Roles of p38\textsubscript{\(\alpha\)} mitogen-activated protein kinase in mouse models of inflammatory diseases and cancer

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Keywords
Cancer; inflammation; mouse models; p38 MAPK; signaling pathways; therapy; tumor initiation; tumor promotion

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(Received 29 December 2014, revised 16 February 2015, accepted 25 February 2015)
doi:10.1111/febs.13250

The p38\textsubscript{\(\alpha\)} mitogen-activated protein kinase pathway not only regulates the production of inflammatory mediators, but also controls processes related to tissue homeostasis, such as cell proliferation, differentiation and survival, which are often disrupted during malignant transformation. The versatility of this signaling pathway allows for the regulation of many specific functions depending on the cell type and context. Here, we discuss mouse models that have been used to identify \textit{in vivo} functions of p38\textsubscript{\(\alpha\)} signaling in the pathogenesis of inflammatory diseases and cancer. Experiments using genetically modified mice and pharmacological inhibitors support that targeting the p38\textsubscript{\(\alpha\)} pathway could be therapeutically useful for some inflammatory diseases and tumor types.

Abbreviations
vAOM, azoxymethane; AP-1, activator protein-1; APC\textsuperscript{\textsubscript{\textsuperscript{min}}}, mice with a point mutation at the Apc gene; ApoE, apolipoprotein E; ASK, apoptosis signal-regulating kinase; CA, constitutively-active form; CAIA, collagen antibody-induced arthritis; CIA, collagen-induced arthritis; CLP, cecal ligation and puncture; COPD, chronic obstructive pulmonary disease; COX-2, cyclooxygenase-2; CRC, colorectal cancer; Cre-ERT2, tamoxifen-inducible Cre; CSS, cigarette smoke solution; CV, Cre-versible allele; CXCL, Chemokine (C-X-C motif) ligand; DC, dendritic cell; DEN, N\textsubscript{\textsuperscript{\textsubscript{diethylnitrosamine}}}; DMBA, 7,12-dimethylbenz[a]anthracene; DN, dominant-negative form; DSS, dextran sodium sulfate; EAE, experimental autoimmune encephalomyelitis; EGFR, epidermal growth factor receptor; ERK, extracellular signal-regulated kinase; F/F, flox/flox conditional allele; HCC, hepatocellular carcinoma; HNF3\textsubscript{\(\beta\}}, hepatocyte nuclear factor 3\textsubscript{\(\beta\)}; HGF, hepatocyte growth factor; IBD, inflammatory bowel disease; ICAM, intercellular adhesion molecule; IEC, intestinal epithelial cell; IFN, interferon; IL, interleukin; JNK, c-Jun N-terminal kinase; K/BxN, mice expressing both the T cell receptor transgene KRN and the major histocompatibility complex class II molecule Alg7; KO, knockout; Ldf, low-density lipoprotein receptor; LPS, lipopolysaccharide; MAPK, mitogen-activated protein kinase; MAP3K, MAPK kinase kinase; MCP, monocyte chemoattractant protein; MIP-1a, macrophage inflammatory protein 1a; MMP, matrix metalloproteinase; MPO, myeloperoxidase; MS, multiple sclerosis; MSK, mitogen- and stress-activated protein kinase; NF-kB, nuclear factor kappa B; Pb, phenobarbital; PMA, phorbol 12-myristate 13-acetate; PTEN, phosphatase and tensin homolog; PyMT, polyoma middle T-antigen; RA, rheumatoid arthritis; ROS, reactive oxygen species; SCC, squamous cell carcinomas; STAT, signal transducer and activator of transcription; TNF, tumor necrosis factor; TPA, 12-O-tetradecanoylphorbol-13-acetate; TS, tobacco smoke; V CAM, vascular cell adhesion molecule; WT, wild-type.
**Introduction**

Mitogen-activated protein kinases (MAPKs) are evolutionarily conserved kinases that control many cellular processes. Eukaryotic cells contain several MAPK pathways that function in parallel and are activated by different extracellular stimuli. The p38 MAPK family includes four members: p38α, p38β, p38δ and p38γ, which are approximately 60% identical in their amino acid sequences, are encoded by different genes, and have different tissue expression patterns. Most cell types express substantial levels of p38α, whereas the other p38 MAPKs have more tissue-specific expression patterns. p38α was originally identified as a protein kinase implicated in stress and inflammatory responses [1–4]. Activation of p38α is usually triggered by the MAPK kinases MKK3 and MKK6, although sometimes by MKK4 or by autophosphorylation independently of MAPK kinases. More than 100 proteins can be directly phosphorylated by p38α, including other protein kinases and many transcription factors [5,6]. The number and variety of p38α substrates identified is consistent with the ability of this signaling pathway to regulate numerous cellular processes. Indeed, the use of pyridinyl imidazole inhibitors such as SB203580 and SB202190, which inhibit p38α and p38β, has allowed the identification of many functions potentially regulated by p38 MAPKs beyond the stress response [7,8].

**p38α MAPK in inflammatory diseases**

There is *in vivo* and *in vitro* evidence linking p38α signaling to the production of inflammatory mediators and pro-inflammatory cytokines in several cell types via transcriptional and post-transcriptional mechanisms [7,16].

Mice deficient for the p38α substrate MK2 provided the first *in vivo* evidence for the implication of this pathway in inflammation. The MK2 KO mice are more resistant to lipopolysaccharide (LPS)-induced endotoxic shock as a result of the reduced production of tumor necrosis factor-α (TNF-α) [17]. Additional studies show that the MK2-related kinase MK3 contributes to regulating LPS-induced TNF-α production *in vivo*, although to a lesser extent than MK2 [18]. The use of mice deficient for p38α either in myeloid cells or in epithelial cells has further supported the implication of this pathway in cytokine production and inflammatory responses *in vivo* [19–21]. The connection of p38α with the production of inflammatory mediators has prompted the use of mouse models to investigate the *in vivo* functions of this pathway in the pathogenesis of inflammatory diseases (Fig. 1 and Table 1). It should be noted that p38β appears to be required neither for the acute, nor chronic inflammatory responses [11,22], whereas myeloid cells deficient in p38γ and p38δ are impaired in the LPS-induced production of several cytokines, which correlates with reduced levels of the MAPK kinase kinase (MAP3K) TPL-2 and extracellular signal-regulated kinase (ERK)1/2 signaling [23]. Interestingly, p38γ activation does not appear to be affected by p38γ and p38δ downregulation [23], suggesting that they regulate the inflammatory response by distinct mechanisms.
Table 1. p38α MAPK signaling in mouse models of inflammatory diseases and cancer. Specificity of mouse lines: Alb, hepatocytes; CD4, T cells; CD11c, dendritic cells; K14, ectoderm and derivatives; Lck, T cells and thymocytes; LysM, myeloid cells; MMTV, breast epithelial cells; More, embryos; Mx-Cre, liver and lymphocytes; RERTn, ubiquitously expressed; Rosa26, ubiquitously expressed; SP-C, type II alveolar epithelial cells; Tie, endothelial cells; Villin, intestinal epithelial cells.

| Mouse lines | Models | Phenotypes | Molecules/processes involved | References |
|-------------|--------|------------|------------------------------|------------|
| p38α T106M (knock-in) MK2−/− | CAIA; p38 MAPK inhibitor CIA | No effect | Not applicable | [22] Arthritis |
| MKK3−/− | K/BxN passive arthritis | Reduced arthritis severity | Reduced P-p38, IL-1β, CXCL-1, IL-6, MMP3 | [29] |
| MKK6−/− | K/BxN passive arthritis | Reduced arthritis, cartilage destruction and bone erosion | Reduced P-p38, P-MK2, P-MSK1, IL-6, MMP3 | [30] |
| ASK1−/− WT | K/BxN passive arthritis; p38 MAPK inhibitor | Reduced arthritis severity | Reduced IL-1β, IL-6, CXCL-1, TNF-α, CCL2 | [31] |
| p38α (F/F) LysM-Cre | K/BxN passive arthritis Antigen-induced arthritis | Enhanced arthritis severity | Enhanced IL-6, IL-1β, P-Stat3 | [32] |
| WT ASK1−/− | EAE; p38 MAPK inhibitors EAE | Reduced EAE severity | Reduced IL-17 | [39,40] EAE |
| p38α−/− Lck-p38α DN (transgenic) MKK3−/− MKK6−/− Lck-MKK6 CA (transgenic) p38α(p38β) Y323F (knock-in) | EAE | Reduced EAE severity | Reduced IL-17 and IL-6 in T cells | [39] |
| p38α (F/F) Rosa26-Cre-ERT2 | EAE | Reduced EAE severity | Reduced MCP-1, RANTES, MIP-1α | [41] |
| p38α (F/F) CD4-Cre p38α (F/F) LysM-Cre p38α (F/F) CD11c-Cre | EAE | Reduced EAE susceptibility | Enhanced IL-17 | [40] |
| p38α (F/F) | EAE and CIA | Reduced EAE and CIA severity | Reduced IGF-1, TNF-α and T-bet expression but enhanced IL-10 | [44] |
| p38α (F/F) LysM-Cre | EAE | Reduced EAE severity | Not applicable | [42] |
| p38α (F/F) | No effect | Not applicable | Reduced IL-6 and Th17 differentiation | [43] |
| MK2−/− | Ldlr−/− | Reduced severity to Atherosclerosis | Reduced VCAM-1, ICAM-1, MCP-1 | [45] Atherosclerosis |
| ApoE−/− | Virus-induced acceleration in ApoE−/− model; p38 MAPK inhibitor ApoE−/− | Reduced viral load and pro-atherogenic molecules | Reduced E-selectin, VCAM-1, ICAM-1, MCP-1 | [46] |
| p38α (F/F) LysM-Cre | No effect on disease initiation enhanced apoptosis and Advanced plaque progression | Not applicable | Reduced AKT activity | [47] |
| p38α (F/F) | ApoE−/− | No effect | Not applicable | [48] |
| p38α (F/F) | No effect | Reduced lung inflammation | Reduced COX-2, IL-6 | [53] COPD and asthma |
| WT | TS-induced COPD; p38 MAPK inhibitor | Reduced disease severity | Increased IL-16, CXCL-1, MMP-12, TCA-3, Leptin | [54] |
Table 1. (Continued).

| Mouse lines | Models | Phenotypes | Molecules/processes involved | References |
|-------------|--------|------------|-----------------------------|------------|
| WT | LPS-induced lung inflammation; p38 MAPK inhibitor | Reduced lung inflammation | Reduced TNF-α, IL-1β and neutrophil accumulation | [55] |
| WT | Ova-induced asthma; p38α antisense oligonucleotide | Reduced disease symptoms | Reduced IL-4, IL-5, IL-13 and eosinophil recruitment | [56] |
| WT | Ova/ ozone-induced asthma; p38 MAPK inhibitor and dexamethasone | Reduced disease symptoms | Reduced TNF-α, IL-13, CXCL-1, GM-CSF and MKP-1 | [57] |
| p38α(F/F) LysM-Cre | SDS- and UVB-induced skin injury | Reduced inflammatory response | Enhanced P-JNK, P-ERK and CREB activity | [20] |
| p38α (F/F) K14-Cre | LPS-induced sepsis | Reduced resistance to sepsis | Reduced TNF-α, IL-6, IL-12, Reduced IL-10 | [33] |
| MSK1−/− MSK2−/− | CLP-induced sepsis | Increased resistance to sepsis | Reduced IL-10 but no differences in IL-6, IL-12, TNF-α | |
| −/− | PMA-induced eczema | Increased inflammation | Enhanced MPO activity and infiltration | |
| p38α (F/F) LysM-Cre | LPS- and CLP-induced sepsis | Increased resistance to sepsis | Reduced TNF-α, AP-1, C/EBP-β and CREB activity | [19] |
| −/− | LPS- induced sepsis | Increased resistance to sepsis | Reduced TNF-α, IFN-γ, IL-6, NO | [17] |
| −/− MK3−/− | LPS- induced sepsis | Not determined | Further reduced TNF-α and TTP compared to MK2−/− | [18] |
| p38α (F/F) Villin-Cre | DSS-induced colitis | Increased colitis | Enhanced apoptosis, increased Bak, IL-6, COX-2 and JNK activation | [21,91,92] |
| p38α (F/F) LysM-Cre | Reduced colitis | Reduced AP-1, NFκB activity, IL-6, COX-2 | | [21] |
| p38α (F/F) Alb-Cre | LPS/TNF-induced liver damage | No effect | Enhanced JNK activation | [86] |
| p38α (F/F) IKK2 (F/F) Alb-Cre | | | | |
| Wip1−/− | MMTV-ErbB2 and MMTV-Hras | Reduced breast tumorigenesis | Enhanced P-p38, reduced proliferation and increased apoptosis | [68] |
| MMTV-Wip1 (transgenic) | MMTV-ErbB2 | Enhanced breast tumorigenesis | Increased proliferation | [69] |
| MMTV-MKK6 (transgenic) | MMTV-MKK6 | Reduced tumorigenesis compared to MMTV-Wip1 | Reduced proliferation | |
| GADD45α−/− | MMTV-Ras | Enhanced breast tumorigenesis | Reduced P-p38 and Ras-induced senescence | [70] |
| WT | MMTV-PyMT; p38 MAPK inhibitor and cisplatin treatment | Reduced tumor growth and malignancy | Enhanced apoptosis and JNK activity | [71] |
| p38α (F/F) | Kras LSL-G12V | Enhanced lung tumorigenesis | Reduced C/EBPα, HNF3β, Increased AKT/EGFR signaling | [67] |
| RERTn-Cre-ERT2 | MK2 (CV/CV) p53 (F/F) | No effect on tumor initiation | Not applicable | [80] |

1844 FEBS Journal 282 (2015) 1841–1857 © 2015 The Authors. FEBS Journal published by John Wiley & Sons Ltd on behalf of FEBS.
| Mouse lines | Models | Phenotypes | Molecules/processes involved | References |
|-------------|--------|------------|-----------------------------|------------|
| Kras LSL-G12D + Adeno-Cre (intratracheal) | MK2/p53 double KO tumors grow faster (tumor progression) | Increased proliferation; increased apoptosis in response to cisplatin | |
| p38α (F/F) Alb-Cre DEN/Pb | Increased liver cancer | Enhanced proliferation and JNK-c-Jun signaling | [66] Liver cancer |
| p38α (F/F) Mx-Cre DEN | Increased liver cancer | Increased ROS, hepatocyte death, IL-α secretion and hepatocyte Compensatory proliferation | [84] |
| p38α (F/F) Alb-Cre Thioacetamide | No effect | Reduced IL-6, IL-1β, HGF | Enhanced SOX-2, c-Jun | [85] |
| p38α (F/F) Villin-Cre AOM/DSS | Increased colon cancer | Altered colon homeostasis and barrier function | [92, 94] Colon cancer |
| p38α (F/F) Villin-Cre-ERT2 p38α (F/F) Alb-Cre | Reduced colon cancer | Reduced proliferation, P-Stat3, IL-6, Mcl-1, increased apoptosis and P-JNK | [92] |
| ASK1<sup>−/−</sup> | AOM/DSS | Increased colitis, macrophage apoptosis and enhanced TNF-α, IL-6, COX2, IL-1β | [95] |
| APC<sup>−/−</sup> | AOM/ACPmin; p38 MAPK inhibitor | Reduced proliferation, enhanced p21, PTEN, nuclear FoxO3A | [96] |
| WT | AOM/DSS; p38 MAPK inhibitor and MEK1 inhibitor | Reduced colon cancer | Enhanced apoptosis, reduced proliferation | [97] |
| PRAK (MK5)<sup>−/−</sup> | DMBA | Increased skin cancer | Impaired Ras-induced senescence, enhanced Ki67, reduced Dcr2, p16 | [107] Skin cancer |
| PRAK (MK5)<sup>−/−</sup> | DMBA/TPA | Reduced skin cancer progression | Impaired angiogenesis, enhanced apoptosis | [108] |
| ASK1<sup>−/−</sup> | DMBA/TPA | Dual function; ASK1 alone- tumor promoting role. Reduced inflammation | Reduced P-p38, P-JNK, TNF-α, IL-6 | [110] |
| ASK2<sup>−/−</sup> | ASK2 in cooperation with ASK1- tumor suppressive role | Reduced P-p38, P-JNK, reduced apoptosis | | |
| GADD45α<sup>−/−</sup> | UV | Increased skin cancer | Reduced apoptosis, P-p38, P-JNK, p53 | [111] |
| p53<sup>−/−</sup> SKH-1 | UV; p38 MAPK inhibitor | Increased P-c-Jun, cyclin D1, NOX-2 | [112] |
| MK2<sup>−/−</sup> | DBMA/TPA | Reduced skin cancer | Increased apoptosis and p53, reduced IL-1β, IL-6, TNF-α | [113] |
| K14-p38α DN (transgenic) | UVB | Reduced skin cancer | Reduced AP-1 activity, reduced COX-2 | [115] |
| K14-p38α DN (transgenic) | Reduced skin cancer | Reduced edema, inflammation and proliferation | [116] |
| MSK1<sup>−/−</sup> MSK2<sup>−/−</sup> | DMBA/TPA | Reduced skin cancer | Enhanced IL-1β, TNF-α, increased MPO activity | [114] |
by reducing the serum levels of interleukin (IL)-6 and TNF-α [28], suggesting that MK2 plays a critical role downstream of p38α signaling in arthritis. Disruption of the p38 MAPK activators MKK3 and MKK6 or the MAP3K apoptosis signal-regulating kinase 1 (ASK1) also protects against experimental arthritis [29–31]. These studies suggest that inhibition of p38 MAPK signaling may have therapeutic potential in arthritis patients. However, a recent study shows that p38α downregulation in myeloid cells exacerbates the severity of arthritis symptoms [32]. This p38α effect could be mediated through the substrates mitogen- and stress-activated protein kinase (MSK)-1 and -2, which control transcriptional activation of the anti-inflammatory cytokine IL-10 [33]. Collectively, p38α signaling appears to have both pro- and anti-inflammatory roles, which could explain the modest effect of p38 MAPK inhibitors in RA patients [34,35]. Targeting of the activators MKK3 and MKK6 or the substrate MK2 has been proposed as alternative therapeutic strategy in RA aiming to avoid the anti-inflammatory effects of p38α [32,36]. In support of this idea, treatment of rats with the MK2 inhibitor PF-3644022 reduces both LPS-induced TNF-α production and chronic inflammation in the streptococcal cell wall-induced arthritis model [37].

**Multiple sclerosis (MS)**

MS is an inflammatory disease of the central nervous system that affects young adults. MS can be modeled in mice by immunization with myelin antigen combined with adjuvant, termed experimental autoimmune encephalomyelitis (EAE). EAE development requires elevated cytokine expression levels, which are also detected in MS patients. Interestingly, p38α is upregulated in MS lesions and the levels of phosphorylated p38 MAPK are enhanced in EAE rat models [38], suggesting the implication of p38 MAPK in EAE. In agreement with this idea, p38 MAPK inhibitors markedly suppress EAE in mouse models, correlating with decreased IL-17 levels [39,40]. Furthermore, downregulation of p38α or its activator ASK1 ameliorates the severity of EAE [39,41,42]. By contrast to the above results, mice deficient in the p38α substrate MK2 show a delayed onset of EAE but prolonged disease activity, which is probably the result of a lack of TNF-α and an altered immune response in the central nervous system [43]. These results suggest a predominant role for p38α substrates other than MK2 in the regulation of EAE development.

Recent studies show that p38α autophosphorylation is required for the production of IL-17 by T cells and impairment of this alternative activation pathway reduces EAE severity in mice [44]. Expression in T cells of a nonphosphorylatable p38α mutant, which is considered to work in a dominant-negative manner, or the deletion of the activators MKK3 and MKK6, greatly reduces phosphorylation of p38 MAPK, production of IL-17 and EAE symptoms in mice [40]. Conversely, forced activation of p38 MAPK in mouse T cells by expression of constitutively active MKK6 results in enhanced IL-17 production and an increased susceptibility to EAE [40]. However, specific deletion of p38α in T cells does not affect EAE development [42]. This might be explained by insufficient downregulation of p38α in T cells or by compensation via other p38 MAPK family members because p38β has a partial redundant role in T cell function [44]. Deletion of p38α in macrophages does not affect EAE development, whereas deletion of p38α in CD11c+ dendritic cells (DCs) reduces EAE symptoms, as well as the expression of IL-6 and differentiation of T cells producing IL-17 (TH17) [42]. These results suggest that p38α-dependent expression of IL-6 in DCs is required for TH17 differentiation and EAE development [42]. Altogether, p38α activation in DCs and T cells appears to be important for the pathogenesis of EAE, suggesting that targeting this pathway might have therapeutic value in MS.

**Atherosclerosis**

Atherosclerosis is a chronic inflammatory cardiovascular disease and a leading cause of both mortality and morbidity worldwide. The atherogenic process has been widely studied using mice deficient either for apolipoprotein E (ApoE), which develop spontaneous atherosclerosis, or for low-density lipoprotein receptor (Ldlr), which need a cholesterol diet to develop hypercholesterolemia and atherosclerosis.

Mice deficient for the p38α substrate MK2, which are impaired in pro-inflammatory cytokine production [17], are resistant to atherosclerosis by reducing vascular lipid deposition and macrophages in hypercholesterolemic Ldlr−/− mice. MK2 also regulates aortic expression of the vascular cell adhesion molecule (VCAM)-1 and the chemokine monocyte chemoattractant protein (MCP)-1, which are key for the recruitment of monocytes/macrophages to the vascular wall [45]. p38 MAPK has also been suggested to regulate the pro-atherogenic molecules VCAM-1 and MCP-1 in ApoE−/− mice [46]. These studies support the implication of p38 MAPK signaling in the development of atherosclerosis, although the cell type responsible remains unclear. Phosphorylated MK2 is detected in the endothelium and macrophage-rich pla-
que areas within aortas of hypercholesterolemic Ldlr\(^{-/-}\) mice, suggesting that atherosclerosis development might involve p38\(\alpha\) activation in these cells. Surprisingly, p38\(\alpha\) downregulation in macrophages does not affect the formation of atherosclerotic plaques or macrophage recruitment in ApoE\(^{-/-}\) mice but, instead, leads to macrophage apoptosis and other markers of advanced plaque progression, which were not checked in the MK2 KO mice, by suppressing AKT activation [47]. It was subsequently shown that the inhibition of p38\(\alpha\) or both MK2 and MK3 impairs the LPS-induced activation of AKT in bone-marrow derived macrophages, although KO of either MK2 or MK3 alone has little effect on AKT phosphorylation [48]. It is therefore possible that p38\(\alpha\) plays a pro-survival role in the macrophages of advanced atherosclerotic plaques, whereas a deficiency of MK2 alone does not affect the AKT survival pathway. Thus, the phenotype of MK2 KO mice might be a result of the role of MK2 in other cells, such as endothelial cells. By contrast to this possibility, a recent study reports that endothelial or macrophage specific-downregulation of p38\(\alpha\) affects neither the development, nor the characteristics of atherosclerotic plaques in ApoE\(^{-/-}\) mice [49]. The controversial findings could be explained by the different genetic backgrounds of the mice used in the studies, which can influence the extent of atherosclerosis in ApoE\(^{-/-}\) mice [50]. More studies are warranted to define the role of p38\(\alpha\) signaling in atherosclerosis, especially regarding the analysis of other cell types that could be involved, such as smooth muscle cells.

**Chronic obstructive pulmonary disease (COPD)**

The p38 MAPK pathway has been linked to lung inflammatory diseases such as COPD and asthma. Phosphorylated p38 MAPK has been detected in both alveolar macrophages and the alveolar walls of COPD patients [51]. Increased activation of p38 MAPK has been also reported in alveolar macrophages of patients with severe asthma [52]. Activation of p38 MAPK in alveolar macrophages may induce the secretion of pro-inflammatory cytokines and chemokines required for the pathogenesis of COPD. Inhibition of p38 MAPK using SD-282 reduces inflammation in a model of tobacco smoke-induced airway inflammation with decreased expression of cyclooxygenase-2 (COX-2) and IL-6 mRNAs [53]. Studies using pharmacological inhibitors have also implicated p38 MAPK in mouse models of COPD, asthma and acute lung inflammation [54–57], suggesting that p38 MAPK inhibition could have therapeutic effects in lung inflammatory diseases.

**p38\(\alpha\) MAPK in cancer**

Cell proliferation, differentiation and survival are tightly regulated under physiological conditions to maintain tissue homeostasis and dysregulation of these processes is a hallmark of cancer. Immune and inflammatory responses are also important for cancer initiation and progression. During tumorigenesis, cells of both the innate (macrophages, neutrophils, DCs) and adaptive (T and B lymphocytes) immune systems infiltrate the tumor microenvironment and regulate tumor cell fate either directly or via the production of extracellular factors. Immune cells rely on the p38 MAPK pathway to regulate multiple functions and to produce cytokines and chemokines [58–61], which may either promote or suppress tumor growth. For example, COX-2, IL-6 and IL-17 can be regulated by p38\(\alpha\) and have important effects on tumorigenesis [62–64]. However, the precise contribution of p38\(\alpha\)-mediated immune responses to tumor initiation and progression is still poorly characterized. This review will focus on the role of p38\(\alpha\) in tumor cells. There is evidence implicating p38\(\alpha\) in the regulation of cell proliferation, differentiation, survival, migration and invasion in various cancer cell lines [7,8,15,16,65]. Initial experiments using mouse models of cancer indicated that p38\(\alpha\) can suppress lung and liver tumor formation in vivo [66,67]. However, additional studies show that p38\(\alpha\) may play tumor suppressor or tumor promoter roles depending on the tissue and the tumorigenesis stage (Fig. 2 and Table 1).

**Breast cancer**

Mouse models have provided in vivo evidence for the implication of p38 MAPK signaling in breast cancer. Studies using mice deficient in Wip1, a phosphatase that can target p38\(\alpha\), show significantly reduced breast tumorigenesis upon expression of Erbb2 or H-Ras, which correlates with higher p38 MAPK activation [68]. The p38\(\alpha\) and p38\(\beta\) inhibitor SB203580 restores the Erbb2 driven tumorigenesis in Wip1 KO mice, suggesting that p38 MAPK hyperactivation contributes to the reduced breast tumorigenesis observed in the absence of Wip1. Conversely, mice overexpressing Wip1 in the breast epithelium are more susceptible to breast tumor development induced by ErbB2, a phenotype that was attenuated upon co-expression of constitutively active MKK6 to activate the p38 MAPK pathway [69]. Mice deficient in Gadd45\(\alpha\), an activator of the c-Jun N-terminal kinase (JNK) and p38 MAPK pathways, also show accelerated breast tumorigenesis induced by Ras, which correlates with reduced activa-
tion of p38 MAPK and reduced levels of Ras-induced senescence [70].

By contrast to the above tumor suppressive role in breast tumor initiation, recent reports suggest that p38 MAPK signaling may also play pro-tumorigenic roles. For example, the p38α and p38β inhibitor PH797804 impairs the growth of breast tumors induced by polyoma middle T (PyMT), which correlates with increased apoptosis and decreased proliferation of tumor cells [71]. Interestingly, p38 MAPK inhibition potentiates the chemotherapeutic drug cisplatin, reducing the size and malignancy of PyMT-induced breast tumors. At the molecular level, inhibition of p38 MAPK results in reactive oxygen species (ROS)-dependent upregulation of the JNK pathway, which in turn mediates cisplatin-induced apoptosis [71]. The inhibitor LY2228820 also reduces tumor growth in a xenograft model based on the MDA-MB-468 breast cancer cell line [72]. These results indicate that p38 MAPK signaling contributes to breast tumor progression in mouse models.

The pro-tumorigenic role of p38 MAPK is also supported by experiments showing that inhibition of this pathway impairs the proliferation of p53 mutant and estrogen receptor-negative breast cancer cell lines in vitro [73]. Of note, both MDA-MB-468 cells and PyMT breast tumors are estrogen receptor-negative. Moreover, high levels of active p38 MAPK have been correlated with invasive and poor prognostic breast cancers, lymph node metastasis and tamoxifen resistance in patients [74–77]. Activation of p38 MAPK signaling downstream of the ubiquitin-conjugating enzyme Ubc13 has been shown to contribute to metastasis and lung colonization by human and mouse breast cancer cells [78]. Taken together, it appears that p38 MAPK inhibitors, either alone or in combination with chemotherapeutic drugs, could help to reduce breast tumor growth and metastasis.

**Lung cancer**

Studies using p38α conditional KO mice have provided in vivo evidence for the involvement of p38 MAPK in lung homeostasis [66,67]. Embryo-specific deletion of p38α results in perinatal death as a result of distorted alveolar structures and massive infiltration of hematopoietic cells in the lungs [66]. Postnatal deletion of p38α results in increased proliferation and defective differentiation of the lung stem and progenitor cells, which can be accounted for by the upregulation of epidermal growth factor receptor (EGFR) and lower expression of the transcription factor C/EBPα [67]. Moreover, p38α signaling in lung stem cells induces the expression of CXCL-12 that activates the stromal fibroblasts, whereas the endogenous p38α in lung fibroblasts is required for the induction of cytokines, which in turn trigger the recruitment of endothelial cells [79]. These results support a key role for p38α in maintaining a functional lung microenvironment, suggesting that disruption of this signaling pathway may lead to lung diseases. In line with this idea, the altered lung homeostasis observed upon p38α downregulation facilitates lung tumorigenesis.
induced by oncogenic K-ras\textsuperscript{G12V} [67]. The p38\textsubscript{a}-deficient lung tumors exhibit poor differentiation and higher mitotic indices, which correlate with reduced levels of the differentiation markers C/EBP\textsubscript{a} and hepatocyte nuclear factor 3\textbeta (HNF3\textbeta), and with increased activation of AKT and EGFR signaling [67]. The phenotype observed in p38\textsubscript{a}-deficient lungs mimics the early stages of K-ras\textsuperscript{G12V} induced transformation, suggesting that the enhanced tumorgenesis might be related to changes in the lung cellular microenvironment rather than to the negative regulation of oncogenic signaling by p38\textsubscript{a} in tumor cells.

Deletion of the p38\textsubscript{a} substrate MK2 has no effect on the initiation of lung tumorigenesis in a similar mouse model, irrespective of the p53 status. However, MK2 restrains the progression of lung tumors in the absence of p53 but has no effect when p53 is expressed. MK2 disruption not only makes p53-deficient lung tumors grow faster, but also sensitizes to DNA damage-inducing drugs such as cisplatin [80].

Increased p38 MAPK phosphorylation has been reported in human lung tumors compared to normal tissue [81], suggesting that p38 MAPK might contribute to lung tumor progression. The regulation of lung inflammation by p38 MAPK signaling may also impinge on tumorigenesis, although it is unclear whether lung inflammatory diseases such as COPD and asthma are linked to increased risk of lung cancer [82]. Further work is required to elucidate whether p38 MAPK inhibition might help lung cancer patients.

Liver cancer

p38\textsubscript{a} negatively regulates hepatocyte proliferation in adult mice during liver regeneration after partial hepatectomy or \textit{N}-nitrosodiethylamine (DEN)-induced liver injury. Inactivation of c-Jun in p38\textsubscript{a} deficient livers results in normal hepatocyte proliferation, suggesting that activation of the JNK-c-Jun pathway is responsible for the enhanced proliferation of p38\textsubscript{a} deficient hepatocytes [66].

Uncontrolled hepatocyte proliferation is considered to be important for liver cancer development. Hepatocellular carcinoma (HCC) is one of the most common forms of primary liver cancer in humans, with 70–90\% of HCC cases occurring in patients with chronic liver diseases and cirrhosis, mainly as a result of hepatitis B virus infection and alcoholic liver disease [83]. To study HCC in mice, DEN is used as an initiator and phenobarbital (Pb) as a promoting agent. Hepatocyte-specific deletion of p38\textsubscript{a} facilitates DEN/Pb-induced HCC, in which upregulation of the JNK-c-Jun pathway plays an important role by enhancing proliferation of p38\textsubscript{a}-deficient tumor cells [66]. p38\textsubscript{a} has been proposed to suppress ROS accumulation by modulating Hsp27 expression and cell death in DEN-treated hepatocytes. Dying hepatocytes release IL-1\alpha, which stimulates DEN-induced hepatocyte proliferation, facilitating HCC development [84]. Similar results have been observed in a model of HCC related to liver cirrhosis, in which p38\textsubscript{a} deficiency in hepatocytes leads to ROS accumulation and enhanced thioacetamide-induced liver damage and fibrosis [85]. Another study using a model of LPS/TNF-induced liver damage has shown that hyperactivation of the JNK pathway in p38\textsubscript{a}-deficient hepatocytes is not sufficient to mediate TNF-induced liver toxicity [86]. However, the combined downregulation of p38\textsubscript{a} and IKK2 in hepatocytes results in liver failure upon LPS injection, suggesting that p38\textsubscript{a} collaborates with the nuclear factor kappa B (NF-kB) pathway to protect the liver from cytokine-induced damage by antagonizing JNK activation [86]. These studies indicate that p38\textsubscript{a} can suppress HCC by regulating different molecular mechanisms depending on the stimuli.

In agreement with the observation that p38\textsubscript{a} suppresses HCC development in mouse models, reduced p38 MAPK and MKK6 activities have been reported in human HCC compared to nontumoral tissue [87]. Moreover, phosphorylation of the p38\textsubscript{a} pathway target Hsp27 has been inversely correlated with tumor size, invasion and tumor stages of human HCCs [88]. By contrast, another study positively correlated p38 MAPK phosphorylation with HCC tumor size and poor survival, although nontumoral areas were not analyzed [89]. A larger cohort of human HCC samples should be analyzed to obtain conclusive data on the role of p38 MAPK signaling in human HCC progression.

Colon cancer

The colon is part of the lower gastrointestinal tract. The intestinal epithelia serve as a barrier and play an important role in protecting the intestinal tract against luminal invading pathogens and ingested toxin, which can promote inflammatory responses. Colon inflammatory diseases such as inflammatory bowel disease (IBD) are associated with higher risk of colorectal cancer (CRC) development [90].

In \textit{vivo} roles of p38\textsubscript{a} in colon homeostasis and tumor development have been studied using mice with p38\textsubscript{a} downregulation in intestinal epithelial cells (IECs) [21,91,92]. These mice appear healthy but show changes in intestinal homeostasis, including increased IEC proliferation, which is associated with increased...
ERK1/2 and EGFR signaling [91], as well as reduced numbers of mucus producing goblet cells [21,91,92]. Moreover, p38α regulates the assembly of intestinal epithelial tight junctions, probably by controlling the expression of ZO-1 and other tight junction molecules [92].

Mice with IEC-specific p38α downregulation are more susceptible to dextran sodium sulfate (DSS)-induced colitis [21,91,92]. DSS is toxic and induces epithelial cell apoptosis, which initiates intestinal inflammation and colitis in mice, and there is evidence that p38α plays a critical role protecting from epithelial apoptosis, thus preventing DSS-induced colitis [21,91,92]. Increased apoptosis correlates with increased JNK activation and accumulation of the pro-apoptotic protein Bak in p38α-deficient IEC [91,92]. Importantly, the enhanced colitis observed in these mice can be rescued by the administration of probiotics, which restore the altered epithelial permeability, supporting that regulation of the epithelial barrier function by p38α is critical for protection against DSS-induced colitis [92]. By contrast to the role of p38α in IEC, downregulation of p38α in myeloid cells reduces inflammatory responses and colon epithelial damage during DSS-induced colitis [21]. This correlates with reduced activity of NF-κB and reduced expression of the inflammatory mediators COX-2 and IL-6 in the DSS-treated mice [21]. Thus, p38α signaling in different cell types appears to affect colitis progression differently. Of note, p38α in IEC not only regulates colon epithelial homeostasis, but also controls the expression of chemokines, which are essential for the recruitment of immune cells such as CD4+ T cells and subsequent clearance of *Citrobacter rodentium* infection [93]. These studies indicate that p38α signaling in IEC is critical for the protection against DSS-induced colitis and mucosal infections.

Chronic infection and inflammation can lead to colon tumor development. The initial stages of inflammation-associated colon tumorigenesis are suppressed by p38α [92,94]. This is probably a result of the ability of p38α to regulate colon homeostasis and the epithelial barrier function [92]. Similarly, mice deficient in the p38α activator ASK1 show enhanced DSS-induced epithelial injury and inflammation and are more susceptible to inflammation-associated colon tumorigenesis [95].

By contrast to the negative role of p38α in colon tumor initiation, p38 MAPK signaling can also perform pro-tumorigenic functions in established colon tumors. Mice xenografted with colon cancer cell lines or expressing APCmin that are treated with the inhibitor SB202190 show reduced tumor growth, which correlates with a switch from HIF1α to FoxO-dependent transcription that affects glycolytic metabolism [96]. Importantly, downregulation of p38α in colon tumor cells or pharmacological inhibition using PH797804 reduces tumor burden in mice, which correlates with activation of the JNK pathway, reduced expression of the anti-apoptotic protein Mcl-1 and downregulation of IL-6/STAT3 signaling [92]. Colon tumor growth is also reduced in azoxymethane-treated APCmin mice by the combined inhibition of p38 MAPK using SB202190 and ERK1/2 signaling using PD0325901 [97]. These studies suggest a dual role for epithelial p38α signaling, suppressing inflammation-associated colon tumor initiation but supporting colon tumor progression.

There is also evidence implicating p38α in colon cancer metastasis. In particular, reduced levels of p38 MAPK activity in colon cancer cells facilitate lung colonization from established liver metastasis by enhancing production of the cytokine PTHLH, which in turn induces endothelial cell death, enabling tumor cell extravasation to the lung [98]. Taken together, p38α signaling appears to control colon tumor cell survival, proliferation and metastasis through distinct mechanisms.

As noted above, IBD patients have higher risk of developing CRC [90]. The activating phosphorylation of p38 MAPK in IBD patients has been evaluated in several studies that yield contradictory results [99–101]. Accordingly, the use of p38 MAPK inhibitors in clinical trials has not shown promising results. In patients with Crohn’s disease, the p38 MAPK and JNK inhibitor CNI-1493 showed some clinical improvement [102], whereas the p38 MAPK inhibitor BIRB796 showed no improvement [103]. Mouse studies indicate that, during DSS-induced colitis, p38α contributes to different functions in various cell types, which could explain the controversial effects reported using p38 MAPK inhibitors for therapy. In human CRC, enhanced levels of phosphorylated p38 MAPK have been reported both in tumor cells and in stromal cells [97,104–106], suggesting a pro-tumorigenic role of p38 MAPK. Moreover, high levels of phosphorylated p38 MAPK have been correlated with resistance to the chemotherapeutic drug irinotecan, as well as with poor overall survival in colon cancer patients [104,106]. Collectively, p38 MAPK inhibition in colon cancer patients appears as an attractive therapeutic possibility, although caution is warranted because p38 MAPK inhibition can result in adverse effects.

**Skin cancer**

Mice deficient for the p38 MAPK substrate PRAK (also known as MK5) show enhanced 7,12-dimethylbenz[a]anthracene (DMBA)-induced skin carcinogene-
sis, which correlates with compromised senescence induction. In primary cells, inactivation of PRAK prevents senescence and promotes oncogenic transformation. The direct phosphorylation of p53 by PRAK has been proposed to mediate these effects [107]. Interestingly, PRAK can also promote the growth of skin tumors induced by DMBA and 12-O-tetradecanoylphorbol-13-acetate (TPA) via regulation of tumor angiogenesis. However, this effect is mediated by PRAK signaling in endothelial cells rather than in keratinocytes. Thus, in endothelial cells, tumor-secreted pro-angiogenic factors activate vascular endothelial growth factor receptor 2, which in turn activates PRAK inducing migration of the endothelial cells and their incorporation into tumor vasculature. This PRAK function may be mediated by the phosphorylation of the focal adhesion kinase FAK and cytoskeletal reorganization [108]. Of note, PRAK has been reported to also be a substrate of the MAPKs ERK3 and ERK4 [109], and further studies are required to validate the contribution of p38α to PRAK activation in skin carcinogenesis. The p38α activator ASK1 has been also proposed to have a dual role in DMBA/TPA-induced skin carcinogenesis, facilitating tumor promotion via regulation of the inflammatory response at the same time as playing a tumor suppressive role by cooperating with ASK2 in keratinocytes [110].

Mice deficient in Gadd45α show increased UV-induced skin carcinogenesis, which correlates with reduced levels of phosphorylated JNK and p38 MAPK, as well as reduced p53 levels and apoptosis [111]. Additionally, inhibition of p38 MAPK signaling has been associated with impaired capacity to repair UV-induced DNA damage, a primary risk factor for human skin cancers. The levels of p38α are decreased in human cutaneous squamous cell carcinomas (SCC) and UV irradiation of p3-deficient A431 keratinocytes (derived from SCC) decreases p38α expression. Consistently, treatment of p53−/− SKH-1 mice with the p38 MAPK inhibitor SB203580 accelerates UV-induced SCC carcinogenesis and increases the expression of the NAPDH oxidase Nox2. These findings support a tumor-suppressive role for p38α in SCC pathogenesis, which is associated with the regulation of Nox2 [112].

By contrast to the above observations, another study has implicated the p38α substrate MK2 in skin tumor development. MK2 deficient mice show reduced skin carcinogenesis after treatment with DMBA/TPA, which has been explained by the implication of MK2 in the production of pro-inflammatory cytokines and in the regulation of p53-dependent apoptosis [113]. Similarly, combined deficiency of the p38α substrates MSK1 and MSK2 results in reduced skin carcinogenesis [114]. However, the expression of IL-1β and TNF-α is upregulated in MSK1/2 double KO mice, probably as a result of weakened negative feedback loops that limit the inflammatory response [33]. Therefore, a defective inflammatory response is unlikely to account for the reduced skin tumorigenesis observed in MSK1/2 double KO mice, which might be a result of impaired p38 MAPK-triggered keratinocyte proliferation. Indeed, p38 MAPK signaling in keratinocytes has been reported to contribute to skin carcinogenesis by inducing activation of the transcription factor activator protein-1 (AP-1) and expression of COX-2, which stimulate the proliferation of UVB-irradiated epidermal keratinocytes [115]. Mice expressing a p38α mutant protein, which may work in a dominant-negative manner, also show reduced skin tumorigenesis in response to solar UV irradiation, suggesting that p38 MAPK activation by solar UV contributes to skin carcinogenesis [116].

**Conclusions**

There is good evidence implicating p38α signaling in inflammatory diseases, as well as during tumor initiation and progression (Table 1). The *in vivo* experiments using genetically modified mice and the use of pharmacological inhibitors suggest that targeting p38α signaling could be useful for the treatment of some inflammatory diseases. Several p38 MAPK inhibitors have been tested in clinical trials but have failed mainly as a result of side effects, such as skin rashes and liver toxicity. However, it is not clear whether these side effects are a result of the systemic inhibition of p38 MAPK signaling or the off-target effects of the inhibitors. Nevertheless, promising results have been obtained in some cases [117], although systemic inhibition of the p38 MAPK pathway may not be beneficial in all the cases. Based on the studies using mouse models, p38α appears to have distinct roles in different cell types even within the same tissue. For example, inhibition of p38α in myeloid cells ameliorates the effects of colitis, whereas inhibition of p38α in IEC can have deleterious effects in the same model. This dual effect could explain the failure of p38 MAPK inhibitors in IBD patients.

Given the contribution of inflammation to tumorigenesis, inhibition of p38α signaling would be expected to benefit inflammation-associated cancers. However, mouse studies indicate that the role of p38α signaling in cancer initiation and progression is cell type- and tumor type-dependent. Because p38α may suppress some type of tumors at the same time as working as a...
tumor promoter in other cancers, the inhibitors should be used with caution. Thus, new strategies to target p38α signaling in cell type or tissue specific manners should be devised. Moreover, considering the cross-talk among signaling pathways, it might be beneficial to use combination therapies for simultaneously targeting p38α and other signaling molecules. It should be noted that genetic analysis in mice have also implicated p38γ and p38δ in the in vivo regulation of colitis-associated colon tumorigenesis [118] and skin cancer [119]. It remains to be established whether different p38 MAPK family members might interplay during tumor development.

Recent studies have improved our understanding of the in vivo roles of p38α signaling in inflammation and cancer. Tumor-suppressing and tumor-promoting functions of the p38α pathway can be temporally and spatially separated during tumor development, depending on the tissue type and the tumor stage. More mechanistic studies are required to define the functions of p38α, as well as its key regulators and targets in mouse models of cancer. Future studies should also focus on the development of new models to regulate the p38 MAPK pathway in a time- and cell type-dependent manner. These new models should provide valuable information on the role of p38α signaling at various stages of the disease and in different cell types, which in turn should be useful for developing improved therapeutic strategies.

Acknowledgements

We are supported by the Fundación BBVA and by grants from the European Commission (ERC 294665), the Spanish MINECO (BFU2010-17850 and CSD2010-0045), Marató TV3 (20133430/31) and AGAUR (2014 SRG-535).

Author contributions

JG and ARN wrote the paper.

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