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REVIEW ARTICLE

The many faces of p38 mitogen-activated protein kinase in progenitor/stem cell differentiation

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Regulation of stem cells is essential for development and adult tissue homoeostasis. The proper control of stem cell self-renewal and differentiation maintains organ physiology, and disruption of such a balance results in disease. There are many mechanisms that have been established as stem cell regulators, such as Wnt or Notch signals. However, the intracellular mechanisms that mediate and integrate these signals are not well understood. A new intracellular pathway that has been reported to be involved in the regulation of many stem cell types is that of p38 MAPK (mitogen-activated protein kinase). In particular, p38α is essential for the proper differentiation of many haematopoietic, mesenchymal and epithelial stem/progenitor cells. Many reports have shown that disruption of this kinase pathway has pathological consequences in many organs. Understanding the extracellular cues and downstream targets of p38α in stem cell regulation may help to tackle some of the pathologies associated with improper differentiation and regulation of stem cell function. In the present review we present a vision of the current knowledge on the roles of the p38α signal as a regulator of stem/progenitor cells in different tissues in physiology and disease.

Key words: cancer, cell specification, cytokine signalling, development, mitogen-activated protein kinase (MAPK), self-renewal.

INTRODUCTION

Embryonic development and maintenance of adult tissue homoeostasis are physiological processes where stem cells, which are characterized by their ability to self-renew and perpetuate themselves, generate differentiated cell types or replenish functional tissue. Furthermore, they have the potential to produce differentiated daughter cells that will eventually become specialized embryonic or adult cells.

Many signalling pathway components are well known as key players in stem cell differentiation and self-renewal. These include growth factors [e.g. FGF (fibroblast growth factor) and BMP (bone morphogenetic protein)], morphogens (e.g. Wnt), cell–cell contact/communication regulators (e.g. Notch), and mediators of the extracellular matrix (e.g. integrin-α6) [1–3], all of which have been reported to control embryonic and adult stem cell homoeostasis. Other pathways have also been identified as modulators or co-modulators of stem cell function.

The p38 MAPK (mitogen-activated protein kinase) pathway is an important mediator of the cellular response to external signals, and in particular to stress. However, there have been many reports connecting this kinase pathway to the regulation of embryonic development and adult tissue turnover.

p38 MAPKs belong to the MAPK family. MAPKs can be classified into three groups: ERKs (extracellular-signal-regulated kinases); JNKs (c-Jun N-terminal kinases) and p38 MAPKs [4]. The present review will primarily focus on the role of p38α in homoeostasis and disease.

p38 MAPKs have been considered as stress-activated protein kinases that respond to cellular stress and cytokines, with roles related to inflammation [5]. They can be divided into two subgroups, dependent on their expression pattern, substrate specificity and sensitivity to pharmacological inhibitors [6]. The first group contains p38α and p38β, which are universally expressed, whereas the second group comprises p38γ and p38δ, which appear to have more tissue-specific expression patterns [7,8]. Strong activation of p38 MAPKs by cytokines and cellular stresses generally promotes the inhibition of cell growth and induces apoptosis [9,10,11]. The different p38 MAPK isoforms have been shown to have redundant, specific or even opposite functions, depending on the cell type involved and the nature of the stimulus [8,12]. The p38α signalling pathway shows the typical kinase cascade of the MAPK family, which results in the regulation of a diverse range of cellular functions [13] (Figure 1).

p38α MAPK is ubiquitously expressed and the most abundant member of the family. It is essential for embryonic development, while also regulating different cellular functions, including proliferation, differentiation, cell death, adhesion and migration, as well as the response to stress and metabolic pathways [14]. It does this through multiple mechanisms, including regulation of transcription, mRNA stability, chromatin remodelling and protein synthesis [14]. More recently, p38α has been found to play important roles in the maintenance of homoeostasis and related pathologies.

p38α IN DEVELOPMENT

p38 MAPKs are widely involved in development, regulating a plethora of processes, including growth, embryonic differentiation and tissue homoeostasis [15,16]. The role of p38 in development was first determined in *Drosophila* embryos, where disruption of p38 signalling by deletion of its upstream activator, MKK [MAPK kinase; lic (licorne)], caused mislocalization of Oskar mRNA and failure to position the embryos anterior–posterior and dorsal–ventral axes [17]. p38α has also been found to play an essential role during development in

Abbreviations used: AP-1, activator protein 1; BMP, bone morphogenetic protein; C/EBP, CAAT/enhancer-binding protein; ESC, embryonic stem cell; IBD, inflammatory bowel disease; IFN, interferon; IL, interleukin; JNK, c-Jun N-terminal kinase; MAPK, mitogen-activated protein kinase; MEF, myocyte enhancer factor; MKK, MAPK kinase; MSC, mesenchymal stem cell; TGF, transforming growth factor; Th, T-cell helper; TNF, tumour necrosis factor.

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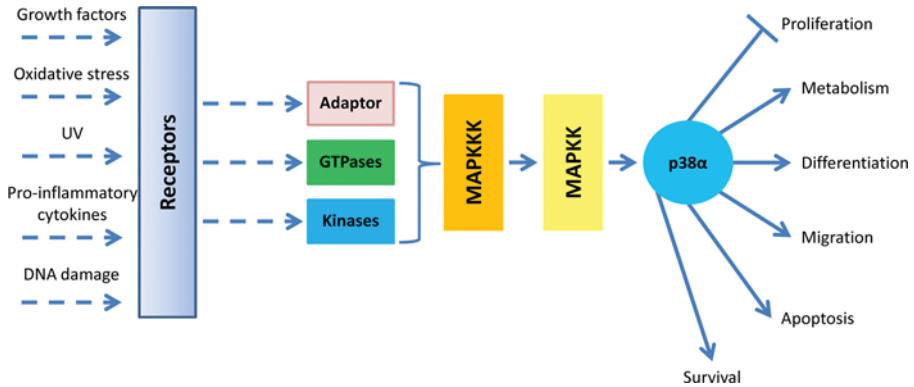

Figure 1 p38α is part of the family of MAPKs

These kinase pathways are activated by external signals, and they form cascades of phosphorylation that lead to the activation of downstream targets and cellular responses. MAPKK, MKK; MAPKKK, MKK kinase.

other animal models. In zebrafish, suppression of the p38 pathway affects the cleavage of the future dorsal side of the embryo and morphogenesis [18,19]. In *Xenopus*, the lack of p38α affects early myogenic development, extending proliferation of the presomitic mesoderm and delaying somitogenesis [20]. In summary, p38 activity in non-mammalian organisms is essential for mesenchymal differentiation, which is required for the proper spatial organization of the animal during development.

Deletion of the mammalian p38α isoform in murine embryos was shown to be lethal at E10.5 (embryonic day 10.5) [12,21,22]. Lethality was due to placental defects causing $p38\alpha^{-/-}$ embryos to die from starvation and low oxygenation. Subsequently, the role of p38α in trophoblast differentiation was demonstrated as the placental defect being overcome following fusion of $p38\alpha^{-/-}$ blastocysts with wild-type tetraploid cells (that only contribute to extraembryonic structures) [12]. Such rescue studies established an important role for the p38α pathway during early placentation, but do not suggest that its activity is required for pre-implantation development. Similarly, disruption of p38 signalling by compound deletion of the p38 upstream activators MKK3 and MKK6 in mice, results in embryonic death due to placental defects [23]. Furthermore, p38α has been shown to be required for the development of the 8–16-cell stage of *in vitro* cultured embryos [24], regulating filamentous actin, as has also been demonstrated in zebrafish [19].

Elucidation of p38 MAPK functions from studies in knockout mice has provided valuable information on their relative importance during embryogenesis, but there is little knowledge about the developmental roles of p38 MAPKs at the cellular level. Embryonic lethality further limits in-depth analysis of the developmental role of p38α at the cellular level in animal models, but generation of $p38\alpha^{-/-}$ ESCs (embryonic stem cells) [25,26] has provided a valuable alternative system. It has been shown that cultured $p38\alpha^{-/-}$ ESCs display several altered properties. These include augmented cell adhesion, which correlates with increased phosphorylation of focal adhesion kinase, and enhanced viability, owing to endogenous activation of Akt [27]. Induced differentiation of ESCs *in vitro* has shown that p38α promotes mesodermal specification, whereas $p38\alpha^{-/-}$ ESCs tend to differentiate into neurons, reducing mesodermal commitment to a greater or lesser degree [28,29].

The apparent discrepancy between the dispensability of p38α for embryo development in knockout animals [12,30,31] and the *in vitro* role for p38α in ESC differentiation, can perhaps be explained by compensation via other p38 isoforms, namely p38β, p38γ or p38δ. One might speculate that p38β, which shares the highest homology with p38α [8], is the most likely candidate in this regard. It is also possible that differences in the *in vitro* set up, such as the use of serum containing undefined factors that would be able to compensate for the loss of function of p38α, may result in the activation of other MAPK pathways [32].

In summary, these studies suggest that p38α deletion may not significantly compromise the potential of ESC differentiation to certain cell types, but it may select for a commitment to specific cell lineages. p38α is a likely activator of transcription factors not only involved in embryonic specification [e.g. Brachyury, MEF2C (myocyte enhancer factor 2C), PPAR (peroxisome-proliferator-activated receptor)] [29,33,34], but also in cross-talk with survival pathways (e.g. Akt) [27] and the regulation of proliferation mediators (e.g. cyclin D1) [35]. The balance between all of these effectors will induce different cellular activities depending on the state of development and cell type, producing apparently opposing outcomes.

More recently, the use of embryonic-specific conditional alleles has revealed specific functions for p38α in later embryonic development, e.g. embryonic lung development, resulting in mice dying shortly after birth, most likely being due to disrupted differentiation of the bronchioalveolar epithelium [32]. Other reports have shown a role for p38α in the branching of the developing lung, as blocking p38 signalling with the inhibitor SB203580, or following p38α knockdown by shRNA (small hairpin RNA), suppressed budding morphogenesis of mouse embryonic lung explants [36]. The use of more specific conditional alleles will allow a better dissection of the functions and mediators of p38α during different stages of embryonic development.

p38α IN ADULT TISSUE HOMOEOSTASIS

The use of conditional floxed alleles and specific small chemical inhibitors has allowed the study of the functions of p38α in adult tissues [14]. This approach has revealed important physiological functions for p38α in lung [37], liver [32], muscle [38], heart [39], haematopoiesis [40], skin [41] and pancreas [42]. In the present review we provide an overview of the recent advances in the study of the role of p38α in regulating adult tissue stem cell homoeostasis.

p38α in haematopoiesis

The role of p38α as a central regulator of haematopoietic homoeostasis is well established. The regulation of proliferation, survival and differentiation of normal haematopoietic cells

by different cytokines and growth factors occurs via p38α signalling [43–46]. In the haematopoietic system, p38α exhibits contradictory functions in different lineages and maturation stages [47]. In thymic development, p38α inhibits differentiation of immature thymocytes at specific stages [48]. In mature $CD4^+$ cells, p38α participates in Th1 (T-cell helper 1) inflammatory response, whereas it needs to be shut down in B-cell pro-activator Th2 cells [49,50].

A role for p38α in mature granulocytes has also been reported. p38α is essential for the survival of neutrophils during inflammation, and suppression of p38α signalling is necessary to eliminate neutrophils in the termination of the inflammatory response [51,52]. The same activation/inactivation process is essential for the survival/apoptosis of eosinophils during the inflammatory response [53]. The function of p38α activity in myeloid cells is paradoxical. Whereas in $CD34^+$ progenitor cells, elevated p38α activity prevents haematopoiesis [54], in other myeloid cells, p38α mediates activin A-mediated differentiation. These opposite effects may be due to the role of p38α as a regulator of transcription factors involved in differentiation and its role in cytokine expression in response to stress [55]. The roles of p38α in haematopoiesis are mediated by its activation of different pools of cell-dependent cytokines [49] or transcription factors [e.g. C/EBP (CAAT/enhancer-binding protein) and GATA-1] [56,57], or mediating differentiation signals [58,59]. The level of p38α activation together with cross-talking to other pathways results in diverse outcomes, such as apoptosis, survival, differentiation or progenitor proliferation [58]. A better understanding of the specific roles of p38α in every stage of haematopoietic development will help in tackling blood-related diseases.

p38α in muscle regeneration

The p38α MAPK pathway is an important regulator of skeletal muscle differentiation (myogenesis) [60,61]. The regulation of myogenesis is essential for normal development, as well as being important in pathological processes (e.g. muscular dystrophies and inflammatory myopathies) in which marked muscle loss and regeneration occurs. The regenerative capacity of adult skeletal muscle has been demonstrated upon acute muscle damage, resulting in the post-trauma generation of myotubes after a few days [62,63]. Early research suggested that budding of myotubes from injured myofibres was the source of new myofibres [63]. Satellite cells have been suggested as being the source for 'dormant myoblasts', responding to muscle damage by re-initiating a process similar to skeletal myogenesis [64]. Satellite cells are activated from quiescence by the p38 MAPK pathway [65].

p38α participates in various stages of adult myogenic differentiation [66]. At early stages, p38α promotes the active heterodimer transcription complex, MyoD/E47 and phosphorylates MEF2, inducing the expression of muscle-specific genes and thereby activating the differentiation program [67,68]. However, at later stages of myogenic differentiation, p38α plays a suppressive role. Phosphorylation of the myogenic factor MRF4 (muscle-regulatory factor 4) reduces its transcriptional activity, affecting essential genes involved in terminal differentiation [69,70]. Nevertheless, the suppressive role of p38α in late myogenesis has only been demonstrated *in vitro* and it requires validation *in vivo*.

The regulation of myoblast proliferation by p38α represents a novel role for the p38 pathway in skeletal myogenesis [38]. $p38\alpha^{-/-}$ myoblasts are characterized by their increased proliferation, a delay in cell-cycle exit, and impaired myoblast differentiation and fusion. p38α is the central p38 MAPK responsible for both *in vitro* and *in vivo* regulation of myogenesis [71].

A key role for p38α in controlling myoblast proliferation is the antagonism of the JNK/c-Jun pathway, probably via MKP-1 (MAPK phosphatase-1) [72]. The cross-talk between the p38 MAPK and JNK signalling pathways, by still undefined mechanisms, has been previously described in different cell types [73–76]. In the context of skeletal myogenesis, two studies have suggested opposite roles for JNK activity in muscle differentiation [77,78]. Importantly, JNK activation has been shown to mediate the increased proliferation potential of p38α-deficient myoblasts, with inhibition of JNK reverting this phenotype. Moreover, enhanced activation of JNK in p38α-deficient myoblasts results in increased levels of its substrate phospho-c-Jun and subsequent induction of c-Jun/AP-1 (activator protein 1)-mediated *c-Jun* gene transcription. This leads to increased recruitment of c-Jun to the cyclin D1 loci in differentiating myoblasts *in vivo*, presumably via the AP-1 sites on the cyclin D1 promoter [79]. p38α controls myoblast proliferation by antagonizing the pro-proliferative activity of JNK [80].

p38α appears to play contradictory roles in muscle differentiation (Figure 2). The availability of specific transcription factors at particular stages of myogenesis, and the effect (activating or inactivating) that p38α-dependent phosphorylation induces, together with the cross-talk with other MAPK pathways, may be responsible for promoting or suppressing differentiation at early or late stages of myogenesis.

p38α in neurogenesis

Most of the known roles of p38α in neurogenesis are related to embryonic development. The roles of p38 in early ESC commitment are due to various insults triggering differentiation that may involve p38 targets, such as repression of Bcl2 expression, leading to neural differentiation [81], or induction of *BMP2* mRNA, to mesodermal [82] differentiation.

In later stages of embryonic development, p38 activity prevents neurogenesis (probably due to p38β activity) in embryonic cortical [83] and oxygen/glucose-deprived hippocampal neurons [84]. However, proliferation of adult hippocampal neural progenitor cells is dependent on adiponectin activation of a p38/GSK3 (glycogen synthase kinase 3)/β-catenin cascade [85]. Furthermore, p38 signalling promotes adult neural differentiation by activating neural transcription factors such as neurogenin 1 [86] and oligodendrocyte progenitor cell progression through Sox10 [SRY (sex-determining region Y)-box 10] activation [87]. The p38α/MEF2C pathway is a survival signal during neural differentiation [88]. In addition, p38 activation by TGF (transforming growth factor)-β promotes differentiation of retinal ganglion cells and neurite outgrowth [89].

Neurogenesis is a clear example of the opposing functions that p38α can show in the same organ. The context, as a combination of the differentiation stage of the cells and the external signals from the environment, will influence the positive or negative outcome of p38 signalling in neural differentiation.

p38α in cardiac homoeostasis

The heart undergoes the least amount of tissue turnover, and regeneration has only been shown in a few species (e.g. newts and zebrafish). Following myocardial infarction, it has been suggested that more than one billion cardiomyocytes per patient would be required for tissue replacement therapy [90]. The zebrafish model has provided a good system to study cardiac self-repair [91,92].

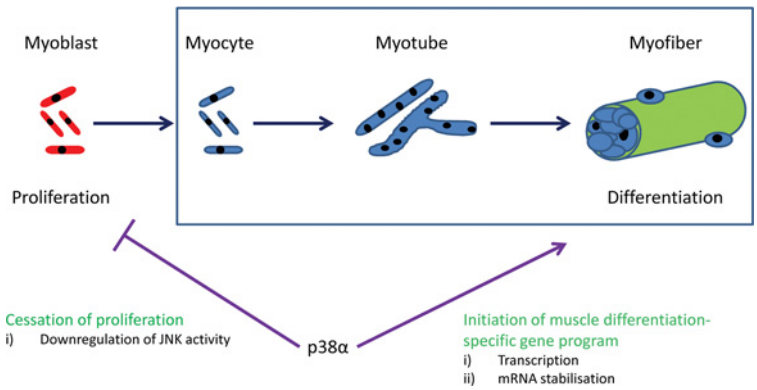

Figure 2 Muscle differentiation model as a paradigm of p38α-dependent tissue stem cell regulation

p38α promotes differentiation and suppresses self-renewal of myoblast progenitors.

The hypothesis of a terminal round of cell division, resulting in the majority of cardiac myocytes exiting the cell cycle shortly after birth [93,94], led to the belief that the mammalian heart was terminally differentiated and lacked the capacity for myocardial self-renewal following injury. However, the identification of cardiac progenitor cells has led to the belief that the heart is also regulated by an adult stem cell compartment [95–101].

p38α has been shown to be a key regulator of mammalian cardiomyogenesis. This includes roles in cardiomyocyte differentiation, division, apoptosis and hypertrophy [102]. Furthermore, p38 MAPK has been shown to control myoblast differentiation at multiple levels, including regulation of transcription factor activity, chromatin remodelling and stability of mRNAs encoding muscle differentiation regulators. p38α regulates cardiac differentiation transcription factors, such as GATA4 [103], MEF2C [104] and SRF (serum-response factor) [105]. Furthermore, it has also been suggested that C/EBPβ and TEF-1 (transcriptional enhancer factor 1) mediate p38 MAPK function in cardiomyocytes following myocardial injury [106], thereby playing a central role in the repair response.

p38α activity in post-injury hearts plays an important role in cellular and myocardial remodelling, affecting both the contractility of myocytes and the extracellular matrix. Dissecting the underlying mechanisms involved in the myocyte cell, autonomous effects as well as the cross-talk interaction between myocytes, fibroblasts and inflammatory cells, should provide a very promising area for future investigation.

p38α in other tissues

p38 also plays roles in other mesenchymal tissues. It has been extensively reported that p38 plays a role in bone regeneration and repair [107]. As in other cellular contexts, the observed roles of p38α in bone differentiation may be contradictory depending on the activation of p38α as an inflammatory mediator or as a regulator of differentiation factors. p38, upon activation by chondrogenic cytokines in MSCs (mesenchymal stem cells), is an essential mediator of bone formation [107–109]. Osteoblast differentiation is regulated by p38 MAPK activation of RUNX1 (Runt-related transcription factor 1) [110]. However, p38α is directly involved in osteoclast differentiation and bone-resorbing activity induced by inflammation [111]. In adipose tissue, there are also opposing reports identifying p38α as an inhibitor [34] or inducer [112] of adipocyte differentiation. In general, early activity of p38 in MSCs promotes bone differentiation [113], but a later activation of the p38 pathway in MSCs leads to their specification into white or brown adipocytes [112,114].

The p38α pathway is also essential for mature differentiation of epithelial tissues. Differentiation of human pancreatic islets regulated by TGF-β or activin A is dependent on p38 activation of the transcription factor PAX6 (paired box 6) [115,116]. The MKK3/p38 cascade regulates the expression of specific pancreatic factors, for example neurogenin-3, which allows pancreatic endocrine cell differentiation [117].

Intestinal homoeostasis can be disrupted by specific deletion of p38α in the colonic epithelium [55]. This intestinal function of p38α maybe mediated through the induction of intestinal genes such as Schlafen-3 [118].

There is also increasing evidence for a pivotal role of p38α at various levels of lung differentiation. p38α is essential in late lung development differentiation, and lack of p38 causes neonatal lethality [32,119]. This role is conserved in the adult lung, and p38α is necessary to maintain adult lung homoeostasis [37]. Furthermore, although p38 can be involved in lung regeneration induced by acute inflammation [120], it is also a mediator of TGF-β-dependent epithelial to mesenchymal transition in bleomycin-induced lung fibrosis [121].

In mammary development, p38α plays a negative role in differentiation by reducing the proliferation needed for ductal expansion and branching morphogenesis [122].

Regulation of caspase 14 in skin by p38 is necessary for normal differentiation of epidermal keratinocytes [123], and shape-induced terminal differentiation of skin stem cells needs p38α activity [124].

In general, the role of p38α in adult epithelial tissues is determined by the prevalence of its inflammatory functions (usually directing to tissue injury) or the activation of differentiation factors allowing tissue homoeostasis.

p38α DISRUPTION IN DISEASE

Cellular behaviour in response to extracellular stimuli is mediated through intracellular signalling pathways, such as the p38 MAPK pathways, and abnormal phosphorylation events can be a cause of, or contribute towards, disease progression in a variety of disorders (Figure 3). The best-known and most widely reported role of p38α in disease is related to its function in cytokine signalling and promotion of pathological inflammation [125]. Several disease models, including rheumatoid arthritis, psoriasis, Alzheimer's disease [126], IBD (inflammatory bowel disease) [127,128],

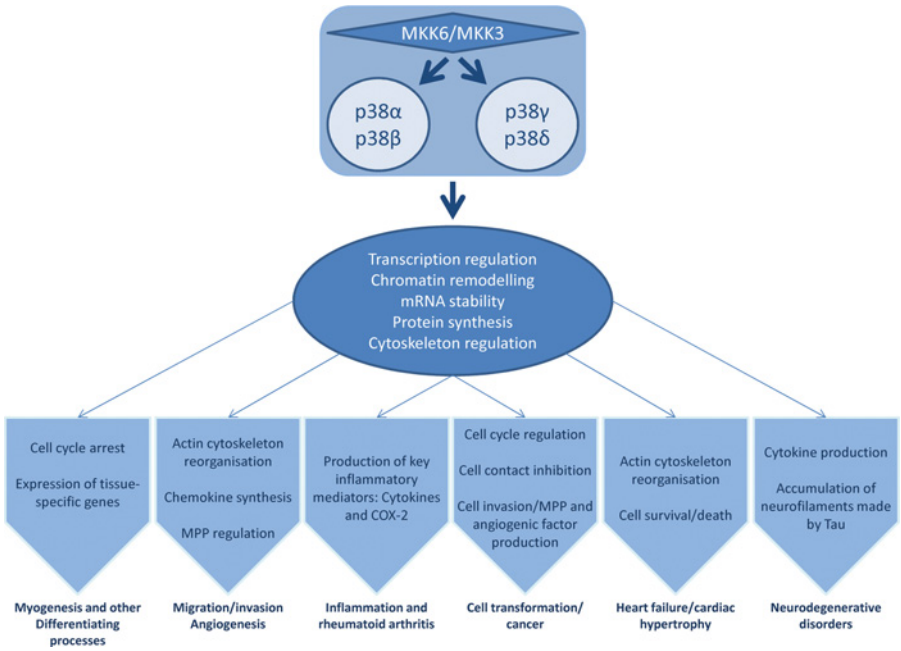

Figure 3 Diversity of cellular processes and physiological functions regulated by the p38 MAPK family

The pathological consequences of the abnormal activation of the pathway are shown at the bottom of the Figure. COX-2, cyclo-oxygenase 2; MPP, Mg^{2+}-dependent protein phosphatase.

Crohn's disease [129], tumorigenesis [14], cardiovascular disease and stroke [130] are all postulated to be mediated, at least in part, by the p38α pathway. Furthermore, previous studies support a role for p38 MAPK in the development, maintenance and/or exacerbation of a number of pulmonary diseases, such as asthma, cystic fibrosis, idiopathic pulmonary fibrosis and COPD (chronic obstructive pulmonary disease) [131]. However, evidence highlights the importance of the differentiation roles of p38α in relation to pathological processes [132].

Many of the inflammation-dependent diseases associated with p38α activity are linked to cytokine-induced differentiation [133]. Activation of p38 MAPK signalling mediates direct or indirect inflammatory cytokine expression, such as IL (interleukin)-1β, IL-6 and TNF (tumour necrosis factor)-α. These cytokines synergistically stimulate the production of other inflammatory cytokines, MMPs (matrix metalloproteinases) and prostanoids [134,135]. p38α has also been involved in the regulation of IL-3, IL-8, MIP1α (macrophage inhibitory protein 1α), GM-CSF (granulocyte/macrophage colony-stimulating factor), VEGF (vascular endothelial growth factor), urokinase-type plasminogen activator and inducible nitric oxide synthase [13,21]. The duration of phosphorylation is crucial in regulating cell fate. Sustained p38α phosphorylation is frequently associated with induction of cellular apoptosis [136,137]; in contrast, transient phosphorylation can be associated with growth-factor-induced survival [138]. Thus the opposite cellular outcome may influence the advance or regression in pathological states.

TNF production in the bone is induced by p38 in rheumatoid arthritis and responsible for bone destruction and inhibition of chondrocyte differentiation, promoting fibrosis in the damaged tissue [139,140]. Increased levels of p38α phosphorylation are seen in the epidermal cells of psoriatic lesions, playing an essential role in promoting the characteristic flaky skin [123]. In asthma, p38 and its downstream target MAPKAPK2 (MAPK-activated protein kinase) are involved in type 2 Th2 cell final activation and differentiation, and production of MCP (monocyte chemoattractant protein)-1 by lung epithelial cells [141,142]. Activation of p38 MAPK induces pro-inflammatory cytokines in IBD, such as IL-1β and TNF-α, both in production and secretion. This regulation takes place in non-immune cells, such as HIMECs (human intestinal microvascular endothelial cells), intestinal epithelium, fibroblasts and myofibroblasts, which participate in IBD and are subject to the direct or indirect effect of p38 MAPK [143,144], and in immune cells such as monocytes and macrophages [145]. Chronic p38α-mediated inflammatory events disrupt homoeostasis and prevent epithelial differentiation, consequently promoting fibroblast maturation and proliferation.

The role of p38α in the neural system has been best demonstrated in relation to neurodegenerative diseases [132]. Disrupted p38 activation has been shown in animal models of neurodegeneration [126] and deposition of tau protein in related pathologies (e.g. Alzheimer's disease) [146]. Although some of the functions are due to the control of inflammatory cytokines released by p38 [147], it has been found that p38α can phosphorylate tau, thereby reducing its ability to promote microtubule assembly [148,149]. In addition, p38α expression in spinal cord neurons seems to be related to neuropathic pain [150,151]. It has also been shown that p38 mediates the survival of cerebellar granule neurons [152].

The p38 MAPK pathway can have both protective and detrimental effects in cardiovascular diseases [132]. It plays an important role in cardiovascular remodelling after injury [153]. After myocardial infarction, p38 activation is a negative regulator of cardiomyocyte proliferation [154]. This potentiates tissue apoptosis [155] and promotes fibrosis [156,157]. Conversely, p38α induces proliferation of vascular smooth muscle cells and vascular regeneration after carotid injury [153].

The complexity of the functions of p38α in the maintenance of haematopoiesis influences its role in haematopoietic diseases. On one hand, p38α is responsible for enhanced stem cell apoptosis, a characteristic of low-grade myelodysplastic syndromes [54,158]. On the other hand, an imbalance towards proliferation may lead to the development of myeloproliferative syndromes, such as leukaemia, lymphomas and myelomas [159–161]. p38 MAPK

is selectively activated by IFNα (interferon α) and mediates the growth-suppressive effects of IFNα in CML (chronic myeloid leukaemia) cells [162].

Finally, the variety of cellular processes involving p38 include many that oppose the oncogenic transformation of solid tissues. As a result, p38α has been considered a tumour suppressor [163,164]. Although most of the suppressor activity is apparently due to promotion of growth arrest and induction of apoptosis [165,166], p38 also contributes to the loss of a malignant phenotype by inducing terminal differentiation of solid epithelial cancer cells [37,167,168].

The paradoxical and contradictory effects of p38α in disease are again closely related to its functions as an inflammatory or differentiation mediator.

CONCLUDING REMARKS

A broad range of intracellular mediators and extracellular insults are involved in p38α activation and function in the cell. They are responsible for the contradictory roles of this pathway not only in different tissues, but also within the same organs and cell types. These opposite roles seem to be related to duration and level of kinase activity. In general, long-term and high levels of p38α activity are involved in the inflammatory response, which usually leads to promotion and progression of disease. High, but transient activation, is linked to apoptosis and may suppress disease (e.g. cancer) or promote pathological processes (e.g. cardiomyopathy). However, constitutive low-level activity promotes differentiation and negatively regulates proliferation. It is this marginal but constant activity that has been reported as being essential for correct stem cell regulation.

Many p38 inhibitors have been developed to tackle inflammatory diseases [6]. Inhibition of p38 prevents the response to inflammatory cytokines and cytokine production at the same time. However, many trials have been stopped owing to toxicities in several tissues. This may be due to the variety of p38α functions and the non-specific cellular inhibition by those drugs [169]. Inhibition of constitutive p38 activity may also interfere with proper cellular turnover and organ physiology. Investigation of the cellular and functional roles of p38α in specific physiological and pathological processes in every organ will allow a better understanding of the responses to drugs targeting this kinase pathway. Cellular and molecular specific drugs directed against mediators of the p38α signalling will improve future use of chemical inhibitors of this pathway in disease therapy.

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