REVIEW

An overview of mammalian p38 mitogen-activated protein kinases, central regulators of cell stress and receptor signaling

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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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**p38 mitogen-activated protein kinases**

p38α (originally named p38) was identified and cloned as a 38 kDa protein that was tyrosine-phosphorylated in response to LPS stimulation in mammalian cells. Sequence comparison, on the day p38α 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 p38α homologue. p38α 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 MK2. There are four members of the p38 group of MAPKs encoded by four different genes in mammals: p38α (MAPK14, chromosome 6p21.31 in humans), p38β (MAPK11, SAPK2b, Chr22q13.33), p38γ (MAPK12, ERK6, SAPK3, Chr22q13.33), and p38δ (MAPK13, SAPK4, Serk4, Chr6p21.31). As can be surmised from their chromosomal locations, MAPK14/p38α and MAPK13/p38δ are physically close and separated by just over 15 kb, as are MAPK11/p38β and MAPK11/p38γ, which are separated by less than 2 kb. All the p38s contain a conserved Thr–Gly–Tyr (TGY) consensus kinase activation loop, and both Thr and Tyr phosphorylation are necessary to fully activate the kinase. However, monophosphorylated p38α Thr180 has some kinase activity in vitro, but a different substrate specificity, when compared with dual-site phosphorylated p38α. p38 group members are expressed ubiquitously, but p38γ and p38δ are enriched in certain cell types and tissues, such as p38γ in skeletal muscle and p38δ in the salivary, pituitary, and adrenal glands. p38β shares more amino acid sequence identity with p38α (~70%), while p38γ and p38δ share ~60% identity with p38α. p38α and p38δ also share high sequence homology with cyclin-dependent kinases (CDKs) and are sensitive to some CDK inhibitors.

**Activation and inactivation of p38**

p38α 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. 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 types. The study of p38 group members other than p38α has been less intensive; however, where it has been examined, the other p38s are frequently co-activated with p38α.

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 activation. Although MKK3 and MKK6 phosphorylate most p38 isoforms in vitro, selective activation and substrate specificity have been observed in vivo. MKK4 has also been reported to phosphorylate p38α and p38δ in specific cell types. A number of MAP3Ks have been reported to participate in p38 activation including TAK1, ASK1, DLK, and MEKK4. 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.

p38α can also be activated by MAP2K-independent mechanisms. TAB1 (TAK1-binding protein 1) directly interacts with p38α and can promote trans autophosphorylation on Thr180 and Tyr182 and thus full activation of p38α. A subsequent study revealed that autophosphorylation of Thr180 and Tyr182 requires a conserved Thr residue. TAB1-dependent p38α activation has been implicated in ischemic myocardial injury and T cell energetic responses. TAB1 is also claimed to play a role in Sestrin-mediated p38α activation. Another MAP2K-independent activation is mediated by ZAP70 after T cell receptor ligation. ZAP70 can directly phosphorylate p38α/β on Tyr182, leading to autophosphorylation on Thr180, one of the dual phosphorylation sites. As discussed, mono-Thr180 phosphorylated p38α still has some kinase activity, and loss of ZAP70-mediated p38 activation in p38αβ−/− double knock-in mice reduces autoimmunity and inflammation in several autoimmune disease models. Interestingly, p38α 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 ZAP70.

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) family. Although several MKPs have been reported to dephosphorylate p38α, MKP1/DUSP1, MKP5/DUSP10, MKP8/DUSP26, and DUSP8 are more potent inhibitors of p38α and JNK than ERK. A recent report showed that DUSP12 is also a p38α phosphatase. While there are a number of p38α DUSPs, no DUSP for p38δ has been reported, and these two p38s are resistant to several known p38α MKPs such as MKP1, 3, 5, and 7. p38α-dependent upregulation of MKP1 was reported and is believed to be part of a negative feedback loop of p38α activation. Other types of phosphatases have also been reported to target p38 MAPks, such as CacyBP/SIP, Wip1, and PP2C. The substrate specificity between p38 and phosphatases and the related physiological functions in vivo still need further investigation. p38γ 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 other. 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 pathway. 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.
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. 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 p38. MNK1/2, kinases that phosphorylate the eukaryotic initiation factor-4e (eIF-4E), are phosphorylated by p38. p38 has also been reported to inactivate murine GSK3β by phosphorylating Ser389, and since GSK3β is required for the continuous degradation of β-catenin in the Wnt signaling pathway, this can lead to an accumulation of β-catenin. It was also reported that p38 negatively regulates insulin secretion by catalyzing an inhibitory phosphorylation of PKD1. 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/EBPβ, 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 stresses. 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   | p38α, p38β, p38γ, p38δ                 | Activates the kinase substrate               | Freshney NW et al., Cell, 1994<sup>6</sup>  
|            |         |                                       | Rouse J et al., Cell, 1994<sup>4</sup>             |
| MAPKAPK3   | p38α, p38β, p38γ, p38δ                 | Activates the kinase substrate               | McLaughlin MM et al., J Biol Chem, 1996<sup>5</sup>  
|            |         |                                       | Waskiewicz AJ et al., EMBO J, 1997<sup>17</sup>    |
| MNK1/2     | p38α    | Activates the kinase substrate         | Deak M et al., EMBO J, 1998<sup>15</sup>  
|            |         |                                       | Pierrat B et al., EMBO J, 1998<sup>17</sup>        |
| PAK6       | p38α    | Activates the kinase substrate         | Kaur R et al., J Biol Chem, 2005<sup>78</sup>      |
| PIP4Kb     | p38α    | Inactivates the kinase substrate       | Jones DR et al., Mol Cell, 2006<sup>79</sup>       |
| RPAK (MK5) | p38α, p38β | Activates the kinase substrate     | New L et al., EMBO J, 1998<sup>58</sup>            |
| PKCε       | p38α, p38β | Completes cytokinesis               | Saurin AT et al., Nat Cell Biol, 2008<sup>80</sup> |
| GSK3β      | p38α    | Inactivates the kinase substrate, activates Wnt pathway. | Bikkavilli RK et al., J Cell Sci, 2008<sup>80</sup>  
|            |         |                                       | Thornton TM et al., Science, 2008<sup>81</sup>     |

GSK3β, 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; PKCε, protein kinase C epsilon type.

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

| Substrate  | Kinase  | Function                              | References                                           |
|------------|---------|---------------------------------------|------------------------------------------------------|
| ATF2       | p38α, p38β, p38γ, p38δ                 | Enhances transcriptional activity               | Cuenda A et al., EMBO J, 1997<sup>81</sup>  
|            |         |                                       | Jiang Y et al., J Biol Chem, 1997<sup>3</sup>       |
| C/EBPα     | p38α    | Enhances transcriptional activity      | Qiao L et al., J Biol Chem, 2006<sup>82</sup>       |
| C/EBPβ     | p38α    | Enhances transcriptional activity      | Engelman JA et al., J Biol Chem, 1998<sup>63</sup>  |
| C/EBPε     | p38α    | Enhances transcriptional activity      | Williamson EA et al., Blood, 2005<sup>84</sup>     |
| CHOP       | p38α, p38β | Enhances transcriptional activity   | Wang XZ et al., Science, 1996<sup>85</sup>         |
| E2F4       | p38α    | Enhances transcriptional activity      | Morillo SM et al., Mol Cell Biol, 2012<sup>85</sup> |
| Elk-1      | p38α    | Enhances transcriptional activity in specific cell types | Janknecht R et al., EMBO J, 1997<sup>86</sup>  
|            |         |                                       | Whitmarsh AJ et al., Mol Cell Biol, 1997<sup>86</sup> |
| ERα        | p38α    | Enhances nuclear localization and transcriptional activity | Lee H et al., Mol Cell Biol, 2002<sup>86</sup>      |
| Fos        | p38α, p38β, p38γ, p38δ                 | Enhances transcriptional activity               | Tanos T et al., J Biol Chem, 2005<sup>87</sup>      |
| FOXO3a     | p38α    | Enhances nuclear relocalization        | Ho KK et al., J Biol Chem, 2012<sup>88</sup>       |
| GR         | p38α    | Enhances transcriptional activity      | Miller AL et al., Mol Endocrinol, 2005<sup>89</sup> |
| IUF1       | p38α, p38β | Enhances transcriptional activity   | Macfarlane WM et al., J Biol Chem, 1997<sup>60</sup> |
| JDP2       | p38α    | N/D                                   | Katz S et al., Biochem J, 2002<sup>91</sup>        |
| c-JUN      | p38α, p38β, p38γ | Enhances transcriptional activity | Humar M et al., Int J Biochem Cell Biol, 2007<sup>52</sup> |


| Substrate | Kinase | Function | References |
|-----------|--------|----------|------------|
| MafA      | p38α, p38β, p38γ, p38δ | Enhances transcriptional activity | Sii-Felice K et al., FEBS Lett, 2005<sup>55</sup> |
| MEF2A     | p38α, p38β, p38γ | Enhances transcriptional activity | Zhao M et al., Mol Cell Biol, 1999<sup>54</sup> |
| MEF2C     | p38α, p38β, p38γ, p38δ | Enhances transcriptional activity | Han J et al., Nature, 1997<sup>12</sup> |
| MEF2D     | p38α | Enhances recruitment of Ash2L to muscle-specific promoters | Zhao M et al., Mol Cell Biol, 1999<sup>54</sup>; Rampalli S et al., Nat Struct Mol Biol, 2007<sup>13</sup> |
| MIF       | p38α | Enhances transcriptional activity | Mansky KC et al., J Biol Chem, 2002<sup>60</sup> |
| MRF4      | p38α | Represses transcriptional activity | Suelves M et al., EMBO J, 2004<sup>56</sup> |
| NFATc1    | p38α | Enhances transcriptional activity and interaction with PU.1 | Matsumoto M et al., J Biol Chem, 2004<sup>57</sup> |
| NFATc4    | p38α, p38β, p38γ | Represses nuclear localization and transcriptional activity | Yang TT et al., Mol Cell Biol, 2002<sup>58</sup> |
| NR4A      | p38α | Enhances transcriptional activity | Sekine Y et al., J Cell Sci, 2011<sup>59</sup> |
| Nur77     | p38α | Disrupts interaction with p65 and represses transcriptional activity | Li L et al., Nat Chem Biol, 2015<sup>100</sup> |
| Osterix   | p38α | Enhances recruitment of coactivators | Ortuño MJ et al., J Biol Chem, 2010<sup>61</sup> |
| p53       | p38α | Increases protein stability and apoptosis | Bulavin DV et al., EMBO J, 1999<sup>59</sup> |
| Pax6      | p38α | Enhances transcriptional activity | Mikkola I et al., J Biol Chem, 1999<sup>102</sup> |
| PPARα     | p38α | Enhances transcriptional activity | Barger PM et al., J Biol Chem, 2001<sup>103</sup> |
| SAP1      | p38α, p38β, p38γ, p38δ | Enhances transcriptional activity | Janknecht R et al., EMBO J, 1997<sup>67</sup> |
| Smad3     | p38α | Enhances nuclear translocation | Hayes SA et al., Oncogene, 2003<sup>104</sup> |
| Snail     | p38α | Increases protein stability and transcriptional activity | Ryu KJ et al., Cancer Res, 2019<sup>105</sup> |
| STAT1     | p38α, p38β | Enhances transcriptional activity | Kovarik P et al., Proc Natl Acad Sci U S A, 1999<sup>106</sup> |
| STAT4     | p38α | Enhances transcriptional activity | Visconti R et al., Blood, 2000<sup>107</sup> |
| TEAD4     | p38α | Enhances cytoplasmic translocation and suppresses transcriptional activity | Lin KC et al., Nat Cell Biol, 2017<sup>106</sup> |
| Twist1    | p38α | Increases protein stability and transcriptional activity | Hong J et al., Cancer Res, 2011<sup>108</sup> |
| USF1      | p38α | Enhances transcriptional activity | Galibert MD et al., EMBO J, 2001<sup>11</sup> |
| Xbp1s     | p38α | Enhances nuclear translocation and transcriptional activity | Lee J et al., Nat Med, 2011<sup>71</sup> |

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; PPARα, 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.
Enhances nucleocytoplasmic transport and represses transcription activity

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 p38β, which enhances mTORC1 activity in response to arsenite-stress\textsuperscript{(13)}, and DEPTOR (mTOR-inhibitory protein) phosphorylation by p38γ and p38δ, leading to its degradation and mTOR hyperactivation\textsuperscript{(14)}. p38α phosphorylation of Tip60 at Thr\textsuperscript{182} promotes senescence and DNA-damage-induced apoptosis\textsuperscript{(15,16)}. Some p38 substrates are cell death regulators. In the ER stress response, p38α 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 death\textsuperscript{(17)}.

### Biological functions of the p38 pathway

#### Embryo development

p38α is required for embryo development, since the mouse Mapk14\textsuperscript{−/−} embryo dies between embryonic days (E) 10.5 and 12.5\textsuperscript{(18–23)}. Mutant mice with a single Thr\textsuperscript{180} to Ala mutation or with the double T180A Y182F mutation are also embryonic lethal\textsuperscript{(22,23)}. Surprisingly, given the importance of the dual phosphorylation for complete p38 activation, substitution of Tyr\textsuperscript{182} with Phe results in mice that have reduced p38 signaling but are nevertheless viable\textsuperscript{(23)}, although this is consistent with previous studies showing that the p38 phosphorylated on Thr\textsuperscript{180} alone retains some activity in vitro\textsuperscript{(17)}. Histological analysis demonstrates that p38α is required for placental angiogenesis, but not embryonic cardiovascular development, and tetraploid rescue of the placental defect in Mapk14\textsuperscript{−/−} embryos confirmed that p38α is

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

| Substrate  | Kinase   | Function                                | References                        |
|------------|----------|-----------------------------------------|-----------------------------------|
| BAF60c     | p38α, p38β | Activates transcription of MyoD-target genes | Simone C et al., Nat Genet, 2004\textsuperscript{(10)} Forcales SV et al., EMBO J, 2012\textsuperscript{(24)} |
| RNF2       | p38α     | Modulates gene expression and histone 2B acetylation | Rao PS et al., Proteomics, 2009\textsuperscript{(24)} |
| EZH2       | p38α     | Promotes cytoplasmic localization        | Anwar T et al., Nat Commun, 2018\textsuperscript{(25)} |
| dAFF2      | p38α, p38β | Disrupts heterochromatin formation       | Seong K-H et al., Cell, 2011\textsuperscript{(26)} |
| CRTC2      | p38α     | Enhances nucleocytoplasmic transport and represses transcription activity | Ma H et al., Mol Cell Biol, 2019\textsuperscript{(27)} |
| E47        | p38α, p38β | Enhances the formation of MyoD/E47 heterodimers | Page JL et al., J Biol Chem., 2004\textsuperscript{(28)} Lluis F et al., EMBO J, 2005\textsuperscript{(29)} |
| HBP1       | p38α     | Increases protein stability and represses transcription | Xiu M et al., Biol, 2003\textsuperscript{(30)} |
| p18(Hamlet) | p38α, p38β | Increases protein stability and enhances transcription | Cuadrado A et al., EMBO J, 2007\textsuperscript{(31)} |
| PGC-1α     | p38α, p38β | Increases protein stability and enhances transcription | Puigserver P et al., Mol Cell, 2001\textsuperscript{(32)} |
| Rb1        | p38α, p38γ | Induces Rb degradation and cell death; suppresses Rb activity and promotes the G0-to-G1 transition | Delston RB et al., Oncogene, 2011\textsuperscript{(33)} Tomás-Loba A et al., Nature, 2019\textsuperscript{(34)} |
| SRC-3      | p38α     | Induces SRC-3 degradation and suppresses RARα-dependent transcription | Gianni M et al., EMBO J, 2006\textsuperscript{(35)} |

CRTC2, CREB-regulated transcription coactivator 2; HBP1, HMG-box transcription factor 1; PGC-1α, 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 |
|-----------|--------|----------|------------|
| Cdc25A    | p38α   | Increases protein stability | Goloudina A et al., Cell Cycle, 2003[32] |
| Cdc25B    | p38α   | Increases protein stability | Lemaire M et al., Cell Cycle, 2006[34] |
| Cyclin D1 | p38α   | Causes ubiquitination and degradation of cyclin D1 | Casanova O et al., J Biol Chem, 2000[35] |
| Cyclin D3 | p38α, p38β p38γ, p38δ | Causes ubiquitination and degradation of cyclin D3 | Casanova O et al., Oncogene, 2004[36] |
| p57kip2   | p38α   | Enhances interaction with CDKs and inhibits CDKs | Joaquin M et al., EMBO J, 2012[37] |
| Bax       | p38α   | Prevents Bcl-2-Bax heterodimer formation, enhances apoptosis | Min H et al., Mol Carcinog, 2012[38] |
| BimEL     | p38α   | Enhances apoptosis | Cai B et al., J Biol Chem, 2006[39] |
| Caspase-3 | p38α   | Inhibits caspase-3 activity and apoptosis | Alvarado-Kristensson M et al., J Exp Med, 2004[40] |
| Caspase-8 | p38α   | Inhibits caspase-8 activity and apoptosis | Alvarado-Kristensson M et al., J Exp Med, 2004[41] |
| Caspase-9 | p38α   | Inhibits caspase-9 activity and apoptosis | Seifert A et al., Cell Signal, 2009[42] |
| Cdt1      | p38α, p38β | Increases protein stability | Chandrasekaran S et al., Mol Cell Biol, 2011[43] |
| Drosha    | p38α   | Enhances nuclear export and degradation | Yang Q et al., Mol Cell, 2015[44] |
| FBP2      | p38α   | Promotes prothrombin mRNA 3’ end processing | Danckwardt S et al., Mol Cell, 2011[45] |
| FBP3      | p38α   | Promotes prothrombin mRNA 3’ end processing | Danckwardt S et al., Mol Cell, 2011[46] |
| H2AX      | p38α, p38β | Promotes serum starvation-induced apoptosis | Lu C et al., FEBS Lett, 2008[47] |
| H3        | p38α   | N/D | Zhong SP et al., J Biol Chem, 2000[48] |
| HuR       | p38α, p38β | Enhances cytoplasmic accumulation and increases mRNA stability | Lafarga V et al., Mol Cell Biol, 2009[49] |
| KSRP      | p38α, p38β | Prevents KSRP-mediated ARE-directed mRNA decay | Briata P et al., Mol Cell, 2005[50] |
| Rps27     | p38α   | N/D | Knight JD et al., Skelet Muscle, 2012[51] |
| SPF45     | p38α   | Inhibits Fas alternative splicing (exon 6 exclusion) | Al-Ayoubi AM et al., Mol Cell Biol, 2012[52] |
| EEA1      | p38α   | Promotes recruitment to endocytic membranes and enhances MOR endocytosis | Macé G et al., EMBO J, 2005[53] |
| Rabenosyn-5 | p38α  | Promotes recruitment to endocytic membranes and enhances MOR endocytosis | Macé G et al., EMBO J, 2005[54] |
| GDI-2     | p38α   | Enhances GDI:Rab5 complex formation and modulates endocytosis | Cavalli V et al., Mol Cell, 2001[55] |
| JIP4      | p38α   | Enhances p38 activity | Kelkar N et al., Mol Cell Biol, 2005[56] |
| Tip60     | p38α   | Enhances the pro-senescent function of Tip60 | Zheng H et al., Mol Cell, 2013[57] |
| TAB1      | p38α   | Inhibits TAK1 activity | Cheung PC et al., EMBO J, 2003[58] |
| TAB3      | p38α   | Inhibits TAK1 activity | Mendoza H et al., Biochem J, 2008[59] |
| FRS2      | p38α   | Downregulates FGF1-induced signaling | Zakrzewska M et al., Int J Mol Sci, 2019[60] |
| Substrate | Kinase | Function | References |
|-----------|--------|----------|------------|
| EGFR      | p38α   | Induces EGFR internalization | Winograd-Katz SE et al., Oncogene, 2006157 |
| FGFR1     | p38α   | Regulates translocation of exogenous FGF1 into the cytosol/nucleus | Sørensen V et al., Mol Cell Biol, 2002158 |
| Nav1.6    | p38α   | Promotes interaction with NEDD-4 and protein degradation | Gasser A et al., J Biol Chem, 2010159 |
| NHE1      | p38α   | Induces intracellular alkalization | Khaled AR et al., Mol Cell Biol, 2001160 |
| PLA2      | p38α   | N/D      | Börsch-Haubold AG et al., J Biol Chem, 1998161 |
| TACE      | p38α, p38β | Increases TACE-mediated ectodomain shedding and TGF-alpha family ligand release | Xu P et al., Mol Cell, 2010162 |
| ZAP70     | p38α   | Phosphorylation of ZAP70 increases stability of T cell receptor | Giardino Torchia ML et al., Proc Natl Acad Sci U S A, 2018163 |
| Caldesmon | p38α   | N/D      | Hedges JC et al., Am J Physiol, 1998164 |
| Hsp27     | p38α   | N/D      | Knight JD et al., Skelet Muscle, 2012165 |
| Keratin 8 | p38α   | Regulates cellular keratin filament reorganization | Ku NO et al., J Biol Chem, 2002166 |
| Lamin B1  | p38α   | Enhances lamin B1 accumulation | Barascu A et al., EMBO J, 2012167 |
| Paxillin  | p38α   | Required for NGF-induced neurite extension of PC-12 cells | Huang C et al., J Cell Biol, 2004168 |
| Stathmin  | p38δ   | N/D      | Parker CG et al., Biochem Biophys Res Commun, 1998169 |
| SAP97     | p38γ   | Modulating the association of this protein with other cytoskeleton proteins | Sabio G et al., EMBO J, 2005170 |
| Tau       | p38α, p38γ, p38δ | Enhances formation of paired helical filaments | Reynolds CH et al., J Neurochem, 1997171 |
| Tensin1   | p38α   | Regulates the binding specificity of tensin1 to different proteins | Hall EH et al., Mol Cell Proteomics, 2010172 |
| DEPTOR    | p38γ, p38δ | Enhances degradation and mTOR hyperactivation | González-Terán B et al., Nat Commun, 2016173 |
| GS        | p38β   | Required for subsequent phosphorylation to inhibit enzyme activity | Kuma Y et al., Biochem J, 2004174 |
| LAMP2A    | p38α   | Activates chaperone-mediated autophagy | Li W et al., Nat Commun, 2017175 |
| Parkin    | p38α   | Decreases its interaction with PINK1 and suppresses mitophagy | Chen J et al., Cell Death Dis, 2018176 |
| p47phox   | p38α   | Promotes NADPH oxidase activation and superoxide production | Makni-Maalej K et al., J Immunol, 2012177 |
| p62       | p38γ, p38δ | Enhances mTORC1 activity | Linares JF et al., Cell Rep, 2015178 |
| Raptor    | p38β   | Enhances mTORC1 activity in response to arsenite stress | Wu X-N et al., J Biol Chem, 2011179 |
| Rpn2      | p38α   | Inhibits proteasome activity | Lee SH et al., J Biol Chem, 2010180 |
| Siah2     | p38α   | Increases Siah2-mediated degradation of PHD3 | Khurana A et al., J Biol Chem, 2006181 |

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-alpha-converting enzyme; TAK1, transforming growth factor β-activated kinase 1; TGF, transforming growth factor.
essential for extraembryonic development\textsuperscript{13,121}. Given the important role that p38 and MK2 play in regulating TNF-induced cell death\textsuperscript{179–182}, it is intriguing that the Mapk14\textsuperscript{–/–} embryonic lethal phenotype is very similar to that observed in other mice with defects in the TNF death pathway. Caspase-8, FADD, and cFLIP knockout 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\textsuperscript{183,184}. Other p38 isoforms are not necessary for embryo development, but p38\(\alpha\) and p38\(\beta\) have overlapping functions, as Mapk14\textsuperscript{–/–} 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\textsuperscript{–/–} Sox2-Cre embryos\textsuperscript{185}. Remarkably, p38\(\alpha\) appears to have a very specific function during embryogenesis because when p38\(\alpha\) was replaced by p38\(\beta\) in the Mapk14 chromosomal locus, which thereby placed p38\(\beta\) under the control of the endogenous p38\(\alpha\) promoter, it was unable to rescue the embryonic lethality induced by loss of p38\(\alpha\)\textsuperscript{185}.

**Immune responses**
p38 is activated by many inflammatory stimuli, and its activity is important for inflammatory responses. Macrophase-specific deletion of Mapk14 inhibits inflammatory cytokine production and protects mice from CLP-induced sepsis\textsuperscript{108}, p38\(\alpha\) controls the production of inflammatory cytokines, such as TNF and IL-6, at many levels. It directly phosphorylates transcription factors, such as MEF2C\textsuperscript{182,186}, and regulators of mRNA stability, such as hnRNPK-homology (KH) type splicing regulatory protein (KSRP)\textsuperscript{187}. MEF2C appears to play an anti-inflammatory role in endothelial cells in vivo\textsuperscript{188}. Via MK2/MK3, p38 also upregulates cytokine mRNA transcription by the serum response transcription factor (SRF)\textsuperscript{189} and similarly, via MK2/MK3, p38 regulates mRNA stability by phosphorylating and inactivating TTP/Zip36, a protein that promotes rapid turnover of AU-rich mRNAs, many of which are cytokine mRNAs\textsuperscript{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\textsuperscript{191–194}. The p38 pathway also regulates adaptive immunity. p38\(\alpha\) participates in antigen processing in CD8\(^+\) cDCs\textsuperscript{195}, and ZAP70-mediated p38\(\alpha/\beta\) activation is important for T cell homeostasis and function\textsuperscript{196,197}. In B cells, p38\(\alpha\) is important for CD40-induced gene expression and proliferation of B cells\textsuperscript{198} and the p38\(\alpha\)-MEF2c axis is believed to be necessary for germinal center B (GCB) cell proliferation and survival\textsuperscript{197,198}. Excessive activation of p38\(\alpha\) has been observed in many inflammatory diseases, such as inflammatory bowel disease (IBD), asthma, rheumatoid arthritis, and steatohepatitis\textsuperscript{199–201}. The other members of the p38 family also play roles in immune responses. For example, p38\(\gamma\) and p38\(\delta\) are required for neutrophil migration to damaged liver in non-alcoholic fatty liver disease\textsuperscript{202} and inhibition of euakaryotic elongation factor 2 in LPS-induced liver damage\textsuperscript{203}. p38\(\delta\) is required for neutrophil accumulation in acute lung injury\textsuperscript{204}. These observations, and the role that p38\(\delta\) 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 diseases\textsuperscript{205}.

**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\(\alpha\) caused mitotic arrest \textit{in vitro}, and an inhibitor of p38\(\alpha/\beta\) suppressed activation of the checkpoint by nocodazole in NIH3T3 cells\textsuperscript{206}. G1 arrest caused by Cdc42 overexpression is also dependent on p38\(\alpha\) in NIH3T3 cells\textsuperscript{207}. Besides, p38\(\gamma\) is specially required for gamma-irradiation-induced G2 arrest\textsuperscript{208}. The link between p38 and cell cycle control has been proposed through the regulation of several p38 substrates. Both p38\(\alpha\) and p38\(\gamma\) regulate cell cycle progression via Rb but in opposite directions\textsuperscript{14,209}. HBP1 represses the expression of cell cycle regulatory genes during cell cycle arrest in a p38-dependent manner\textsuperscript{209}; p53 and p21 activation by p38\(\alpha\) prevented G1 progression through blockade of CDK activity\textsuperscript{210,211}. The p38 pathway is also involved in cell cycle progression, as it is essential for self-renewal of mouse male germine stem cells\textsuperscript{213} and its regulation of G1-length plays a role in cell size uniformity\textsuperscript{214}.

**Cell differentiation**
Participation of p38 in cell differentiation has been reported in certain cell types. p38\(\alpha\) activity is essential for neuronal differentiation in PC-12 cells and EPO-induced differentiation in SKT6 cells\textsuperscript{3,121}. Treatment of 3T3-L1 fibroblasts with specific p38\(\alpha/\beta\) inhibitors prevents their differentiation into adipocytes by reducing C/EBP\(\beta\) phosphorylation\textsuperscript{16} and p38\(\alpha\)-dependent phosphorylation of MEF2C and BAF60 is critical for myogenic differentiation\textsuperscript{10,218}. Intestinal epithelial cell-specific deletion of p38\(\alpha\) also influences goblet cell differentiation in a Notch-dependent manner\textsuperscript{20}.

**Cell metabolism**
p38 group members participate in many cellular events related to metabolism. The p38\(\beta\)-PRAK axis specifically phosphorylates Rheb and suppresses mTORC1 activity under energy depletion conditions\textsuperscript{22}. DEPTOR, an inhibitor of mTORC, can be phosphorylated by p38\(\gamma\) and p38\(\delta\), leading to its degradation\textsuperscript{223}. Meanwhile, p38\(\delta\) directly phosphorylated p62 to enhance mTORC1 activity in response to amino acids\textsuperscript{175}. In brown adipocytes, p38\(\alpha\) functions as a central mediator in \(\beta\)-adrenergic-induced UCP1 expression\textsuperscript{17,174}, while in white adipocytes, p38\(\alpha\) inactivation leads to elevated white-to-beige adipocyte reprogramming and resistance to diet-induced obesity\textsuperscript{219,220}. In hepatocytes, p38\(\alpha\) controls lipolysis and protects against nutritional steatohepatitis. Thus, mice with hepatectomy-specific loss of p38\(\alpha\) developed more severe steatohepatitis than wild type mice when fed high-fat or -cholesterol diets. Intriguingly, macrophase 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 macrophages\textsuperscript{209}. p38\(\alpha\) also directly phosphorylates Xbp1\(\alpha\) to enhance its nuclear migration for maintaining glucose homeostasis in obesity\textsuperscript{175}. However, p38\(\alpha\) also functions as a negative regulator of AMPK signaling in maintaining gluconeogenesis, and hepatic p38\(\alpha\) could be a drug target for hyperglycemia\textsuperscript{211}. It was also reported that p38\(\gamma\) directly phosphorylated p62 under imidazole propionate stimulation to promote mTORC1 activity in hepatocytes\textsuperscript{216}.
Interestingly, AMPK also triggers the recruitment of p38α to scaffold protein TAB1 for p38α autoactivation in human T cells224.

**Cell senescence**

p38α appears to play a pivotal role in senescence. Constitutive activation of the p38 pathway by active MKK3 or MKK6 induces senescence in several cell types225,226, and p38α activity is responsible for senescence induced by multiple stimuli, such as telomere shortening227,228, H₂O₂ exposure229,230, and chronic oncogene activation230,231,232. p38α/β-specific inhibitors have been successfully used to prevent cellular senescence in cultured human corneal endothelial cells233. Since cellular senescence is considered a defense strategy against oncogene activation, the p38 pathway plays important roles in tumorigenesis234. Meanwhile, p38α 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 senescence233–235.

**Cell survival and death**

The role of the p38 pathway in cell fate is cell type and stimulus dependent. For example, p38α becomes activated upon NGF withdrawal in PC-12 cells, and p38α activated by overexpression of MKK3 induced apoptosis in NGF differentiated PC-12 cells236. Similarly, inhibition of p38 with PD169316 blocked NGF withdrawal-induced apoptosis in PC-12 cells237,238. The interplay between the p38 pathway and caspases, the central regulators/executors of apoptosis, is complicated because p38α activity can be elevated in a caspase-dependent manner in death stimulus treated cells239,240, and caspase activity can also be elevated in MKK6E (dominant active form) overexpressed cells239,240. In contrast, inhibition of caspase-8 and caspase-3 by p38α-mediated phosphorylation in neutrophils was also reported241. Recent studies show that p38-activated MK2 directly phosphorylates RIPK1 in TNF-treated cells or pathogen-infected cells, limiting TNF-induced cell death242–244. 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 mRNAs245. Aberrant p38α activity is observed in many tumor cells, and inhibition of p38α/β enhances cell death in these cells246,247.

**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 genes248. 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)249,250, inflammation (>8,000)250–254, and infections (>3,600)255,256 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 clinically252–254. In 2011, the European Commission approved Esbriet (pirfenidone), which was described as a p38γ inhibitor, for the treatment of idiopathic pulmonary fibrosis257. 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 settings258, 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

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**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, NCT00683767 |
| 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-37198   | 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-582947   | p38α   | Rheumatoid arthritis            | Phase 2  | NCT00605735         |

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| Drug | Target | Condition or disease | Status | NCT number |
|------|--------|----------------------|--------|------------|
| BMS-582949 | p38α | Vascular diseases (atherosclerosis) | Phase 2 | NCT00570752 |
| CHF6297 | p38α | Chronic obstructive pulmonary disease | Phase 1/2 | NCT02815488 |
| Losmapimod (GS856553) | p38α/β | Acute coronary syndrome | Phase 1/2/3 | NCT01756495 NCT02145468 NCT00910962 |
| Losmapimod (GS856553) | p38α/β | Chronic obstructive pulmonary disease | Phase 2 | NCT00642148 NCT01541852 |
| Losmapimod (GS856553) | p38α/β | Depressive disorder, major | Phase 2 | NCT00976560 NCT00569062 |
| Losmapimod (GS856553) | p38α/β | Glomerulosclerosis, focal segmental | Phase 2 | NCT02000440 |
| Losmapimod (GS856553) | p38α/β | Pain, neuropathic | Phase 2 | NCT011110057 NCT00969059 |
| LY3007113 | p38 | Metastatic cancer | Phase 1 | NCT01463631 |
| Neflamapimod (VX-745) | p38α | Alzheimer's disease | Phase 2 | NCT03402659 NCT02423200 NCT02423122 |
| Neflamapimod (VX-745) | p38α | Dementia with Lewy bodies | Recruiting | NCT04001517 |
| P38 inhibitor (4) | p38 | Rheumatoid arthritis | Phase 2 | NCT00303563 NCT00316771 |
| PF-03715455 | p38α | Asthma | Phase 2 | NCT02219048 |
| PF-03715455 | p38α | Chronic obstructive pulmonary disease | Phase 2 | NCT02366637 |
| PF-03715455 | p38α | Healthy | Phase 1 | NCT01226693 |
| PH-797804 | p38α/β | Rheumatoid arthritis | Phase 2 | NCT00383188 NCT00620685 |
| Ralimetinib (LY2228820) | p38α/β | Adult glioblastoma | Phase 1/2 | NCT02364206 |
| Ralimetinib (LY2228820) | p38α/β | Advanced cancer | Phase 1 | NCT01393990 |
| Ralimetinib (LY2228820) | p38α/β | Epithelial ovarian cancer Fallopian tube cancer Primary peritoneal cancer | Phase 1/2 | NCT01663857 |
| Ralimetinib (LY2228820) | p38α/β | Postmenopausal metastatic breast cancer | Phase 2 | NCT02322853 |
| SB-681323 | p38 | Acute lung injury | Phase 2 | NCT00996840 |
| 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 |
| Talmipimod (SCIO-469) | p38α | Bone marrow diseases Myelodysplastic syndromes Hematologic diseases Bone marrow neoplasms | Phase 2 | NCT00113893 |
| Talmipimod (SCIO-469) | p38α | Multiple myeloma | Phase 2 | NCT00095680 NCT00087867 |
| Talmipimod (SCIO-469) | p38α | Rheumatoid arthritis | Phase 2 | NCT00043732 NCT00089921 |
| VX-702 | p38α | 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 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 killing. 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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