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Systematic Review

Isoform-specific and cell/tissue-dependent effects of p38 MAPKs in regulating inflammation and inflammation-associated oncogenesis

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Abstract

p38 MAPK (mitogen-activated protein kinases) family proteins (α, β, γ and δ) are key inflammatory kinases and play an important role in relaying and processing intrinsic and extrinsic signals in response to inflammation, stress, and oncogene to regulate cell growth, cell death and cell transformation. Recent studies in genetic mouse models revealed that p38α in epithelial cells mostly suppresses whereas in immune cells it promotes inflammation and inflammation-associated oncogenesis. On the contrary, p38γ and p38δ signaling in immune and epithelial cells is both pro-inflammatory and oncogenic. This review summarizes recent discoveries in this field, discusses possible associated mechanisms, and highlights potentials of systemically targeting isoform-specific p38 MAPKs. Understanding of p38 MAPK isoform-specific and cell/tissue- and perhaps stage-dependent effects and their integrated regulated activity in inflammation and in inflammation-associated oncogenesis is essential for effectively targeting this group of kinases for therapeutic intervention.

Keywords: p38 MAPKs; Isoform-specific and cell/tissue-dependent effects; Inflammation; Inflammation-associated oncogenesis

1. Introduction

p38 mitogen-activated protein kinases (MAPKs) (α, β, γ and δ) are encoded by four different genes in four different chromosomes [1]. p38 MAPKs are dual-phosphorylated on tyrosine and threonine residues within a conserved Thr-Pro-Tyr (TPY) motif by MAPK kinase 3 (MKK3) and/or MKK6, which in turn phosphorylate a substrate typically containing a ST/P motif (Ser or Thr residue, followed by Pro [1]). p38α and p38β phosphorylate more than 100 substrates [2], and many of them are not phosphorylated by p38γ and p38δ that have specific and non-overlapping substrates and are therefore called alternative p38 MAPKs [3–5]. Although distinct substrates may play a role in an isoform-specific effect of p38 MAPKs, how p38 MAPK family members signal via common and unique substrates are largely unknown [2,4]. We will review recent discoveries from genetic studies about isoform-specific and cell/tissue-dependent effects of p38 MAPKs in inflammation and in inflammation-associated oncogenesis and discuss potentials of targeting a specific p38 isoform in therapeutic intervention.

p38α is expressed universally in all tissues and/or cells, whereas other p38 family proteins are only detectable in certain tissues and/or cells [1,2]. Although all p38 MAPKs can be activated similarly in response to inflammation, stress and oncogenic signaling, they can also be activated distinctively [1,2,6–9]. Oncogene RAS, for example, stimulates p38α (also called p38) phosphorylation but increases RNA/protein levels of p38γ (and not other p38 MAPKs), indicating that p38 MAPKs are activated by Ras oncogene by an isoform-specific mechanism [6,7,10–12]. Furthermore, elevated p38γ gene expression was demonstrated in human breast, colon, and pancreatic cancers, which is correlated with decreased patient survival, indicating its potential roles in malignant development and progression in clinic [9,10,12–15]. In addition, treatment of mice with the inflammation stimulus dextran sulfate sodium (DSS) preferably stimulates p38γ phosphorylation (as compared to p38α) in intestinal epithelial tissues/cells [16], whereas p38α (to a less extent for p38δ) is predominantly activated by lipopolysaccharide (LPS) [17] and tumor necrosis factor (TNF) [18]. In patients with chronic inflammation (arthritis), however, p38α and p38γ, but not other p38s, are both activated [19]. A distinct activation-pattern of p38 family proteins by different stimuli may play an important role in their different biological outcomes and an elevated p38γ RNA/protein in Ras-transformed cells and in cancers indicates its potential as a sustainable therapeutic target for pharmacological intervention.

p38 family MAPK proteins also differently activate their downstream substrates such as kinases and transcription factors [2,4]. Several kinases, including p38 regulated/activated kinase (PRAK), and mitogen-activated protein kinase–interacting kinase 1 (MNK1), are phosphorylated by p38α and/or p38β *in vitro* and in cells, but not by other p38 isoforms, whereas MAP kinase-activated protein kinase 2 (MK2) is activated by all p38 family proteins [1,4]. Transcription factors myocyte enhancer factor 2C (MEF2C) and activating transcription factor-2 (ATF2) are activated by all p38 family proteins [3,4]. Although c-Jun is

activated by p38α and p38γ, this occurs via distinct mechanism: c-Jun is activated by p38α through phosphorylation of the AP-1 partner proteins Sap-1α and ATF2 [1] but activated by p38γ via AP-1-dependent transcription [20–22]. The different effects of p38 family proteins on downstream kinases and transcription factors may play an important role in their isoform-specific and cell/tissue-dependent activities.

p38γ protein has a unique structure among p38 family proteins, which may determine its capacity to phosphorylate a specific substrate and to signal via a specific pathway through interacting with different proteins [1,15, 23,24]. Specifically, p38γ C-terminal contains a PDZ-binding motif that interacts with PDZ-domain containing proteins including its substrate SAP90 [25] and its phosphatase protein tyrosine phosphatase H1 (PTPH1) [11,15]. Moreover, PDZ motif is required for p38γ to interact with c-Jun in cells [20], which may be important for p38γ to activate AP-1-dependent gene transcription, including c-Jun, matrix metalloproteinase (MMP9) [20], Nanog [21], and epidermal growth factor receptor (EGFR) [22]. Furthermore, p38γ depends on PDZ motif to bind, phosphorylate and activate PTPH1 [26], which is important for PTPH1 to catalyze EGFR dephosphorylation and to promote KRAS-dependent growth [22,27]. In addition, p38γ binds and/or phosphorylates several proliferative proteins, including DNA topoisomerase IIα (Topo IIα) and estrogen receptor α (ER) in breast cancer [8,9], heat shock protein 90 (Hsp90) and β-catenin in colon cancer [13,16], and glucose transporter 2 (Glut2) and phosphofructokinase-2/fructose-2,6-bisphosphatase 3 (PFKFB3) in pancreatic cancer [12]. It is not known, however, if PDZ binding is directly and indirectly involved in p38γ interacting with this group of proliferative proteins. These results together indicate that p38γ may execute its oncogenic activity through interaction with other proliferative proteins dependent and independent of PDZ binding [28].

2. Effects of p38α/β knockout on inflammation and inflammation-associated oncogenesis

Cell culture studies showed p38α inhibits Ras proliferative activity in NIH3T3 fibroblasts by negative feedback in which transient transfection of oncogenic Ras ($HRAS^{G61L}$) stimulates phosphorylation of each member of the co-transfected p38α pathway MKK6 (MAPK kinase 6), p38α, and PRAK (p38-related/activated protein kinase)/MAPK-activated protein kinase 2 (MK2), which in turn suppresses Ras proliferative response [6]. The p38α suppressive activity on Ras oncogene was further demonstrated pharmacologically in intestinal epithelial cells (IEC) in which Ras-dependent soft-agar growth was increased by treatment with the p38α/β inhibitor SB203586 [29]. Moreover, the p38 upstream activator MKK6 and down-stream kinase PRAK and MK2 were further shown to suppress Ras proliferative activity and/or Ras-induced transformation in different *in vitro* and *in vivo* systems [6,30–35], although recent MK2 knockout studies showed its promoting role in colitis-associated cancer [36]. These results together indicate that the p38α pathway activities in target cells (fibroblasts and epithelial cells) are inhibitory to Ras proliferative activity and oncogenic transformation in cell culture [7] (Table 1, Ref. [12,16,34,37–64]).

Systemic effects of p38α in inflammation and in inflammation-associated oncogenesis have been investigated by knockout (KO) studies in mice. Because global p38α KO is embryonic lethal [65,66], inducible and/or conditional p38α KO was developed. Specific p38α KO in macrophages leads to changes in pro-inflammatory cytokines TNF, IL-6, and anti-inflammatory cytokine IL-10 in bone marrow-derived macrophages (BMDM) in a manner dependent of stimuli and of treatment time, which is blocked by IL-10 antibody, indicating a proinflammatory response [56]. Further, myeloid p38α KO decreases colitis, inhibits colitis-associated cancer (CAC) [42], and prolongs survival of IL-$10^{-/-}$ mice, indicating that myeloid p38α is pro-inflammatory and oncogenic [56]. A pro-inflammatory role of p38α is also demonstrated by a decrease in 2,4-dinitrofluorobenzene (DNFB)-induced ear swelling in mice with p38α KO in dendritic cells (DCs) and in T cells, although myeloid-specific p38α KO had an opposite effect [48]. Moreover, p38α KO in DCs inhibits dextran sodium sulfate (DSS)-induced colitis and attenuates DSS/azoxymethane (AOM)-induced CAC in association with decreased neutrophil infiltration and with changes in multiple cytokines in colon tissues [54], further indicating the pro-inflammatory and oncogenic role of p38α in immune cells (Fig. 1). This conclusion is further supported by decreased lethality in mice after the treatment with lipopolysaccharide (LPS) in which p38α is specifically deletion in macrophage in association with reduced blood levels of pro-inflammatory cytokines TNF, IL-12, and IL-18 [55]. Moreover, there is attenuated colitis and decreased inflammatory cytokine expression (after DSS) in mice with myeloid-specific p38α KO [41]. Myeloid p38α is also important for DSS-induced skin inflammation [46] and p38α KO in DCs, but not in macrophages or T cells, inhibits T_H17 differentiation, decreases IL-17 levels, and suppresses autoimmune inflammation [67]. In addition, inhibition of p38α activity by expressing a dominant negative (dn) mutant in CD4 T cells decreases IL-17 expression and reduces the severity of allergic encephalomyelitis (EAE) [57]. Studies with a CRISPR-Cas9 screening of primary T cells further showed that p38α deletion increases the efficacy of mouse anti-tumor T cells [50,68], thus demonstrating an oncogenic role of p38α in T cells. A recent study further showed that p38α activity (the phospho-p38α/total p38α ratio) in leukocytes isolated from the patient peripheral blood with metastatic melanoma is increased as compared to those without metastasis, and predicts decreased

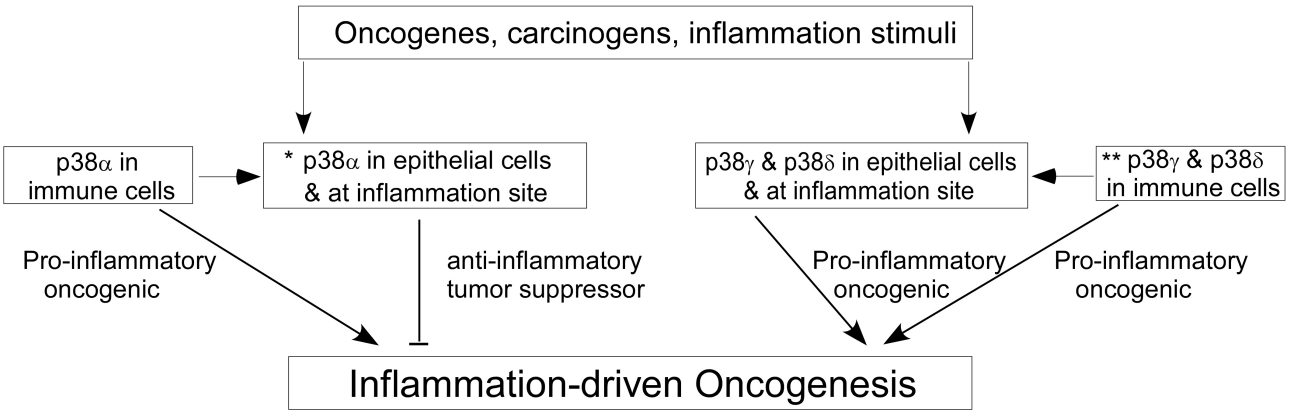

Fig. 1. p38 (α, β, γ, and δ) family proteins regulate inflammation and inflammation-associated oncogenesis by isoform-specific and cell/tissue-dependent mechanism. p38α activity in immune cells is mostly proinflammatory and oncogenic while in epithelial cells (and other target cells such as MEFs) is anti-inflammatory and tumor suppressive. p38γ and p38δ activity in immune and epithelial cells is both proinflammatory and oncogenic. * Biphasic effects of inducible p38α KO in intestinal epithelial cells and in lung epithelial projector cells, i.e., p38α is a tumor suppressor in cancer initiation stage but is oncogenic in advanced stage likely via tumor-stromal interactions. No p38β studies on inflammation and/or cancer have been reported. ** Only studies of conditional p38δ and combined p38γ/p38δ KO in myeloid cells were reported.

patient survival, and that p38α KO specifically in fibroblasts attenuates lung metastasis of melanoma in mice [51]. Moreover, specific deletion of p38α from fibroblasts also inhibits KRAS-induced lung tumorigenesis [52]. These results together indicate that p38α activity in stromal cells (immune cells and fibroblasts) overall is pro-inflammatory and/or oncogenic [48,54,67] (Fig. 1) (Tables 1,2).

Studies with specific p38α KO in epithelial cells in which tumor develops, however, showed that p38α is anti-inflammatory with a tumor suppressor activity [40,41,43,44,49]. Experiments in mice with intestinal epithelial cell (IEC)-specific p38α KO, for example, showed increased IEC proliferation, enhanced colitis severity and/or colon tumorigenesis after the treatment with DSS $\pm$ azoxymethane (AOM) as compared to control mice [41,43,44]. An increase in the carcinogen diethyl nitrosamine (DEN)-induced liver tumorigenesis was also observed in mice with hepatic-specific p38α KO [40,49]. Moreover, studies in H-Ras-transformed or immortalized fibroblasts showed increased *in vivo* xenograft formation of mouse embryonic fibroblasts (MEFs) lacking p38α [38] and its activator MKK3 and MKK6 [34]. Moreover, experiments with inducible p38α global knockout revealed that p38α KO increases lung stem cell proliferation and KRAS-induced lung tumorigenesis [37]. In addition, co-injection of p38α-deleted mesenchymal stem cells (MSCs) increases xenograft growth of human colon cancer cells in nude mice in association with enhanced angiogenesis [39]. However, inhibition of p38α nuclear translocation by a peptide attenuates AOM/DSS-induced colon cancer, likely through targeting p38α in multiple cell-types and tissues [69]. These results together indicate that p38α activity in target cells (epithelial, fibroblasts) and in co-injected MSCs is anti-inflammatory and/or tumor-suppressive in response to carcinogen, inflammation stimulus and/or RAS oncogene (Fig. 1).

Recent studies further showed that inducible p38α KO at a late stage in intestinal epithelial cells (65 days after AOM/DSS administration to induce colon tumor) and in alveolar epithelial progenitor cells (20 weeks after induction of $KRAS^{G12V}$ expression in lungs) decreases tumorigenesis, despite the initial increase in tumorigenesis in both tissues [44,45]. Mechanisms involved however are mostly unclear and may involve epithelial p38α signaling interaction with stromal once tumor reaches a certain size [52,70]. This speculation is supported by the fact that p38α silencing in pancreatic cancer cells inhibits the cell growth *in vitro* but increases the xenograft formation of the same cells in mice [71] and that p38α in fibroblasts promotes lung metastasis of melanoma [51] and lung tumorigenesis [52]. These results indicate a stage-specific role of epithelial p38α in tumorigenesis and metastasis likely through signaling interactions with stromal tissues. Although studies also showed a distinct role of p38α vs p38β in cell survival and cell death [71,72], p38β is generally believed to be redundant and its global KO did not show major phenotypes [73]. These results together indicate that p38α in epithelial cells has a dual role in oncogenesis, i.e., anti-inflammatory as a tumor suppressor at the tumor initiation but oncogenic once tumor is established or becomes metastatic (Fig. 1) (Tables 1,2).

3. Effects of p38γ/δ knockout on inflammation and inflammation-associated oncogenesis

Genetic studies showed that mice with global p38γ and/or p38δ knockout are phenotypically nor-

Table 1. Effects of knockout of p38 MAPKs on inflammation and inflammation-associated oncogenesis.

p38 knockout (KO)	Major phenotype	Reference
$^{-/-}$ (inducible KO)	increased lung tumorigenesis (KRAS)	[37]
$^{-/-}$ (KO in MEFs)	increased transformation by Ras and other oncogenes	[38]
$^{-/-}$ (inducible KO in MSCs)	increased xenograft growth co-injected with p38α-deleted mesenchymal stromal cells (MSCs)	[39]
liver-specific KO	increased liver tumorigenesis (Den-induced)	[40]
IEC-specific KO	increased colitis (DSS)	[41]
myeloid-specific KO	decreased colitis (DSS)	
myeloid-specific KO	decreased colitis-associated tumorigenesis (AOM/DSS)	[42]
IEC-specific KO	increased colitis and colitis-associated cancer (CAC) (AOM/DSS)	[43]
IEC-specific KO*	biphasic; increased colon tumorigenesis early and decreased tumor growth later	[44]
Alveolar epithelial type II* (AE II-specific KO)	biphasic, increased tumorigenesis early and decreased tumor formation later (KRAS)	[45]
myeloid-specific KO	decreased skin inflammation to SDS increase skin inflammation to UVB increased skin inflammation to TPA	[46]
keratinocyte specific KO	decreased skin inflammation to UVB	[45]
DC specific KO	no effect on skin inflammation to UVB	
keratinocyte specific KO	increased skin inflammation to LPS/TPA	[48]
myeloid specific KO	increased skin inflammation to LPS/TPA	
DC specific KO	decreased skin inflammation to LPS/TPA	
T cell specific KO	decreased skin inflammation to LPS/TPA	
Hepatic-specific KO	increased liver tumorigenesis (Den-induced)	[49]
T cell specific KO (CRISPR-Cas9)	increased adoptive immunotherapy increased anti-tumor activity of T cells	[50]
$^{-/-}$ (inducible) &	decreased lung metastatic of melanoma	[51]
Fibroblasts-specific KO	decreased lung metastatic of melanoma	
Fibroblast-specific KO	decreased lung tumorigenesis (KRAS model)	[52]
DC-specific KO	decreased T_H-17 cell differentiation and decreased IL-23/IL-6 expression	[53]
DC-specific KO	decreased colitis/colon tumors (AOM/DSS), increased JNK, IL-10, IFN-γ and decreased IL-6, TNF, IL-1β, and IL-17	[54]
Macrophage specific KO	decreased LPS-induced TNFα, IL-12 and IL-18	[55]
Macrophage specific KO	decreased colitis in IL-10$^{-/-}$ mice	[56]
Keratinocyte-specific KO	decreased skin inflammation (to UVB)	
MKK3/6$^{-/-}$ in CD4T cells	decreased IL-17	[57]
p38α dn Tg in CD4T cells	decreased IL-17	
MKK3/6$^{-/-}$ in MEFs	increased xenograft in immortalized cells	[34]
p38β	No studies reported	

Table 1. Continued.

p38 knockout (KO)	Major phenotype	Reference
p38γ		
$^{-/-}$	decreased TNFα, IL-β and IL-10 in response to LPS	[58]
$^{-/-}$**	decreased colon tumorigenesis when combined with p38$\delta^{-/-}$ (AOM/DSS)	[59]
$^{-/-}$**	decreased skin tumorigenesis when combined with p38$\delta^{-/-}$ (DMBA/TPA)	[60]
$^{-/-}$	slowed T-cell differentiation (p38$\gamma^{-/-}$ more affects in $CD4^+/CD8^+$ cells) (p38$\delta^{-/-}$ more affects in $CD4^-/CD8^-$ cells)	[61]
IEC-specific KO	decreased colitis and CAC (AOM/DSS model)	[16]
Hepatic-specific KO	Decreased liver tumorigenesis (Den model)	[62]
pancreas-specific KO	Decreased pancreatic tumorigenesis (KPC model)	[12]
p38δ		
$^{-/-}$	decreased skin tumorigenesis (DMBA model)	[63]
$^{-/-}$**	decreased colon tumorigenesis When combined with p38$\gamma^{-/-}$ (AOM/DSS model)	[59]
$^{-/-}$**	decreased skin tumorigenesis when combined with p38$\gamma^{-/-}$ (DMBA/TPA)	[60]
$^{-/-}$	decreased mammary tumorigenesis (PyMT model)	[64]

The global knockout is indicated by a sign "$^{-/-}$", whereas conditional knockout (KO) is shown as cell/tissue-specific KO through the Cre recombinase technology. Tumors were induced by transgenic expression of the indicated oncogene and/or by treatment of mice with the indicated carcinogen ± inflammation stimuli (please see details in the indicated references). *indicates a biphasic effect with enhanced tumorigenesis by inducible p38α conditional KO during tumor initiation and with decreased tumor growth and/or metastasis after tumor established, and **shows similar phenotypes in p38γ KO and p38δ KO mice, which is more substantial in their double KO mice. Effects of p38γ in experimental and clinic cancer were recently reviewed [74] and results from this table are summarized in Table 2.

Table 2. Summary of p38 MAPKs in inflammation and cancer.

	Pro-inflammatory		Anti-inflammatory		Tumor-suppressive		Oncogenic		Oncogenic	Others
Knockout	Epithelial	Immune cells	Epithelial	Immune cells	Epithelial	Immune cells	Epithelial	Immune cells	Fibroblast	
p38α		**X***	**X**	**X***	**X**			**X**	**X**	
p38β										**?**
p38γ	**X**	**X**					**X**			
p38δ	**X**	**X**					**X**			

*Response differs in a stimulus- and cell/tissue-specific manner.

mal, which however results in a decrease in multiple cytokines in response to lipopolysaccharide [LPS, a toll-like receptor 4 (TLR4) ligand] in bone marrow-derived macrophages (BMDM) [58,75]. Although global p38γ knockout alone has no significant effect on 7,12-dimethylbenz(a)anthracene (DMBA)/tetradecanoyl-phorbol-13-acetate (TPA)-induced skin tumorigenesis as compared with wild-type (WT) mice, there is attenuated tumorigenesis in p38δ KO mice with a more substantial effect in mice with its combined KO with p38γ [60].

In colon cancer studies, p38γ and p38δ global KO has no major impact on chronic inflammation but decreases acute inflammation in intestine tissues in response to DSS [59]. Moreover, mice with myeloid-specific p38γ and/or p38δ KO are resistant to diet-induced fatty liver, hepatic triglyceride, and glucose intolerance in association with defective migration of neutrophils to the damaged liver [76]. Analyses of global p38γ and/or p38δ KO mice further showed that p38δ and p38γ KO differentially regulates T cell differentiation at different stages as compared with WT mice [61]. Separate studies showed that both myeloid-specific and global p38δ KO decreased alveolar neutrophil accumulation and attenuated acute lung injury [77], whereas combined p38γ/p38δ myeloid-specific and global KO protects mice against fungal infection and inhibits leukocyte recruitment to infected kidneys [78]. These results together indicate that systemic p38γ and p38δ activity and their signaling in immune cells (only KO data available in myeloid cells) are mostly pro-inflammatory and/or oncogenic (Fig. 1).

Recent genetic studies in mouse cancer models further showed that systemic and epithelial p38γ in gastrointestinal (GI) system is essential for tumorigenesis. Global p38γ and p38δ KO attenuates colitis-associated cancer (CAC) with their combined KO having more significant effects than either alone, indicating a cooperative oncogenic activity of systemic p38γ and p38δ [59]. Moreover, IEC-specific p38γ KO alone decreases pro-inflammatory cytokines (IL-6, IL-1β and TNF), inhibits the β-catenin/Wnt pathway in colonic tissues, and attenuates DSS-induced colitis and AOM/DSS-induced CAC [16]. Importantly, oral application of a p38γ selective pharmacological inhibitor pirfenidone (PFD) [79,80] depends on epithelial p38γ to decrease p38γ phosphorylating its substrates and to reduce cytokine's levels in tumor tissues, and to inhibit tumorigenesis, suggesting a novel strategy to block colon tumorigenesis by targeting epithelial p38γ [16]. p38γ was further shown to phosphorylate RB and to drive cell cycle progression, and hepatic p38γ KO and systemic application of PFD both block diethyl nitrosamine (DEN)-induced liver tumorigenesis [62]. Our recent studies further showed that p38γ mediates KRAS oncogene signaling to activate the glycolytic pathway in pancreatic ductal cancer cells (Pdac) and that specific p38γ KO in pancreatic epithelial cells inhibits pancreatitis, reduces cytokine levels, and decreases pancreatic tumorigenesis in KPC mice [12]. Moreover, epithelial p38γ is required for PFD to suppress glycolytic pathways, to block pancreatic tumorigenesis in KPC mice, and to inhibit Pdac xenograft growth [12]. Together, these results demonstrate that epithelial p38γ is essential for colon, liver and pancreatic tumorigenesis and its pharmacological inhibitor PFD may have therapeutic potentials to block their development, growth, and progression (Fig. 1) (Tables 1,2).

Studies also showed that p38δ is required for tumorigenesis in certain tissues. An early study showed that global p38δ KO blocks DMBA/TPA-induced skin tumorigenesis [63]. Studies from Cuenda lab further showed that global p38δ KO alters expression of several cytokines in response to DSS [59]. Although combined global p38γ/p38δ KO appears to achieve more substantial effects in regulating cytokines and in inhibiting CAC than either alone in DSS/AOM mouse model, analyses of chimeric mice of WT with p38γ/p38$\delta^{-/-}$ animals revealed a critical role of hematopoietic, but not epithelial, p38γ/p38δ in regulation of inflammatory mediators and immune cell recruitment [59]. A protective effect of global p38δ KO on DMBA/TPA-induced skin tumorigenesis was observed in association with decreased cytokines and chemokines in skin tissues, which are further enhanced in p38γ/δ double KO mice [60]. A recent study further showed that conditional knockout of p38δ in mammary epithelial cells decreases the viral oncogene PyMT-induced breast tumorigenesis in mice [64]. These results together indicate that systemic and epithelial p38δ, as in the case with p38γ, is pro-inflammatory and oncogenic (Fig. 1) (Tables 1,2).

4. Implications of cell/tissue-type dependent and isoform-specific effects of p38 MAPKs in inflammation and in inflammation-associated oncogenesis

Mechanisms for cell/tissue-dependent and isoform-specific roles of p38 family proteins in inflammation and inflammation-associated oncogenesis are largely unknown. Although different p38 MAPK isoforms may regulate different sets of inflammation mediators and/or different groups of downstream molecules in response to different stimuli and/or in different cells/tissues, there is still a lack of experimental evidence to support this hypothesis. While it is difficult to systemically compare intrinsic activities of p38 family proteins in immune cells due to lack of genetic evidence, p38α and p38γ in epithelial cells appear to be antagonistic. This effect has been observed at the level of protein, cell, and disease. At protein level, for example, p38α and p38γ both phosphorylate the tumor suppressor Rb at different sites leading to an opposite effect on cell-cycle progression. Specifically, p38γ phosphorylates Rb at S807/S811 and stimulates G1/S transition [62], whereas p38α phosphorylates Rb at S429/T252 and slows cell-cycle progression [81]. Although Rb phosphorylation at these different sites is not known to be sufficient to trigger the opposite effect on cell-cycle progression, this mechanism may contribute to the tumor suppressor activity of p38α and oncogenic activity of p38γ. At cellular level, we showed an antagonizing effect of p38α and p38γ in stress response and in KRAS transformation in which p38α transfection directly depletes cellular p38γ protein by a ubiquitination-dependent mechanism [82] and that inhibition of p38α activity with SB203580 increases p38γ protein levels [20]. At disease level, increased p-p38α in pancreatic cancer tis-

sues couples with increased patient's survival, indicating its tumor-suppressive activity [83], whereas upregulated p38γ in the same cancer predicts decreased patient survival, suggesting its oncogenic effect [12]. Thus, p38γ and p38α can antagonize each other toward a protein substrate in stress or oncogene-induced cellular outcome and in clinical cancer development and progression. This cross-restrained activity of p38α and p38γ could complicate therapeutic gain when their isoform-specific pharmacological inhibitors are used in systemic intervention. Please see recent outstanding reviews about p38 MAPKs and inhibitors [2,84].

Cell/tissue-specific effects of p38 family proteins will also have important implications for using their pharmacological inhibitors to regulate inflammation and inflammation-driven oncogenesis systemically. Although p38α in immune cells is pro-inflammatory, application of its inhibitor SB203580 does not improve clinical symptoms of DSS-induced colitis in mice [41]. This might occur as an integration of its inhibition of pro-inflammatory p38α activity in immune system and of its blockade of anti-inflammatory effect of p38α in intestinal epithelial cells (Fig. 1) [41]. These experimental results are consistent with a poor outcome of clinical trials using an oral p38α inhibitor BIRB in the treatment of Crohn' disease [85]. On the other hand, p38γ activity in immune cells and in epithelial cells is both pro-inflammatory and oncogenic (Fig. 1) and its inhibitor PFD therefore showed a significant and consistent inhibitory effect on inflammation and inflammation-associated oncogenesis as observed in mouse models of colon, liver, and pancreatic cancer [12,16,62]. Considering of cell/tissue-dependent and isoform-specific effects of p38 family proteins is therefore critical for development of effective small molecular p38 inhibitors against inflammation and inflammation-driven cancer in therapeutic intervention.

Abbreviations

AOM, azoxymethane; ATF2, activating transcription factor-2; BMDM, bone marrow-derived macrophages; DMBA, 12-dimethylbenz(a)anthracene; DCs, dendritic cells; DNFB, 2,4-dinitrofluorobenzene; DSS, dextran sulfate sodium; EGFR, epidermal growth factor receptor; ER, estrogen receptor α; Hsp90, heat shock protein 90 alpha; IEC, intestinal epithelial cell; "$^{-/-}$", global deletion; KO, knockout; MAPKs, mitogen-activated protein kinases; MEFs, mouse embryonic fibroblasts; MEF2C, myocyte enhancer factor 2C; MKK3 or 6, MAPK kinase 3 and/or 6; MMP9, matrix metalloproteinase; LPS, lipopolysaccharide; KPC, *LSL-Kras*$^{G12D/+}$: *LSL-Trp53*$^{R172H/+}$: *Pdx1-Cre* mice; MAPK, mitogen-activated protein kinase; p38α MAPK, MAPK14; p38β, MAPK11; p38γ, MAPK12; p38δ, MAPK13; PRAK, p38 regulated/activated kinase; MK2, MAP kinase-activated protein kinase 2; MNK1, mitogen-activated protein kinase-interacting kinase 1; PFKFB3, phosphofructokinase-2/fructose-2,6-bisphosphatase 3; PTPH1, protein tyrosine phosphatase H1; PyMT, polyomavirus middle T antigen; TPA, 12-tetradecanoylphorbol-13-acetate; WT, wild-type.

Author contributions

JZQ, GC—concept development and manuscript writing; HX, XMQ—discussion of the manuscript and figure preparation.

Ethics approval and consent to participate

Not applicable.

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Conflict of interest

The authors declare no conflict of interest. GC is serving as one of the Editorial Board members of this journal. We declare that GC had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to GP.

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