Nuclear P38

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One of the hallmarks of MAPK signaling is the nuclear translocation of some of its components upon stimulation. This is important for the regulation of transcription, activation of enzymes and stabilisation of proteins that lead to the induced processes involved in the response to the particular stimulation or pathologies. Here we describe the nuclear function regulation and mechanism of translocation of two central MAPKs, namely P38α/β that are involved in the regulation of a variety of processes including mainly stress response.

Keywords: p38MAPK ; nuclear translocation ; β-like importins ; inflammation ; cancer

The p38 mitogen-activated protein kinase (p38MAPK, termed here p38) cascade is a central signaling pathway that transmits stress and other signals to various intracellular targets in the cytoplasm and nucleus. More than 150 substrates of p38α/β have been identified, and this number is likely to increase. The phosphorylation of these substrates initiates or regulates a large number of cellular processes including transcription, translation, RNA processing and cell cycle progression, as well as degradation and the nuclear translocation of various proteins. Being such a central signaling cascade, its dysregulation is associated with many pathologies, particularly inflammation and cancer. One of the hallmarks of p38α/β signaling is its stimulated nuclear translocation, which occurs shortly after extracellular stimulation. Although p38α/β do not contain nuclear localization or nuclear export signals, they rapidly and robustly translocate to the nucleus, and they are exported back to the cytoplasm within minutes to hours.

1. Introduction

The p38 mitogen-activated protein kinase (p38MAPK, termed here p38) is a signaling protein kinase that operates within a signaling cascade to transmit extracellular signals to their intracellular targets. The p38 cascade is one of four similar cascades that are all key communication lines between the plasma membranes and the nucleus, and thereby, it is involved in fundamental cellular processes, including stress response, proliferation, differentiation and others [1][2][3]. The four MAPK cascades are extracellular signal-regulated kinase (ERK) 1/2 [4], c-Jun N-terminal kinase (JNK [5]), p38 [6], and ERK5 [7]. The MAPK cascades transmit signals via a sequential activation of protein kinases, which are organized in 3–5 tiers (MAP4K, MAP3K, MAPKK, MAPK, and MAPK activated protein kinases (MAPKAPKs also termed MKs)). Each of these tiers includes more than one kinase (e.g., 4 isoforms at the p38 tier), and the components involved, while the number of tiers may vary between cell lines or under different conditions (see the scheme of the MAPK cascades in ref [8]). In this review, we focus on p38 [9][10], whose cascade is composed of many kinases at the MAP4K and MAP3K levels, MKK3/6, and perhaps MKK4 at the MAPKK tier, p38α-d at the MAPK tier, and several MKs at the next tier (MNK1/2, MSK1/2, MK2/3, and MK5). Interestingly, unlike the other MAPKs, p38 can also be activated via MKK-independent pathways, either by ZAP/LCK-mediated Tyr phosphorylation [11] or by interaction with TAB1 [12]. The downregulation/inactivation of the p38 cascade is regulated by various phosphatases, among them are several dual specificity phosphatases termed MAPK phosphatases (MKPs) that operate directly on the MAPKs [13]. As in all MAPK cascades, p38 transmits signals initiated by various agents, including cytokines and environmental queues, but it is known to operate mainly as a mediator of stress responses. Thus, the kinase is a key regulator of metabolic, oxidative, and endoplasmic reticulum (ER) stresses, but it plays an important role in other physiological processes such as cell cycle, senescence, differentiation, and several aspects of immunological processes.

Being responsible for the various distinct and even opposing fundamental cellular processes, the p38 cascade needs to be tightly regulated. Indeed, several regulatory mechanisms that determine the specificity of the cascade have been identified, including the duration and strength of the signals [13][14], which are controlled mainly by dual specificity phosphatases [15][16], scaffold proteins [17], and dynamic subcellular localization of the cascade's components [18]. Importantly, the central roles of the cascade suggest that its dysregulation may cause various diseases. Indeed, p38 was shown to participate in the induction of pathologies such as inflammation-related diseases [19], autoimmune diseases [20], some types of cancer, and other pathologies, as specified later in this review. Interestingly, unlike other MAPKs, p38 demonstrates distinct and even opposing effects in different cancers, as it was shown to serve either as a tumor

suppressor [21] or tumor promoter [22]. It was also shown that in some cases, it can perform both activities in different stages of cancer development [23]. Although all p38 isoforms have been implicated in the processes listed above, they can be divided into two somewhat distinct subgroups: p38α and p38β (p38α/β) versus p38g and p38d. In this review, we focus on p38α/β, mainly discussing the physiological and pathological roles of these protein kinases, providing information on nuclear p38α/βs and their substrates as well as the importance of their phosphorylation specificity. We also describe the mechanisms involved in the nuclear translocation of p38α/β and compare it to other mechanisms of nuclear shuttling. The fact that p38α/β has so many nuclear targets indicates that the prevention of their nuclear translocation may affect their physiological and pathological functions. Indeed, we show that prevention of the nuclear translocation can be used as a tool to combat inflammation and cancer.

2. Physiological Roles of Nuclear p38α/β

The p38α/β are best known for their involvement in stress signaling, and indeed, these kinases as well as JNKs were initially termed stress-activated protein kinases (SAPKs [24]). However, it was established that their activity is not confined to stress responses, and under some conditions, the p38α/β may participate in the regulation of other processes, such as proliferation, differentiation, immune response, migration, and apoptosis. In many cases, p38α/β mediate their effects by activating and regulating transcription factors. One interesting example is the modulation of endoplasmic reticulum (ER) stress in breast cancer cells, which is mediated by the p38α/β-dependent activation of the transcription factor XBP-1 that decreases the expression of the ER protein ERp29 [25]. Another example is the transcriptional inhibition of autophagy genes downstream of p38α/β in response to oxidative stress in HeLa cells [26]. Other stresses such as UV radiation translational inhibition and others were shown to operate by p38α/β-activated transcription factors, such as ATF, MEF2, Elk1, and p53. However, p38α/β can also affect other regulators (e.g., MKs, proteasome, EGFR [27]) to coordinate their signaling. Notable transcription factor-independent targets that exert p38α/β functions are cell cycle regulators that modulate (usually inhibiting) cell cycle progression. Thus, various stresses induce the downregulation of cyclinD, thereby arresting cells at G1 [28]. In addition, p38α/β cascades were shown to induce the expression of CDK inhibitors, activate p53, or inhibit the transcription factor E2F and the G2/M regulator Cdc25B phosphatase, all leading to the inhibition of cell cycle progression [29]. By contrast, in some systems, p38α/β seem to enhance proliferation. For example, such effects were detected in hematopoietic cells and in some cancer cell lines [30]. These differential effects may be mediated by changes in the duration of p38α/β signals, where transient signals lead to fibroblasts' proliferation, while sustained signals induce cell cycle arrest [31]. However, the molecular mechanisms by which p38α/β are involved in proliferation have not been fully deciphered yet. Thus, the effects of p38α/β on the regulation of stress response or cell cycle progression are well-reviewed (e.g., [32][33]), and we will not elaborate on these effects. However, not less important are the roles of p38α/β in regulating protein degradation and the translocation of proteins upon stimulation. The molecular mechanisms involved are described in detail next.

2.1. 38a/b Regulation of Protein Degradation

The role of p38α/β in the regulation of protein degradation is widespread, mainly upon stress signals, and may involve several distinct mechanisms in both the cytoplasm and the nucleus. One such mechanism that mostly occurs in the nucleus involves phosphorylation of ubiquitin E3 ligases, such as Siah2, which is known to regulate PHD3 that further controls the stability of the transcription factor HIF1 α. p38α/β phosphorylate Siah2 on Ser24 and Thr29, thereby facilitating its activity towards degradation of PHD, and in turn destabilization of HIF1 α [34][35]. Similarly, p38α/β phosphorylate the E3 ligase Skp2 at Ser64, leading to enhanced degradation of the transcription factor Nkx3-1 and thereby blocking its effects on estrogen receptor-mediated gene expression [36]. Another mechanism involves the phosphorylation of the ubiquitination target which can either facilitate or inhibit the ubiquitination process. Examples for enhanced degradation are the phosphorylation of RBP-Jk at Thr339 which subsequently induces its degradation [37], or phosphorylation of p300 at Ser 1834 (together with AKT) that induces its degradation to allow DNA repair [38]. On the other hand, phosphorylation of the inflammation regulator TRIM9s at Ser76/80 stabilizes it, thereby causing a positive feedback loop for the degradation of the upstream MKK6 [39]. Interestingly, p38α/β may also regulate proteasomal activity and localization to govern protein stability in general. It was shown that osmotic stress inhibits proteasome by p38α/β-dependent phosphorylation of the proteasome subunit Rpn2 at Thr273, which is important for peptide degrading activity [40]. This inhibitory effect was supported by the finding that p38 inhibitors elevate proteasome activity under varying conditions [41]. In addition, p38α/β may regulate the subcellular localization of the proteasome by phosphorylating the proteasome-binding protein PI31. Consequently, this phosphorylation facilitates the association of the proteasome with the motor dynein complex, and regulates its transport on axons [42]. Other proteins whose stability is regulated by direct p38 phosphorylation are Cdt1, HBP1, p18Hamlet, Rb1, SRC3, CDC25A/B, CyclineD1/3, TACE, p53, Snail, Twist, Nav1.6, PGC1 α, HuR and Drosha [43]. Thus, p38α/β use various molecular mechanisms to regulate stimulation-dependent proteins stability.

2.2. p38a/b Regulation of Stimulated Nuclear Translocation

Another important process that is regulated by p38α/β is the dynamic change of protein localization upon stimulation. As described above regarding the regulation of protein degradation, the effect of p38α/β on nuclear translocation can be either global or specific to certain phosphorylated proteins. The global effects may be derived by p38α/β phosphorylation of either nuclear pore proteins or of karyopherins (importins/exportins). Indeed, it was shown that the nuclear pore proteins Nup62, Nup153, and Nup214 are phosphorylated by p38 (or ERK), and this phosphorylation inhibits the global nuclear protein shuttling initiated by viruses that affect the heart such as the encephalomyocarditis virus [44]. A similar effect was detected in cardiomyocytes of failing hearts in rats and humans, where p38α/β phosphorylation mediates the rearrangement of nuclear pores, leading to a decreased uptake of nuclear localization signal (NLS)-containing proteins [45]. As for karyopherins, it was shown that p38α/β regulate the expression of the beta-like importins (Imp) Imp7 and Imp8 [46], which are important for the nuclear translocation of various signaling proteins. Aside from the global changes, p38α/β is known to phosphorylate the translocating proteins themselves to mediate either nuclear accumulation or nuclear export. For example, the active SMAD3 phosphorylation by p38α/β upon TGF β stimulation reduces the rate of its nuclear translocation [47]. A similar effect was detected for FOXO3 α, which is phosphorylated by p38α/β at Ser7 to promote its nuclear localization [48]. The nuclear translocation of RhoA due to p38 phosphorylation upon LPS treatment and of actin upon TPA stimulation [49] was reported as well [50]. On the other hand, p38α/β phosphorylation may be responsible for the nuclear export of proteins; the most famous among them are its downstream MKs. It was shown that MK2/3 contain an NLS, which directs them to the nucleus of resting cells. Following phosphorylation by p38α/β, MK2/3 are exported to the cytoplasm, due to unmasking of the C-terminal NES of the MK2/3 (reviewed in [51]). Moreover, MK5 contains an NLS as well, and can be found in the nucleus under certain conditions. However, its export after p38α/β phosphorylation seems to be mediated not only by exposure of NES but also by anchoring to ERK3/4 [52]. Other proteins whose localization is directly regulated by p38α/β phosphorylation are retinoic acid receptor-g, [53], androgen receptor [54], estrogen receptor-α [55], 5-lipoxygenase [56], the Hippo pathway transcription factor TEAD4 [57], as well as other proteins (NFATc4, Xbp1s, Drosha, CRTC2, HuR, Rabenosyn5, Lamin-B, FGFR1, PIP4K2B, EZH2, and Tripeptidyl-Peptidase II) as specified in previous reviews. Thus, p38α/β use several distinct mechanisms for the regulation of nuclear translocation of proteins upon various stimulations.

3. Role of Nuclear p38α/β in Pathologies.

Abnormal activity and dysregulation of the p38α/β cascade are associated with a variety of diseases. Indeed, p38α/β were implicated in the induction and maintenance of several pathologies such as inflammation [19], cancer , and autoimmune diseases mentioned above, but also Friedreich's ataxia [58], Parkinson's disease [59], Alzheimer's disease [60], cardiac hypertrophy [61], hypoxic nephropathy [62], and diabetes [63]. In many cases, the role of p38α/β is not direct, but it is mediated by p38α/β-regulated inflammation, which in turn contributes to the development of the diseases. For example, Parkinson's disease is induced in part by neuroinflammation associated with glial cells [61], and colorectal cancer often develops due to initial inflammatory disease of the colon [64]. Moreover, p38α was first identified due to its involvement in the production of pro-inflammatory cytokines upon endotoxin treatment, mainly via nuclear processes [65]. It was later found that p38α/β are involved in the production of pro-inflammatory cytokines, such as TNF-α, IL-1 β, IL-2 IL-6, IL-7, and IL-8, and also in the regulation of other inflammation mediators such as Cox2 [66][67]. Although many of these effects involve nuclear processes in some instances, it may be regulated also by translation, due to AU-rich elements (ARE) in the 3′ untranslated region of their mRNA. The presence of these elements is known to shorten the half-life of mRNA containing them or block their translation, mainly due to the phosphorylation of ARE binding proteins such as HuR [68] by MK2 downstream of p38α/β [69]. The pro-inflammatory cytokines are known players in many inflammation-related diseases such as inflammatory bowel diseases (IBD), psoriasis asthma, rheumatoid arthritis, inflammation-induced cancer, and more [66]. However, the actual trigger for inflammation in some systems, either acute or chronic, is not known, but it still requires p38α/β for its mediation. The means by which p38α/β are involved in these processes and the upstream components involved need further investigation. Due to the involvement of p38α/β in several inflammatory diseases, it became clear that specific inhibitors of these kinases should become a beneficial therapeutic approach. Indeed, in the past decade, more than 20 specific inhibitors of p38α/β were developed and proven very effective in pre-clinical investigations, demonstrating good tolerability and efficacy in several mouse models [70][71]. However, when subjected to clinical trials, the effects were much less favorable. Apparently, except for one inhibitor, pirfenidone, which by itself demonstrated a weak and unselective effect, no durable therapeutic effects have been detected for any of the others tested. The reasons for these failures among the different drugs are numerous, and while in some cases they were toxic, the more common problem was that after an initial good response, there was a rebound effect that increased inflammation within weeks. The reason for this rebound is still not clear and is currently under investigation.

In the past decade, substantial research has been devoted to studying the role of p38α/β in cancer, confirming that these kinases can act either as tumor promotors, or more frequently, as tumor suppressors. The tumor suppressor effects were corroborated by immortalized MKK3/6 knockout fibroblasts that were shown to have a higher tendency to develop xenografts in nude mice[72]. Moreover, it was shown that the expression of MKK3/6, or other components of the cascade, is reduced in many cancers [73]. The function of p38α/β as tumor suppressors usually affect early stages of tumor initiation, and it generally involves either an inhibition of cell cycle progression, enhanced apoptosis, senescence, or differentiation. Similar to the effects in non-transformed cells, the inhibition of cell cycle by p38α/β in tumors can be mediated by the direct or indirect phosphorylation of several nuclear substrates. Among them are CyclinD, whose inhibition may cause apoptosis in colorectal cancer cells, p53, that leads to the upregulation of p21Cip1/WAF1, GADD45, and 14-3-3 proteins to cause cell cycle arrest [74], RB1, which prevents the metastasis of prostate cancer [75], and others. Additionally, it was shown that p38α/β facilitate the production of apoptotic cytokines such as TNF-α [76]. The terminal differentiation of cancer was detected in rhabdomyosarcoma cells overexpressing MKK3 or MKK6 [77], and premature senescence was related to p38α/β-induced phosphorylation of the transcription factor HBP1 [78]. Some other effects on tumor promotion, although less frequent, may be mediated via inflammation in relevant cancers. Other mechanisms that may initiate cancer by p38α/β are elevated migration/invasion, increased angiogenesis , or a direct effect on proliferation [79][80]. As mentioned above, p38α/β are central regulators of inflammation, which in many cases is involved in cancer initiation and progression [81]. Indeed, some of the specific p38α/β inhibitors that have been developed over the years, although having failed in inflammation-related clinical trials, were proven useful in treating cancers [82]. Interestingly, in some cancer cells, p38α/β may facilitate migration by several mechanisms, including an enhanced production of chemoattractants [83] or reduced expression of fibulin 3, which is a cell migration blocker [84]. Finally, the involvement of p38α/β in angiogenesis, which supplies blood vessels to the tumors and enhances their growth, was shown to occur in head and neck cancer [85]. Some reports have shown that the molecular mechanisms involved include expression of vascular endothelial growth factor (VEGFA) and hypoxia-inducible factor 1 α (HIF1 α . Interestingly, in models of colorectal cancer, p38α/β may act as either tumor suppressors or promoters in different stages of cancer development.

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