the FEBS Journal

STATE-OF-THE-ART REVIEW

Roles of p38α mitogen-activated protein kinase in mouse models of inflammatory diseases and cancer

Jalaj Gupta[1,*] and Angel R. Nebreda[1,2]

1 Institute for Research in Biomedicine (IRB Barcelona), Barcelona, Spain
2 Institució Catalana de Recerca i Estudis Avançats (ICREA), Barcelona, Spain

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

Correspondence
A. R. Nebreda, IRB Barcelona, Baldiri Reixac 10, 08028 Barcelona, Spain
Fax: +34 9340 20595
Tel: +34 9340 31379
E-mail: angel.nebreda@irbbarcelona.org

*__Present address:__
Georg-Speyer-Haus, Institute for Tumor Biology and Experimental Therapy, 60596 Frankfurt am Main, Germany

(Received 29 December 2014, revised 16 February 2015, accepted 25 February 2015)

doi:10.1111/febs.13250

The p38α 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 *in vivo* functions of p38α signaling in the pathogenesis of inflammatory diseases and cancer. Experiments using genetically modified mice and pharmacological inhibitors support that targeting the p38α pathway could be therapeutically useful for some inflammatory diseases and tumor types.

Abbreviations
vAOM, azoxymethane; AP-1, activator protein-1; APC^{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*-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; HNF3β, hepatocyte nuclear factor 3β; 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 A(g7); KO, knockout; Ldlr, 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; VCAM, 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]. *In vivo* physiological roles for p38 MAPK signaling have been determined by the generation of genetically modified mice. Of note, p38α knockout (KO) mice are embryonic lethal as a result of a defect in placenta morphogenesis [9,10], whereas the KOs for other p38 MAPKs are viable [11,12]. The double KO for MKK3 and MKK6 is also embryonic lethal and shows a similar phenotype to the p38α KO [13]. Moreover, there is evidence that p38α and p38β play overlapping *in vivo* functions during mouse development [14]. Genetically modified mice have provided evidence showing that p38α signaling plays an important role controlling inflammation, as well as the proliferation, differentiation and survival of different cell types [15,16]. Here, we discuss the roles of p38α in mouse models of inflammatory diseases and cancer.

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, p38α activation does not appear to be affected by p38γ and p38δ downregulation [23], suggesting that they regulate the inflammatory response by distinct mechanisms.

Rheumatoid arthritis (RA)

RA is an autoimmune and chronic inflammatory disorder that affects the joints of hands and feet. Both p38 MAPK and the activators MKK3 and MKK6 are phosphorylated in their activation residues in synovial tissue from RA patients [24,25], suggesting the implication of p38 MAPK signaling in RA. In a collagen-induced model of experimental arthritis (CIA), the p38 MAPK inhibitor SD-282 attenuates disease progression and reverses cartilage and bone destruction [26,27]. There is evidence that only p38α but not p38β is involved in collagen-antibody or TNF-α-driven arthritis [22]. Deficiency of MK2 protects against CIA

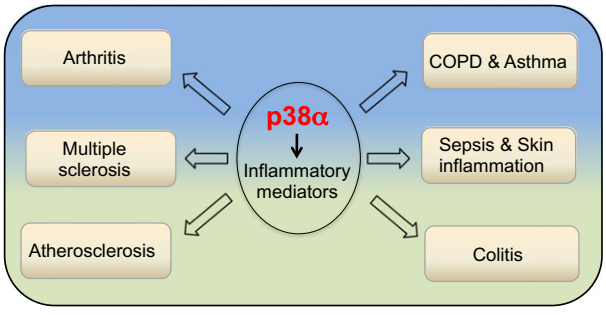

Fig. 1. Implication of p38α MAPK in mouse models of inflammatory diseases. For details, see Table 1.

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)	CAIA; p38 MAPK inhibitor	No effect	Not applicable	[22]	Arthritis
MK2$^{-/-}$	CIA	Reduced arthritis severity and incidence	Reduced TNF-α, IL-6	[28]	
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$^{-/-}$	K/BxN passive arthritis	Reduced arthritis, cartilage destruction and bone erosion	Reduced IL-1β, IL-6, CXCL-1, TNF-α, CCL2	[31]	
WT	K/BxN passive arthritis; p38 MAPK inhibitor				
p38α (F/F) LysM-Cre	K/BxN passive arthritis Antigen-induced arthritis	Enhanced arthritis severity	Enhanced IL-6, IL-1β, P-Stat3	[32]	
WT	EAE; p38 MAPK inhibitors	Reduced EAE severity	Reduced IL-17	[39,40]	EAE
ASK1$^{-/-}$	EAE	Reduced EAE severity	Reduced MCP-1, RANTES, MIP-1α	[41]	
p38α$^{+/-}$	EAE	Reduced EAE severity	Reduced IL-17	[39]	
Lck-p38α DN (transgenic)	EAE	Reduced EAE severity	Reduced IL-17 and P-p38 in T cells	[40]	
MKK3$^{-/-}$ MKK6$^{+/-}$					
Lck-MKK6 CA (transgenic)		Enhanced EAE susceptibility	Enhanced IL-17		
p38α/p38β Y323F (knock-in)	EAE and CIA	Reduced EAE and CIA severity	Reduced IFN-γ, TNF-α and T-bet expression but enhanced IL-10	[44]	
p38α (F/F) Rosa26-Cre-ERT2	EAE	Reduced EAE severity	Not determined	[42]	
p38α (F/F) CD4-Cre		No effect	Not applicable		
p38α (F/F) LysM-Cre		No effect	Not applicable		
p38α (F/F) CD11c-Cre		Reduced EAE	Reduced IL-6 and Th17 differentiation		
MK2$^{-/-}$	EAE	Delayed EAE onset and prolonged activity	Reduced TNF-α, FasR, enhanced leukocyte infiltration and reduced apoptosis	[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	Reduced viral load and pro-atherogenic molecules	Reduced E-selectin, VCAM-1, ;ICAM-1, MCP-1	[46]	
p38α (F/F) LysM-Cre	ApoE$^{-/-}$	No effect on disease initiation	Not applicable	[47]	
		enhanced apoptosis and Advanced plaque progression	Reduced AKT activity		
p38α (F/F) LysM-Cre p38α (F/F) Tie-Cre-ERT2	ApoE$^{-/-}$	No effect	Not applicable	[49]	
WT	TS-induced COPD; p38 MAPK inhibitor	Reduced lung inflammation	Reduced COX-2, IL-6	[53]	COPD and asthma
SP-C-MKK6 CA (transgenic)	CSS/LPS- induced COPD	Enhanced 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 p38α (F/F) K14-Cre	SDS- and UVB-induced skin injury	Reduced inflammatory response	Enhanced P-JNK, P-ERK and Reduced CXCL-1, CXCL-2, IL-10	[20]	Sepsis and skin inflammation
$MSK1^{-/-}$ $MSK2^{-/-}$	LPS-induced sepsis	Reduced resistance to sepsis	Enhanced TNF-α, IL-6, IL-12, Reduced IL-10	[33]	
	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]	
$MK2^{-/-}$	LPS- induced sepsis	Increased resistance to sepsis	Reduced TNF-α, IFN-γ, IL-6, NO	[17]	
$MK2^{-/-}$ $MK3^{-/-}$	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]	Colitis
p38α (F/F) LysM-Cre		Reduced colitis	Reduced AP-1, NFkB activity, IL-6, COX-2	[21]	
p38α (F/F) Alb-Cre	LPS/TNF-induced liver damage	No effect	Enhanced JNK activation	[86]	Liver damage
p38α (F/F) IKK2 (F/F) Alb-Cre		Enhanced liver toxicity	Enhanced hepatocyte apoptosis, Reduced c-FLIP(L) levels		
$Wip1^{-/-}$	MMTV-ErbB2 and MMTV-Hras	Reduced breast tumorigenesis	Enhanced P-p38, reduced proliferation and increased apoptosis	[68]	Breast cancer
MMTV-Wip1 (transgenic)	MMTV-ErbB2	Enhanced breast tumorigenesis	Increased proliferation	[69]	
MMTV-MKK6 (transgenic)		No effect	Increased Wip1		
MMTV-Wip1 MMTV-MKK6 (transgenic)		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) RERTn-Cre-ERT2	Kras LSL-G12V	Enhanced lung tumorigenesis	Reduced C/EBPα, HNF3β, Increased AKT/EGFR signaling	[67]	Lung cancer
MK2 (CV/CV) p53 (F/F)		No effect on tumor initiation	Not applicable	[80]	

Table 1. (Continued).

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 p38α (F/F) Mx-Cre	DEN/Pb	Increased liver cancer	Enhanced proliferation and JNK-c-Jun signaling	[66]	Liver cancer
p38α (F/F) Alb-Cre	DEN	Increased liver cancer	Increased ROS, hepatocype death, IL-α secretion and hepatocyte Compensatory proliferation	[84]	
p38α (F/F) Mx-Cre		No effect	Reduced IL-6, IL-1β, HGF		
p38α (F/F) Alb-Cre	Thioacetamide	Increased liver cancer	Enhanced SOX-2, c-Jun	[85]	
p38α (F/F) Villin-Cre p38α (F/F) Villin-Cre-ERT2	AOM/DSS	Increased colon cancer	Altered colon homeostasis and barrier function	[92,94]	Colon cancer
p38α (F/F) Villin-Cre-ERT2	p38α deletion in AOM/DSS-induced colon tumors	Reduced colon cancer	Reduced proliferation, P-Stat3, IL-6, Mcl-1, increased apoptosis and P-JNK	[92]	
ASK1$^{-/-}$	AOM/DSS	Increased colon cancer	Increased coltitis, macrophage apoptosis and enhanced TNF-α, IL-6, COX2, IL-1β	[95]	
APC^{min}	AOM/APCmin; p38 MAPK inhibitor	Reduced colon cancer	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) $^{-/-}$	DMBA	Increased skin cancer	Impaired Ras-induced senescence, enhanced Ki67, reduced DcR2, p16	[107]	Skin cancer
PRAK (MK5) $^{-/-}$	DMBA/TPA	Reduced skin cancer progression	Impaired angiogenesis, enhanced apoptosis	[108]	
ASK1$^{-/-}$	DMBA/TPA	Dual function; ASK1 alone- tumor promoting role. Reduced inflammation	Reduced P-p38, P-JNK, TNF-α, IL-6	[110]	
ASK2$^{-/-}$		ASK2 in cooperation with ASK1- tumor suppressive role	Reduced P-p38, P-JNK, reduced apoptosis		
GADD45α$^{-/-}$	UV	Increased skin cancer	Reduced apoptosis, P-p38, P-JNK, p53	[111]	
p53$^{-/-}$ SKH-1	UV; p38 MAPK inhibitor	Increased skin cancer	Increased P-c-Jun, cyclin D1, NOX-2	[112]	
MK2$^{-/-}$	DMBA/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)	Solar UV	Reduced skin cancer	Reduced edema, inflammation and proliferation	[116]	
MSK1$^{-/-}$ MSK2$^{-/-}$	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 (or allergic) 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 p38α activation in these cells. Surprisingly, p38α 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 p38α 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 p38α 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 p38α 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 p38α 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.

p38α 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 p38α 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 p38α and have important effects on tumorigenesis [62–64]. However, the precise contribution of p38α-mediated immune responses to tumor initiation and progression is still poorly characterized. This review will focus on the role of p38α in tumor cells. There is evidence implicating p38α 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 p38α can suppress lung and liver tumor formation *in vivo* [66,67]. However, additional studies show that p38α 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 p38α, show significantly reduced breast tumorigenesis upon expression of Erbb2 or H-Ras, which correlates with higher p38 MAPK activation [68]. The p38α and p38β 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 Gadd45α, 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-

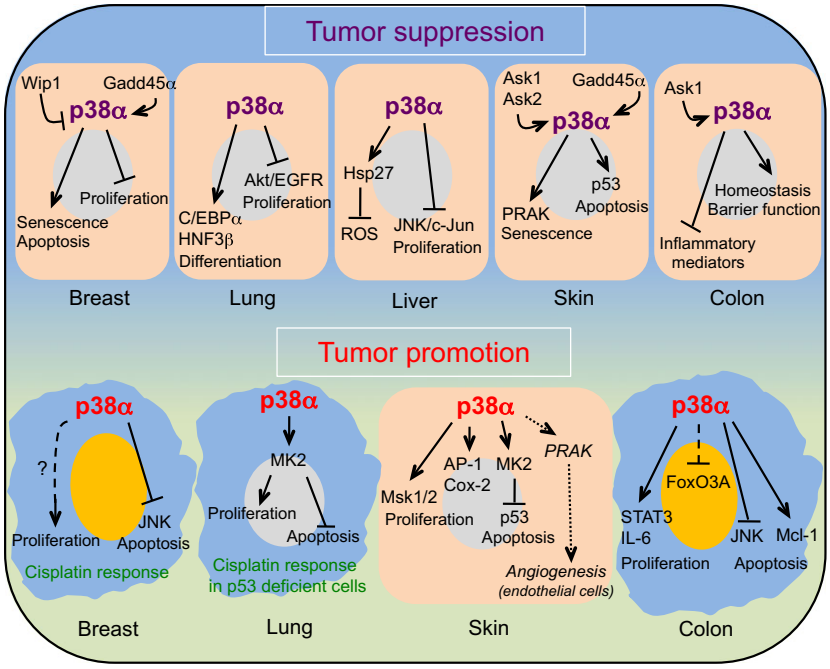

Fig. 2. Regulation of tumorigenesis by p38α MAPK in mouse models of cancer. Key molecules and processes are indicated. For further details, see Table 1. Normal cells are indicated in beige and tumor cells are indicated in blue. Breast and lung tumor cells treated with cisplatin rely on p38α for survival. The link between PRAK and angiogenesis has been reported in endothelial cells.

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^{G12V} [67]. The p38α-deficient lung tumors exhibit poor differentiation and higher mitotic indices, which correlate with reduced levels of the differentiation markers C/EBPα and hepatocyte nuclear factor 3β (HNF3β), and with increased activation of AKT and EGFR signaling [67]. The phenotype observed in p38α-deficient lungs mimics the early stages of K-ras^{G12V} induced transformation, suggesting that the enhanced tumorigenesis might be related to changes in the lung cellular microenvironment rather than to the negative regulation of oncogenic signaling by p38α in tumor cells.

Deletion of the p38α 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

p38α negatively regulates hepatocyte proliferation in adult mice during liver regeneration after partial hepatectomy or *N*-nitrosodiethylamine (DEN)-induced liver injury. Inactivation of c-Jun in p38α deficient livers results in normal hepatocyte proliferation, suggesting that activation of the JNK-c-Jun pathway is responsible for the enhanced proliferation of p38α 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 p38α facilitates DEN/Pb-induced HCC, in which upregulation of the JNK-c-Jun pathway plays an important role by enhancing proliferation of p38α-deficient tumor cells [66]. p38α has been proposed to suppress ROS accumulation by modulating Hsp27 expression and cell death in DEN-treated hepatocytes. Dying hepatocytes release IL-1α, 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 p38α 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 p38α-deficient hepatocytes is not sufficient to mediate TNF-induced liver toxicity [86]. However, the combined downregulation of p38α and IKK2 in hepatocytes results in liver failure upon LPS injection, suggesting that p38α 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 p38α can suppress HCC by regulating different molecular mechanisms depending on the stimuli.

In agreement with the observation that p38α 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 p38α 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 vivo roles of p38α in colon homeostasis and tumor development have been studied using mice with p38α 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-kB 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 APC^{min} 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 APC^{min} 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 p53-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.

References

1 Freshney NW, Rawlinson L, Guesdon F, Jones E, Cowley S, Hsuan J & Saklatvala J (1994) Interleukin-1 activates a novel protein kinase cascade that results in the phosphorylation of Hsp27. *Cell* **78**, 1039–1049.

2 Lee JC, Laydon JT, McDonnell PC, Gallagher TF, Kumar S, Green D, McNulty D, Blumenthal MJ, Heys JR, Landvatter SW *et al.* (1994) A protein kinase involved in the regulation of inflammatory cytokine biosynthesis. *Nature* **372**, 739–746.

3 Rouse J, Cohen P, Trigon S, Morange M, Alonso-Llamazares A, Zamanillo D, Hunt T & Nebreda AR (1994) A novel kinase cascade triggered by stress and heat shock that stimulates MAPKAP kinase-2 and phosphorylation of the small heat shock proteins. *Cell* **78**, 1027–1037.

4 Han J, Lee JD, Bibbs L & Ulevitch RJ (1994) A MAP kinase targeted by endotoxin and hyperosmolarity in mammalian cells. *Science* **265**, 808–811.

5 Trempolec N, Dave-Coll N & Nebreda AR (2013) SnapShot: p38 MAPK substrates. *Cell* **152**, 924–924.e1.

6 Trempolec N, Dave-Coll N & Nebreda AR (2013) SnapShot: p38 MAPK signaling. *Cell* **152**, 656–656.e1.

7 Cuenda A & Rousseau S (2007) p38 MAP-kinases pathway regulation, function and role in human diseases. *Biochim Biophys Acta* **1773**, 1358–1375.

8 Cuadrado A & Nebreda AR (2010) Mechanisms and functions of p38 MAPK signalling. *Biochem J* **429**, 403–417.

9 Adams RH, Porras A, Alonso G, Jones M, Vintersten K, Panelli S, Valladares A, Perez L, Klein R & Nebreda AR (2000) Essential role of p38alpha MAP kinase in placental but not embryonic cardiovascular development. *Mol Cell* **6**, 109–116.

10 Mudgett JS, Ding J, Guh-Siesel L, Chartrain NA, Yang L, Gopal S & Shen MM (2000) Essential role for p38alpha mitogen-activated protein kinase in placental angiogenesis. *Proc Natl Acad Sci USA* **97**, 10454–10459.

11 Beardmore VA, Hinton HJ, Eftychi C, Apostolaki M, Armaka M, Darragh J, McIlrath J, Carr JM, Armit LJ, Clacher C *et al.* (2005) Generation and characterization of p38beta (MAPK11) gene-targeted mice. *Mol Cell Biol* **25**, 10454–10464.

12 Sabio G, Arthur JS, Kuma Y, Peggie M, Carr J, Murray-Tait V, Centeno F, Goedert M, Morrice NA & Cuenda A (2005) p38gamma regulates the localisation of SAP97 in the cytoskeleton by modulating its interaction with GKAP. *EMBO J* **24**, 1134–1145.

13 Brancho D, Tanaka N, Jaeschke A, Ventura JJ, Kelkar N, Tanaka Y, Kyuuma M, Takeshita T, Flavell RA & Davis RJ (2003) Mechanism of p38 MAP kinase activation in vivo. *Genes Dev* **17**, 1969–1978.

14 del Barco Barrantes I, Coya JM, Maina F, Arthur JS & Nebreda AR (2011) Genetic analysis of specific and redundant roles for p38alpha and p38beta MAPKs during mouse development. *Proc Natl Acad Sci USA* **108**, 12764–12769.

15 Han J & Sun P (2007) The pathways to tumor suppression via route p38. *Trends Biochem Sci* **32**, 364–371.

16 Wagner EF & Nebreda AR (2009) Signal integration by JNK and p38 MAPK pathways in cancer development. *Nat Rev Cancer* **9**, 537–549.
17 Kotlyarov A, Neininger A, Schubert C, Eckert R, Birchmeier C, Volk HD & Gaestel M (1999) MAPKAP kinase 2 is essential for LPS-induced TNF-alpha biosynthesis. *Nat Cell Biol* **1**, 94–97.
18 Ronkina N, Kotlyarov A, Dittrich-Breiholz O, Kracht M, Hitti E, Milarski K, Askew R, Marusic S, Lin LL, Gaestel M *et al*. (2007) The mitogen-activated protein kinase (MAPK)-activated protein kinases MK2 and MK3 cooperate in stimulation of tumor necrosis factor biosynthesis and stabilization of p38 MAPK. *Mol Cell Biol* **27**, 170–181.
19 Kang YJ, Chen J, Otsuka M, Mols J, Ren S, Wang Y & Han J (2008) Macrophage deletion of p38alpha partially impairs lipopolysaccharide-induced cellular activation. *J Immunol* **180**, 5075–5082.
20 Kim C, Sano Y, Todorova K, Carlson BA, Arpa L, Celada A, Lawrence T, Otsu K, Brissette JL, Arthur JS *et al*. (2008) The kinase p38 alpha serves cell type-specific inflammatory functions in skin injury and coordinates pro- and anti-inflammatory gene expression. *Nat Immunol* **9**, 1019–1027.
21 Otsuka M, Kang YJ, Ren J, Jiang H, Wang Y, Omata M & Han J (2010) Distinct effects of p38alpha deletion in myeloid lineage and gut epithelia in mouse models of inflammatory bowel disease. *Gastroenterology* **138**, 1255–1265.
22 O'Keefe SJ, Mudgett JS, Cupo S, Parsons JN, Chartrain NA, Fitzgerald C, Chen SL, Lowitz K, Rasa C, Visco D *et al*. (2007) Chemical genetics define the roles of p38alpha and p38beta in acute and chronic inflammation. *J Biol Chem* **282**, 34663–34671.
23 Risco A, del Fresno C, Mambol A, Alsina-Beauchamp D, MacKenzie KF, Yang HT, Barber DF, Morcelle C, Arthur JS, Ley SC *et al*. (2012) p38gamma and p38delta kinases regulate the Toll-like receptor 4 (TLR4)-induced cytokine production by controlling ERK1/2 protein kinase pathway activation. *Proc Natl Acad Sci USA* **109**, 11200–11205.
24 Chabaud-Riou M & Firestein GS (2004) Expression and activation of mitogen-activated protein kinase kinases-3 and -6 in rheumatoid arthritis. *Am J Pathol* **164**, 177–184.
25 Schett G, Tohidast-Akrad M, Smolen JS, Schmid BJ, Steiner CW, Bitzan P, Zenz P, Redlich K, Xu Q & Steiner G (2000) Activation, differential localization, and regulation of the stress-activated protein kinases, extracellular signal-regulated kinase, c-JUN N-terminal kinase, and p38 mitogen-activated protein kinase, in synovial tissue and cells in rheumatoid arthritis. *Arthritis Rheum* **43**, 2501–2512.
26 Medicherla S, Ma JY, Mangadu R, Jiang Y, Zhao JJ, Almirez R, Kerr I, Stebbins EG, O'Young G, Kapoun AM *et al*. (2006) A selective p38 alpha mitogen-activated protein kinase inhibitor reverses cartilage and bone destruction in mice with collagen-induced arthritis. *J Pharmacol Exp Ther* **318**, 132–141.
27 Mihara K, Almansa C, Smeets RL, Loomans EE, Dulos J, Vink PM, Rooseboom M, Kreutzer H, Cavalcanti F, Boots AM *et al*. (2008) A potent and selective p38 inhibitor protects against bone damage in murine collagen-induced arthritis: a comparison with neutralization of mouse TNFalpha. *Br J Pharmacol* **154**, 153–164.
28 Hegen M, Gaestel M, Nickerson-Nutter CL, Lin LL & Telliez JB (2006) MAPKAP kinase 2-deficient mice are resistant to collagen-induced arthritis. *J Immunol* **177**, 1913–1917.
29 Inoue T, Boyle DL, Corr M, Hammaker D, Davis RJ, Flavell RA & Firestein GS (2006) Mitogen-activated protein kinase kinase 3 is a pivotal pathway regulating p38 activation in inflammatory arthritis. *Proc Natl Acad Sci USA* **103**, 5484–5489.
30 Yoshizawa T, Hammaker D, Boyle DL, Corr M, Flavell R, Davis R, Schett G & Firestein GS (2009) Role of MAPK kinase 6 in arthritis: distinct mechanism of action in inflammation and cytokine expression. *J Immunol* **183**, 1360–1367.
31 Mnich SJ, Blanner PM, Hu LG, Shaffer AF, Happa FA, O'Neil S, Ukairo O, Weiss D, Welsh E, Storer C *et al*. (2010) Critical role for apoptosis signal-regulating kinase 1 in the development of inflammatory K/BxN serum-induced arthritis. *Int Immunopharmacol* **10**, 1170–1176.
32 Guma M, Hammaker D, Topolewski K, Corr M, Boyle DL, Karin M & Firestein GS (2012) Antiinflammatory functions of p38 in mouse models of rheumatoid arthritis: advantages of targeting upstream kinases MKK-3 or MKK-6. *Arthritis Rheum* **64**, 2887–2895.
33 Ananieva O, Darragh J, Johansen C, Carr JM, McIlrath J, Park JM, Wingate A, Monk CE, Toth R, Santos SG *et al*. (2008) The kinases MSK1 and MSK2 act as negative regulators of Toll-like receptor signaling. *Nat Immunol* **9**, 1028–1036.
34 Cohen SB, Cheng TT, Chindalore V, Damjanov N, Burgos-Vargas R, Delora P, Zimany K, Travers H & Caulfield JP (2009) Evaluation of the efficacy and safety of pamapimod, a p38 MAP kinase inhibitor, in a double-blind, methotrexate-controlled study of patients with active rheumatoid arthritis. *Arthritis Rheum* **60**, 335–344.
35 Damjanov N, Kauffman RS & Spencer-Green GT (2009) Efficacy, pharmacodynamics, and safety of VX-702, a novel p38 MAPK inhibitor, in rheumatoid arthritis: results of two randomized, double-blind, placebo-controlled clinical studies. *Arthritis Rheum* **60**, 1232–1241.

36 Gaestel M, Kotlyarov A & Kracht M (2009) Targeting innate immunity protein kinase signalling in inflammation. *Nat Rev Drug Discov* **8**, 480–499.
37 Mourey RJ, Burnette BL, Brustkern SJ, Daniels JS, Hirsch JL, Hood WF, Meyers MJ, Mnich SJ, Pierce BS, Saabye MJ *et al.* (2010) A benzothiophene inhibitor of mitogen-activated protein kinase-activated protein kinase 2 inhibits tumor necrosis factor alpha production and has oral anti-inflammatory efficacy in acute and chronic models of inflammation. *J Pharmacol Exp Ther* **333**, 797–807.
38 Krementsov DN, Thornton TM, Teuscher C & Rincon M (2013) The emerging role of p38 mitogen-activated protein kinase in multiple sclerosis and its models. *Mol Cell Biol* **33**, 3728–3734.
39 Namiki K, Matsunaga H, Yoshioka K, Tanaka K, Murata K, Ishida J, Sakairi A, Kim J, Tokuhara N, Shibakawa N *et al.* (2012) Mechanism for p38alpha-mediated experimental autoimmune encephalomyelitis. *J Biol Chem* **287**, 24228–24238.
40 Noubade R, Krementsov DN, Del Rio R, Thornton T, Nagaleekar V, Saligrama N, Spitzack A, Spach K, Sabio G, Davis RJ *et al.* (2011) Activation of p38 MAPK in CD4 T cells controls IL-17 production and autoimmune encephalomyelitis. *Blood* **118**, 3290–3300.
41 Guo X, Harada C, Namekata K, Matsuzawa A, Camps M, Ji H, Swinnen D, Jorand-Lebrun C, Muzerelle M, Vitte PA *et al.* (2010) Regulation of the severity of neuroinflammation and demyelination by TLR-ASK1-p38 pathway. *EMBO Mol Med* **2**, 504–515.
42 Huang G, Wang Y, Vogel P, Kanneganti TD, Otsu K & Chi H (2012) Signaling via the kinase p38alpha programs dendritic cells to drive TH17 differentiation and autoimmune inflammation. *Nat Immunol* **13**, 152–161.
43 Tietz SM, Hofmann R, Thomas T, Tackenberg B, Gaestel M & Berghoff M (2014) MK2 and Fas receptor contribute to the severity of CNS demyelination. *PLoS One* **9**, e100363.
44 Jirmanova L, Giardino Torchia ML, Sarma ND, Mittelstadt PR & Ashwell JD (2011) Lack of the T cell-specific alternative p38 activation pathway reduces autoimmunity and inflammation. *Blood* **118**, 3280–3289.
45 Jagavelu K, Tietge UJ, Gaestel M, Drexler H, Schieffer B & Bavendiek U (2007) Systemic deficiency of the MAP kinase-activated protein kinase 2 reduces atherosclerosis in hypercholesterolemic mice. *Circ Res* **101**, 1104–1112.
46 Tang-Feldman YJ, Lochhead SR, Lochhead GR, Yu C, George M, Villablanca AC & Pomeroy C (2013) Murine cytomegalovirus (MCMV) infection upregulates P38 MAP kinase in aortas of Apo E KO mice: a molecular mechanism for MCMV-induced acceleration of atherosclerosis. *J Cardiovasc Transl Res* **6**, 54–64.
47 Seimon TA, Wang Y, Han S, Senokuchi T, Schrijvers DM, Kuriakose G, Tall AR & Tabas IA (2009) Macrophage deficiency of p38alpha MAPK promotes apoptosis and plaque necrosis in advanced atherosclerotic lesions in mice. *J Clin Invest* **119**, 886–898.
48 McGuire VA, Gray A, Monk CE, Santos SG, Lee K, Aubareda A, Crowe J, Ronkina N, Schwermann J, Batty IH *et al.* (2013) Cross talk between the Akt and p38alpha pathways in macrophages downstream of Toll-like receptor signaling. *Mol Cell Biol* **33**, 4152–4165.
49 Kardakaris R, Gareus R, Xanthoulea S & Pasparakis M (2011) Endothelial and macrophage-specific deficiency of P38alpha MAPK does not affect the pathogenesis of atherosclerosis in $ApoE^{-/-}$ mice. *PLoS One* **6**, e21055.
50 Dansky HM, Charlton SA, Sikes JL, Heath SC, Simantov R, Levin LF, Shu P, Moore KJ, Breslow JL & Smith JD (1999) Genetic background determines the extent of atherosclerosis in ApoE-deficient mice. *Arterioscler Thromb Vasc Biol* **19**, 1960–1968.
51 Renda T, Baraldo S, Pelaia G, Bazzan E, Turato G, Papi A, Maestrelli P, Maselli R, Vatrella A, Fabbri LM *et al.* (2008) Increased activation of p38 MAPK in COPD. *Eur Respir J* **31**, 62–69.
52 Bhavsar P, Hew M, Khorasani N, Torrego A, Barnes PJ, Adcock I & Chung KF (2008) Relative corticosteroid insensitivity of alveolar macrophages in severe asthma compared with non-severe asthma. *Thorax* **63**, 784–790.
53 Medicherla S, Fitzgerald MF, Spicer D, Woodman P, Ma JY, Kapoun AM, Chakravarty S, Dugar S, Protter AA & Higgins LS (2008) p38alpha-selective mitogen-activated protein kinase inhibitor SD-282 reduces inflammation in a subchronic model of tobacco smoke-induced airway inflammation. *J Pharmacol Exp Ther* **324**, 921–929.
54 Amano H, Murata K, Matsunaga H, Tanaka K, Yoshioka K, Kobayashi T, Ishida J, Fukamizu A, Sugiyama F, Sudo T *et al.* (2014) p38 Mitogen-activated protein kinase accelerates emphysema in mouse model of chronic obstructive pulmonary disease. *J Recept Signal Transduct Res* **34**, 299–306.
55 Brando Lima AC, Machado AL, Simon P, Cavalcante MM, Rezende DC, Sperandio da Silva GM, Nascimento PG, Quintas LE, Cunha FQ, Barreiro EJ *et al.* (2011) Anti-inflammatory effects of LASSBio-998, a new drug candidate designed to be a p38 MAPK inhibitor, in an experimental model of acute lung inflammation. *Pharmacol Rep* **63**, 1029–1039.
56 Duan W, Chan JH, McKay K, Crosby JR, Choo HH, Leung BP, Karras JG & Wong WS (2005) Inhaled

p38alpha mitogen-activated protein kinase antisense oligonucleotide attenuates asthma in mice. *Am J Respir Crit Care Med* **171**, 571–578.
57 Liang L, Li F, Bao A, Zhang M, Chung KF & Zhou X (2013) Activation of p38 mitogen-activated protein kinase in ovalbumin and ozone-induced mouse model of asthma. *Respirology* **18** (Suppl 3), 20–29.
58 Rincon M & Davis RJ (2009) Regulation of the immune response by stress-activated protein kinases. *Immunol Rev* **228**, 212–224.
59 Arthur JS & Ley SC (2013) Mitogen-activated protein kinases in innate immunity. *Nat Rev Immunol* **13**, 679–692.
60 Alam MS, Gaida MM, Ogawa Y, Kolios AG, Lasitschka F & Ashwell JD (2014) Counter-regulation of T cell effector function by differentially activated p38. *J Exp Med* **211**, 1257–1270.
61 Lanna A, Henson SM, Escors D & Akbar AN (2014) The kinase p38 activated by the metabolic regulator AMPK and scaffold TAB1 drives the senescence of human T cells. *Nat Immunol* **15**, 965–972.
62 Mantovani A, Allavena P, Sica A & Balkwill F (2008) Cancer-related inflammation. *Nature* **454**, 436–444.
63 Hussain SP & Harris CC (2007) Inflammation and cancer: an ancient link with novel potentials. *Int J Cancer* **121**, 2373–2380.
64 Bailey SR, Nelson MH, Himes RA, Li Z, Mehrotra S & Paulos CM (2014) Th17 cells in cancer: the ultimate identity crisis. *Front Immunol* **5**, 276.
65 del Barco Barrantes I & Nebreda AR (2012) Roles of p38 MAPKs in invasion and metastasis. *Biochem Soc Trans* **40**, 79–84.
66 Hui L, Bakiri L, Mairhorfer A, Schweifer N, Haslinger C, Kenner L, Komnenovic V, Scheuch H, Beug H & Wagner EF (2007) p38alpha suppresses normal and cancer cell proliferation by antagonizing the JNK-c-Jun pathway. *Nat Genet* **39**, 741–749.
67 Ventura JJ, Tenbaum S, Perdiguero E, Huth M, Guerra C, Barbacid M, Pasparakis M & Nebreda AR (2007) p38alpha MAP kinase is essential in lung stem and progenitor cell proliferation and differentiation. *Nat Genet* **39**, 750–758.
68 Bulavin DV, Phillips C, Nannenga B, Timofeev O, Donehower LA, Anderson CW, Appella E & Fornace AJ Jr (2004) Inactivation of the Wip1 phosphatase inhibits mammary tumorigenesis through p38 MAPK-mediated activation of the p16(Ink4a)-p19(Arf) pathway. *Nat Genet* **36**, 343–350.
69 Demidov ON, Kek C, Shreeram S, Timofeev O, Fornace AJ, Appella E & Bulavin DV (2007) The role of the MKK6/p38 MAPK pathway in Wip1-dependent regulation of ErbB2-driven mammary gland tumorigenesis. *Oncogene* **26**, 2502–2506.
70 Tront JS, Hoffman B & Liebermann DA (2006) Gadd45a suppresses Ras-driven mammary tumorigenesis by activation of c-Jun NH2-terminal kinase and p38 stress signaling resulting in apoptosis and senescence. *Cancer Res* **66**, 8448–8454.
71 Pereira L, Igea A, Canovas B, Dolado I & Nebreda AR (2013) Inhibition of p38 MAPK sensitizes tumour cells to cisplatin-induced apoptosis mediated by reactive oxygen species and JNK. *EMBO Mol Med* **5**, 1759–1774.
72 Campbell RM, Anderson BD, Brooks NA, Brooks HB, Chan EM, De Dios A, Gilmour R, Graff JR, Jambrina E, Mader M *et al.* (2014) Characterization of LY2228820 dimesylate, a potent and selective inhibitor of p38 MAPK with antitumor activity. *Mol Cancer Ther* **13**, 364–374.
73 Chen L, Mayer JA, Krisko TI, Speers CW, Wang T, Hilsenbeck SG & Brown PH (2009) Inhibition of the p38 kinase suppresses the proliferation of human ER-negative breast cancer cells. *Cancer Res* **69**, 8853–8861.
74 Esteva FJ, Hortobagyi GN, Sahin AA, Smith TL, Chin DM, Liang SY, Pusztai L, Buzdar AU & Bacus SS (2001) Expression of erbB/HER receptors, heregulin and P38 in primary breast cancer using quantitative immunohistochemistry. *Pathol Oncol Res* **7**, 171–177.
75 Esteva FJ, Sahin AA, Smith TL, Yang Y, Pusztai L, Nahta R, Buchholz TA, Buzdar AU, Hortobagyi GN & Bacus SS (2004) Prognostic significance of phosphorylated P38 mitogen-activated protein kinase and HER-2 expression in lymph node-positive breast carcinoma. *Cancer* **100**, 499–506.
76 Gutierrez MC, Detre S, Johnston S, Mohsin SK, Shou J, Allred DC, Schiff R, Osborne CK & Dowsett M (2005) Molecular changes in tamoxifen-resistant breast cancer: relationship between estrogen receptor, HER-2, and p38 mitogen-activated protein kinase. *J Clin Oncol* **23**, 2469–2476.
77 Salh B, Marotta A, Wagey R, Sayed M & Pelech S (2002) Dysregulation of phosphatidylinositol 3-kinase and downstream effectors in human breast cancer. *Int J Cancer* **98**, 148–154.
78 Wu X, Zhang W, Font-Burgada J, Palmer T, Hamil AS, Biswas SK, Poidinger M, Borcherding N, Xie Q, Ellies LG *et al.* (2014) Ubiquitin-conjugating enzyme Ubc13 controls breast cancer metastasis through a TAK1-p38 MAP kinase cascade. *Proc Natl Acad Sci U S A* **111**, 13870–13875.
79 Ruiz EJ, Oeztuerk-Winder F & Ventura JJ (2014) A paracrine network regulates the cross-talk between human lung stem cells and the stroma. *Nat Commun* **5**, 3175.
80 Morandell S, Reinhardt HC, Cannell IG, Kim JS, Ruf DM, Mitra T, Couvillon AD, Jacks T & Yaffe MB (2013) A reversible gene-targeting strategy identifies synthetic lethal interactions between MK2 and p53 in

the DNA damage response in vivo. *Cell Rep* **5**, 868–877.
81 Greenberg AK, Basu S, Hu J, Yie TA, Tchou-Wong KM, Rom WN & Lee TC (2002) Selective p38 activation in human non-small cell lung cancer. *Am J Respir Cell Mol Biol* **26**, 558–564.
82 Powell HA, Iyen-Omofoman B, Baldwin DR, Hubbard RB & Tata LJ (2013) Chronic obstructive pulmonary disease and risk of lung cancer: the importance of smoking and timing of diagnosis. *J Thorac Oncol* **8**, 6–11.
83 El-Serag HB & Rudolph KL (2007) Hepatocellular carcinoma: epidemiology and molecular carcinogenesis. *Gastroenterology* **132**, 2557–2576.
84 Sakurai T, He G, Matsuzawa A, Yu GY, Maeda S, Hardiman G & Karin M (2008) Hepatocyte necrosis induced by oxidative stress and IL-1 alpha release mediate carcinogen-induced compensatory proliferation and liver tumorigenesis. *Cancer Cell* **14**, 156–165.
85 Sakurai T, Kudo M, Umemura A, He G, Elsharkawy AM, Seki E & Karin M (2013) p38alpha inhibits liver fibrogenesis and consequent hepatocarcinogenesis by curtailing accumulation of reactive oxygen species. *Cancer Res* **73**, 215–224.
86 Heinrichsdorff J, Luedde T, Perdiguero E, Nebreda AR & Pasparakis M (2008) p38 alpha MAPK inhibits JNK activation and collaborates with IkappaB kinase 2 to prevent endotoxin-induced liver failure. *EMBO Rep* **9**, 1048–1054.
87 Iyoda K, Sasaki Y, Horimoto M, Toyama T, Yakushijin T, Sakakibara M, Takehara T, Fujimoto J, Hori M, Wands JR *et al.* (2003) Involvement of the p38 mitogen-activated protein kinase cascade in hepatocellular carcinoma. *Cancer* **97**, 3017–3026.
88 Yasuda E, Kumada T, Takai S, Ishisaki A, Noda T, Matsushima-Nishiwaki R, Yoshimi N, Kato K, Toyoda H, Kaneoka Y *et al.* (2005) Attenuated phosphorylation of heat shock protein 27 correlates with tumor progression in patients with hepatocellular carcinoma. *Biochem Biophys Res Commun* **337**, 337–342.
89 Wang SN, Lee KT, Tsai CJ, Chen YJ & Yeh YT (2012) Phosphorylated p38 and JNK MAPK proteins in hepatocellular carcinoma. *Eur J Clin Invest* **42**, 1295–1301.
90 Gillen CD, Walmsley RS, Prior P, Andrews HA & Allan RN (1994) Ulcerative colitis and Crohn's disease: a comparison of the colorectal cancer risk in extensive colitis. *Gut* **35**, 1590–1592.
91 Caballero-Franco C, Choo MK, Sano Y, Ritprajak P, Sakurai H, Otsu K, Mizoguchi A & Park JM (2013) Tuning of protein kinase circuitry by p38alpha is vital for epithelial tissue homeostasis. *J Biol Chem* **288**, 23788–23797.
92 Gupta J, Del Barco Barrantes I, Igea A, Sakellariou S, Pateras IS, Gorgoulis VG & Nebreda AR (2014) Dual function of p38alpha MAPK in colon cancer: suppression of colitis-associated tumor initiation but requirement for cancer cell survival. *Cancer Cell* **25**, 484–500.
93 Kang YJ, Otsuka M, van den Berg A, Hong L, Huang Z, Wu X, Zhang DW, Vallance BA, Tobias PS & Han J (2010) Epithelial p38alpha controls immune cell recruitment in the colonic mucosa. *PLoS Pathog* **6**, e1000934.
94 Wakeman D, Schneider JE, Liu J, Wandu WS, Erwin CR, Guo J, Stappenbeck TS & Warner BW (2012) Deletion of p38-alpha mitogen-activated protein kinase within the intestinal epithelium promotes colon tumorigenesis. *Surgery* **152**, 286–293.
95 Hayakawa Y, Hirata Y, Nakagawa H, Sakamoto K, Hikiba Y, Otsuka M, Ijichi H, Ikenoue T, Tateishi K, Akanuma M *et al.* (2010) Apoptosis signal-regulating kinase 1 regulates colitis and colitis-associated tumorigenesis by the innate immune responses. *Gastroenterology* **138**, 1055–1067.
96 Chiacchiera F, Matrone A, Ferrari E, Ingravallo G, Lo Sasso G, Murzilli S, Petruzzelli M, Salvatore L, Moschetta A & Simone C (2009) p38alpha blockade inhibits colorectal cancer growth in vivo by inducing a switch from HIF1alpha- to FoxO-dependent transcription. *Cell Death Differ* **16**, 1203–1214.
97 Chiacchiera F, Grossi V, Cappellari M, Peserico A, Simonatto M, Germani A, Russo S, Moyer MP, Resta N, Murzilli S *et al.* (2012) Blocking p38/ERK crosstalk affects colorectal cancer growth by inducing apoptosis in vitro and in preclinical mouse models. *Cancer Lett* **324**, 98–108.
98 Urosevic J, Garcia-Albeniz X, Planet E, Real S, Cespedes MV, Guiu M, Fernandez E, Bellmunt A, Gawrzak S, Pavlovic M *et al.* (2014) Colon cancer cells colonize the lung from established liver metastases through p38 MAPK signalling and PTHLH. *Nat Cell Biol* **16**, 685–694.
99 Docena G, Rovedatti L, Kruidenier L, Fanning A, Leakey NA, Knowles CH, Lee K, Shanahan F, Nally K, McLean PG *et al.* (2010) Down-regulation of p38 mitogen-activated protein kinase activation and proinflammatory cytokine production by mitogen-activated protein kinase inhibitors in inflammatory bowel disease. *Clin Exp Immunol* **162**, 108–115.
100 Waetzig GH, Seegert D, Rosenstiel P, Nikolaus S & Schreiber S (2002) p38 mitogen-activated protein kinase is activated and linked to TNF-alpha signaling in inflammatory bowel disease. *J Immunol* **168**, 5342–5351.
101 Malamut G, Cabane C, Dubuquoy L, Malapel M, Derijard B, Gay J, Tamboli C, Colombel JF & Desreumaux P (2006) No evidence for an involvement

of the p38 and JNK mitogen-activated protein in inflammatory bowel diseases. *Dig Dis Sci* **51**, 1443–1453.

102 Hommes D, van den Blink B, Plasse T, Bartelsman J, Xu C, Macpherson B, Tytgat G, Peppelenbosch M & Van Deventer S (2002) Inhibition of stress-activated MAP kinases induces clinical improvement in moderate to severe Crohn's disease. *Gastroenterology* **122**, 7–14.

103 Schreiber S, Feagan B, D'Haens G, Colombel JF, Geboes K, Yurcov M, Isakov V, Golovenko O, Bernstein CN, Ludwig D *et al.* (2006) Oral p38 mitogen-activated protein kinase inhibition with BIRB 796 for active Crohn's disease: a randomized, double-blind, placebo-controlled trial. *Clin Gastroenterol Hepatol* **4**, 325–334.

104 Fan XJ, Wan XB, Fu XH, Wu PH, Chen DK, Wang PN, Jiang L, Wang DH, Chen ZT, Huang Y *et al.* (2014) Phosphorylated p38, a negative prognostic biomarker, complements TNM staging prognostication in colorectal cancer. *Tumour Biol* **35**, 10487–10495.

105 Hardwick JC, van den Brink GR, Offerhaus GJ, van Deventer SJ & Peppelenbosch MP (2001) NF-kappaB, p38 MAPK and JNK are highly expressed and active in the stroma of human colonic adenomatous polyps. *Oncogene* **20**, 819–827.

106 Paillas S, Boissiere F, Bibeau F, Denouel A, Mollevi C, Causse A, Denis V, Vezzio-Vie N, Marzi L, Cortijo C *et al.* (2011) Targeting the p38 MAPK pathway inhibits irinotecan resistance in colon adenocarcinoma. *Cancer Res* **71**, 1041–1049.

107 Sun P, Yoshizuka N, New L, Moser BA, Li Y, Liao R, Xie C, Chen J, Deng Q, Yamout M *et al.* (2007) PRAK is essential for ras-induced senescence and tumor suppression. *Cell* **128**, 295–308.

108 Yoshizuka N, Chen RM, Xu Z, Liao R, Hong L, Hu WY, Yu G, Han J, Chen L & Sun P (2012) A novel function of p38-regulated/activated kinase in endothelial cell migration and tumor angiogenesis. *Mol Cell Biol* **32**, 606–618.

109 Cargnello M & Roux PP (2011) Activation and function of the MAPKs and their substrates, the MAPK-activated protein kinases. *Microbiol Mol Biol Rev* **75**, 50–83.

110 Iriyama T, Takeda K, Nakamura H, Morimoto Y, Kuroiwa T, Mizukami J, Umeda T, Noguchi T, Naguro I, Nishitoh H *et al.* (2009) ASK1 and ASK2 differentially regulate the counteracting roles of apoptosis and inflammation in tumorigenesis. *EMBO J* **28**, 843–853.

111 Hildesheim J, Bulavin DV, Anver MR, Alvord WG, Hollander MC, Vardanian L & Fornace AJ Jr (2002) Gadd45a protects against UV irradiation-induced skin tumors, and promotes apoptosis and stress signaling via MAPK and p53. *Cancer Res* **62**, 7305–7315.

112 Liu L, Rezvani HR, Back JH, Hosseini M, Tang X, Zhu Y, Mahfouf W, Raad H, Raji G, Athar M *et al.* (2014) Inhibition of p38 MAPK signaling augments skin tumorigenesis via NOX2 driven ROS generation. *PLoS One* **9**, e97245.

113 Johansen C, Vestergaard C, Kragballe K, Kollias G, Gaestel M & Iversen L (2009) MK2 regulates the early stages of skin tumor promotion. *Carcinogenesis* **30**, 2100–2108.

114 Chang S, Iversen L, Kragballe K, Arthur JS & Johansen C (2011) Mice lacking MSK1 and MSK2 show reduced skin tumor development in a two-stage chemical carcinogenesis model. *Cancer Investigat* **29**, 240–245.

115 Dickinson SE, Olson ER, Zhang J, Cooper SJ, Melton T, Criswell PJ, Casanova A, Dong Z, Hu C, Saboda K *et al.* (2011) p38 MAP kinase plays a functional role in UVB-induced mouse skin carcinogenesis. *Mol Carcinog* **50**, 469–478.

116 Liu K, Yu D, Cho YY, Bode AM, Ma W, Yao K, Li S, Li J, Bowden GT & Dong Z (2013) Sunlight UV-Induced skin cancer relies upon activation of the p38alpha signaling pathway. *Cancer Res* **73**, 2181–2188.

117 Goldstein DM, Kuglstatter A, Lou Y & Soth MJ (2010) Selective p38alpha inhibitors clinically evaluated for the treatment of chronic inflammatory disorders. *J Med Chem* **53**, 2345–2353.

118 Del Reino P, Alsina-Beauchamp D, Escos A, Cerezo-Guisado MI, Risco A, Aparicio N, Zur R, Fernandez-Estevez M, Collantes E, Montans J *et al.* (2014) Pro-oncogenic role of alternative p38 mitogen-activated protein kinases p38gamma and p38delta, linking inflammation and cancer in colitis-associated colon cancer. *Cancer Res* **74**, 6150–6160.

119 Schindler EM, Hindes A, Gribben EL, Burns CJ, Yin Y, Lin MH, Owen RJ, Longmore GD, Kissling GE, Arthur JS *et al.* (2009) p38delta Mitogen-activated protein kinase is essential for skin tumor development in mice. *Cancer Res* **69**, 4648–4655.