

Atypical p38

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The mitogen-activated protein kinase (MAPK) p38 is an essential family of kinases, regulating responses to environmental stress and inflammation. There is an ever-increasing plethora of physiological and pathophysiological conditions attributed to p38 activity, ranging from cell division and embryonic development to the control of a multitude of diseases including retinal, cardiovascular, and neurodegenerative diseases, diabetes, and cancer. Despite the decades of intense investigation, a viable therapeutic approach to disrupt p38 signaling remains elusive. A growing body of evidence supports the pathological significance of an understudied atypical p38 signaling pathway. Atypical p38 signaling is driven by a direct interaction between the adaptor protein TAB1 and p38 α , driving p38 autophosphorylation independent from the classical MKK3 and MKK6 pathways.

MAPK

p38

atypical signaling

vascular disease

GPCRs

kinases

mechanisms

1. Introduction

The p38 mitogen-activated protein kinase (MAPK) family are critical cellular signaling regulators that drive many physiological and pathophysiological pathways. Therefore, it is not surprising that since their discovery in 1994 ^[1], over 45,000 research articles and reviews have been published describing the mechanism of p38 activation and the role of p38 during development and disease progression. The broader MAPK family includes c-Jun activated Kinase (JNK), extracellular signal-related kinase 1 and 2 (ERK1/2), and protein kinase B, also known as AKT kinase (AKT), all of which are critical in regulating a multitude of cellular processes from cell division to cell death and everything in between. Cellular stimuli/stress induces the activation of MAPKs, including hormones, growth factors, and cytokines, as well as environmental stressors such as osmotic shock, UV radiation, and ischemic injury ^[2]. As such, p38 MAPKs have been the subject of intense study to generate clinically effective therapeutics. Despite ongoing clinical trials for many diseases, including ischemic cardiac damage, COPD, multiple cancers, various neuropathies, and ARDS/COVID-19, only one non-selective p38 inhibitor (pirfenidone) has been approved for clinical use to treat idiopathic pulmonary fibrosis ^{[3][4]}. An underlying contributor to the loss of efficacy and on-target toxicity of these drugs is thought to be due to the ubiquitous and critical role p38 plays in normal physiology. Additionally, almost all current approaches have centered around therapeutics that target the ATP-binding site of p38 resulting in blockade of all p38 activity, both physiological and pathophysiological, regardless of the stimulus. Therefore, there is an increased focus on researching the downstream signaling targets of p38 induced only during disease progression, such as the critical inflammatory kinase MAPK-activated protein kinase 2 (MK2), or the alternative p38 activation pathways selectively induced during inflammation and disease progression (see [Figure 1](#)).

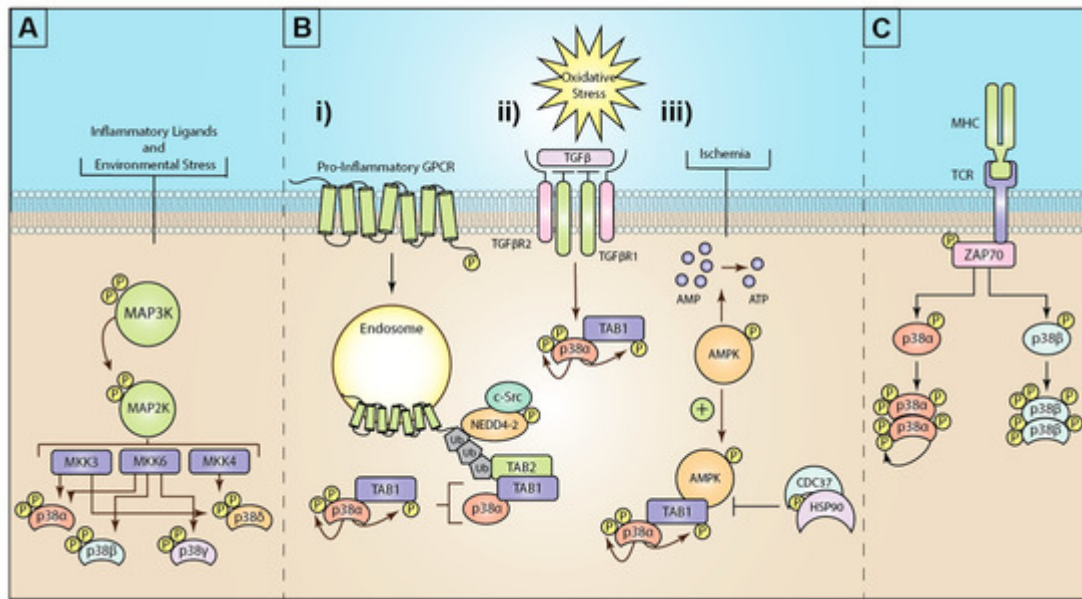


Figure 1. Mechanisms of mitogen-activated protein kinase (MAPK) p38 activation: **(A)** Inflammatory ligands and environmental stress trigger the activation of a three-tiered kinase cascade. Environmental or inflammatory ligands induce the activation of MAP3Ks through a complex array of different mechanisms. MAP3Ks then activate the critical MAP2Ks, MKK3, MKK6, or (less commonly) MKK4. These MAP2Ks can then differentially activate the four isoforms of p38 (α , β , γ , and δ). **(B)** The known mechanisms for atypical p38 signaling are (i) GPCR stimulation triggers G-protein dependent c-Src phospho-activation of the E3 ubiquitin ligase neural precursor cell expressed developmentally downregulated 4-2 (NEDD4-2). GPCRs recruit and are ubiquitinated by NEDD4-2. K63 ubiquitin chains recruit the ubiquitin-binding adaptor protein TAK1-binding protein 2 (TAB2). In turn, TAB2 then recruits TAB1, which binds and induces autophosphorylation of p38 α . (ii) Oxidative stress triggers TGF β activation, which drives TAB1 and p38 activation, although the exact mechanism is unclear. (iii) Ischemia or hypoxia events drive activation of AMP-activated protein kinase (AMPK), which in turn promotes the formation of the TAB1-p38 α complex and p38 α autophosphorylation. This process is negatively regulated by the heat shock protein 90 (HSP90)-Cdc37 complex. **(C)** T-cell receptor (TCR) ligation to major histocompatibility complex (MHC) drives intracellular activation of the src-family zeta-chain-associated protein kinase 70 (Zap70). Zap70 phosphorylates p38 at tyrosine 323, enabling autophosphorylation of p38 α , or β .

In light of the sheer volume of p38 research articles and the wealth of excellent reviews available, it would be impractical and redundant to cover all aspects of p38 MAPK signaling. Therefore, this review will initially provide a brief overview of the history of p38 and the many roles it plays in disease progression. This will be followed by a more focused examination of the novel atypical p38 activation pathways, specifically including atypical p38 activation by GPCRs, their implications for disease progression, and therapeutic intervention. In comparison to classical p38 activity, atypical p38 signaling has been understudied with only 44 publications, however, this growing body of work represents a fresh perspective on p38 activity and function in disease.

2. Mechanisms of Atypical p38 Activation

MKK3/6 kinase activity is widely considered to be the primary mechanism for p38 phosphorylation. Nevertheless, there is a growing body of evidence to support alternative mechanisms for p38 activation ([Figure 1](#)). Two “atypical” or MKK3/6 independent mechanisms exist that facilitate activation of the p38 α through autophosphorylation in cis, true autophosphorylation rather than phosphorylation of a neighboring p38 [\[5\]](#). The first example of atypical p38 signaling was discovered in 2002, when p38 α was shown to directly associate with transforming growth factor β -activated kinase 1 (TAK1) binding protein 1 (TAB1), an adaptor protein critical for both TGF β and TAK1 signaling [\[6\]](#). During osmotic stress responses [\[7\]](#), TAB1 is responsible for oligomerization and autophosphorylation of TAK1 after O-glycosylation, leading to TAK1 activation [\[8\]\[9\]](#). Conversely, in atypical p38 signaling, TAB1 binds directly and selectively to two discrete binding domains on p38 α . Specifically, TAB1 residues 404–412 interact at a canonical site used by other p38 substrates, including MKK3 and MEF2a, and residues 389–394 bind to a non-canonical binding site on the c-terminal lobe of p38 α . This site does not exist on any of the other p38 isoforms, and at the time of writing, no other proteins have been shown to bind to the same site on p38 α [\[10\]\[11\]](#). The direct interaction of TAB1 with p38 α induces a conformational change moving the active loop into the catalytic domain and enhancing ATP-binding, thus enabling cis-autophosphorylation of the active loop at Thr180 and Tyr182 [\[5\]](#). Consequently, this leads to p38-induced phosphorylation of TAB1 at Ser423, downregulating TAB1 binding to TAK1 and inhibiting TAK1-mediated MKK3/6 activation [\[12\]](#). Additional studies have also shown that TAB1 phosphorylation can alter its intracellular localization, where increased phosphorylation at S452/453/456/457 blocks its nuclear translocation causing TAB1 retention in the cytosol [\[13\]](#). Intriguingly, TAB1 remains bound to p38 α during atypical p38 activity, potentially suppressing the capacity of p38 nuclear translocation [\[11\]](#).

Reactive oxygen species are thought to be the initial driving force behind atypical p38 signaling in cardiac ischemia-reperfusion damage [\[11\]\[5\]](#). Similarly, cigarette smoke extract (CSE) induced oxidative stress in fetal tissue upregulating TGF β production and resulting in TAB1-mediated p38 phosphorylation in a manner independent of TAK1 signaling or the ASK1-signalosome [\[14\]](#). In a separate cardiac ischemia model, the TAB1-p38 interaction is upregulated in an AMPK-dependent manner [\[15\]](#) ([Figure 1B ii](#)). The interaction is negatively regulated by the HSP90/CDC37 chaperone complex in myocytes [\[16\]](#). TAB1 expression is also negatively regulated by the E3 ligase itch through ubiquitin-mediated degradation. Where itch-deficient mice display dramatically increased dermal inflammation levels in an MKK3/6-independent manner [\[17\]](#). The WW-domain in itch binds directly to a conserved PPXY motif in TAB1 (aa145–148). This interaction drives TAB1 K⁴⁸-linked ubiquitination to regulate TAB1 turnover/degradation. TAB1 expression is significantly elevated in the absence of itch, leading to enhanced atypical p38 activation and increased cytokine production, including interleukin-6 (IL-6), interleukin-1 β (IL-1 β), interleukin-11 (IL-11), and interleukin-19 (IL-19). Critically, Wang et al. in 2013 developed a peptide inhibitor fused to the HIV-TAT peptide, generating a cell-penetrating peptide inhibitor that selectively disrupts the TAB1 interaction with p38, substantially attenuating atypical p38 activation [\[18\]\[19\]](#). When used in the itch^{-/-} mice, the peptide blocked atypical p38 α signaling and dermal inflammation was significantly suppressed [\[17\]](#). Further studies have shown that mutation of a critical proline proximal to the p38 binding peptide of TAB1 (P419) blocks TAB1 binding to p38 α and prevents atypical p38 α signaling [\[20\]\[5\]\[21\]](#), as does mutation of four key residues within the p38 α -binding peptide of TAB1 (V390A, Y392A, V408G, and M409A) [\[11\]\[5\]](#). Critically, unlike the systemic knockout of TAB1 or p38 α , which

are embryonically lethal [\[22\]\[23\]](#), the TAB1 knock-in (TAB1-KI) mouse displays no physiological abnormalities but is protected from myocardial ischemic damage [\[11\]](#).

This critical interaction provides a novel opportunity to further develop the peptide inhibitors or screen for small molecule inhibitors to target atypical p38 signaling selectively. Indeed, using a virtual small fragment screen, a group of functionalized adamantanes, specifically 3-amino-1-adamantanol, was found to bind to a critical hydrophobic pocket, forming hydrogen bonds with two key residues, leucine 222 and 234, in the non-canonical TAB1 binding site on p38 α . Further screening found there to be three distinct fragment binding sites within the non-canonical binding site. Linking sulfonamide scaffolds to the adamantanol generated a small molecule with a high affinity to the three regions in the non-canonical binding site [\[10\]](#). Additional development of these compounds will hopefully yield a viable therapeutic. However, it remains to be shown whether these lead hits can block atypical p38 signaling in cells or in vivo.

Despite these detailed studies describing the exact molecular mechanism of TAB1-p38 α interaction and degradation, there are significant gaps in our understanding, specifically for how osmotic stress, oxidative stress, LPS, or inflammatory cytokines such as TNF- α and IL-1 β initiate the TAB1-p38 α interaction and atypical p38 signal transduction. Conversely, recent studies have shown that a family of G protein-coupled receptors (GPCRs) can initiate the TAB1-p38 interaction through a novel ubiquitin-driven pathway (described below and [Figure 1B](#)). This is the first example of a clearly defined mechanism for the induction of atypical p38 signaling and demonstrates conservation of the mechanism for at least four GPCRs critical for vascular inflammatory signaling and vascular homeostasis [\[20\]\[24\]\[25\]](#).

In addition to TAB1, a second discrete mechanism for p38 autophosphorylation has also been demonstrated through src-family zeta-chain-associated protein kinase 70 (Zap70). This pathway is critical for T-cell activation through a T-cell receptor (TCR) specific mechanism [\[26\]](#). In contrast to TAB1-mediated autophosphorylation, p38 α and p38 β isoforms are phosphorylated at Tyr323 by ZAP70, leading to dimerization and mutual trans-autophosphorylation of the kinases at Thr180 alone. Tyr323 is located on the L16 loop of p38, facilitating this autophosphorylation by inducing a shift in the flexible phosphorylation lip of p38 (residues 171–183) [\[27\]](#). Together, both TAB1- and ZAP70-mediated autophosphorylation of p38 reveal the kinase's atypical activation in an MKK3/6-independent manner. The functional significance of these distinct activation mechanisms is still unclear. Additional studies are required to elucidate how atypical activation alters p38 α substrate activation and induction of distinct signal transduction events. Notably, p38 α is phosphorylated at the same sites in both classical MKK3/6-mediated and TAB1-mediated signaling, indicating that differential downstream signaling may instead be regulated in a spatiotemporal context rather than kinase functionality.

3. Activation of Atypical p38 by GPCRs

As the most extensive and versatile family of membrane proteins, G protein-coupled receptors (GPCRs) regulate many cellular pathways by activating MAPKs via G protein-dependent and -independent mechanisms [\[28\]\[29\]\[30\]\[31\]\[32\]](#). Many of the GPCR families can activate p38 α , but until recently, the mechanism for GPCR-mediated p38 α

activation remained unclear or was predicted to be controlled through the classical MKK3/6 pathway. However, several recent studies have linked vascular inflammatory GPCRs to the activation of the TAB1-dependent atypical p38 signaling pathway [20][24][6][25][33][34]. The initial studies examined thrombin-mediated activation of the protease-activated receptor 1 (PAR1) in vascular endothelial cells. The authors noted that after activation, PAR1 was ubiquitinated, despite being trafficked and degraded in a ubiquitin-independent manner [33][35][36][37]. α -Thrombin, activation of PAR1 induces the receptor to couple to the G protein subunits $G\alpha_q$ or $G\alpha_{12/13}$ to induce activation of the proto-oncogene tyrosine-protein kinase c-Src (Src short for sarcoma) and subsequent activation of the E3 ubiquitin ligase, neural precursor cell expressed developmentally downregulated 4-2 (NEDD4-2) [24]. NEDD4-2 is one of a family of nine Homologous to E6-AP Carboxy Terminus (HECT) domain-containing E3 ligases and mediates the covalent coupling of ubiquitin to the intracellular c-tail or intracellular loops of GPCRs [20][25]. C-Src activates NEDD4-2 through tyrosine phosphorylation of a critical tyrosine residue, Y485, on a linker peptide between WW domain 2 and 3 (2,3 peptide). This 2, 3-linker peptide acts as a molecular switch that holds NEDD4-2 in an inactive conformation. Phosphorylation of Y485 by c-Src induces a conformational change that releases NEDD4-2 from an autoinhibited state. After activation, most likely at the plasma membrane, NEDD4-2 is recruited to PAR1, leading to PAR1 ubiquitination [24], although the exact mechanism as to how NEDD4-2 is recruited to PAR1 is unknown. Traditionally, GPCR ubiquitination serves as a sorting signal to cause endolysosomal trafficking and protein degradation [20][33]. However, in this case, NEDD4-2-mediated ubiquitination drives the recruitment of the TAB2-TAB1-p38 signaling complex [20][24][25][33]. TAB2 has an NP14 zinc finger (NZF) domain that binds to the lysine 63-linked NEDD4-2 ubiquitin chains and functions as an adaptor protein. It is predicted but has not been conclusively shown that TAB2 subsequently binds to and recruits TAB1 and p38 α , inducing p38 α autophosphorylation and TAB1 phosphorylation [20][38]. Interestingly, a structural homolog to TAB2, TAB3, is also able to bind to TAB1 to produce p38 pro-inflammatory signaling by GPCRs. However, it is not known what the contribution of each homolog is when expressed in the same cell or whether they are functionally redundant [25]. As stated above, the ubiquitinated endosomal receptors nucleate the formation and activation of the TAB1-p38 α complex and increase TAB1 phosphorylation and stability [20]. It is still unclear whether GPCR-activated TAB1 sequesters p38 in the cytosol. Likewise, it is not known how TAB1-p38 signaling is terminated.

Importantly, this pathway is not unique just to PAR1 and α -thrombin. NEDD4-2 dependent regulation of atypical p38 signaling is also conserved for the purinergic receptor P2Y1. Furthermore, a recent study also demonstrated that the pathway is conserved for prostaglandin E2 (PGE2), histamine, ADP, and α -thrombin-mediated p38 activation and inflammatory cytokine production in primary human microvascular and macrovascular endothelial cells [25]. Additional studies are required to determine how many GPCRs utilize this pathway, whether atypical p38 signaling is critical for all cells, and how it selectively contributes to pathophysiological responses.

4. Pathophysiological Implications of Atypical p38 Signaling

Contrary to the highly studied MKK3/6-dependent pathway, the impact of TAB1-p38-dependent signaling in physiology and disease remains largely understudied with just 44 research articles on the subject (Table 1). As mentioned above, the recent development of the viable p38 α -KI mouse [39] or the TAB1-KI mouse [11] suggests that

perturbation of the atypical pathway is less critical for developmental and physiological signaling compared to the embryonically lethal systemic knockout of p38 α or TAB1 [22][23]. It is perhaps then not surprising that atypical p38 activation has so far only been identified as a contributor to disease progression, which will be discussed below.

Table 1. Physiological roles of TAB1-dependent atypical p38 signaling.

| Disease | Mechanism of p38 Autophosphorylation | Model | Specific Cell or Animal Line |
|--|--------------------------------------|---|--|
| Cardiovascular ischemia and reperfusion | TAB1-mediated | Murine in vivo [11][15][18][40][41] | MKK3 ^{-/-} [15][41]; C57BL/6 [15][40]; Sprague Dawley [15]; Wistar [18]; TAB1 KI [11] |
| | | Murine in vitro [11][5][18][40][41][42] | H9c2 [41]; Sprague Dawley [18][40][42]; Wistar [18]; C57BL/6 [11][5] |
| | | Human in vitro [11][18][19][40][39] | HEK293 [11][18][40][39] |
| | | Structural modeling [10] | |
| | | Murine in vivo [43] | Sprague Dawley |
| Myocardial infarction, amyloidosis, and cardiomyopathy | TAB1-mediated | Murine in vitro [16][43][44] | H9c2 [43]; Wistar [44] |
| | | Human in vitro [44] | Patient heart |
| | | Zebrafish in vivo [45] | |
| | | Murine in vivo [20][17][46] | BALB/c [46]; CD1/CD1 [20]; C57BL/6, Itch ^{-/-} [17] |
| General inflammation and cancer | TAB1-mediated | Murine in vitro [20][17][46] | V β 8.1, OT-II [46]; TAB1 ^{-/-} [20]; C57BL/6, Itch ^{-/-} [17] |
| | | Human in vitro [20][24][25] | HUVEC [20][24][25]; HEK293 [20]; HDMEC [25] |
| | | Structural modeling [27][47] | |
| | | Murine in vivo [48] | BALB/c |
| Parasitic infection | TAB1-mediated | Murine in vivo [48] | BALB/c |
| | | Murine in vitro [48][49][50] | RAW264.9 [48]; MKK3 ^{-/-} [49]; |

| Disease | Mechanism of p38 Autophosphorylation | Model | Specific Cell or Animal Line |
|-----------------------------------|--------------------------------------|---|--|
| Viral infection | TAB1-mediated | | BALB/c [50] |
| | | Murine in vitro [51] | C57BL/6, BC-1 |
| | | Human in vitro [52] | Huh7.5.1, HEK293, patient liver |
| Bacterial infection | TAB1-mediated | Human in vitro [53] | HPMEC |
| | | Shrimp [54] | |
| Diabetes | TAB1-mediated | Murine in vitro [55] [56] | β-TC6 [55] [56] ; Sprague Dawley, NMR1 [56] |
| | | Human in vitro [56] | Islet |
| | | Murine in vivo [57] | vβ8.1 |
| Leukocyte dysfunction | TAB1-mediated | Murine in vitro [57] | 2B4 |
| | | Human in vitro [58] [59] [60] | Patient blood |
| Pregnancy complications | TAB1-mediated | Murine in vitro [61] | CD-1 |
| | | Human in vitro [14] [61] | Patient placenta |
| | | Murine in vitro [62] [63] | MKK3 ^{-/-} /6 ^{-/-} [62] ; MKK3 ^{-/-} [63] |
| Other | TAB1-mediated | Human in vitro [6] [13] [21] [64] | HEK293 [6] [13] [21] [64] ; MDA231 [64] |
| | | Structural modeling [65] | |
| Immune system (T-Cell) modulation | Zap70-mediated | Murine in vivo [26] | P116 |
| | | Murine in vitro [66] [67] [68] [69] | Gadd45a ^{-/-} [66] ; CD4SP [67] ; C57BL/6 [68] [69] |

Atypical p38 plays a key role in multiple pro-inflammatory pathologies. The interaction of atypical p38 with TAB1 has been demonstrated in ischemic cardiac damage, ischemia-reperfusion injury, and amyloidosis. In an MKK3^{-/-} ischemic mouse, the TAB1-p38 interaction was a leading contributor to necrosis in cardiomyocytes [\[41\]](#). The role of atypical p38 was further confirmed in the progression of ischemic damage when a cell-penetrating inhibitor peptide was developed that reduced infarct size in ischemic rats

| [18] | Disease | Mechanism of p38 Autophosphorylation | Model | Specific Cell or Animal Line | Genetically |
|---|---|--------------------------------------|---|------------------------------|--------------------------------------|
| | transphosphorylation of TAB1 was disabled [11] , and prevent apoptosis in cardiomyocytes during IR [40] | | Human in vitro [26] [70] [71] [72] [73] | Jurkat, P116 | more, the |
| | | | Chicken in vitro [72] | [16] DT40 | l-p38α to ylation is 90 during |
| cardiac stress is thought to dissociate p38α from p38α, enabling TAB1 interaction and p38α autophosphorylation to drive IL-6 and TNFα expression and cardiomyocyte apoptosis [16] . Additional studies have also shown that in a zebrafish model of amyloid light-chain (AL-LC) amyloidosis, AL-LC drives TAB1-p38α signaling causing cardiotoxic signaling, impaired cardiac function, pericardial edema, cell death, and subsequent heart failure [44] [45] . | | | | | |

Aside from the heart, p38 autophosphorylation has also been indicated in pathological inflammation in dermal disorders, preterm birth, and more broadly in vascular inflammation. In the *itch*^{-/-} mice, TAB1 expression is significantly enhanced, leading to robust p38 autophosphorylation and subsequent increases in inflammatory cytokine expression, immune cell recruitment, and spontaneous skin lesions [17]. The use of the cell-penetrating peptide inhibitor significantly reduced these phenotypes, suggesting that *itch*-mediated p38 signaling could be exploited therapeutically [17]. In the field of reproductive biology, term and preterm parturition are tied to oxidative-stress and inflammatory TGF-β-induced TAB1-p38 activity resulting in amniochorion senescence [14]. Atypical p38 is also considered an essential component of the careful balance of endothelial mesenchymal transition (EndoMT) and mesenchymal endothelial transition (MEndoT) in human and murine amnion cells that contributes to the timing of parturition [61].

Vascular inflammation also directly activates GPCR-dependent p38 signaling in endothelial cells. In these studies, GPCR ligand α-thrombin induces endothelial barrier disruption driving vascular leakage and permeability. Additionally, recent studies of GPCR-mediated TAB1-p38 activity have demonstrated that it is conserved in multiple endothelial vascular beds and activated by a family of GPCR ligands associated with inflammation such as histamine, PGE2, ADP, and potentially many others [20][24][25]. While it has not yet been definitively shown, it stands to reason that any cell that expresses these GPCR receptors has the potential to induce atypical p38 signaling. This being the case, it will be essential to understand the role of GPCR signaling in fibroblasts, epithelial cells, mural/pericyte cells, and neuronal cells. Therefore, the impact of GPCR-induced atypical signaling is likely to play an, as of yet, undiscovered or overlooked role in many other vascular inflammatory diseases.

Beyond the vasculature, the role of atypical p38 is also explored in the modulation of the immune system by inflammatory ligands, attenuation of the TCR, and response to pathogens. Basophils and eosinophils isolated from healthy patients undergo p38 autophosphorylation in response to cytokine exposure from TNFα and GM-CSF, contributing to prolonged inflammation like that seen in pulmonary inflammatory disorders [58]. Conversely, TAB1-p38 interaction is also associated with maintaining anergic CD4⁺ T-cells through increased expression of TAB1 following antigen exposure and abrogating TCR [57]. Similarly, TAB1-p38 drives T-cell senescence via an AMPK-dependent regulatory pathway, resulting in downregulation of TCR signalosome [59]. AMPK also plays an essential role in the TAB1-p38 activation of HSP27 in simulated sepsis, maintaining vascular integrity [53]. Intracellular infection leading to TAB1-p38 activity was first shown in macrophages in mice infected with *Toxoplasma*

gondii, resulting in pro-inflammatory IL-12 production specific to atypical signaling [49]. *Leishmania* infection results in parasite GP63-induced degradation of TAB1 to reduce p38 activation [50], the reversal of which sharply attenuates infection [48]. These studies suggest a vital role for the TAB1-p38 interaction in the host defense during intracellular pathogen infection.

Another example of atypical p38 activation comes from a recent study that demonstrated that multiple viruses utilize atypical p38 signaling to drive viral infections. Inhibition of TAB1-dependent p38 activation impaired hepatitis C virus (HCV) assembly and viral replication. This was also confirmed for severe fever with thrombocytopenia syndrome virus (SFTSV), herpes simplex virus type 1 (HSV-1), and severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [52]. Indeed, the p38 inhibitor losmapimod is currently in a clinical trial to treat SARS-CoV-2 (ClinicalTrials.gov ID: NCT04511819). It will be important for future studies to understand how atypical p38 signaling contributes to viral and bacterial infections and whether selective atypical p38 inhibitors could support current therapeutic regimens.

In the realm of type 1 diabetes, a link was found for TAB1-p38 interaction in the apoptosis of beta cells via oxidative stress by NO [55] and cytokine-induced beta-cell death [56]. These investigators noted that the effect of TAB1 signaling was specific to the TAB1 α splicing product of the TAB1 gene located on chromosome 22, which has also been linked to systemic sclerosis and type 2 diabetes, hinting at a potential genetic component involving TAB1 mutation in the initiation of these diseases.

Contrary to TAB1-dependent signaling, Zap70-dependent activation of p38 is exclusive to T-cell activation via the TCR response, which is negatively regulated by p38 phosphorylation of upstream Zap70 [26][27]. However, a recent study also showed that TCR-mediated p38 activation occurs simultaneously through a classical kinase cascade and inflammatory augmentation by the alternative, atypical p38 activation. Intriguingly, it is suggested that uncoupling of the classical p38 activation mediated by the adaptor protein LAT and the guanine nuclear exchange factor, Son of Sevenless 1/2 (SOS1/2), reduced T-cell development and exacerbated autoimmune disease in mice [72]. At the same time, the genetic blockade of the TAB1-Zap70 suppressed T helper cell activation (T_H1 and T_H17) and expression of IFN γ and IL17. Indicating that both the classical and atypical p38 activation pathways could work synergistically to induce a balance between pro- and anti-inflammatory responses [72]. It is currently unclear whether there are some cases when TAB1-p38 activation may work in consort with MKK3/6, albeit in a TAK1-independent manner as TAB1 phosphorylation by p38 during atypical p38 signaling blocks TAB1's interaction with TAK1 preventing TAB1-TAK1 dependent MKK3/6 activation [12].

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