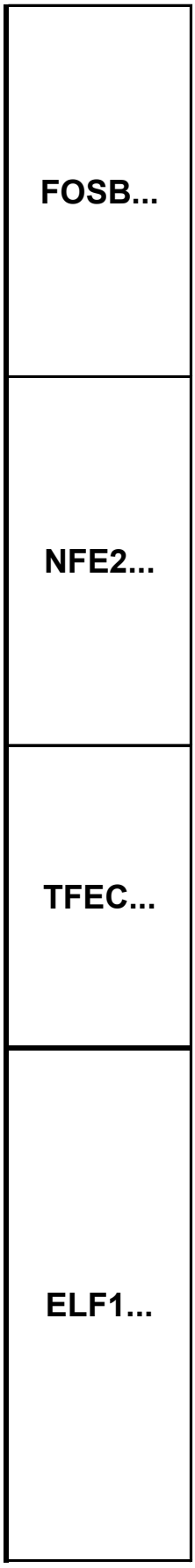
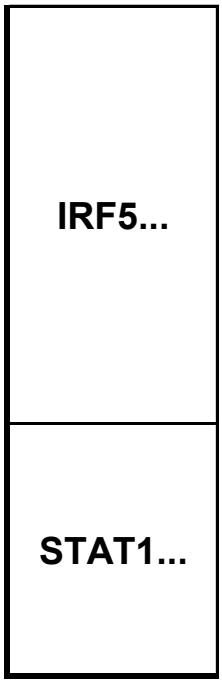

BCL6...
CREB5...
KLF6...


FOSB...
NFE2...
TFEC...
ELF1...


IRF5...
STAT1...

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

B Cell Lymphoma 6 (BCL6) is a critical transcription factor in regulating and promoting T Follicular cell identify and function. In addition, promotes B cell proliferation and plays a critical role in the initiation and maintenance in the formation of germinal centres.

cAMP response element binding 5 (CREB5) Is a member of the CREB (cAMP response element binding) family of TFs. All CREB/ATF family members are characterised with functional domains that have high binding affinity to the CRE motif found in the promotor region of a wide range of cellular processes (4). CREB function has been widely reported to regulate a diverse range of cellular function including proliferation, differentiation, survival, glucose homeostasis, mitochondrial homeostasis, protein homeostasis, circadian rhythm control and synaptic plasticity associated with the development of memory. There is also significant evidence highlighting the role of CREB members in immune cell function. CREB members act as co-activators which in concert with other transcription factors initiate target gene transcription. CREB5 specifically binds to CRE motifs either as a homodimer or heterodimer with cJun or ATF2 (5).

Kruppel like factor 6 (KLF6) is a member of the Kruppel family of transcription factors, KLF6 acts primarily as a transcriptional activator. KLF6 can modulate a number of cellular processes; i) During embryonic and tissue development. KLF6 is also expressed across a range of tissues and is involved in the expansion and maintenance of haematopoietic stem cells. ii) KLF6 directly activates TGFb and associated transcripts including COL1A, PLAU and ENG highlighting a role in wound healing and repair processes in addition to promoting fibrosis. iii) KLF6 has also been identified as a modulator of immune and inflammatory responses (10).

FOSB belongs to 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 (14).

Nuclear Factor Eryhtorid 2 (NFE2) also known as NFE related factor 2 (NRF2) 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) supression of inflammation including via repression of the NLRP3 inflammasome, iii) promote mitochondrial autophagy and degradation. Additionally NRF2 promotes erythroid and megakaryocyte poesis and differentiation (17).

Transcription Factor EC (TFEC) Is part of the microphthalmia associated transcription factor family (MiT) that as a group exert multiple biologically relevant functions. Unlike other members of this family TFEC expression is primarily restricted to monocytes and macrophages where TFEC recognised to upregulate transcription of myosin heavy chain alpha (21).

E74 Like ETS Transcription Factor 1 (ELF1) is a member of the ETS family of transcription factors that is highly expressed in haematopoietic cells, organs as well as epithelial / endothelial cells with several principle functions (25,26). i) It is an important promotor of haematopoiesis and haematopoietic cell gene expression. Amongst haematopoietic cells, i) it is highly expressed and modulates lymphocyte development and function modulating the expression of IL-2ra, IL-3, CD2, CD4 and immunoglobulin heavy chains. In addition regulates GM-CSF expression in activated T cells (25, 26). ii) It is also known to play a role in angiogenesis and blood vessel development promoting expression of regulators including Tie1/2, angio-poietin-2 and VEGFR1 (27) and iii) is upregulated and implicated in the progression of several cancer and associated with increased tumour cell invasiveness and epithelial-mesenchymal transition. Finally iv) confers an antiviral effect where ELF1 is upregulated in response to IFNb and viral infection and controls viral replication in vitro and in vivo. However this antiviral effect does not require STAT1 signalling. ELF1 upregulates a distinct pattern of anti-viral proteins distinct from both early and late ISG responses (28) and specifically appears to synergise with IFNb to promote expression of OAS1 (29).

Interferon Regulatory Fator 5 (IRF5) is a member of the IRF family of transcription factors. IRF5 is activated and undergoes nuclear translocation following viral infection, TLR 3,4, 7-9 signalling and DNA damage. In innate immunity IRF5 activates transcription of T1 IFNs and additional pro-inflammatory cytokines in response to these stimuli. IRF5 unlike IRF3/7 can specifically initiate additional pro-inflammatory cytokine expression post viral infection and in response to bacterial infection and PAMPS including IL-12, IL-6 and TNF-a (30). IRF5 has been shown to play roles beyond innate immunity with IRF5 upregulating genes associated with neuropathic pain in microglia (31) and contributes to insulin resistance and adipose tissue deposition in obese mice (32). Additionally IRF5 can promote cell cycle arrest and expression of pro-apoptotic transcripts suggesting a role as a tumour suppressor gene (33).

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.

Glossary

Arg1

ATF

BMDM

CCL

Chi3l

COX

CPG

CRE

GM-CSF

HIF1a

IEG

IL

IFN

JUN

KO

LPS

MAPK

MRC1

MSK

mt

NADPH

NFkB

NO

OAS1
PMA
PPARy
PRDM1
RBC
Retina
ROS
TF
TH2
TLR
TNF
VEGFR
WT

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

BMDM from BCL6-/- mice had increased expression of CCL2/CCL7 and IL1a although no difference in CCL3 or IL-12 expression following stimulation with LPS. BCL6 -/- mice are prone to fatal TH2 mediated inflammation (1) 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 (2). 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 binding of the BCL6 to its DNA motif which overlaps with STAT binding and exerts in anti-inflammatory effects by preventing STAT binding (3).

Whilst the actions of CREB5 specifically has not been explored the functional impact of other CREB family members on monocyte / macrophage function are described (4). CREB5 is observed to be most highly expressed in classical monocytes compared to intermediate and non classical monocytes although its specific function was not explored (6). In monocytes (and macrophages) CREB family members may i) interfere with the TF p300/CBP to inhibit NFKb signalling following TLR activation (7). Several mechanisms through which CREB represse NFkB signalling in monocytes and macrophages have been proposed (7). ii) TLR signalling results in MAPK and MSK1/2 pathways - the latter promotes CREB phosphorylation and activation resulting in IL-10 transcription in BMDM (8). Additionally several mechanisms of CREB mediated IL-10 transcription have been identified beyond TLR-MSK1/2 signalling (4). iii) CREB promotes anti-apoptotic pathways in macrophages in response to TLR4/NFkB signalling again via MSK1/2 resulting in CREB mediated transcription of antiapoptotic genes (9) minimising pathogen mediated immune escape.

KLF6 modulates monocyte and macrophage function towards a pro-inflammatory state. i) LPS and IFNy induce upregulation of KLF6 whilst IL-4/IL-13 downregulate KLF6 expression in human and murine BMDM, ii) KLF6 overexpression augments proinflammatory cytokine expression (IL1a, IL1b, TNFa, CCL2, CCL3, COX2) by acting as a coactivator of NFkB and represses M2 like gene transcripts, (Arg1, MRC1, Chi3l3 and Retina) by inhibiting the expression of PPARy. Whilst deletion has the opposite effect in both macrophage cell lines and BMDM (11). KLF6 also supresses BCL6 expression by increasing PRDM1 expression, thereby limiting BCL6 repression of pro-inflammatory cytokine expression (12). In (12) KLF6 deficiency in a macrophage specific KLF6 KO mouse reduced macrophage migration and recruitment to sites of inflammation. A further study identified KLF6 promotes HIF1a expression, with macrophage specific KLF6 deficiency impairing both HIF1a expression, proinflammatory cytokine expression and a switch to glycolytic metabolism in several murine models in response to LPS, heat inactivated candida and hypoxia (13).

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 (15). A single study identified FOSB as upregulated in repones to a number of factors including ionomycin and ATP resulting in AP-1 complex expression in myeloid cells. FOSB knockdown in a related osteoblast cell line resulted in downregulation of COX-2 expression (16).

NRF2 confers a anti-inflammatory phenotype in macrophages; macrophages from NRF2 -/- mice have increased ROS, activation of TLR, IRF3 and NFkB signalling following LPS and increased pro-inflammatory cytokine production (18) via NADPH oxidase. The anti-inflammatory effects of NRF2 are mediated by both a redox (anti-oxidant) dependent (19) and independent mechanisms (18). 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 polymerase mediated transcription (20). Specific increased NRF2 activity (by depletion of its repressor Keap1) in myeloid cells protects against caecal puncture induced sepsis, with lower mortality and pro-inflammatory marker expression compared to wild type and NRF2-/- models (20).

TFEC expression is limited to cells of the monocyte/macrophage lineage. TFEC protein expression is upregulated by IL-4 stimulation in a STAT6 dependent manner in BMDM. Whilst LPS stimulation resulted in TFEC mRNA expression however protein expression was not observed suggesting TFEC expression is upregulated by IL-4 and M2 like cytokines rather than M1 / pro-inflammatory cytokines (23). A further study demonstrated the TFEC binding motif in the promotor region of the IL-4receptor and a reduction in IL-4r expression with a mutation of the TFEC motif in the promotor region suggesting TFEC and IL-4 signalling can exert a feed forward loop (24).

ELF1 can regulate and promote expression of GMCSF which has been explored in activated T cells following TCR signalling however the effects of ELF1 mediated GM-CSF expression on myeloid cells was not explored. No additional studies investigating ELF1 function in monocytes or macrophages were identified.

IRF5 is widely expressed on immune cells including macrophages, monocytes, DCs and B cells. Splenic macrophages from IRF5-/- mice have reduced expression TNFa, IL-6, and IL-12 following TLR stimulation and are resistant to CPG and LPS induced endotoxin shock (34). Similarly IRF5 promotes differentiation of monocytes towards an M1 phenotype. Whilst macrophages converting from an M2 to M1 phenotype resulted in increased IRF5 expression which was shown to directly modulate upregulation of pro-inflammatory cytokines and repression of IL-10 and TGFb via recruitment of IRF5 to promotor regions (35). IRF5 cooperates with the NfkB subunit protein RELa to be recruited to promotor regions of pro-inflammatory genes upregulated following LPS stimulation (36).
Transduces and promotes T1 and T2 Interferon signalling and promotes proinflammatory cytokine expression following both IFN stimulation and LPS. Promotes an M1 like macrophage phenotype with antimicrobial and antiviral functions (37,38).

Arginase 1

Activating Transcription Factor

Bone Marrow Derived Macrophage

CC Motif Chemokine Ligand

Chitinase like protien 3 ligand

Cyclooxygenase

Cysteine Phosphate Guanine

CAMP Responsive Element

Granulocyte Macrophage Colony Stimulating Factor

Hypoxia Inducible Factor 1

Immediate Early Gene

Interleukin

Interferon

JUN Proto-Oncogene

Knock Out

Lipopolysacchiride

Mitogen-activated protein kinase

Mannose Receptor C-type

Mitogen- and Stress-activated protein Kinases

mitochondrial

Nicotinamide Adenine Dinucleotide Phosphate

Nuclear Factor kappa B

Nitric Oxide

Ornithine Acid Synthase 1
Phorbol 12-Myristate 13-Acetate
Peroxisome Proliferator Activated Receptor
PR domain zinc finger Protein 1
Red Blood Cell
Resistin-like alpha
Reactive Oxygen Species
Trancription Factor
T helper 2
Toll Like Receptor
Tumor Necrosis Factor
Vascular Endothelial Growth Factor Receptor
Wild Type

Summary of transcription factor function in monocytes
BLC6 is induced by TLR signalling but confers an anti-inflammatory role supressing the effects NFkB signalling
CREB family TFs primarily exert an anti-inflammatory effect, opposing NFkB signalling and promoting IL-10 transcription. However in bacterial infection promotes macrophage survival to minimise pathogen mediated escape
Exertes a proinflammatory effect on monocytes / macrophages, upregualates proinflammatory signalling as a NFkB coavtivator, promotes HIF1a transcription (thereby promotes pro-inflammatory cytokine expression) and represses BCL6 activity

A heterodimer partner to JUN family TFs fotming AP-1 which promote pro-inflammatory responses and cytokine expression. Although limited data on the specific function FOSB heterodimers
Anti-inflammatory effect principally, represses proinflammatory cytokine expression, an important regulator of ROS hoemeostasis therefore reduces inflammasome activation, and protects against oxidative stress
Is upregulated in reponse to IL-4 and promotes its expression in a feed forward manner, skewing towards an M2 phenotype
No specific studies in macrophages / monocytes however is upregulated downstream of GM-CSF which induces a proifnlammatory phenotype of macrophage in vitro. ELF-1 also promotes expression of type 1/ type 2 IFNs and anti-viral proteins independent of STAT signalling

Unlike IRF3/7 will promote pro-inflammatory cytokine and IFN signalling pathways downstream
Critical mediator of type 1 and type 2 IFN signalling promoting pro-inflammatory and anti viral effects of IFN signalling. Also enhances IFN signalling in feed forward loop