separately overexpression of cFos in RAW 264.7 cells has been linked to suppression of pro-inflammatory cytokine expression following LPS stimulation indicating a potentially immune regulatory effect in this macrophage like cell line (83).

ATP Binding Cassette Subfamily A Member 1
Alveolar Macrophage

Acute Myeloid Leukaemia
Apolipoprotein C
Apolipoprotein E
Arginase 1
alpha smooth muscle actin
Bone Marrow Derived Macrophage
CC Motif Chemokine Ligand
Coronavirus
Cyclooxygenase
CAMP Responsive Element Binding Protein
Colony Stimulating Factor 2
Colony Stimulating Factor 3
CXC motif chemokine ligand
Extra Cellular Matrix
Epithelial Growth Factor
Epithelial Mesenchymal Transition
Endoplasmic Reticulum
Fatty Acid Synthetase
Fibroblast Growth Factor
Cysteine Rich secreted protein
Fims receptor related Tyrosine Kinase 3
Granulocyte Colony Stimulating Factor
Growth Phase 0
Growth Phase 1
Glucose-6-Phosphatase Catalytic
Gamm activated Sequence
Granulocyte Macrophage Colony Stimulating Factor
Hypoxia Inducible Factor 1
Interferon gamma
Interleukin
Interferon
Interferon beta
inducible Nitric Oxide Synthase
Interferon Regulatory Factor
Interferon Stimulated Gene
Interferon Sensitive Response Element
JUN Proto-Oncogene
Knock Out
Lipopolysaccharide
Liver X Receptor
Nuclear Factor kappa B
Natural Killer
Phosphoenolpyruvate carboxykinase 1
Platelet Derived Growth Factor

Platelet Derived Growth Factor Beta
Phosphoinositide-3-Kinase
Stem Cell Factor
SPHK1 Interactor, AKAP Domain Containing
Tyrosine Aminotransferase
Transcription Factor
Transforming Growth Factor b
T helper
Tumour Necrosis Factor
Vascular Endothelial Growth Factor
WNT1-inducible-signaling pathway protein genes
Wild Type

Summary of transcription factor function in macrophages
Anti-inflammatory effect, ATF3 is induced after pro inflammatory activation but works to repress the inflammatory response
Important in cholesterol efflux, is induced by efferocytosis and has a immune repressive effect esp. if activated following stim with pro inflammatory cytokines

Context specific response in Macrophages and can induce pro and anti inflammatory effects. More commonly associated with anti inflammatory effects in the literature

Broad anti-inflammatory effect but in TAMs where it has been studied
Supresses Pro-inflammatory and IFN signalling
Specific function in macrophages not explored but in related osteoblasts promotes a pro fibro genic effect

ISG upregulated with INF signalling - primarily limits the IFN response
ISG also a negative regulator of IFN response although in certain context appear to promote proinflammatory responses in macrophages
Promoted T1 IFN signalling and fine tune the inflammatory response towards an antiviral response by downregulating associated pro-inflammatory cytokine expression
Critical mediator of T1 and T2 IFN signalling promoting pro-inflammatory and anti viral effects of INF signalling. Also enhances IFN signalling in feed forward loop

Mediates IFNAR signalling and limits the ISG response via upregulation of IL-10. Implicated as a profibrotic mediator also. Can mediate both pro and anti inflammatory effects.
Promotes monocyte to macrophage differentiation, in THP-1 cells induces glycolysis, pro-inflammatory cytokine production and antibacterial properties. Overall a pro-inflammatory effect
Limited studies but effects appear context dependent to a degree in macrophages but in TAMs induces an M2 alternatively activated phenotype with increase IL-10, Arg 1 and Fizz1 expression

No specific studies in macrophages but in other cell types appears to promote fibrosis
May be upregulated in this population due to monocyte contamination induces a anti-inflammatory effect
Promotes an anti-inflammatory profibrotic phenotype

Not explored in macs but in other cell types promotes and pro-fibrotic phenotype, is upregulated by TGF-b signalling and through an unknown mechanism result in activation of neighbouring fibroblasts
STAT5A promotes pro-inflammatory signalling, antigen presentation (via effects of GM-CSF) with downregulation of pro-fibrotic gene sets.
Promote AM proliferation, AM residency programmes and in inflammatory lung conditions pro-inflammatory responses mediated via HIF1

Ltd Data on lung macrophages, restricts fibrotic responses by inhibiting TGFb. Whilst known to restrict Wnt.b-catenin and NFkB signalling by promote tissue inflammation by limiting the immune regulatory effects of TGFb.
CBFB is required to maintain AM self renewal capacity and proliferation
Inhibits the pro-inflammatory effects of HIF-1a and exerts immune regulatory effect
Ltd data on lung macrophages, in a single study cFOS expression was associated with proinflammatory signalling in activated macrophages. However in vitro cFOS expression appears to confer an immunomodulatory role.

Cluster	Cholesterol / Lipid Metabolism	Proliferation/ self renewal	Pro Inflam.
FABP4^{hi} AM	NR1H3		
IGF1^{+} AM			
CD206^{hi} FN^{hi} AM			
CXCL10^{+} AM			
mono SPP1^{+} mac			ATF2 STAT5A
Pan AM	BHLHE40	BHLHE40 CBFB TCF7L2	BHLHE40 SMAD7 FOS

Counter Inflam.	Pro IFN	Counter IFN	Pro-Fibrotic	Counter-Fibrotic	UD function
ATF3 NR3C1					GTF2F1
					E2F4 LEF1
CEBPA NFE2		NFE2	PRDM5. CEBPA		MAFF
	STAT1 STAT2 IRF7	STAT3 IRF2 ETV7			
ELK4 FOXP1			MAF RREB1		EP300
TCF7L2				SMAD7	