Role of p38α in apoptosis: implication in cancer development and therapy

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1- Introduction

The family of p38 mitogen-activated protein kinases (MAPKs) belongs to the MAPK superfamily. They are strongly activated by different stress signals and inflammatory cytokines, although non-stressful stimuli also activate p38 MAPKs leading to the regulation of cellular functions such as proliferation, differentiation and survival. Four different p38 MAPK family members have been identified so far: p38α, β, γ and δ, also known as stress-activated kinase 2a (SAPK2a), SAPK2b, SAPK3 and SAPK4, respectively, which may have both overlapping and specific functions (reviewed by Cuenda and Rousseau, 2007; Kyriakis and Avruch, 2001; Nebreda and Porras, 2000; Ono and Han, 2000). p38α was initially identified as a 38 KDa protein, which became phosphorylated in Tyr in response to the bacterial endotoxin LPS in macrophages (Han et al., 1994). In parallel, other two groups identified p38α as a kinase activated by stress and IL1, able to phosphorylate and activate MAPKAP-K2 (MAPK-activated protein kinase 2) (Freshney et al., 1994; Rouse et al., 1994). p38α (encoded by MAPK14 gene) is broadly expressed and is also the most abundant p38 isoform present in most cell types. Targeted inactivation of the mouse p38α gene results in embryonic death due to a placental defect (Adams et al., 2000; Mudgett et al., 2000; Tamura et al., 2000). p38 MAPKs are mainly activated by MKK3 and MKK6 through dual phosphorylation in Tyr and Thr, although MKK4 can sometimes activate p38α (Cuenda and Rousseau, 2007).

MKK3 and MKK6 are in turn activated by phosphorylation by a MAPK kinase kinase (MKKK) such as MLKs, ASK1, TAK1 or MEKKs, which are activated by small and heterotrimeric G proteins (Cuenda and Rousseau, 2007; Wagner and Nebreda, 2009).

p38α can be also activated through MKK-independent pathways such as that involving p38α autophosphorylation upon interaction with TAB1 (Cuenda and Rousseau, 2007).

Once p38 MAPKs are activated, they phosphorylate different transcription factors such as p53, ATF2, MEF2 or C/EBPβ and protein kinases, including MAPKAP-K1 and MAPKAP-K3 (also known as MK-2 and MK-3), MSK-1 (mitogen- and stress-activated protein kinase 1) and MNK-1 and MNK-2 (MAP kinase-interacting serine/threonine kinase 1 and 2) (Cuenda and Rousseau, 2007; Wagner and Nebreda, 2009).

The analysis of the function of p38α has been initially based on the effect of chemical inhibitors such as SB203580 and SB202190, which inhibit p38α but can also inhibit p38β at a higher dose (reviewed by Nebreda and Porras, 2000). Therefore, the main effects observed upon treatment with those inhibitors are a consequence of p38α inhibition, sometimes are also due to p38β inhibition. The generation of mice with specific genetic inactivation of the different p38 isoforms or the use of interference RNA technology during the last few years has allowed a more precise study of the role played by each isoform and they have been essential to establish the role of p38α in different cellular processes.
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Figure 1. p38 MAPK signaling pathway. A variety of stimuli, mainly stress stimuli, activate p38 MAPK through complex kinase cascades including a MAP3K that phosphorylates a MAPK2 that, in turn, phosphorylates p38MAPKs. Cellular intermediates, like GTPases, receptor adapter proteins or cell cycle checkpoint proteins, among others, transmit the stimulus to the kinase cascades. Once activated, the different p38MAPKs either phosphorylate cytoplasmic targets or translocate into the nucleus leading to the regulation of transcription factors involved in cellular responses. MKK6 is the major activator of all p38 MAPK isoforms, while MKK3 and MKK4 are more specific and can only activate some isoforms.

2- Dual role of p38 MAPK in cell death: function of p38α in apoptosis

p38 MAPK can play a dual role as a regulator of cell death, thus it can either mediate cell survival or cell death through different mechanisms, including apoptosis. Therefore, the specific function of p38 MAPKs in apoptosis appears to depend on the cell type, the stimuli and/or the isoform (reviewed by Nebreda and Porras, 2000; Wagner and Nebreda, 2009).

As indicated above, some studies have been based on the using of chemical inhibitors such as SB203580 which is able to inhibit p38α and p38β, thus the participation of the p38β isoform in apoptosis can not be excluded. In fact, there is a good evidence for a role of p38α and/or p38β MAPKs as mediators of apoptosis in several cell types such as neurons (Ciesielski-Treska et al., 2001; De Zutter and Davis, 2001; Ghata et al., 2000; Le-Niculescu et al., 1999) or cardiac cells (Mackay and Mochly-Rosen, 1999; Saurin et al., 2000; Wang et al., 1998). Moreover, the induction of apoptosis by many types of stimuli such TNF-α(Valladares et al., 2000), TGF-β (Edlund et al., 2003) or oxidative stress (Zhuang et al., 2000) involves one of these p38MAPKs. p38α is a mediator of apoptosis in response to a number of cellular stresses through transcriptional and posttranscriptional mechanisms, which can involve the regulation of apoptotic and/or survival pathways (reviewed by Wagner and Nebreda, 2009).

For example, p38α sensitizes cardiomyocytes and MEFs-derived cell lines to apoptosis induced by different stimuli through both, up-regulation of the pro-apoptotic proteins Fas and Bax and down-regulation of the activity of ERKs and Akt survival pathways (Porras et al., 2004; Zuluaga et al., 2007a). According to this, overexpression of p38α enhances apoptosis induced by the constitutive active mutant MKK3bE in cardiomyocytes, while overexpression of p38β promotes cell survival (Nebreda and Porras, 2000). p38α is also a negative regulator of survival in embryonic stem (ES) (Guo and Yang, 2006). In addition, p38α is able to suppress tumor initiation induced by H-ras oncogene through induction of apoptosis (Dolado et al., 2007). Upon expression of oncogenic H-Ras, ROS are generated leading to p38α activation and apoptotic cell death.
Moreover, p38α MAPK plays an important role in the apoptosis induced by some chemotherapeutic drugs. For example, it is essential for cisplatin-induced apoptosis in the colon carcinoma derived cell line, HCT116 (Bragado et al., 2007).

On the other hand, anti-apoptotic roles of p38 MAPKs have been described in DNA-damaged fibroblasts (Héron-Milhavet and LeRoith, 2002), differentiating neurons (Okamoto et al., 2000) and activated macrophages (Park et al., 2002). In some cases, p38α has been identified as the isoform responsible for this survival effect. For example, in pulmonary arterial endothelial cells exposed to anoxia-reoxygenation during ischemia-reperfusion, carbon monoxide (CO) protects from apoptosis through p38α activation (Zhang et al., 2003; Zhang et al., 2005). In response to H$_2$O$_2$, p38α also mediates cell survival in MEFs, while p38α mediates apoptosis triggered by serum deprivation (Gutiérrez-Uzquiza et al., 2010). In both situations, C3G acts as a negative regulator of p38α. This crosstalk between the C3G and the p38α pathways has been also observed in CML cell line K562, where p38α mediates STI-571-induced apoptosis (Maia et al., 2009).

In contrast to the apoptotic role of p38 in CML cells treated with STI-571, p38 MAPK pathway exerts an antiapoptotic role in CML cells, as well as acute promyelocytic leukemia cells (APL), treated with arsenic trioxide (AT) (Verma et al., 2002b). In some tumor cells p38α can also induce a pro-survival effect known as tumor dormancy, which maintains cells in a quiescent state related to drug resistance (reviewed by Aguirre-Ghiso, 2007). In addition, p38α can also induce cell survival of colorectal cancer cells through inhibition of autophagy (Comes et al., 2007).

3- Pathways regulating p38α apoptotic function

There are different signaling pathways that are involved in the regulation of p38 apoptotic function. Some of them can be considered classical and/or canonical, while others such as C3G-Rap1 or PKC are novel or less known.

Classically, two small GTPases from the Rho family, Rac1 and Cdc42, have been described to be activators of p38α MAPK (Nobes and Hall, 1995). The existence of a functional crosstalk between Rac and p38 MAPK has been largely reported in relation with different cellular functions. p38 can act either as an effector or as an activator of Rac. In particular, in cardiomyocytes p38α acts as a positive or a negative regulator of Rac1 depending on the presence of growth factors (Zuluaga et al., 2007b). On the other hand, Rac-GTP induces p38 activation in many systems (Nobes and Hall, 1995). For example, Rac-1 is an upstream regulator of p38 in retinoic acid-induced differentiation and apoptosis of malignant NB-4 (acute pro-myelocytic leukemia) and MCF-7 (breast carcinoma) cell lines (Alsayed et al., 2001).

Recent novel findings support the participation of another member of the Ras family, the GTPase Rap1, in the regulation of p38α function in apoptosis (Gutiérrez-Uzquiza et al., 2010; Maia et al., 2009). Rap1 can either activate or inhibit p38α depending on the cell context. In CML cells, the C3G-Rap1 pathway downregulates the pro-apoptotic activity of p38αMAPK as a mediator of STI effects (Maia et al., 2009). In contrast, in MEFs C3G is a negative regulator of p38α MAPK activity and Rap1 a positive one, leading to pro- or anti-apoptotic effects depending on the stress stimulus (Gutiérrez-Uzquiza et al., 2010).

There are also evidences of a cross-talk between PKCs and p38 MAPK in order to regulate apoptosis. For example, in LNCaP prostate cancer cells, PMA induces apoptosis through a mechanism, which involves PKCα and d-mediated p38α/β activation (Tanaka et al., 2003). An autocrine pro-apoptotic loop is also generated in these cells by PKCδ, which is mediated by death receptor ligands through a mechanism dependent on caspase-8, FADD, p38α/β MAPK and JNK (Gonzalez-Guerrico and Kazanian, 2005). In addition, in vascular smooth muscle cells activation of PKCδ leads to apoptotic cell death involving p53 induction through a mechanism partially dependent on p38α/β MAPK (Ryer et al., 2005).

4- Targets of p38α in the regulation of apoptosis

The mechanisms by which p38α can mediate apoptosis or cell survival, include those involving the regulation of the expression and/or activity of different members of the Bcl-2 family.

Bax is a pro-apoptotic member of the Bcl-2 family, which can be regulated by p38α through different mechanisms. In cardiomyocytes derived cell lines, p38α mediates an up-regulation of Bax mRNA and protein, which sensitizes cells to apoptosis induced by different stimuli (Porras et al., 2004). In addition, in primary neonatal cardiomyocytes p38 α/β mediated Bax translocation to mitochondria upon simulated ischemia (Capano and Crompton, 2006). This p38 α/β)-induced Bax translocation was also observed in a human hepatoma cell line (HepG2) treated with different pro-apoptotic stimuli (Kim et al., 2006). In contrast, in the anoikis-induced apoptosis in mammary epithelial cells, p38α is not required for Bax mitochondrial translocation, but it acts as a part of a mitochondrial complex allowing Bax activation and cytochrome-c release (Owens et al., 2009).

Bimlevels (Cai and Xia, 2008) and activity (Cai et al., 2006) are also positively regulated by p38α, which contributes to induce apoptosis. Thus, in PC12 cells treated with sodium arsenite, p38α induces FOXO3anuclear translocation, which stimulates Bim transcription, leading to an increase in BimEL protein levels (Cai and Xia, 2008). In addition, p38α
contributes to BimEL phosphorylation in Ser65 (Cai et al., 2006).

Bcl-2 has been shown to be phosphorylated by p38α upon NGF withdrawal in memory B lymphocytes, which leads to inhibition of its anti-apoptotic activity and to induction of cytochrome-c release (Tourian et al., 2004). Similarly, H₂O₂ induces p38α-mediated Bcl-2 phosphorylation in adult rat cardiac myocytes contributing to apoptosis (Markou et al., 2009).

p38α can also mediate survival through regulation of the expression and/or activity of proteins from the Bcl-2 family. For example, carbon monoxide protects from ischemia-reperfusion lung injury through a p38α-dependent up-regulation of Bcl-2 and Bcl-xLprotein levels (Zhang et al., 2003). According to this, UVA-induced p38α (α/β) activation in a human keratinocyte cell line (HaCaT cells) results in an increase in Bcl-xL protein levels through post-transcriptional mechanisms mediated by the 3′-untranslated region (UTR) (Bachelor and Bowden, 2004). In addition, in primary human trophoblasts p38α appears to mediate EGF-mediated Bad phosphorylation in Ser 112, which protects from hypoxia-induced apoptosis (Humphrey et al., 2008).

p38α is also involved in the stimulation of Fas and FasL expression, which can contribute to apoptosis in a number of cellular systems. p38α was shown to participate in the anti-CD3-induced upregulation of Fas and FasL expression in T cells, although p38α alone was unable to increase Fas expression (Hsu et al., 1999). Similarly, p38 MAPK is a mediator of hepatitis B virus X protein-induced Fas and FasL expression (Wang et al., 2004). p38α activation also mediates Fas expression through phosphorylation of STAT1 in Ser 727 in cardiac myocytes exposed to ischemia/reperfusion (Stephanou et al., 2001). According to this, Fas expression is down-regulated in p38α-deficient embryonic cardiomyocytes under basal conditions which contributes to sensitize cells to apoptosis (Porras et al., 2004). In contrast, p38α downregulates Fas expression through inhibition of NF-κB in human melanoma cells (Ivanov and Ronai, 2000).

Apart from the role of p38α in the regulation of Fas/FasL expression, p38α mediates caspase 8 activation in Fas-activated Jurkat cells by inhibiting the phosphorylation and presence of c-FLIPs in the DISC (Tourian et al., 2004). p38α also mediates TGF-β-induced activation of caspase 8 (Schrantz et al., 2001) as well as the regulation of membrane blebbing and nuclear condensation (Deschesnes et al., 2001).

The tumor suppressor protein p53, which is a relevant mediator of apoptosis in response to a great variety of stimuli, is also an important p38 target. In fact, there are a number of evidences supporting a role for p38α in the regulation of p53. For example, in response to different chemotherapeutic drugs such as cisplatin p38α phosphorylates and/or activates p53 leading to onset of apoptosis (Bragado et al., 2007; Sánchez-Prieto et al., 2000). p38α can also induce apoptosis through p53 in response to other stimuli. Thus, p53 phosphorylation by p38α is essential in the apoptosis induced by the HIV-1 envelope (Perfettini et al., 2005). In addition to this role of p38α as a direct regulator of p53, p38α also acts through phosphorylation and stabilization of the p53 coactivator, p18Hamlet (Cuadrado et al., 2007). In response to DNA damage p18Hamlet is accumulated, which contributes to induce apoptosis through the stimulation of some p53-regulated genes, such as Noxa. Other alternative mechanisms are involved in p38α-mediated apoptosis. For example, phosphorylation of H2AX by p38α has been shown to be required for serum starvation-induced apoptosis (Lu et al., 2008).

In addition to the above referred effects of p38α through direct regulation of pro- and/or antiapoptotic proteins, p38α is also a negative regulator of PI3K/Akt and ERKs survival pathways. Thus, in p38α-deficient derived cardiomyocytes or MEFs cell lines ERKs and Akt activities are increased, which contributes to the enhanced survival of these cells (Porras et al., 2004; Zuluaga et al., 2007a). In particular, in cardiomyocytes p38α can negatively modulate Akt activity, independently of PI3K, favoring the interaction between caveolin-1 and PP2A and the activation of PP2A through a mechanism dependent on cell attachment (Zuluaga et al., 2007a).

There are additional mechanisms that can be involved in the p38α-induced survival, such as the activation of the ATF6α-Rheb-mTOR survival pathway (Schewe and Aguirre-Ghiso, 2008). Other mechanisms include the p38α mediated induction of antioxidant enzymes expression in response to oxidative stress (unpublished data from our group). In addition, the increase in BNIP-3 levels and the low Bim/Bcl-xL ratio induced by p38α would contribute to this survival effect upon H₂O₂ treatment (Gutiérrez-Uzquiza et al., 2010).
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5- Disregulation of p38α function in apoptosis: involvement in human diseases

Different evidences from the literature indicate that the pro-apoptotic function of p38α is deregulated in some human diseases such as cancer, although recent findings have also linked p38 signaling with neurodegenerative diseases such as Alzheimer's disease (AD), Parkinson disease (PD) and amyotrophic lateral sclerosis (ALS) (reviewed by Kim and Choi, 2010).

5.1- Role of p38α in cancer: implication in cancer development and therapy

5.1.1- p38α as a tumor suppressor and/or mediator

Several data indicate that p38α can act as a tumour suppressor (Review by Wagner and Nebreda, 2009). In particular, p38α negatively regulates malignant transformation induced by Ras through different mechanisms including apoptosis induction. For example, in MEFs expressing H-RasV12, sustained activation of p38α MAPK inhibits transformation through a mechanism involving ROS-induced apoptosis (Dolado et al., 2007). H-RasV12-induced ROS is only able to trigger apoptosis in MEFs expressing p38α, but not in those deficient in this protein. As a consequence, p38α-deficient MEFs transformed by Ras accumulate high levels of ROS which contributes to tumour progression. This type of response is produced in the transformation induced by different oncogenes able to generate ROS. In fact, many human cancer cell lines have developed mechanisms to uncouple ROS generation to p38α activation and therefore induction of apoptosis. However, as referred above, p38α can also induce a survival state known as tumor dormancy in some cancer cells such as those from squamous carcinoma, which maintains cells in a quiescent state related to drug resistance through mechanisms including activation of the p38α-ATF6α-Rheb-mTOR survival pathway (reviewed by Aguirre-Ghiso, 2007; Schewe and Aguirre-Ghiso, 2008).

5.1.2- Role of p38α in chronic myeloid leukemia and other hematopoietic malignancies

p38 MAPK, mainly the p38α isoform, is a key player in the maintenance of hematopoiesis homeostasis, as it balances both proliferative and growth inhibitory signals triggered by the growth factors and cytokines that regulate normal hematopoiesis (Feng et al., 2009; Uddin et al., 2004). Alterations in this p38 MAPK-
controlled balance may result in either overproduction or depletion of myelosuppressive cytokines leading to the development of certain bone marrow failure syndromes. For example, p38α is responsible for the enhanced stem cell apoptosis characteristic of low grade myelodysplastic syndromes (MDSs) (Navas et al., 2006; Zhou et al., 2007). On the other hand, imbalance toward the proliferative side may conduct to the development of myeloproliferative syndromes (MPSs), such as leukemia, lymphomas and myelomas.

The role played by different members of the p38 kinase family in the regulation of acute leukemia blasts growth (myeloid and lymphoid), is not well defined, although they seem to participate in the generation of resistance to chemotherapeutic agents (Feng et al., 2009; Platanias, 2003) In contrast, the participation of the p38 MAPK pathways in the pathogenesis and pathophysiologpy of chronic leukemias have been extensively studied, although its role is contradictory. On one side, p38 is activated by the Rho-GEF domain of Bcr, contributing to transformation through the regulation of NF-κB activation (Korus et al., 2002). On the other side, p38 MAPK is selectively activated by IFNα and mediates the growth suppressive effects of IFNα in CML cells (Mayer et al., 2001) as well as in normal hematopoiesis (Verma et al., 2002a).

p38 MAPK also seems to play a role in chronic lymphocytic leukemia (CLL). p38 and its effector MK-2 (MAP kinase-activated protein kinase-2) are activated by rituximab in cultures of CLL cells and contributes to the generation of the antileukemic effects of rituximab in CLL (Pedersen et al., 2002). Finally, there are evidences supporting the participation of p38 in cell proliferation and adhesion of lymphomas and multiple myelomas in response to growth factors (Feng et al., 2009; Platanias, 2003).

Another important function of p38α MAPK in hematopoiesis is to promote cell differentiation. Curiously, while GTP-induced erythroid differentiation of K562 cells is mediated through p38-dependent caspase activation (Moosavi et al., 2007), caspases do not participate in STI-571-induced erythroid differentiation in CML cells, where STI-571-mediated apoptosis and differentiation are independent events (Jacquel et al., 2007). The differentiation-inducing therapy may be a good therapeutic alternative for CML patients that develop resistance to STI-571.

5.2- Role of p38α in neurodegenerative diseases

Recent findings support the involvement of p38 MAPK signaling pathway in neurodegenerative diseases. Thus, persistent activation of the p38 MAPK signaling has been suggested to contribute to neuronal apoptosis in Alzheimer's disease (AD), Parkinson disease (PD) and Amyotrophic lateral sclerosis (ALS).

Alzheimer’s disease is an incurable, neurodegenerative disease characterized by a progressive deterioration of the cognitive, memory and learning ability including lost of motor coordination at advanced stages. AD is the result of the accumulation of plaques containing amyloidogenic Aβ proteins and tangles containing the microtubule-associated protein tau in a hyperphosphorylated state (Giacobini and Becker, 2007). The ASK1-MKK6-p38 signaling pathway participates in amyloid precursor protein (APP) and tau phosphorylation in response to oxidative stress and contributes to the expression of the β-secretase gene (Galvan et al., 2007) and the induction of neuronal apoptosis triggered by ROS (D'Amico et al., 2000; Puig et al., 2004; Tamagno et al., 2003).

Parkinson disease is a degenerative disorder of the central nervous system characterized by muscle rigidity, tremor and loss of physical movement caused by a progressive loss of dopaminergic neurons. A number of specific genetic mutations causing Parkinson’s disease have been discovered, being the mutations in α-Synuclein (a major constituent of Lewy bodies) among the best characterized (Gandhi and Wood, 2005). α-Synuclein activates p38 MAPK in human microglia promoting a potent inflammatory stimulation of microglial cells (Klegeris et al., 2008). The p38 MAPK is also activated in PD cellular and animal models and plays a role in dopaminergic neural apoptosis through the phosphorylation of p53 and expression of the pro-apoptotic protein Bax (Karunakaran et al., 2008; Mathiasen et al., 2004; Silva et al., 2005).

Amyotrophic lateral sclerosis is a progressive, lethal, degenerative disorder of motor neurons in the brain and spinal cord, leading to paralysis of voluntary muscles. Aberrant chemistry and oxidative stress have been described to be involved in ALS development, being SOD1 (superoxide dismutase 1) the most frequently mutated gene in the inherited cases of ALS. Numerous evidences point to a role of p38 MAPK in the development and progression of ALS induced by mutations in SOD1 gene (Bendotti et al., 2004; Bendotti et al., 2005; Dewil et al., 2007; Holasek et al., 2005; Tortarolo et al., 2003). Mutant SOD1 provokes aberrant oxyrdical reactions that increase the activation of p38 MAPK in motor neurons and glial cells. This increase in active p38 MAPK may phosphorylate cytoskeletal proteins and activate cytokines and nitric oxide, thus contributing to neurodegeneration through different mechanisms including apoptosis (Bendotti et al., 2005; Tortarolo et al., 2003).

5.3- p38α in cancer therapy

p38α can act as a tumor suppressor in the initial phases of malignant transformation, which involves apoptosis induction. Similarly, p38α is also a mediator of apoptosis upon treatment with many chemotherapeutical drugs such as cisplatin, arsenic trioxide or others. Therefore, p38α can be considered as a target in the treatment of cancer, although sometimes is also responsible for the resistance to some of these treatments.

It is well established that p38 MAPK mediates the responses to several DNA-damaging agents, such as...
UV radiation, cisplatin (CDDP) and Ara-C through activation of p53-dependent and independent responses (Bulavin et al., 1999; Huang et al., 1997; Sánchez-Prieto et al., 2000). Cisplatin is an anti-cancer drug that induces apoptosis in a number of cancer cell lines through mechanisms that in many cases are p38 dependent. In the colon carcinoma cell line HCT116, the activation of p38α was shown to be necessary for CDDP-induced apoptosis, upon activation by p53-mediated ROS production (Bragado et al., 2007). Once p38α MAPK is activated, it contributes to further activation of p53, which leads to a positive feedback loop. So, a p53/ROS/p38α MAPK cascade is essential for cisplatin-induced cell death and the subsequent p38α/p53 positive feedback loop strongly enhances the initial p53 activation in HCT116 cells. In other cancer cell lines, c-Abl is required for CDDP-induced p38 activation and for its antitumoral effect. Thus, CDDP-induced cell death appears to be dependent on c-Abl expression, rather than on its tyrosine kinase activity, and on stabilization of MKK6 protein levels (Galán-Moya et al., 2008). This pro-apoptotic effect of CDDP is not selective for tumoral cells. Hence, in NIH3T3 cells, which are non-transformed cells, an involvement of p38α/β MAPK was described as mediator of CDDP-induced apoptosis through a mechanism dependent on the phosphorylation of p53 in Ser33 and the subsequent p53 transcriptional activation (Sánchez-Prieto et al., 2000).

Similarly to CDDP, other anticancer drugs also lead to the generation of ROS as an important mechanism to induce apoptosis in cancer cells, being p38α a relevant mediator. Thus, diamine, a thiol-oxidizing compound, induces apoptosis in a gastric human adenocarcinoma cell line (AGS) through a mechanism dependent on Trx1/p38α/p53 pathway, while CaCo2 cells are resistant to this compound due to the absence of a functional p53 (Piccirillo et al., 2009).

As previously mentioned, activation of p38 MAPK plays a key role in some hematopoietic malignancies by different mechanisms including increasing resistance to chemotherapeutic agents (Feng et al., 2009). Ara-C is a classic anti-neoplastic agent widely used in the treatment of CML blast crisis, which provides a typical example of genotoxic stress mediated through c-Abl-p38 MAPK pathway (Huang et al., 1997; Pandey et al., 1996; Stadheim et al., 2000). Although p38 MAPK is activated by c-Abl in response to CDDP in some cancer cell lines (Galán-Moya et al., 2008) and by overexpression of Bcr-Abl, Ara-C (1-β-D-arabinofuranosylcytosine) is unable to activate p38 MAPK in cells with constitutive expression of Bcr-Abl such as the CML derived cell line K562 (Sánchez-Arévalo Lobo et al., 2005). In those cells, Bcr-Abl induces a sustained activation of the p38 MAPK pathway (not related to increased apoptosis), rendering them insensitive to further activation in response to Ara-C. Therefore, Bcr-Abl mediated p38 MAPK activation is a key mechanism to explain resistance to Ara-C. In fact, lack of p38 MAPK activation is a general mechanism for Ara-C resistance, as it had been previously proposed (Stadheim et al., 2000). This could provide a clue for new therapeutic approaches based on the combined use of specific Abl and p38 MAPK inhibitors.

In contrast, p38 MAPK signaling cascade mediates the antiproliferative effects of STI-571 (or imatinib, the current drug used in CML treatment) and cisplatin on Bcr-Abl expressing cells (Galán-Moya et al., 2008; Parmar et al., 2004). Moreover, we have recently found a functional relationship between C3G and p38 in CML, so that the pro-apoptotic activity of p38α MAPK, as a mediator of STI-571 effects, is downregulated by the C3G-Rap1 pathway and the antitumoral effects of STI-571 could be improved by C3G gene silencing as it enhances p38α activation and pro-apoptotic activity (Maia et al., 2009).

In contrast, p38 appears to be a negative regulator of the antitumoral effects of all-trans-retinoic acid (RA), which induces differentiation and growth arrest in several malignant cell types, including acute promyelocytic leukemia (APL) and breast carcinoma. The Rac-p38 MAPK-MK2 pathway is activated by RA and negatively regulates RA-effects in NB-4 APL and MCF-7 breast cancer cell lines, as p38α/β inhibitor SB203580 enhances RA-dependent cell differentiation and apoptosis. Therefore, pharmacological inhibition of p38α/β may prevent resistance to RA that is developed in nearly all cases (Alsayed et al., 2001).

Arsenic trioxide (AT), which also induces differentiation and apoptosis of leukemia cells in vitro and in vivo, activates the Rac-p38 MAPK-MK2 pathway, which can act as a negative regulator of AT functions, suggesting a possible role of p38 MAPK pathways in AT-induced resistance (Verma et al., 2002b). However, AT can sensitize human promonocytic cells U937 to TNF-α-induced apoptosis, which is dependent on p38α/β activation (Amran et al., 2007). AT increases the levels of TNF-α receptor leading to an enhancement of TNF-α-induced apoptosis. The role of p38 MAPK in resistance to chemotherapeutic agents is also observed in an experimental model of head and neck cancer, where lower activation or lack of activation of p38 MAPK correlates with a more resistant phenotype (Losá et al., 2003).

Therefore, based on all these data described here and other published data, p38α would play a dual role in cancer treatment. Depending on the type of tumour and the chemotherapeutic agent, p38α can either induce apoptosis or survival, leading to the disappearance of the tumour or making it resistant to chemotherapy.

Concluding remarks

p38α MAPK (encoded by MAPK14 gene) is broadly expressed and is also the most abundant p38 isoform present in most cell types. It can be activated by several
extracellular signals, including stress stimuli, leading to the regulation of different cellular processes, which includes cell death. Although in many cases p38α is a mediator of apoptosis, recent data indicate that it can also have a pro-survival role. Therefore, p38α would play a dual role in apoptosis, which is dependent on the cell context and/or stimulus.

p38α regulates apoptosis through transcriptional and posttranscriptional mechanisms, being of particular relevance the modulation of proteins from the Bcl-2 family and proteins involved in the death receptor pathway such as Fas and FasL.

p38α-mediated apoptosis or survival is deregulated in a number of pathologies. For example, some neurodegenerative diseases are linked to an enhanced apoptosis mediated by p38α. p38α can also act as a tumour suppressor in the initial stages of malignant transformation through activation of apoptosis. In addition, the antitumoral effects of a number of chemotherapeutical drugs are based on the activation of p38α. However, it should be notice that in some tumours p38α MAPK is involved in chemotherapeutical resistance.

We apologize to the authors whose original work is not included in the references due to extension constrains.

References


Han J, Lee JD, Biblos L, Ulevitch RJ. A MAP kinase targeted by endotoxin and hyperosmorality in mammalian cells. Science. 1994 Aug 5;265(5173):808-11


Valladares A, Alvarez AM, Ventura JJ, Roncero C, Benito M, Porras A. p38 mitogen-activated protein kinase mediates tumor
necrosis factor-alpha-induced apoptosis in rat fetal brown adipocytes. Endocrinology. 2000 Dec;141(12):4383-95


Porras A, Guerrero C.


Dewil M, dela Cruz VF, Van Den Bosch L, Robberecht WM. Inhibition of p38 mitogen activated protein kinase and mutant SOD1(G93A)-induced motor neuron death. Neurobiol Dis. 2007 May;26(2):332-41


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Porras A, Guerrero C


Cai B, Xia Z. p38 MAP kinase mediates arsenite-induced apoptosis through FOXO3a activation and induction of Bim transcription. Apoptosis. 2008 Jun;13(6):803-10


Markou T, Dowling AA, Kelly T, Lazou A. Regulation of Bcl-2 phosphorylation in response to oxidative stress in cardiac myocytes. Free Radic Res. 2009 Sep;43(9):809-16


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