



REVIEW

An overview of mammalian p38 mitogen-activated protein kinases, central regulators of cell stress and receptor signaling [version 1; peer review: 2 approved]

Jiahuai Han¹, Jianfeng Wu¹, John Silke ^{2,3}

¹State Key Laboratory of Cellular Stress Biology, Innovation Center for Cell Biology, School of Life Sciences, Xiamen University, Xiamen, Fujian, 361005, China

²The Walter and Eliza Hall Institute, IG Royal Parade, Parkville, Victoria, 3052, Australia

³Department of Medical Biology, University of Melbourne, Parkville, Victoria, 3050, Australia

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Abstract

The p38 family is a highly evolutionarily conserved group of mitogen-activated protein kinases (MAPKs) that is involved in and helps co-ordinate cellular responses to nearly all stressful stimuli. This review provides a succinct summary of multiple aspects of the biology, role, and substrates of the mammalian family of p38 kinases. Since p38 activity is implicated in inflammatory and other diseases, we also discuss the clinical implications and pharmaceutical approaches to inhibit p38.

Keywords

p38, MAPK, inflammation, signalling

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- 1 **Jonathan Ashwell**, National Cancer Institute, National Institutes of Health, Bethesda, USA
- 2 **Guadalupe Sabio**, Centro Nacional de Investigaciones Cardiovasculares (CNIC), Madrid, Spain

Any comments on the article can be found at the end of the article.

Corresponding authors: Jiahuai Han (jiahuaihan@xmu.edu.cn), John Silke (silke@wehi.edu.au)

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p38 mitogen-activated protein kinases

p38 α (originally named p38) was identified and cloned as a 38 kDa protein that was tyrosine-phosphorylated in response to LPS stimulation in mammalian cells^{1,2}. Sequence comparison, on the day p38 α was cloned, revealed that it belonged to the mitogen-activated protein kinase (MAPK) family and that a *Saccharomyces cerevisiae* osmotic response protein kinase HOG1 was a p38 α homologue³⁻⁵. p38 α was also named cytokine suppressive drug binding protein (CSBP) because it was identified as the target of a series of anti-inflammatory pyridinyl-imidazole compounds and as reactivating kinase (RK) because it phosphorylated and activated MK2³⁻⁵. There are four members of the p38 group of MAPKs encoded by four different genes in mammals: p38 α (*MAPK14*, chromosome 6p21.31 in humans), p38 β (*MAPK11*, *SAPK2b*, Chr22q13.33)⁶, p38 γ (*MAPK12*, *ERK6*, *SAPK3*, Chr22q13.33)^{7,8}, and p38 δ (*MAPK13*, *SAPK4*, *Serk4*, Chr6p21.31)^{9,10}. As can be surmised from their chromosomal locations, *MAPK14/p38 α* and *MAPK13/p38 δ* are physically close and separated by just over 15 kb, as are *MAPK12/p38 β* and *MAPK11/p38 γ* , which are separated by less than 2 kb. All the p38s contain a conserved Thr–Gly–Tyr (TGY) dual phosphorylation motif within the kinase activation loop, and both Thr and Tyr phosphorylation are necessary to fully activate the kinase¹¹. However, monophosphorylated p38 α Thr¹⁸⁰ has some kinase activity *in vitro*, but a different substrate specificity, when compared with dual-site phosphorylated p38 α ¹². p38 group members are expressed ubiquitously, but p38 γ and p38 δ are enriched in certain cell types and tissues, such as p38 γ in skeletal muscle and p38 δ in the salivary, pituitary, and adrenal glands¹³. p38 β shares more amino acid sequence identity with p38 α (~70%), while p38 γ and p38 δ share ~60% identity with p38 α . p38 γ and p38 δ also share high sequence homology with cyclin-dependent kinases (CDKs) and are sensitive to some CDK inhibitors¹⁴.

Activation and inactivation of p38

p38 α is involved in the response to almost all stressful stimuli, including LPS, UV light, heat shock, osmotic shock, inflammatory cytokines, T cell receptor ligation, glucose starvation, and oncogene activation^{2,4,5,15-20}. Under certain circumstances, it is also activated upon growth factor stimulation. It should be noted that the activation of p38 in some cases is cell type specific, since an activating stimulus in one cell type may inhibit p38 in other cell types²¹. The study of p38 group members other than p38 α has been less intensive; however, where it has been examined, the other p38s are frequently co-activated with p38 α ²².

Like other MAPK signaling pathways, the activation of all p38s is mediated by a kinase cascade: MAPKKK (MAP3K), which activates MAPKK (MAP2K), which in turn activates MAPK. The MAP2K kinases MKK3 and MKK6 are the major upstream kinases for p38 activation²³⁻²⁵. Although MKK3 and MKK6 phosphorylate most p38 isoforms *in vitro*, selective activation and substrate specificity have been observed *in vivo*²⁶. MKK4 has also been reported to phosphorylate p38 α and p38 δ in specific

cell types⁹. A number of MAP3Ks have been reported to participate in p38 activation including TAK1²⁷, ASK1²⁸, DLK²⁹, and MEKK4^{29,30}. Low-molecular-weight GTP-binding proteins in the Rho family, such as Rac1 and Cdc42, can activate p38 through binding to MEK1 or MLK1, which function as upstream activators of MAP3K^{31,32}.

p38 α can also be activated by MAP2K-independent mechanisms. TAB1 (TAK1-binding protein 1) directly interacts with p38 α and can promote trans autophosphorylation on Thr¹⁸⁰ and Tyr¹⁸² and thus full activation of p38 α ³³. A subsequent study revealed that autophosphorylation of Thr¹⁸⁰ and Tyr¹⁸² requires a conserved Thr¹⁸⁵ residue³⁴. TAB1-dependent p38 α activation has been implicated in ischemic myocardial injury and T cell anergy^{35,36}. TAB1 is also claimed to play a role in Sestrin-mediated p38 α activation¹². Another MAP2K-independent activation is mediated by ZAP70 after T cell receptor ligation. ZAP70 can directly phosphorylate p38 α/β on Tyr^{323/18}, leading to autophosphorylation on Thr¹⁸⁰, one of the dual phosphorylation sites. As discussed, mono-Thr¹⁸⁰ phosphorylated p38 still has some kinase activity³⁷, and loss of ZAP70-mediated p38 activation in p38 $\alpha\beta$ ^{Y323F} double knock-in mice reduces autoimmunity and inflammation in several autoimmune disease models³⁸⁻⁴⁰. Interestingly, p38 α also phosphorylates ZAP70, resulting in a decrease in the size and persistence of the T cell receptor signaling complex, and therefore acts as a feedback regulator of ZAP70⁴¹.

Conversely, de-phosphorylation of both threonine and tyrosine residues in the activation loop inactivates MAPKs, and this is mainly carried out by dual-specificity phosphatases of the MAPK phosphatase (MKP)/dual specificity phosphatase (DUSP) family⁴². Although several MKPs have been reported to dephosphorylate p38 α , MKP1/DUSP1, MKP5/DUSP10, MKP8/DUSP26, and DUSP8 are more potent inhibitors of p38 α and JNK than ERK⁴³. A recent report showed that DUSP12 is also a p38 α phosphatase⁴⁴. While there are a number of p38 α DUSPs, no DUSP for p38 γ or p38 δ has been reported, and these two p38s are resistant to several known p38 α MKPs such as MKP1, 3, 5, and 7⁴⁵. p38 α -dependent upregulation of MKP1 was reported and is believed to be part of a negative feedback loop of p38 α activation⁴⁶. Other types of phosphatases have also been reported to target p38 MAPKs, such as CacyBP/SIP⁴⁷, Wip1⁴⁸, and PP2C^{49,50}. The substrate specificity between p38 and phosphatases and the related physiological functions *in vivo* still need further investigation. p38 γ has also been reported to be degraded by a p38/JNK/ubiquitin-proteasome-dependent pathway, which represents an additional mechanism by which p38 kinases may cross regulate each other⁵¹. Yet other ways of regulating p38 are suggested from studies in *Caenorhabditis elegans*, where a genetic screen for resistance against bacterial infection identified RIOK-1, an atypical serine kinase and human RIO kinase homolog, as a suppressor of the p38 pathway⁵². As RIOK-1 is a transcriptional target of the p38 pathway in *C. elegans*, this suggests that RIOK-1 is part of a negative feedback loop. A brief summary of the p38 pathway is shown in [Figure 1](#).

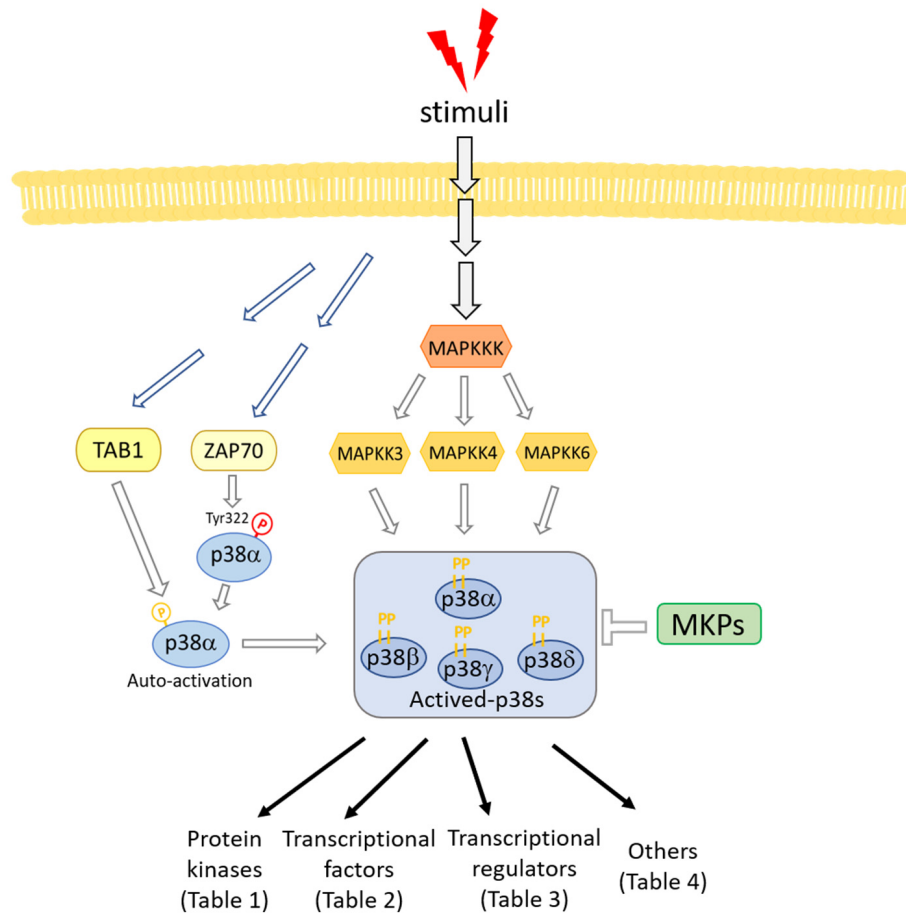


Figure 1. A diagram of the p38 pathway. MKP, mitogen-activated protein kinase phosphatase; TAB1, TAK1-binding protein 1; Tyr, tyrosine.

Downstream substrates of p38

Protein kinases

The p38 MAPK cascade does not end at p38. Members of the MAPK-activated protein kinase (MAPKAPK) family such as MK2, MK3, and MK5 (PRAK) are all p38 substrates^{3,4,53-55}. The MKs have a broad range of substrates that extend the range of functions regulated by p38 kinases. Mitogen- and stress-activated protein kinase-1/2 (MSK1/2), which are important for CREB activation and chromosome remodeling, have also been identified as substrates of p38⁵⁶. MNK1/2, kinases that phosphorylate the eukaryotic initiation factor-4e (eIF-4E), are phosphorylated by p38^{57,58}. p38 α has also been reported to inactivate murine GSK3 β by phosphorylating Ser³⁸⁹, and since GSK3 β is required for the continuous degradation of β -catenin in the Wnt signaling pathway, this can lead to an accumulation of β -catenin^{59,60}. It was also reported that p38 δ negatively regulates insulin secretion by catalyzing an inhibitory phosphorylation of PKD1⁶¹. A number of p38 protein kinase substrates are summarized in [Table 1](#).

Transcription factors

p38 targets a large number of transcription factors, including myocyte-specific enhancer factor 2 (MEF2) family members, cyclic AMP-dependent transcription factor 1, 2, and 6 (ATF-1/2/6), CHOP (growth arrest and DNA damage inducible gene 153, or GADD153), p53, C/EBP β , MITF1, DDIT3, ELK1/4, NFAT, and STAT1/4. p38 phosphorylation of transcription factors predominantly leads to enhanced transcriptional activity. However, in some cases, it represses transcription, and this is summarized in [Table 2](#). Transcription factor phosphorylation by p38 is often stimulus and cell type dependent and plays a role in the cellular response to inflammation, DNA damage, metabolic stress, and many other stresses⁶²⁻⁷⁶. The effects of p38 on transcription seem to constitute the major part of p38's responses to stress stimuli.

Transcriptional regulators

A large number of transcriptional regulators, including epigenetic enzymes, are substrates of p38, and these are summarized

Table 1. Substrates of p38 group members – kinases.

Substrate	Kinase	Function	References
MAPKAPK2 (MK2)	p38 α , p38 β , p38 γ , p38 δ	Activates the kinase substrate	Freshney NW <i>et al.</i> , <i>Cell</i> , 1994 ⁴ Rouse J <i>et al.</i> , <i>Cell</i> , 1994 ³
MAPKAPK3 (MK3)	p38 α , p38 β , p38 γ , p38 δ	Activates the kinase substrate	McLaughlin MM <i>et al.</i> , <i>J Biol Chem</i> , 1996 ⁵⁴
MNK1/2	p38 α	Activates the kinase substrate	Fukunaga R <i>et al.</i> , <i>EMBO J</i> , 1997 ⁵⁸ Waskiewicz AJ <i>et al.</i> , <i>EMBO J</i> , 1997 ⁵⁷
MSK1/2	p38 α	Activates the kinase substrate	Deak M <i>et al.</i> , <i>EMBO J</i> , 1998 ⁵⁶ Pierrat B <i>et al.</i> , <i>J Biol Chem</i> , 1998 ⁷⁷
PAK6	p38 α	Activates the kinase substrate	Kaur R <i>et al.</i> , <i>J Biol Chem</i> , 2005 ⁷⁸
PIP4Kb	p38 α	Inactivates the kinase substrate	Jones DR <i>et al.</i> , <i>Mol Cell</i> , 2006 ⁷⁹
RPAK (MK5)	p38 α , p38 β	Activates the kinase substrate	New L <i>et al.</i> , <i>EMBO J</i> , 1998 ⁵⁵
PKC ϵ	p38 α , p38 β	Completes cytokinesis	Saurin AT <i>et al.</i> , <i>Nat Cell Biol</i> , 2008 ⁸⁰
GSK3 β	p38 α	Inactivates the kinase substrate, activates Wnt pathway.	Bikkavilli RK <i>et al.</i> , <i>J Cell Sci</i> , 2008 ⁶⁰ Thornton TM <i>et al.</i> , <i>Science</i> , 2008 ⁵⁹

GSK3 β , glycogen synthase kinase 3 beta; MAPKAPK, mitogen-activated protein kinase activated protein kinase; MSK1/2, mitogen- and stress-activated protein kinase; PAK6, p21-activated kinase 6; PIP4Kb, phosphatidylinositol 5 phosphate 4-kinase; PKC ϵ , protein kinase C epsilon type.

Table 2. Substrates of p38 group members – transcription factors.

Substrate	Kinase	Function	References
ATF2	p38 α , p38 β , p38 γ , p38 δ	Enhances transcriptional activity	Cuenda A <i>et al.</i> , <i>EMBO J</i> , 1997 ⁸¹ Jiang Y <i>et al.</i> , <i>J Biol Chem</i> , 1997 ⁹
C/EBP α	p38 α	Enhances transcriptional activity	Qiao L <i>et al.</i> , <i>J Biol Chem</i> , 2006 ⁸²
C/EBP β	p38 α	Enhances transcriptional activity	Engelman JA <i>et al.</i> , <i>J Biol Chem</i> , 1998 ⁸³
C/EBP ϵ	p38 α	Enhances transcriptional activity	Williamson EA <i>et al.</i> , <i>Blood</i> , 2005 ⁸⁴
CHOP	p38 α , p38 β	Enhances transcriptional activity	Wang XZ <i>et al.</i> , <i>Science</i> , 1996 ⁶⁸
E2F4	p38 α	Enhances transcriptional activity	Morillo SM <i>et al.</i> , <i>Mol Cell Biol</i> , 2012 ⁸⁵
Elk-1	p38 α	Enhances transcriptional activity in specific cell types	Janknecht R <i>et al.</i> , <i>EMBO J</i> , 1997 ⁶⁷ Whitmarsh AJ <i>et al.</i> , <i>Mol Cell Biol</i> , 1997 ⁶⁶
ER α	p38 α	Enhances nuclear localization and transcriptional activity	Lee H <i>et al.</i> , <i>Mol Cell Biol</i> , 2002 ⁸⁶
Fos	p38 α , p38 β , p38 γ , p38 δ	Enhances transcriptional activity	Tanos T <i>et al.</i> , <i>J Biol Chem</i> , 2005 ⁸⁷
FOXO3a	p38 α	Enhances nuclear relocalization	Ho KK <i>et al.</i> , <i>J Biol Chem</i> , 2012 ⁸⁸
GR	p38 α	Enhances transcriptional activity	Miller AL <i>et al.</i> , <i>Mol Endocrinol</i> , 2005 ⁸⁹
IUF1	p38 α , p38 β	Enhances transcriptional activity	Macfarlane WM <i>et al.</i> , <i>J Biol Chem</i> , 1997 ⁹⁰
JDP2	p38 α	N/D	Katz S <i>et al.</i> , <i>Biochem J</i> , 2002 ⁹¹
c-JUN	p38 α , p38 β , p38 γ	Enhances transcriptional activity	Humar M <i>et al.</i> , <i>Int J Biochem Cell Biol</i> , 2007 ⁹²

Substrate	Kinase	Function	References
MafA	p38 α , p38 β , p38 γ , p38 δ	Enhances transcriptional activity	Sii-Felice K <i>et al.</i> , <i>FEBS Lett</i> , 2005 ⁹³
MEF2A	p38 α , p38 β , p38 δ	Enhances transcriptional activity	Zhao M <i>et al.</i> , <i>Mol Cell Biol</i> , 1999 ⁹⁴
MEF2C	p38 α , p38 β , p38 γ , p38 δ	Enhances transcriptional activity	Han J <i>et al.</i> , <i>Nature</i> , 1997 ⁵²
MEF2D	p38 α	Enhances recruitment of Ash2L to muscle-specific promoters	Zhao M <i>et al.</i> , <i>Mol Cell Biol</i> , 1999 ⁹⁴ Rampalli S <i>et al.</i> , <i>Nat Struct Mol Biol</i> , 2007 ⁷³
MITF	p38 α	Enhances transcriptional activity	Mansky KC <i>et al.</i> , <i>J Biol Chem</i> , 2002 ⁹⁵
MRF4	p38 α	Represses transcriptional activity	Suelves M <i>et al.</i> , <i>EMBO J</i> , 2004 ⁹⁶
NFATc1	p38 α	Enhances transcriptional activity and interaction with PU.1	Matsumoto M <i>et al.</i> , <i>J Biol Chem</i> , 2004 ⁹⁷
NFATc4	p38 α , p38 β , p38 γ	Represses nuclear localization and transcriptional activity	Yang TT <i>et al.</i> , <i>Mol Cell Biol</i> , 2002 ⁹⁸
NR4A	p38 α	Enhances transcriptional activity	Sekine Y <i>et al.</i> , <i>J Cell Sci</i> , 2011 ⁹⁹
Nur77	p38 α	Disrupts interaction with p65 and represses transcriptional activity	Li L <i>et al.</i> , <i>Nat Chem Biol</i> , 2015 ¹⁰⁰
Osterix	p38 α	Enhances recruitment of coactivators	Ortuño MJ <i>et al.</i> , <i>J Biol Chem</i> , 2010 ¹⁰¹
p53	p38 α	Increases protein stability and apoptosis	Bulavin DV <i>et al.</i> , <i>EMBO J</i> , 1999 ⁶⁹
Pax6	p38 α	Enhances transcriptional activity	Mikkola I <i>et al.</i> , <i>J Biol Chem</i> , 1999 ¹⁰²
PPAR α	p38 α	Enhances transcriptional activity	Barger PM <i>et al.</i> , <i>J Biol Chem</i> , 2001 ¹⁰³
SAP1	p38 α , p38 β , p38 γ , p38 δ	Enhances transcriptional activity	Janknecht R <i>et al.</i> , <i>EMBO J</i> , 1997 ⁶⁷
Smad3	p38 α	Enhances nuclear translocation	Hayes SA <i>et al.</i> , <i>Oncogene</i> , 2003 ¹⁰⁴
Snail	p38 α	Increases protein stability and transcriptional activity	Ryu KJ <i>et al.</i> , <i>Cancer Res</i> , 2019 ¹⁰⁵
STAT1	p38 α , p38 β	Enhances transcriptional activity	Kovarik P <i>et al.</i> , <i>Proc Natl Acad Sci U S A</i> , 1999 ¹⁰⁶
STAT4	p38 α	Enhances transcriptional activity	Visconti R <i>et al.</i> , <i>Blood</i> , 2000 ¹⁰⁷
TEAD4	p38 α	Enhances cytoplasmic translocation and suppresses transcriptional activity	Lin KC <i>et al.</i> , <i>Nat Cell Biol</i> , 2017 ⁷⁶
Twist1	p38 α	Increases protein stability and transcriptional activity	Hong J <i>et al.</i> , <i>Cancer Res</i> , 2011 ¹⁰⁸
USF1	p38 α	Enhances transcriptional activity	Galibert MD <i>et al.</i> , <i>EMBO J</i> , 2001 ⁷¹
Xbp1s	p38 α	Enhances nuclear translocation and transcriptional activity	Lee J <i>et al.</i> , <i>Nat Med</i> , 2011 ⁷⁵

ATF2, activating transcription factor 2; C/EBP, CCAAT/enhancer binding protein; CHOP, CCAAT/enhancer-binding protein homologous protein; ER, estrogen receptor; GR, glucocorticoid receptor; IUF1, insulin upstream factor 1; JDP2, Jun dimerization protein 2; MEF, myocyte-specific enhancer factor; MITF, microphthalmia transcription factor; MRF, muscle regulatory factor; NFAT, nuclear factor of activated T cells; Pax6, paired box 6; PPAR α , peroxisome proliferator-activated receptor alpha; TEAD4, TEA domain family transcription factor 4; USF1, upstream transcription factor 1; Xbp1s, spliced form of X-box binding protein 1.

in **Table 3**. The SWI–SNF complex subunit BAF60 is phosphorylated and inactivated by p38 during skeletal myogenesis^{109,110}, and EZH2, the catalytic component of the Polycomb Repressive Complex 2 (PRC2), was also found to be phosphorylated by p38, particularly in ER-negative breast cancer samples¹¹¹. Besides its transcriptional function, dATF-2 is also involved in heterochromatin formation, and stress-induced phosphorylation of dATF-2 by p38 disrupts heterochromatin in *Drosophila*¹¹².

Other substrates

Given the wide range of responses that p38 is involved in, it is not surprising that many p38 substrates cannot be so easily categorized into groups, and these miscellaneous substrates are summarized in **Table 4**. Some of them are involved in metabolism such as Raptor phosphorylation by p38 β , which enhances mTORC1 activity in response to arsenite-stress¹¹³, and DEPTOR (mTOR-inhibitory protein) phosphorylation by p38 γ and p38 δ , leading to its degradation and mTOR hyperactivation¹¹⁴. p38 α phosphorylation of Tip60 at Thr¹⁵⁸ promotes senescence and DNA-damage-induced apoptosis^{115,116}. Some p38 substrates are

cell death regulators. In the ER stress response, p38 α locates to the lysosome and phosphorylates the chaperone-mediated autophagy (CMA) receptor LAMP2A, leading to activation of CMA and thus protecting cells from ER stress-induced death¹¹⁷.

Biological functions of the p38 pathway

Embryo development

p38 α is required for embryo development, since the mouse *Mapk14*^{-/-} embryo dies between embryonic days (E) 10.5 and 12.5^{118–121}. Mutant mice with a single Thr¹⁸⁰ to Ala mutation or with the double T180A Y182F mutation are also embryonic lethal^{122,123}. Surprisingly, given the importance of the dual phosphorylation for complete p38 activation, substitution of Tyr¹⁸² with Phe results in mice that have reduced p38 signaling but are nevertheless viable¹²³, although this is consistent with previous studies showing that the p38 phosphorylated on Thr¹⁸⁰ alone retains some activity *in vitro*³⁷. Histological analysis demonstrates that p38 α is required for placental angiogenesis, but not embryonic cardiovascular development, and tetraploid rescue of the placental defect in *Mapk14*^{-/-} embryos confirmed that p38 α is

Table 3. Substrates of p38 group members – transcriptional regulators.

	Substrate	Kinase	Function	References
Chromatin remodeling regulators	BAF60c	p38 α , p38 β	Activates transcription of MyoD-target genes	Simone C <i>et al.</i> , <i>Nat Genet</i> , 2004 ¹⁰⁹ Forcales SV <i>et al.</i> , <i>EMBO J</i> , 2012 ¹¹⁰
	RNF2	p38 α	Modulates gene expression and histone 2B acetylation	Rao PS <i>et al.</i> , <i>Proteomics</i> , 2009 ¹²⁴
	EZH2	p38 α	Promotes cytoplasmic localization	Anwar T <i>et al.</i> , <i>Nat Commun</i> , 2018 ¹¹¹
	dAFF2	p38 α , p38 β	Disrupts heterochromatin formation	Seong K-H <i>et al.</i> , <i>Cell</i> , 2011 ¹¹²
Other regulators	CRTC2	p38 α	Enhances nucleocytoplasmic transport and represses transcription activity	Ma H <i>et al.</i> , <i>Mol Cell Biol</i> , 2019 ¹²⁵
	E47	p38 α , p38 β	Enhances the formation of MyoD/E47 heterodimers	Page JL <i>et al.</i> , <i>J Biol Chem</i> , 2004 ¹²⁶ Lluís F <i>et al.</i> , <i>EMBO J</i> , 2005 ¹²⁷
	HBP1	p38 α	Increases protein stability and represses transcription	Xiu M <i>et al.</i> , <i>Biol</i> , 2003 ¹²⁸
	p18(Hamlet)	p38 α , p38 β	Increases protein stability and enhances transcription	Cuadrado A <i>et al.</i> , <i>EMBO J</i> , 2007 ¹²⁹
	PGC-1 α	p38 α , p38 β	Increases protein stability and enhances transcription	Puigserver P <i>et al.</i> , <i>Mol Cell</i> , 2001 ¹³⁰
	Rb1	p38 α , p38 γ	Induces Rb degradation and cell death; suppresses Rb activity and promotes the G0-to-G1 transition	Delston RB <i>et al.</i> , <i>Oncogene</i> , 2011 ¹³¹ Tomás-Loba A <i>et al.</i> , <i>Nature</i> , 2019 ¹⁴
	SRC-3	p38 α	Induces SRC-3 degradation and suppresses RAR α -dependent transcription	Gianni M <i>et al.</i> , <i>EMBO J</i> , 2006 ¹³²

CRTC2, CREB-regulated transcription coactivator 2; HBP1, HMG-box transcription factor 1; PGC-1 α , peroxisome proliferator-activated receptor gamma co-activator 1 alpha; RAR, retinoic acid receptor; RNF2, ring finger protein 2.

Table 4. Substrates of p38 group members – others.

	Substrate	Kinase	Function	References
Cell-cycle regulators	Cdc25A	p38 α	Increases protein stability	Goloudina A <i>et al.</i> , <i>Cell Cycle</i> , 2003 ¹³³
	Cdc25B	p38 α	Increases protein stability	Lemaire M <i>et al.</i> , <i>Cell Cycle</i> , 2006 ¹³⁴
	Cyclin D1	p38 α	Causes ubiquitination and degradation of cyclin D1	Casanovas O <i>et al.</i> , <i>J Biol Chem</i> , 2000 ¹³⁵
	Cyclin D3	p38 α , p38 β p38 γ , p38 δ	Causes ubiquitination and degradation of cyclin D3	Casanovas O <i>et al.</i> , <i>Oncogene</i> , 2004 ¹³⁶
	p57kip2	p38 α	Enhances interaction with CDKs and inhibits CDKs	Joaquin M <i>et al.</i> , <i>EMBO J</i> , 2012 ¹³⁷
Cell-death regulators	Bax	p38 α	Prevents Bcl-2–Bax heterodimer formation, enhances apoptosis	Min H <i>et al.</i> , <i>Mol Carcinog</i> , 2012 ¹³⁸
	BimEL	p38 α	Enhances apoptosis	Cai B <i>et al.</i> , <i>J Biol Chem</i> , 2006 ¹³⁹
	Caspase-3	p38 α	Inhibits caspase-3 activity and apoptosis	Alvarado-Kristensson M <i>et al.</i> , <i>J Exp Med</i> , 2004 ¹⁴⁰
	Caspase-8	p38 α	Inhibits caspase-8 activity and apoptosis	Alvarado-Kristensson M <i>et al.</i> , <i>J Exp Med</i> , 2004 ¹⁴⁰
	Caspase-9	p38 α	Inhibits caspase-9 activity and apoptosis	Seifert A <i>et al.</i> , <i>Cell Signal</i> , 2009 ¹⁴¹
DNA/RNA binding proteins	Cdt1	p38 α , p38 β	Increases protein stability	Chandrasekaran S <i>et al.</i> , <i>Mol Cell Biol</i> , 2011 ¹⁴²
	Drosha	p38 α	Enhances nuclear export and degradation	Yang Q <i>et al.</i> , <i>Mol Cell</i> , 2015 ¹⁴³
	FBP2	p38 α	Promotes prothrombin mRNA 3' end processing	Danckwardt S <i>et al.</i> , <i>Mol Cell</i> , 2011 ¹⁴⁴
	FBP3	p38 α	Promotes prothrombin mRNA 3' end processing	Danckwardt S <i>et al.</i> , <i>Mol Cell</i> , 2011 ¹⁴⁴
	H2AX	p38 α , p38 β	Promotes serum starvation-induced apoptosis	Lu C <i>et al.</i> , <i>FEBS Lett</i> , 2008 ¹⁴⁵
	H3	p38 α	N/D	Zhong SP <i>et al.</i> , <i>J Biol Chem</i> , 2000 ¹⁴⁶
	HuR	p38 α , p38 β	Enhances cytoplasmic accumulation and increases mRNA stability	Lafarga V <i>et al.</i> , <i>Mol Cell Biol</i> , 2009 ¹⁴⁷
	KSRP	p38 α , p38 β	Prevents KSRP-mediated ARE-directed mRNA decay	Briata P <i>et al.</i> , <i>Mol Cell</i> , 2005 ¹⁴⁸
	Rps27	p38 α	N/D	Knight JD <i>et al.</i> , <i>Skelet Muscle</i> , 2012 ¹⁴⁹
	SPF45	p38 α	Inhibits Fas alternative splicing (exon 6 exclusion)	Al-Ayoubi AM <i>et al.</i> , <i>Mol Cell Biol</i> , 2012 ¹⁵⁰
Endocytosis regulators	EEA1	p38 α	Promotes recruitment to endocytic membranes and enhances MOR endocytosis	Macé G <i>et al.</i> , <i>EMBO J</i> , 2005 ¹⁵¹
	Rabenosyn-5	p38 α	Promotes recruitment to endocytic membranes and enhances MOR endocytosis	Macé G <i>et al.</i> , <i>EMBO J</i> , 2005 ¹⁵¹
	GDI-2	p38 α	Enhances GDI:Rab5 complex formation and modulates endocytosis	Cavalli V <i>et al.</i> , <i>Mol Cell</i> , 2001 ¹⁵²
MAPK pathway regulator	JIP4	p38 α	Enhances p38 activity	Kelkar N <i>et al.</i> , <i>Mol Cell Biol</i> , 2005 ¹⁵³
	Tip60	p38 α	Enhances the pro-senescent function of Tip60	Zheng H <i>et al.</i> , <i>Mol Cell</i> , 2013 ¹¹⁵
	TAB1	p38 α	Inhibits TAK1 activity	Cheung PC <i>et al.</i> , <i>EMBO J</i> , 2003 ¹⁵⁴
	TAB3	p38 α	Inhibits TAK1 activity	Mendoza H <i>et al.</i> , <i>Biochem J</i> , 2008 ¹⁵⁵
	FRS2	p38 α	Downregulates FGF1-induced signaling	Zakrzewska M <i>et al.</i> , <i>Int J Mol Sci</i> , 2019 ¹⁵⁶

	Substrate	Kinase	Function	References
Membrane proteins	EGFR	p38 α	Induces EGFR internalization	Winograd-Katz SE <i>et al.</i> , <i>Oncogene</i> , 2006 ¹⁵⁷
	FGFR1	p38 α	Regulates translocation of exogenous FGF1 into the cytosol/nucleus	Sørensen V <i>et al.</i> , <i>Mol Cell Biol</i> , 2008 ¹⁵⁸
	Nav1.6	p38 α	Promotes interaction with NEDD-4 and protein degradation	Gasser A <i>et al.</i> , <i>J Biol Chem</i> , 2010 ¹⁵⁹
	NHE1	p38 α	Induces intracellular alkalinization	Khaled AR <i>et al.</i> , <i>Mol Cell Biol</i> , 2001 ¹⁶⁰
	PLA2	p38 α	N/D	Börsch-Haubold AG <i>et al.</i> , <i>J Biol Chem</i> , 1998 ¹⁶¹
	TACE	p38 α , p38 β	Increases TACE-mediated ectodomain shedding and TGF- α family ligand release	Xu P <i>et al.</i> , <i>Mol Cell</i> , 2010 ¹⁶²
	ZAP70	p38 α	Phosphorylation of ZAP70 increases stability of T cell receptor	Giardino Torchia ML <i>et al.</i> , <i>Proc Natl Acad Sci U S A</i> , 2018 ⁴¹
Structure proteins	Caldesmon	p38 α	N/D	Hedges JC <i>et al.</i> , <i>Am J Physiol</i> , 1998 ¹⁶³
	Hsp27	p38 α	N/D	Knight JD <i>et al.</i> , <i>Skelet Muscle</i> , 2012 ¹⁴⁹
	Keratin 8	p38 α	Regulates cellular keratin filament reorganization	Ku NO <i>et al.</i> , <i>J Biol Chem</i> , 2002 ¹⁶⁴
	Lamin B1	p38 α	Enhances lamin B1 accumulation	Barascu A <i>et al.</i> , <i>EMBO J</i> , 2012 ¹⁶⁵
	Paxillin	p38 α	Required for NGF-induced neurite extension of PC-12 cells	Huang C <i>et al.</i> , <i>J Cell Biol</i> , 2004 ¹⁶⁶
	Stathmin	p38 δ	N/D	Parker CG <i>et al.</i> , <i>Biochem Biophys Res Commun</i> , 1998 ¹⁶⁷
	SAP97	p38 γ	Modulating the association of this protein with other cytoskeleton proteins	Sabio G <i>et al.</i> , <i>EMBO J</i> , 2005 ¹⁶⁸
	Tau	p38 α , p38 γ , p38 δ	Enhances formation of paired helical filaments Inhibits amyloid- β toxicity in Alzheimer's mice	Reynolds CH <i>et al.</i> , <i>J Neurochem</i> , 1997 ¹⁶⁹ Ittner A <i>et al.</i> , <i>Science</i> , 2016 ¹⁷⁰
	Tensin1	p38 α	Regulates the binding specificity of tensin 1 to different proteins	Hall EH <i>et al.</i> , <i>Mol Cell Proteomics</i> , 2010 ¹⁷¹
Others	DEPTOR	p38 γ , p38 δ	Enhances degradation and mTOR hyperactivation	González-Terán B <i>et al.</i> , <i>Nat Commun</i> , 2016 ¹¹⁴
	GS	p38 β	Required for subsequent phosphorylation to inhibit enzyme activity	Kuma Y <i>et al.</i> , <i>Biochem J</i> , 2004 ¹⁷²
	LAMP2A	p38 α	Activates chaperone-mediated autophagy	Li W <i>et al.</i> , <i>Nat Commun</i> , 2017 ¹¹⁷
	Parkin	p38 α	Decreases its interaction with PINK1 and suppresses mitophagy	Chen J <i>et al.</i> , <i>Cell Death Dis</i> , 2018 ¹⁷³
	p47 ^{phox}	p38 α	Promotes NADPH oxidase activation and superoxide production	Makni-Maalej K <i>et al.</i> , <i>J Immunol</i> , 2012 ¹⁷⁴
	p62	p38 γ , p38 δ	Enhances mTORC1 activity	Linares JF <i>et al.</i> , <i>Cell Rep</i> , 2015 ¹⁷⁵ Koh A <i>et al.</i> , <i>Cell</i> , 2018 ¹⁷⁶
	Raptor	p38 β	Enhances mTORC1 activity in response to arsenite stress	Wu X-N <i>et al.</i> , <i>J Biol Chem</i> , 2011 ¹¹³
	Rpn2	p38 α	Inhibits proteasome activity	Lee SH <i>et al.</i> , <i>J Biol Chem</i> , 2010 ¹⁷⁷
	Siah2	p38 α	Increases Siah2-mediated degradation of PHD3	Khurana A <i>et al.</i> , <i>J Biol Chem</i> , 2006 ¹⁷⁸

CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; FBP1, far upstream binding protein; FGF1, fibroblast growth factor 1; FGFR1, fibroblast growth factor receptor 1; FRS2, fibroblast growth factor receptor substrate 2; GDI, GDP dissociation inhibitor; KSRP, hnRNPK-homology type splicing regulatory protein; MAPK, mitogen-activated protein kinase; mTORC1, mammalian target of rapamycin complex 1; NADPH, nicotinamide adenine dinucleotide phosphate; NGF, nerve growth factor; NHE1, Na⁺/H⁺ exchanger isoform 1; PHD3, prolyl hydroxylase 3; PLA2, phospholipase A2; SAP97, synapse-associated protein 97; TAB, transforming growth factor- β -activated protein kinase-1-binding protein; TACE, tumor necrosis factor- α -converting enzyme; TAK1, transforming growth factor β -activated kinase 1; TGF, transforming growth factor.

essential for extraembryonic development^{120,121}. Given the important role that p38 and MK2 plays in regulating TNF-induced cell death^{179–182}, it is intriguing that the *Mapk14*^{-/-} embryonic lethal phenotype is very similar to that observed in other mice with defects in the TNF death pathway. Caspase-8, FADD, and cFLIP knock-out mice also die at E10.5, and this is due to TNF-dependent endothelial cell death and disruption of the vasculature in the yolk sac^{183,184}. Other p38 isoforms are not necessary for embryo development, but p38 α and p38 β have overlapping functions, as *Mapk14*^{loxp/loxp}*Mapk11*^{-/-}*Sox2-Cre* embryos die before E16.5 with spina bifida that correlates with neural hyperproliferation and increased apoptosis in the liver, which was not observed in *Mapk14*^{Δ/Δ}*Sox2-Cre* embryos¹⁸⁵. Remarkably, p38 α appears to have a very specific function during embryogenesis because when p38 α was replaced by p38 β in the *Mapk14* chromosomal locus, which thereby placed p38 β under the control of the endogenous p38 α promoter, it was unable to rescue the embryonic lethality induced by loss of p38 α ¹⁸⁵.

Immune responses

p38 is activated by many inflammatory stimuli, and its activity is important for inflammatory responses. Macrophage-specific deletion of *Mapk14* inhibits inflammatory cytokine production and protects mice from CLP-induced sepsis¹⁸⁶. p38 α controls the production of inflammatory cytokines, such as TNF and IL-6, at many levels. It directly phosphorylates transcription factors, such as MEF2C^{62,186}, and regulators of mRNA stability, such as hnRNP-K-homology (KH) type splicing regulatory protein (KSRP)¹⁸⁷. MEF2C appears to play an anti-inflammatory role in endothelial cells *in vivo*¹⁸⁸. Via MK2/MK3, p38 also upregulates cytokine mRNA transcription by the serum response transcription factor (SRF)¹⁸⁹, and similarly, via MK2/MK3, p38 regulates mRNA stability by phosphorylating and inactivating TTP/Zfp36, a protein that promotes rapid turnover of AU-rich mRNAs, many of which are cytokine mRNAs^{187,190}. p38 activation also induces the expression of inflammatory mediators such as COX-2, MMP9, iNOS, and VCAM-1, which are involved in tissue remodeling and oxidation regulation^{191–194}. The p38 pathway also regulates adaptive immunity. p38 α participates in antigen processing in CD8⁺ cDCs¹⁹⁵, and ZAP70-mediated p38 α / β activation is important for T cell homeostasis and function¹⁸. In B cells, p38 α is important for CD40-induced gene expression and proliferation of B cells¹⁹⁶, and the p38 α -MEF2c axis is believed to be necessary for germinal center B (GCB) cell proliferation and survival^{197,198}. Excessive activation of p38 α has been observed in many inflammatory diseases, such as inflammatory bowel disease (IBD), asthma, rheumatoid arthritis, and steatohepatitis^{199–201}. The other members of the p38 family also play roles in immune responses. For example, p38 γ and p38 δ are required for neutrophil migration to damaged liver in non-alcoholic fatty liver disease²⁰² and inhibition of eukaryotic elongation factor 2 in LPS-induced liver damage²⁰³. p38 δ is required for neutrophil accumulation in acute lung injury²⁰⁴. These observations, and the role that p38s play in TNF production, led to enormous pharmaceutical efforts to develop p38 inhibitors to treat chronic inflammatory diseases. However, unfortunately, these drugs were not efficacious in these diseases²⁰⁵.

Cell cycle

p38 has been implicated in G1 and G2/M phases of the cell cycle in several studies. The addition of activated recombinant p38 α caused mitotic arrest *in vitro*, and an inhibitor of p38 α / β suppressed activation of the checkpoint by nocodazole in NIH3T3 cells²⁰⁶. G1 arrest caused by Cdc42 overexpression is also dependent on p38 α in NIH3T3 cells²⁰⁷. Besides, p38 γ is specially required for gamma-irradiation-induced G2 arrest²⁰⁸. The link between p38 and cell cycle control has been proposed through the regulation of several p38 substrates. Both p38 α and p38 γ regulate cell cycle progression via Rb but in opposite directions^{14,209}. HBP1 represses the expression of cell cycle regulatory genes during cell cycle arrest in a p38-dependent manner²¹⁰; p53 and p21 activation by p38 α prevented G1 progression through blockade of CDK activity^{211,212}. The p38 pathway is also involved in cell cycle progress, as it is essential for self-renewal of mouse male germline stem cells²¹³ and its regulation of G1-length plays a role in cell size uniformity²¹⁴.

Cell differentiation

Participation of p38 in cell differentiation has been reported in certain cell types. p38 α activity is essential for neuronal differentiation in PC-12 cells and EPO-induced differentiation in SKT6 cells^{20,215}. Treatment of 3T3-L1 fibroblasts with specific p38 α / β inhibitors prevents their differentiation into adipocytes by reducing C/EBP β phosphorylation⁸³, and p38 α -dependent phosphorylation of MEF2C and BAF60 is critical for myogenic differentiation^{110,216}. Intestinal epithelial cell-specific deletion of p38 α also influences goblet cell differentiation in a Notch-dependent manner²⁰⁰.

Cell metabolism

p38 group members participate in many cellular events related to metabolism. The p38 β -PRAK axis specifically phosphorylates Rheb and suppresses mTORC1 activity under energy depletion conditions²². DEPTOR, an inhibitor of mTORC, can be phosphorylated by p38 γ and p38 δ , leading to its degradation¹²³. Meanwhile, p38 δ directly phosphorylates p62 to enhance mTORC1 activity in response to amino acids¹⁷⁵. In brown adipocytes, p38 α functions as a central mediator in β -adrenergic-induced UCP1 expression^{217,218}, while in white adipocytes, p38 α inactivation leads to elevated white-to-beige adipocyte reprogramming and resistance to diet-induced obesity^{219,220}. In hepatocytes, p38 α controls lipolysis and protects against nutritional steatohepatitis. Thus, mice with hepatocyte-specific loss of p38 α developed more severe steatohepatitis than wild type mice when fed high-fat or -cholesterol diets. Intriguingly, macrophage specific deletion of p38 had the opposite effect in the same high-fat diets and resulted in less steatohepatitis than in wild type mice, which probably reflects the inflammatory role of p38 in macrophages¹⁹⁹. p38 α also directly phosphorylates Xbp1s to enhance its nuclear migration for maintaining glucose homeostasis in obesity⁷⁵. However, p38 α also functions as a negative regulator of AMPK signaling in maintaining gluconeogenesis, and hepatic p38 α could be a drug target for hyperglycemia²²¹. It was also reported that p38 γ directly phosphorylates p62 under imidazole propionate stimulation to promote mTORC1 activity in hepatocytes¹⁷⁶.

Interestingly, AMPK also triggers the recruitment of p38 α to scaffold protein TAB1 for p38 α autoactivation in human T cells²²².

Cell senescence

p38 α appears to play a pivotal role in senescence. Constitutive activation of the p38 pathway by active MKK3 or MKK6 induces senescence in several cell types^{223,224}, and p38 α activity is responsible for senescence induced by multiple stimuli, such as telomere shortening^{225,226}, H₂O₂ exposure^{227,228}, and chronic oncogene activation^{19,223,229}. p38 α / β -specific inhibitors have been successfully used to prevent cellular senescence in cultivated human corneal endothelial cells²³⁰. Since cellular senescence is considered a defense strategy against oncogene activation, the p38 pathway plays important roles in tumorigenesis²³¹. Meanwhile, p38 α activity is important for senescence-associated secretory phenotype (SASP), and its inhibition markedly reduces the secretion of most SASP factors, suggesting multiple roles for the p38 pathway in senescence^{232–235}.

Cell survival and death

The role of the p38 pathway in cell fate is cell type and stimulus dependent. For example, p38 α becomes activated upon NGF withdrawal in PC-12 cells, and p38 α activated by overexpression of MKK3 induced apoptosis in NGF differentiated PC-12 cells²¹¹. Similarly, inhibition of p38 with PD169316 blocked NGF withdrawal-induced apoptosis in PC-12 cells^{236,237}. The interplay between the p38 pathway and caspases, the central regulators/executors of apoptosis, is complicated because p38 α activity can be elevated in a caspase-dependent manner in death stimulus treated cells^{238,239}, and caspase activity can also be elevated in MKK6E (dominant active form) overexpressed cells^{239,240}. In contrast, inhibition of caspase-8 and caspase-3 by p38 α -mediated phosphorylation in neutrophils was also reported¹⁴⁰. Recent studies show that p38-activated MK2 directly phosphorylates RIPK1 in TNF-treated cells or pathogen-infected cells, limiting TNF-induced cell death^{180–182}. This represents an interesting link between cytokine production induced by TNF and

cell death because TNF-induced MK2/MK3 phosphorylation of tristetraprolin/Zfp36 inactivates it and leads to increased stability of cytokine mRNAs¹⁹⁰. Aberrant p38 α activity is observed in many tumor cells, and inhibition of p38 α / β enhances cell death in these cells^{241,242}.

Perspectives

p38 is one of the most researched of all proteins, let alone kinases, and a search in PubMed for p38 MAPK or p38 kinase returns more than 36,000 publications, which is a higher number than some proteins listed in a review of the “top 10” most studied genes²⁴³. By contrast, searches for the kinases Raf and Src return about 17,000 and 25,000 hits, respectively. In 2018, there were more than 2,000 publications that mention p38, and it is clearly impractical to summarize such a vast amount of literature. As might be surmised from the preceding commentary, the studies are on a wide range of topics; however, the publications are more concentrated in some areas than others. The role of the p38 pathway in cancers (>10,000)^{244–246}, inflammation (>8,000)^{247–249}, and infections (>3,600)^{250,251} was intensively studied. About 1,600 publications include the specific term “p38 inhibitor”. This reflects the previously mentioned enormous interest of the pharmaceutical industry in developing p38 inhibitors to treat chronic inflammatory diseases, such as rheumatoid arthritis. Yet other publications report natural products that can activate or inhibit p38, with the ultimate aim of using them clinically^{252–258}. In 2011, the European Commission approved Esbriet (pirfenidone), which was described as a p38 γ inhibitor, for the treatment of idiopathic pulmonary fibrosis²⁵⁹. However, when this drug was approved by the FDA in 2014 for treating the same disease, it was described as a compound that acts on multiple pathways. In 2008, there were 27 clinical trials listed testing the use of p38 inhibitors in inflammatory disease settings²⁰⁵, while a search today for p38 inhibitors in clinicaltrials.gov returns 44 studies for conditions as diverse as pain, asthma, cognitive impairment, rheumatoid arthritis, cancer, myelodysplastic syndrome, and depression (Table 5). This indicates that there remains clinical interest in targeting the pathway

Table 5. Clinical trials of p38 inhibitors.

Drug	Target	Condition or disease	Status	NCT number
ARRY-371797	p38	Ankylosing spondylitis	Phase 2	NCT00811499
ARRY-371797	p38	Dental pain	Phase 2	NCT00542035 NCT00663767
ARRY-371797	p38	Healthy	Phase 1	NCT00790049
ARRY-371797	p38	LMNA-related dilated cardiomyopathy	Phase 2	NCT02351856 NCT02057341
ARRY-371797	p38	Osteoarthritis of the knee	Phase 2	NCT01366014
ARRY-371798	p38	Rheumatoid arthritis	Phase 1	NCT00729209
ARRY-614	p38 and Tie2	Myelodysplastic syndromes	Phase 1	NCT01496495 NCT00916227
AZD7624	p38	Corticosteroid-resistant asthma	Phase 2	NCT02753764
BIRB 796 BS	p38	Healthy	Phase 1	NCT02211170
BMS-582949	p38 α	Rheumatoid arthritis	Phase 2	NCT00605735

Drug	Target	Condition or disease	Status	NCT number
BMS-582949	p38 α	Vascular diseases (atherosclerosis)	Phase 2	NCT00570752
CHF6297	p38 α	Chronic obstructive pulmonary disease	Phase 1/2	NCT02815488
Losmapimod (GS856553)	p38 α/β	Acute coronary syndrome	Phase 1/2/3	NCT01756495 NCT02145468 NCT00910962
Losmapimod (GS856553)	p38 α/β	Chronic obstructive pulmonary disease	Phase 2	NCT00642148 NCT01541852
Losmapimod (GS856553)	p38 α/β	Depressive disorder, major	Phase 2	NCT00976560 NCT00569062
Losmapimod (GS856553)	p38 α/β	Glomerulosclerosis, focal segmental	Phase 2	NCT02000440
Losmapimod (GS856553)	p38 α/β	Pain, neuropathic	Phase 2	NCT01110057 NCT00969059
LY3007113	p38	Metastatic cancer	Phase 1	NCT01463631
Neflamapimod (VX-745)	p38 α	Alzheimer's disease	Phase 2	NCT03402659 NCT02423200 NCT02423122
Neflamapimod (VX-745)	p38 α	Dementia with Lewy bodies	Recruiting	NCT04001517
P38 inhibitor (4)	p38	Rheumatoid arthritis	Phase 2	NCT00303563 NCT00316771
PF-03715455	p38 α	Asthma	Phase 2	NCT02219048
PF-03715455	p38 α	Chronic obstructive pulmonary disease	Phase 2	NCT02366637
PF-03715455	p38 α	Healthy	Phase 1	NCT01226693
PH-797804	p38 α/β	Rheumatoid arthritis	Phase 2	NCT00383188 NCT00620685
Ralimetinib (LY2228820)	p38 α/β	Adult glioblastoma	Phase 1/2	NCT02364206
Ralimetinib (LY2228820)	p38 α/β	Advanced cancer	Phase 1	NCT01393990
Ralimetinib (LY2228820)	p38 α/β	Epithelial ovarian cancer Fallopian tube cancer Primary peritoneal cancer	Phase 1/2	NCT01663857
Ralimetinib (LY2228820)	p38 α/β	Postmenopausal metastatic breast cancer	Phase 2	NCT02322853
SB-681323	p38	Acute lung injury	Phase 2	NCT00996840
SB-681323	p38	Coronary heart disease	Phase 2	NCT00291902
SB-681323	p38	Chronic obstructive pulmonary disease	Phase 1/2	NCT00564746 NCT00144859
SB-681323	p38	Pain, neuropathic	Phase 2	NCT00390845
SB-681323	p38	Rheumatoid arthritis Inflammation	Phase 1/2	NCT00419809 NCT00439881 NCT00134693
Talmapimod (SCIO-469)	p38 α	Bone marrow diseases Myelodysplastic syndromes Hematologic diseases Bone marrow neoplasms	Phase 2	NCT00113893
Talmapimod (SCIO-469)	p38 α	Multiple myeloma	Phase 2	NCT00095680 NCT00087867
Talmapimod (SCIO-469)	p38 α	Rheumatoid arthritis	Phase 2	NCT00043732 NCT00089921
VX-702	p38 α	Rheumatoid arthritis	Phase 2	NCT00395577 NCT00205478

and that there is therefore a need for more specific inhibitors of each of the p38 group members and more basic research to fully understand how the pathway, especially how each member of the p38 family, is utilized and regulated.



One consequence of the massive pharmaceutical effort over the last 20 years is a large number of very specific, well-tolerated, and readily bioavailable drugs that can enable such basic research. For example, one study using a boutique panel of kinase inhibitors was able to demonstrate that 11 potent and specific p38 inhibitors synergized with Smac-mimetic drugs to kill a subset of AML leukemias, providing the strongest evidence implicating p38 in Smac-mimetic-induced killing¹⁷⁹. Since several of these p38 inhibitors had already been clinically trialed, this presents an opportunity to fast-track such combinations into

the clinic. In our opinion, it is likely that this is where the future of p38 research and p38 inhibitors lies, in revealing the intricate web of inter-connections and inter-dependencies of this core and central regulator of cell stress. We also believe that greater efforts to genetically assess the role of p38 and p38 isoforms in the pathophysiology of inflammatory and other diseases need to be made in order to push forward the clinical application of our burgeoning knowledge.

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