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p38 MAP Kinases in Heart

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1. Introduction

p38 kinases are members of the mitogen-activated protein kinases (MAPK) which are also referred to as stress-activated serine/threonine-specific kinases (SAPKs) with established involvement in a wide range of signaling pathways and different biological processes. The prototypic p38 MAPK, p38α MAPK, was originally identified as a tyrosine phosphorylated protein detected in LPS-stimulated macrophages with essential function for inflammatory cytokine production (Han, Lee, Bibbs, & Ulevitch, 1994; Han, Lee, Tobias, & Ulevitch, 1993) and as an upstream activating kinase of MAPK-activated protein kinase 2 (MK2) in cells stimulated with arsenite, heat shock, or interleukin-1 (Freshney et al., 1994; Rouse et al., 1994). Extensive studies have now revealed that p38 MAPKs have critical roles in many different tissues far beyond immune regulation and inflammatory responses. In this review, we will focus on the structure and molecular biology of p38 MAP kinases, and their specific roles in heart, especially regarding myocyte proliferation, apoptosis, and hypertrophic responses (Rose, Force, & Wang, 2010).

2. Molecular Structure of p38 MAPK

In human and mammals, there are four isoforms in the p38 MAPK sub-family including p38α , p38β , p38γ and p38δ isoforms. Human p38 MAP Kinases are encoded by MAPK14 for α (NCBI Gene ID: 1432, chromosome 6), MAPK11 for β (NCBI Gene ID: 5600, chromosome 22), MAPK12 for γ (NCBI Gene ID: 6300, chromosome 22), and MAPK13 δ (NCBI Gene ID: 5603, chromosome 6), respectively. They have high degree of sequence homologies at amino acid level (>60% identity among isoforms) (Figure 1). In addition, p38α MAPK mRNAs have 4 transcript variants due to alternative splicing (NM_001315.2, NM_139012.2, NM_139013.2, and NM_139014.2), resulting in protein variants with different sequences at the C-terminus (Figure 2). Each p38 MAPK isoform has different tissue-specific expression pattern (M. Li, Liu, & Zhang, 2011). p38α MAPK is ubiquitously expressed in many cell types, in contrast p38β MAPK is highly expressed in brain and lung,

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p38γ MAPK is mostly detected in skeletal muscle and nerve system, and p38δ MAPK is enriched in uterus and pancreas (Ono & Han, 2000). All isoforms possess the same conserved domains (from I to X) and a Thr-Gly-Tyr (TGY) dual phosphorylation motif that serves as activation switch for the kinases (Figure 1). As a shared mechanism among all MAP kinase families, p38 MAPKs are activated by upstream kinases (MAPKK) via targeted phosphorylation of the TGY motif, although autophosphorylation mediated activation mechanism is also reported (Han et al., 1994; Lu et al., 2006). The structures of human p38α in inactive and active states have been solved by X-ray crystallography. The phosphorylated TGY motif and the length of the activation loop are identified to be different from members of the other two MAPK branches i.e. extracellular signal-regulated kinases (ERK) and c-jun N-terminal kinases (JNK). This unique signature likely confers substrate specificity to each MAPK subfamilies (Roux & Blenis, 2004). Based on phylogenic and gene synteny analysis of MAPK 11,12,13 and 14 genes across different species, it is speculated that MAPK11/12 cluster is the gene duplication product of MAPK13/14 cluster, and MAPK12 is originated from MAPK11 also by gene duplication (M. Li et al., 2011). p38 MAPKs form functional complexes with substrates and modulators in cells. For example, MK2 is a binding partner p38α MAPK, interacting in a “head-to-head’ manner, and present active sites of both kinases with extensive intermolecular interactions that dictate substrate and intracellular localization (White, Pargellis, Studts, Werneburg, & Farmer, 2007). p38α MAPK is also reported to be a client protein for Hsp90/Cdc37 which constitutively binds and modulates its non-canonical activation by TAB1 (Ota, Zhang, Ping, Han, & Wang, 2010) Numerous inhibitors against p38 MAPKs have been reported with diverse chemical structures. Most inhibitors such as SB203580, VX745, RO3201195, and AMG548 bind competitively to the ATP binding site. On the other hand, BIRB796 inhibit p38 MAPK activity by conformational change that exclude ATP binding (J. Zhang, Shen, & Lin, 2007).

3. Cellular function of p38 MAP Kinases

3.1. Subcellular localization of p38 MAPK

Under basal conditions, p38 MAPKs are detected in both the nucleus and the cytoplasm. However, upon activation, p38 MAPKs are trans-located into the nucleus (Zarubin & Han, 2005) and inactivated p38 MAPKs are exported to the cytoplasm. This translocation process depends on p38 MAPK phosphorylation but not its own catalytic activity, suggesting the involvement of upstream kinases (Wood, Thornton, Sabio, Davis, & Rincon, 2009). This extracellular stimulation-dependent translocation of p38 MPAKs is an essential process for its functions in various cell types. In addition to its phosphorylation, microtuble- and dynein-dependent processes are reported to be involved in p38 MAPK translocation (Gong, Ming, Deng, & Jiang, 2010). In addition, MK2 is also involved in subcellular localization of p38 MAPK s. Activated MK2 forms a complex with p38 MAPKs in the nucleus and then triggers the export p38/MK2 complex to cytoplasm, hence directing p38 MAPK activities to cytosolic downstream targets (Ben-Levy, Hooper, Wilson, Paterson, & Marshall, 1998). Different p38 MAPK isoforms also have distinct subcellular localization patterns. p38-regulated/activated protein kinase (PARK) interacts with p38α MAPK and localizes in the nucleus, whereas p38β-PARK complex localizes in the cytosol. This differential localization is determined by specific motifs between amino acid 145 and 156 in both p38 MAPK

isoforms (Q. Li et al., 2008). In addition to the translocation between nucleus and cytosol, p38 MAPK also translocates to mitochondria. p38 MAPK is known to activate p53 and then promote apoptosis by inducting expression and translocation of Bax in mitochondria (S. J. Kim, Hwang, Shin, Kang, & Chun, 2002; Mayr, Hu, Hainaut, & Xu, 2002). In neuronal cell, p38 MAPK was shown to translocate to mitochondria in response to nerve growth factor withdrawal, resulting in phosphorylation of Bcl-2 and inactivation of its anti-apoptotic effects (Torcia et al., 2001).

3.2. Activation/deactivation of p38 MAPK

Activation of p38 MAPK pathway has been implicated in a variety of stress response in addition to inflammation, including osmotic shock, heat, and oxidative stress (Johnson & Lapadat, 2002; Kyriakis & Avruch, 2001; Ono & Han, 2000). The canonical pathway for p38 MAPK activation involves cascades of MAP3Ks and MAP2Ks as upstream kinases, including MAP kinase kinase kinases (MEKK1-4), TGFβ-activated kinase (TAK1), thousand-and-one amino acid 1-3 (TAO1-3), mixed-lineage kinase 2/3 (MLK2/3), and apoptosis signal-regulating kinase 1/2 (ASK1/2) at the MAP3K level, and MKK 3, 6 and 4 at the MAP2K level (Figure 3). Phosphorylation of p38 MAPKs at the threonie/tyrosine residues (TGY) in the kinase activation loop resulted in a conformational change which induces the kinase catalytic activity and binding to substrates (Cuadrado & Nebreda, 2010). Other than MKK dependent activation, TAK1-binding protein 1 (TAB1), ZAP70 and HSP90/Cdc37 have been reported to regulate non-canonical activation of p38 MAPK via autophosphorylation (Ge et al., 2002; Ota et al., 2010; Salvador et al., 2005; Tanno et al., 2003). Uniquely, ZAP70 phosphorylates p38α on Tyr323 before it is further activated by autophoshorylation (Salvador et al., 2005). Furthermore, acetylation of p38 at lys-53 in the ATP-binding pocket also enhances p38 MAPK activity during cellular stress (Pillai et al., 2011). Therefore, p38 MAPKs can be induced by varies stresses via different mechanisms.

Inactivation of p38 MAPK is primarily carried out through the dephosphorylation of the TGY motif. Several phosphatases from protein phosphatase (PP) family, protein tyrosine phosphatase (PTP) family, and dual-specificity phosphatase (DUSP) family are implicated in this process. For example, ser/thr phosphatases PP2Cα /β suppress activity of p38 MAPKs through direct interaction as well as suppression of MKKs/TAK1 in mammalian cell (Hanada et al., 1998; Takekawa, Maeda, & Saito, 1998). PTPs, such as hematopoietic PTP (HePTP) and striatal-enriched phosphatase (STEP), are known to bind to MAPKs through a kinase-interaction motif (KIM) and inactivate p38 MAPK s by dephosphorylating the phosphotyrosine residue in their activation loop (Pulido, Zuniga, & Ullrich, 1998; Saxena, Williams, Brockdorff, Gilman, & Mustelin, 1999; Saxena, Williams, Gilman, & Mustelin, 1998). DUSPs, which have a docking domain to MAPKs and dual-specific phosphatase activity, bind to p38 MAPK s and dephosphorylate both phosphotyrosine and phosphothreonine residues in the TXY motif (reviewed in (Cuadrado & Nebreda, 2010)). In addition to these phosphatases, molecular chaperones such as Hsp90-Cdc37 complex can also modulate p38 MAPK autophosphorylation activity and non-canonical activation (Ota et al., 2010).

3.3. Downstream targets of p38 MAPK

Diverse functions of p38 MAPKs are mediated through a large variety of downstream substrates. As reviewed by Young et al, p38 MAPK target molecules are first characterized by using p38 MAPK specific inhibitors, SB203580 and SB202190, and more recently in gene deletion mouse models. Inhibition/deficiency of p38 MAPKs causes changes in cell survival/apoptosis, proliferation, differentiation, migration, mRNA stability, and inflammatory response in different cell types (Young, 2013). Although a vast majority of the literature focus on p38α MAPK isofrom function, a significant number of studies have been conducted to demonstrate the different functions of the distinct isoforms of p38 MAPK, For instance, p38β MAPK contributes to regulate Store Operated Calcium Entry (SOCE) and permeability responses in endothelial cell and bladder cancer cell migration through STIM1 and Hsp27, respectively (Sundivakkam, Natarajan, Malik, & Tiruppathi, 2013; Yu et al., 2014). Although distinct roles of p38γ and δ MAPK isoforms are not well-known, several evidences have been provided that they have critical roles in biological processes such as tumorigenesis (Del Reino et al., 2014). p38γ regulates G2-M transition in mitotic processs via stabilizing chromosome and an energetic signaling in skeletal muscle contraction (Brault, Pizzimenti, Dentel, & Wiseman, 2013; Kukkonen-Macchi et al., 2011). p38δ MAPK plays a role of differentiating monocyte to bone-forming monoosteophils in bone repair process and insulin secretion and survival of pancreastic β cells (Sumara et al., 2009; Z. Zhang & Shively, 2013). From the p38 MAPK isoform knockouts study, deficiency of p38α MAPK isoform in mouse leads to embryonic death as a result of defective placental development, whereas that of other isofoms shows subtle phentypes (Allen et al., 2000; Beardmore et al., 2005; Mudgett et al., 2000; Sabio et al., 2005; Tamura et al., 2000). Considering the severity of phenotypes in isoform specific knockout mice, p38α MAPK seems to be the major isofom of the family at least during development and inflammatory responses, although p38β MAPK, p38γ MAPK, and p38δ MAPK have also pivotal roles under other conditions. (Aouadi, Binetruy, Caron, Le Marchand-Brustel, & Bost, 2006; Xing, Bachstetter, & Van Eldik, 2013).

Many kinases are activated by p38 MAPKs such as MK2/3, PARK, MAPK interacting protein kinases 1/2 (MNK1/2), mitogen and stress activated protein kinase 1/2 (MSK1/2), and eukaryotic elongation factor 2 kinase (eEF2k) (Cuadrado & Nebreda, 2010; Gallo & Johnson, 2002). MK2 is one of the well-studied downstream targets of p38 MAPKs and its activity in turn can regulate cell survival/apoptosis, proliferation, differentiation, mRNA stability and inflammatory response. In addtion, MK2/p38 complex stabilizes each other (Gaestel, 2006; Kotlyarov et al., 2002; Sudo, Kawai, Matsuzaki, & Osada, 2005). p38/MK2-dependent cellular processes are regulated by numerous downstream substrates such as small heat shock protein 27 (HSP27), lymphocyte-specific protein1 (LSP1), cAMP response element-binding protein (CREB), cyclooxygenase 2 (COX2), activating transcription factor 1 (ATF1), serum response factor (SRF), and mRNA-binding protein tristetraprolin (TTP) (Rose et al., 2010; Zarubin & Han, 2005). CREB and TTP can regulate mRNA stability and transcriptional factor activity in a MK2-dependent manner (Rolli, Kotlyarov, Sakamoto, Gaestel, & Neininger, 1999; Stoecklin et al., 2004). MK3 is highly homologous to MK2 and these two kinases have similar functions (Cargnello & Roux, 2011). Another well-studied downstream target of p38 MAPKs is MSK1/2, which is thought to regulate the subcellular

localization of p38 MAPK and ERK1/2 (Cargnello & Roux, 2011). These kinases are involved in the transcriptional regulation by CREB, STAT3, NFkB-dependent transcription and chromatin remodeling (Drobic, Perez-Cadahia, Yu, Kung, & Davie, 2010; Pierrat, Correia, Mary, Tomas-Zuber, & Lesslauer, 1998; Vermeulen, De Wilde, Van Damme, Vanden Berghe, & Haegeman, 2003; Wierenga, Vogelzang, Eggen, & Vellenga, 2003).

In addition to protein kinases such as MK2/3 and MSK1/2, many transcription factors are direct downstream targets of p38 MAPKs, including ATF1/2/6, c-MYC, c-FOS, GATA4, MEF2A/C, SRF, STAT1, and CHOP. ATF2 isa member of the ATF/cAMP response element-binding protein family and a regulator of tumorgenesis. It can be activated by p38 MAPKs as well as JNK through phosphorylation on threonine 69 and 71 (Raingeaud et al., 1995; Vlahopoulos et al., 2008). ATF2 regulates other transcription factors in extracellular stresses; genes related with growth and tumorgenesis; and genes associated with homeostasis (Bhoumik, Lopez-Bergami, & Ronai, 2007). Furthermore, ATF2 has a negative feedback mechanism for p38 MAPK regulation through DUSPs (Breitwieser et al., 2007). In short, upstream and downstream signaling molecules constitute the signaling network of p38 MAPKs as activators, modulators and effectors (Figure 3).

4. Function of p38 MAPK in Cardiovascular System

4.1. Regulation of cardiomyocyte proliferation

Whereas fetal and neonatal cardiomyocytes have a high mitotic activity, terminally differentiated cardiomyocytes in adult heart have diminished capacity to proliferate. Myocyte proliferation is dynamically regulated during cardiac maturation in postnatal heart and is an important area of investigation for cardiac regeneration after injury. Recently, several lines of evidence have indicated that cell cycle reentry and progression can be induced in adult myocytes while cell proliferation can be enhanced in neonatal and progenitor cardiomyocyte by inhibition of p38 MAPK activities. Engel *et al.* first showed that binucleation of cardiomyocyte is regulated by p38 MAPK which accumulates at the mid-body during myocyte cytokinesis and disrupts anillin localization (Engel, Schebesta, & Keating, 2006). They also demonstrated that p38 MAPK inhibition in serum-treated cardiomyocyte up-regulated core components of the central spindle and resulted in the mid-body formation. Combination FGF1 stimulation and p38 MAPK inhibitor up-regulates cell cycle regulating genes including cyclin A2, cdc2a, and cyclin B, resulting in induction of mitosis in both adult and fetal cardiomyocyte (Engel, Hsieh, Lee, & Keating, 2006; Engel et al., 2005). Therefore, p38 MAPK is associated with cell-cycle arrest in mammalian cardiomyocytes and its inhibition may represent a strategy to promote cardiac regeneration in response to injury.

4.2. Apoptotic roles in the heart

Under stressed conditions such as ischemia and oxidative injury, cardiomyocytes suffer from apoptotic death in heart. Myocardial ischemia is a potent inducer of p38 MAPK activation. Using both *in vivo* and *ex-vivo* cardiac ischemia/reperfusion (I/R) injury models, p38 MAPK inhibition has been demonstrated to blunt apoptosis in I/R injured hearts. Similar cardioprotection is also observed in a transgenic heart expressing a dominant negative

mutant of p38α MAPK (Ma et al., 1999; Ren, Zhang, Kovacs, Wang, & Muslin, 2005). Consistent with these studies, overexpression of p38α MAPK reduced anti-apoptotic protein Bcl-xl expression in cultured neonatal cardiomyocyes and p38 inhibition reduced stress-induced apoptosis in cultured cardiomyocyes (Kaiser et al., 2004; Sharov et al., 2003). It is reported that p38 MAPK dependent apoptosis in heart is mediated via downstream events mediated by STAT1, CHOP, FAK, SMAD, cytochrome c, NF-kB, PTEN, and p53 (Eiras et al., 2006; Fiordaliso et al., 2001; Ghosh, Das, Manna, & Sil, 2009; Qian et al., 2012; Schroder, Heger, Piper, & Euler, 2006; Stephanou et al., 2001; Zhao et al., 2010). However, some reports demonstrated that p38 MAPK also involves in anti-apoptotic effect via phosphorylation of α β-Crystallin or induction of Pim-3 during early response to oxidative stress or anoxic preconditioning respectively (Aggeli, Beis, & Gaitanaki, 2008; D. Liu et al., 2009; Mitra, Ray, Datta, Sengupta, & Sarkar, 2014). More interestingly, p38α MAPK and p38β MAPK appear to have an opposite role in apoptosis (Wang et al., 1998). Whereas p38α MAPK has a pro-apoptotic role via p53 activation, p38β MAPK has a pro-survival role via inhibition of ROS formation (J. K. Kim, Pedram, Razandi, & Levin, 2006; H. Liu, Pedram, & Kim, 2011). Interestingly, a recent report suggests that the protective effect of estrogen against oxidative stress via manganese superoxide dismutase induction is mediated by active mitochondrial localized p38β MAPK in cardiomyocytes (H. Liu, Yanamandala, Lee, & Kim, 2014). Therefore distinct function of p38α MAPK and p38β MAPK in cardiac apoptosis regulation is potentially contributed by their distinct intracellular localization, . Under ischemic condition, chronic insulin exposure and metabolic stresses induce p38 MAPK activation and promote insulin receptor substrate 1/2 (IRS1/2) degradation, resulting in AKT inactivation and subsequent myocyte apoptosis and heart failure (Qi et al., 2013). In general, chronic activation of p38 MAPK activity is viewed as pathological and pro-apoptotic, and inhibition of p38 MAPK activity is in clinical evaluation as a potential therapy to mitigate acute injury in ischemic heart failure (Marber, Rose, & Wang, 2011).

4.3. Cardiac Hypertrophy Regulation

Cardiac hypertrophy is a significant component of pathological remodeling in the diseased hearts and a major risk factor for heart failure and advert outcome. In past decade, numerous reports have demonstrated that p38 MAPK inhibition using pharmacological inhibitors or dominant negative p38 MAPK mutant expression can attenuate cardiomyocyte growth in response to hypertrophic stimuli *in vitro* (Liang & Molkentin, 2003; Nemoto, Sheng, & Lin, 1998; Wang et al., 1998; Zechner, Thuerauf, Hanford, McDonough, & Glembotski, 1997). In addition to inhibitory studies, chronic activation of p38 MAPK pathway by overexpression upstream kinases has indicated that p38 MAPK activation is sufficient to induce hypertrophic response in cultured cardiomyocytes (Nemoto et al., 1998; Wang et al., 1998; Zechner et al., 1997). Adenoviral infection of constitutive active mutant of MKK3 or MKK6 in neonatal rat ventricular myocytes (NRVMs) result in characteristic hypertrophic responses, including an increase in cell size, enhanced sarcomeric organization, and elevated atrial natriuretic factor expression. Furthermore, the hypertrophic response by MKK3/6 is enhanced by co-infection of an adenoviral vector expressing p38β MAPK, and was suppressed by the p38β MAPK dominant negative mutant (Wang et al., 1998). In addition, adenoviral infection of p38α MAPK in NRVMs upregulated fibrosis related gene expression, whereas that of p38β MAPK upregulated BNP gene at transcriptional level

(Koivisto et al., 2011). As mentioned above, p38α MAPK enhanced MKK3 activation-induced apoptotic activity. Taken together, these observations indicate that p38α MAPK and p38β MAPK have distinct roles in cardiac hypertrophy and pathological remodeling *in vitro*.

Despite the evident *in vitro* impacts of p38 MAPK activation on hypertrophic response, the *in vivo* impact is far from uniformed. Cardiac-specific overexpression of active MKK3 and MKK6 mice do not show the significant increase in cardiomyocyte size, although they show marked cardiac interstitial fibrosis, ventricular wall thinning, left ventricular dysfunction, immature death, and expression of fetal marker genes characteristic of cardiac failure (Liao et al., 2001). In addition, cardiac-specific overexpression of dominant negative p38α MAPK in mice promotes cardiomyocyte growth (Braz et al., 2003). In contrast with these reports, acute activation of endogenous p38 MAPK in adult heart using cardiac-specific and inducible expression of a constitutively active MKK3 results in cardiac hypertrophy and fibrosis (Streicher, Ren, Herschman, & Wang, 2010). This discrepancy might be caused by developmental timing and the duration of p38 MAPK activation. Because our unpublished data and other report suggest p38 MAPK involves in post-natal cardiac maturation and proliferation (Engel et al., 2005), In addition, cardiac-specific p38 MAPK dominant negative transgenic mice and cardiac-specific p38α knockout mouse showed an elevated cardiac hypertrophy in response to pressure overload (Nishida et al., 2004; S. Zhang et al., 2003). Recent studies have reported that p38 MAPK also plays critical roles in the development of physiological hypertrophy. Using ASK1 knockout and cardiac – specific p38α MAPK knockout mice, Taniike *et al* demonstrate that loss of p38α MAPK results in enhanced physiological hypertrophy through an increase in AKT activity in response to swimming exercise (Taniike et al., 2008). On the other hand, the transgenic mice expressing p38α MAPK dominant negative mutant do not show the enhancement in physiological hypertrophy in response to swimming exercise (Watanabe et al., 2007). Taken together with pressure overload and swimming exercise studies, loss of function through cardiac-specific knockout and transgenic dominant negative p38α MAPK expression yield distinct outcome in response to hypertrophic stimuli. Therefore, although p38 MAPK activation is related to cardiac hypertrophy, its role *in vivo* is controversial and remains to be further elucidated. More mechanistic studies regarding isoform specific function and stress-specific response are needed before a targeted therapy can be developed for heart diseases.

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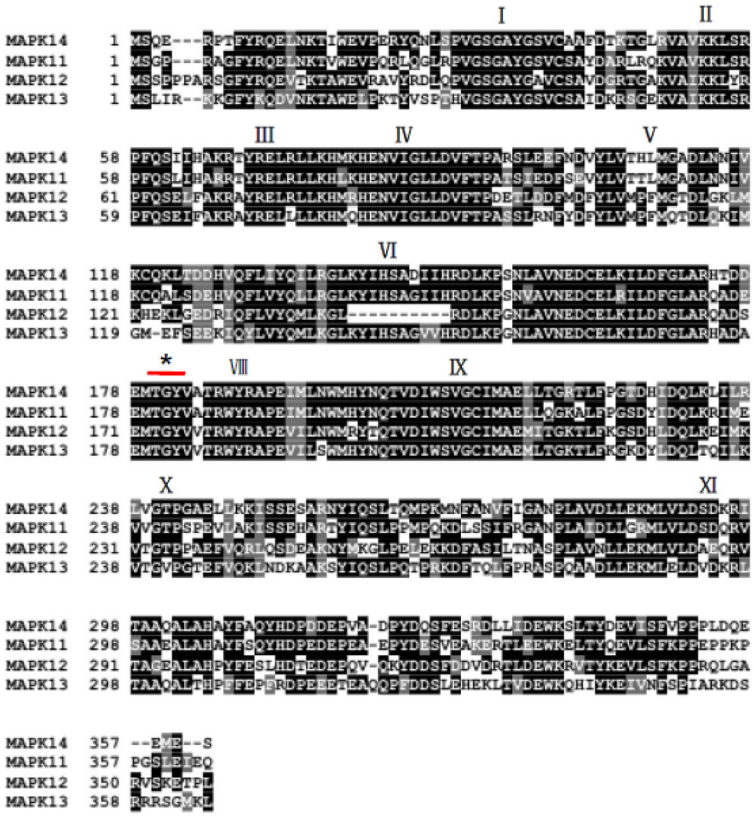

Figure 1. Primary sequence of human p38 MAPK isoforms

Shaded blocks are conserved domains from I to XI. * indicates the TGY motif in the kinase activation loop.

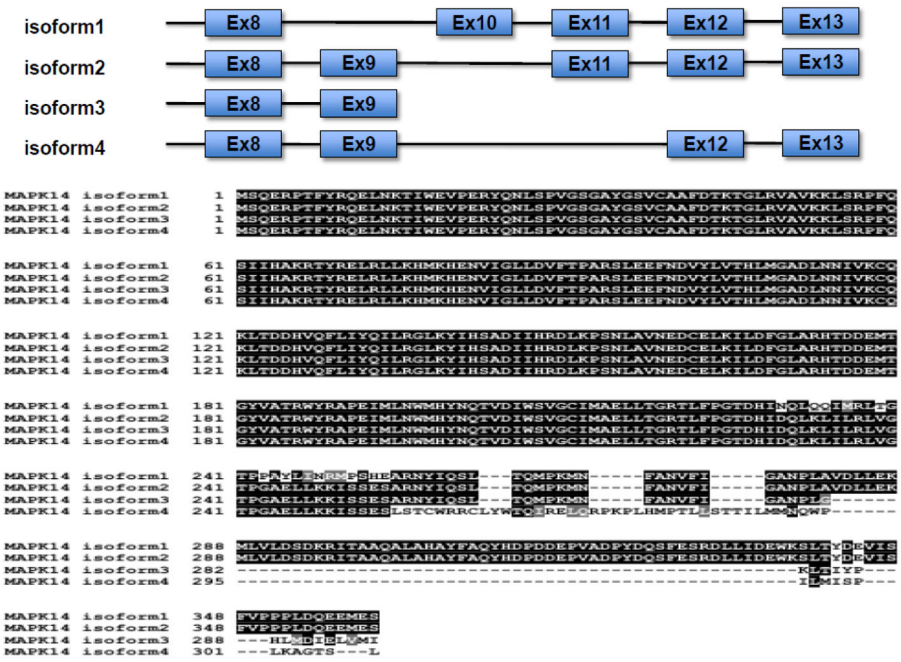

Figure 2. Human p38α MAPK (MAPK14) transcription variants

Top panel: Isoform specific exon utilization of p38α MAPK variants. **Bottom panel:** amino acid sequences of p38α MAPK variants.

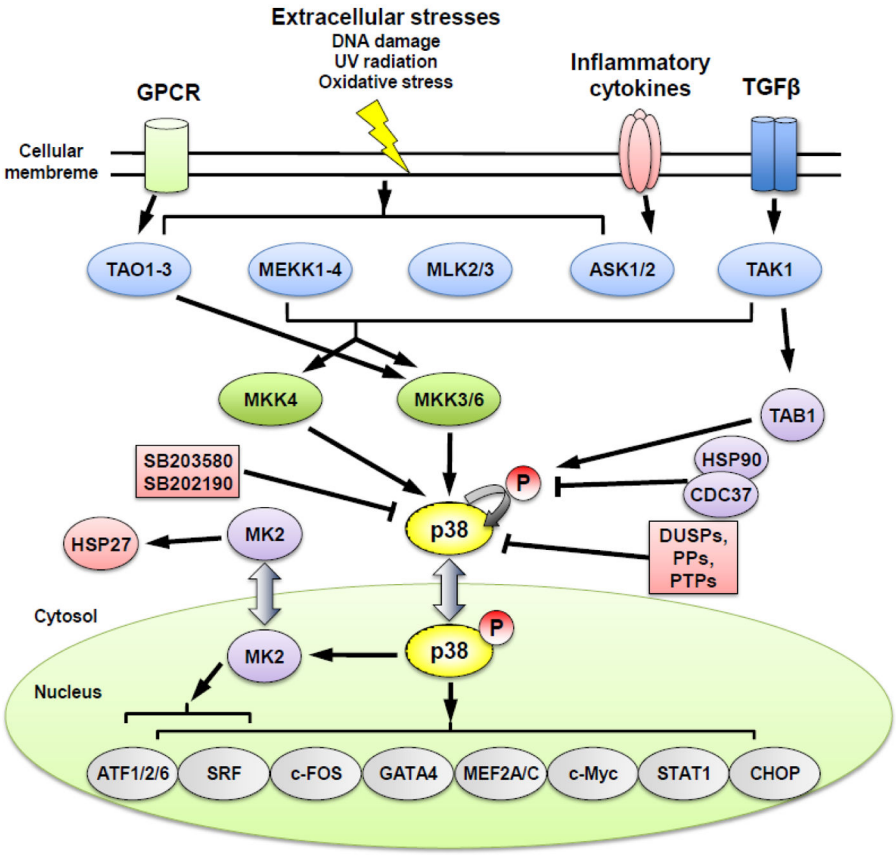

Figure 3.

Signaling pathways and molecular network of p38 MAPK activation and downstream targets.