Proteasome- and p38-dependent Regulation of ERK3 Expression*

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Proteasome inhibition leads to accumulation of transcription factors, heat shock proteins, cyclins, and other proteasome substrate proteins by blocking their proteolytic degradation. An increase in gene transcription upon proteasome inhibition was found for a group of proteins, including p21WAF1/CIP1, ubiquitin, and transcription factors. In this study, we have demonstrated selective up-regulation of extracellular signal-regulated kinase 3 (ERK3) mRNA and protein expression upon treatment with peptide-based proteasome inhibitors or lactacystin. ERK3 is a family member of the mitogen-activated protein kinases (also called ERK) that are key mediators of signal transduction from the cell surface to the nucleus. ERK3 up-regulation is independent of the p53, Bcl2, and caspase 3 status of cells. p38 pathway kinase inhibitors prevent proteasome-dependent ERK3 induction and enhance the antiproliferative effect of proteasome inhibitors. MCF-7 cells expressing ERK3 ectopically show increased resistance toward proteasome inhibition. The results indicate that ERK3 expression is a consequence of p38 pathway activation and most probably represents an intracellular defense or rescue mechanism against cell stress and damage induced by proteasome inhibition.

Proteasome inhibition leads to an increase in the expression of a large number of proteins by both posttranslational and transcriptional mechanisms. Various proteins crucial for cell cycle regulation and stress response, such as cyclins and transcription factors, are substrates of the ubiquitin-proteasome proteolytic pathway and directly accumulate in a polyubiquitylated state after proteasome inhibitor treatment. On the other hand, proteasome inhibition has been reported to increase transcription and translation of a group of genes, including p21WAF1/CIP1 (1), and a number of proteins involved in heat shock response (2) and transcriptional regulation, such as Gadd153, ATF3, and MAD1 (3).

As reported previously, we have used a quantitative fluorescent cDNA hybridization approach to identify genes regulated transcriptionally in response to proteasome inhibitor treatment. Changes in mRNA expression of 7900 genes from the UniGene collection were compared upon exposure of cells to the proteasome inhibitors lactacystin, lactacytin-β-lactone, or MG132 by means of microarray-based cDNA hybridization (3). All these inhibitors block the proteolytic activity of the 26 S proteasome without influencing its ATPase or isopeptidase activities. The three gene expression profiles were very similar, revealing 52 genes that are induced more than 5-fold and 34 genes that are repressed more than 5-fold by at least one of the inhibitors.

A gene raising interest and found to be up-regulated on all three cDNA array chips was ERK3, a MAP1 kinase of the extracellular signal-regulated kinase (ERK) subfamily. MAP kinases are serine/threonine kinases that are phosphorylated and thereby activated in response to a wide array of stimuli and are part of sequentially acting complex protein kinase cascades. They modulate many cellular events including mitogen-induced cell cycle progression through the G1 phase, regulation of embryonic development and cell and neuronal differentiation (4, 5). A controlled regulation of the MAP kinase cascade is involved in cell proliferation and differentiation, whereas an uncontrolled activation can result in oncogenesis. In vertebrate cells, two additional, distinct kinase cascades have been discovered to date targeting Jun N-terminal kinases/stress-activated protein kinases and p38 (6). The Jun N-terminal kinases and p38 kinases are preferentially transferred to the nucleus in their active phosphorylated form by cellular stresses including proteasome inhibition (7).

Based on characteristic features of its sequence, ERK3 is categorized as one of six members of the ERK subfamily (8). It retains a much greater similarity to ERK1 and ERK2, particularly in the phosphorylation lip, than to the other known family members. ERK3 is ubiquitously expressed in a variety of tissues and mammalian cell lines. ERK3 mRNA, like ERK1 and ERK2 mRNA, is detectable in numerous tissues, including heart, brain, placenta, lung, liver, skeletal muscle, kidney, and pancreas tissues and human skin fibroblasts, with its highest level in skeletal muscle (8). Several properties of ERK3, however, distinguish it from all other known ERK homologs, indicating that ERK3 appears to represent a distinct evolutionary branch of ERK/MAP kinases and that it could be controlled by other cell signaling pathways. ERK3 is constitutively nuclear (9), is not translocated in response to a stimulus, and does not retain the activating tyrosine phosphorylation site, a hallmark of the ERK family. Upstream ERK3-activating mechanisms are not yet known, and concerning ERK3 substrates, studies are contradictory (10, 11).

In this study, we have characterized time- and dose-dependent ERK3 mRNA and protein overexpression upon treatment with different proteasome inhibitors in a variety of cell lines. ERK3 overexpression was independent of the intracellular p53, caspase 3, and Bcl-2 statuses but was accompanied by activation of the p38 and MEK3/6 kinases. Moreover, ERK3 induction was completely blocked upon preincubation with selective inhibitors of the p38 pathway. We demonstrate that cells ectopically expressing ERK3 are more resistant toward proteasome inhibitors. We further demonstrate that cells treated with a specific inhibitor of the p38 pathway are more sensitive.

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1 The abbreviations used are: MAP, mitogen-activated protein; ERK, extracellular signal-regulated kinase; PCR, polymerase chain reaction; GAPDH, glyceraldehyde-3-phosphate dehydrogenase.
toward proteasome inhibitor treatment, suggesting that ERK3 overexpression protects cells from the anti-proliferative effect induced by proteasome inhibition.

EXPERIMENTAL PROCEDURES

Cell Culture—The human adenocarcinoma cell lines MCF-7, MDA MB231, MDA MB468, and the human prostate cell line DU145 (all from the American Tissue Culture Collection) were cultured at 37 °C in a 5.5% CO2 atmosphere in minimal essential medium with ribonucleosides and deoxyribonucleosides, supplemented with 10% fetal calf serum, 2 mM t-glutamine, 1 mM sodium pyruvate, 0.1 mM nonessential amino acids, and 0.01 mg/ml gentamycin (Life Technologies, Inc.). The human leukemic cell line HL-60 and the human non-small cell lung cancer cell line NCI-H1299 (obtained from American Tissue Culture Collection) were cultured in RPMI 1640 medium containing 10% fetal calf serum in a 5.5% CO2 atmosphere at 37 °C. Stable Bcl-2-transfected MDA-MB-453 cells were generated and supplied by Markus Wartmann (Novartis Pharma AG, Basel, Switzerland). Subconfluent cells were treated with proteasome or kinase inhibitors, staurosporine, rotenone, or doxorubicin, respectively, for indicated times and doses. Z-Ile-Glu(O-t-butyl)-Ala-Leu-H (PSI), Z-Leu-Leu-Nva-H (MG115), Z-Leu-Leu-Leu-H (MG132), lactacystin, and lactacystin-β-lactone were purchased from AFFINITI Research Products Ltd. (Mamhead Castle, UK). Staurosporine was obtained from Kamiya (Seattle, WA). PD169316, SB202190, and SB203580 were purchased from Alexis (Lausen, Switzerland). Doxorubicin was obtained from Sigma. PS341 was a gift of Carlos Garcia-Echeverria (Novartis Pharma AG, Basel, Switzerland).

Cell proliferation was measured using the MTS assay kit from Promega (Wallisellen, Switzerland) according to the recommendations of the manufacturer. Fig. 1 shows the chemical structures of the compounds utilized in this study.

Stable Transfection—MCF-7 cells were stably transfected with expression vector pEYD-1/GS-ERK3(His)6 (clone H-L77964M) carrying a zeocin resistance gene (Invitrogen, Groningen, Netherlands) using the Effectene transfection kit (Qiagen AG, Basel, Switzerland). pGreen Lantern (Life Technologies, Inc.) was cotransfected for green fluorescent protein expression to control for transfection efficiency by means of fluorescence microscopy. Stable transfected clones (100 μg/ml zeocin resistance) were picked and cultured, and histidine-tagged ERK3 expression was confirmed by Western blot.

Real Time Reverse Transcription-Polymerase Chain Reaction—The PCR primers and TaqMan probes to amplify and detect ERK3 mRNA were designed using Primer Express software version 1.0 (PerkinElmer Life Sciences) based on the sequence reported in GenBank™ as follows: ERK3 forward primer, 5’-GAATGCAAAATCTGGCATAATT-3’; ERK3 reverse primer, 5’-ACAGTCCCTCACCACCTCA-3’; ERK3 probe, 6-carboxyfluorescein-5’-CCTTGATACCAGTCCTTCTGAGCCA-3’.
Western Blot Analysis—Cells were washed twice with phosphate-buffered saline (Life Technologies, Inc.), lysed with M-PER (Pierce), and boiled for 5 min. The protein concentration was normalized to the determination of the total protein amount in the supernatant using the BCA protein assay kit (Pierce). 40 μg of total protein per lane was separated by electrophoresis in SDS-polyacrylamide gels (Bio-Rad) and transferred to Protran nitrocellulose membranes (Schleicher & Schuell). All primary antibodies and secondary horseradish peroxidase-conjugated antibodies were purchased from Santa Cruz Biotechnology Inc. (Santa Cruz, CA), except an anti-polystrene antibody, which was from Sigma. Proteins were detected by chemoluminescence with SuperSignal substrate (Pierce).

RESULTS

Proteasome Inhibition Leads to ERK3 mRNA and ERK3 Protein Overexpression—To systematically elucidate pathways linked to proteasome inhibition, we treated MCF-7 breast carcinoma cells for 14 h with the three chemically different proteasome inhibitors Z-Leu-Leu-Leu-H (MG132), lactacystin, or lactacystin-β-lactone at 10 μM compound concentration or with Me2SO as a control (3). Less than 10% residual proteasome activity was measurable in protein extracts derived from MCF-7 cells treated with either one of the proteasome inhibitors under those conditions (data not shown). In addition, to compare expression profiles of proteasome inhibitors with those of apoptosis-inducing compounds, not the proteasome-targeting compounds, a control experiment with trapoxin A was performed. NCI-H1299 cells were treated for 24 h with 1 μM trapoxin A. Trapoxin A is a histone deacetylase inhibitor that has been shown to have an impact on gene expression (13) and to have antitumor activity (14). The transcriptional response was examined by means of microarray-based differential fluorescent cDNA hybridization. In principle, the technology has been described (15, 16). Comparison of the three expression profiles of proteasome inhibitors revealed a high degree of similarity, indicating that the observed changes in gene expression were indeed a consequence of blocked proteasome activity. Most of the genes whose expression was influenced by proteasome inhibitors were not influenced by trapoxin A. ERK3 was one of the genes found to be significantly up-regulated (Fig. 2A): 2.9-fold by MG132, 3.4-fold by lactacystin, and 2.1-fold by lactacystin-β-lactone. ERK3 mRNA levels, however, did not change after trapoxin A treatment, suggesting that ERK3 is not generally up-regulated upon apoptosis induction. Induction of ERK3 gene expression upon MG132 treatment was further confirmed by means of real time reverse transcription-PCR (Fig. 2B). A fast response in MCF-7 cells was observed. ERK3 mRNA reached maximal induction between 12 h (3.4-fold) and 24 h (3.9-fold), peaked at 16 h (4.2-fold), and started to decrease from 24 h onwards. Several factors, including the site of mRNA synthesis, its stability and half-life, the translation efficiency, and the half-life of translated ERK3, determine intracellular ERK3 protein levels. The up-regulation of the mRNA was confirmed to be accompanied by an increase in protein expression at the protein level. A dose-dependent increase in the ERK3 protein level is shown in Fig. 2C for MCF-7 cells that were incubated for 7 h with MG132. ERK3 protein was 6.6-fold increased after treatment with 50 μM MG132 compared with cells treated with Me2SO (Fig. 2D).

Selectivity of ERK3 Induction—To prove that ERK3 overexpression was due to proteasome inhibition and was not an
unrelated side effect of the peptide-based inhibitor MG132, MCF-7 cells were treated with different proteasome inhibitors for 3.5 and 14 h. ERK3 protein expression was analyzed by immunoblotting (Fig. 3A). Protein expression of ERK3 was markedly increased after exposure to proteasome inhibitors for 14 h but not for the shorter incubation time of 3.5 h, suggesting that ERK3 transcription and translation required more than 3.5 h. The observed ERK3 overexpression was independent of the proteasome inhibitor type. Despite their chemical divergence, MG132, MG115, PS341, lactacystin, lactacystin-b-lactone, and PSI caused a similar degree of ERK3 up-regulation after 14 h. To address specificity, other apoptosis-inducing compounds were tested for their ability to induce ERK3 expression in MCF-7 cells. In contrast to the proteasome inhibitor MG132, trapoxin A, doxorubicin, staurosporine, and rotenone did not induce ERK3 even after 14 h (Fig. 3B).

**Selectivity of ERK3 Induction within the ERK Family**—Based on the homology of its protein sequence, ERK3 belongs to the ERK family, a group of proteins involved in cell signaling, proliferation, and differentiation control. Overexpression of ERK3 could represent a general response to cell stress, and other members of the ERK family might be induced by proteasome inhibitions as well. Immunoblotting of protein extracts from MCF-7 cells treated with different proteasome inhibitors revealed no induction of ERK1/2 (Fig. 3C) and no induction of ERK5 or ERK6 (data not shown) after 3.5, 7, or 14 h of exposure.

**ERK3 Induction Is Independent of p53, Caspase 3, and Ectopic Bcl-2 Expression**—Apoptosis induced by inhibition of the proteasome involves mechanisms independent of p53 (1) and Bcl-2 (17). In this context it was important to establish a possible relationship between proteasome inhibitor-induced ERK3 expression and the genetic background of the cell lines used to study the induction. ERK3 induction was studied in a number of cell lines with different p53 statuses. MCF-7 cells have wild type p53 (18); HL-60 cells are p53 null (19); and the other cell lines, MDA MB231 (20), MDA MB468 (21), and DU145 (22), have mutations in p53. Moreover, MCF-7 cells, but not the other cell lines tested, are deficient in caspase 3 (23). MG132 and lactacystin treatment increased the ERK3 protein level in all cell lines tested (Fig. 4A), independent of the p53 and caspase 3 statuses.

Recently, a functional link has been discussed between Bcl-2 and the proteasome (17). Moreover, Bcl-2 appears to be a substrate for the ubiquitin-proteasome pathway (24). To test the effect of Bcl-2 overexpression on ERK3 induction, MDA MB453 cells were stably transfected either with Bcl-2, producing MDA MB453-Bcl-2 cells, or with a control vector (MDA MB453-neo). Bcl-2 was present at very low levels in MDA MB453-neo cells but was readily detected by Western blotting in MDA MB453-Bcl-2 (Fig. 4B). Following exposure to MG132 or lactacystin, ERK3 was induced in both cell lines regardless of the Bcl-2 expression level. Moreover, the induction of ERK3 appears not to be dependent on the presence of functional Bcl-2. MDA MB468 cells are deficient in Bcl2 expression (25), but ERK3 was induced upon proteasome inhibition (Fig. 4A).

**ERK3 Is Controlled by the p38 Pathway**—It has been reported previously that proteasome inhibition leads to activation of p38 (7). Moreover, p38 is activated by the mitogen-activated/extracellular response kinase kinases MEK3 and
MEK6 (26). As shown in Fig. 5 A, by Western blotting with activation state-specific antibodies, p38 and MEK3/6, but not ERK1/2, are phosphorylated and thereby activated in a time-dependent manner in MCF-7 cells treated with 10 μM MG132, in agreement with published data (7). Overall p38 expression levels were not affected (Fig. 5 B). Is there a link between p38 activation and ERK3 induction? To address this question we tested whether ERK3 induction could be blocked by preincubation with selective p38 kinase inhibitors. The kinase inhibitors SB202190, SB203580, and PD169316 are specific inhibitors of the p38 pathway (26, 27). MCF-7 cells were pretreated for 3 h with these inhibitors to disable p38 activation and were subsequently incubated with the proteasome inhibitor MG132 for an additional 14 h. Immunoblotting revealed no induction of
ERK3 in cotreated cells (Fig. 5C), suggesting that ERK3 is controlled by the p38 pathway. Recently, it has been published that two transcription factors, GADD153 and ATF3, are induced by inhibition of the proteasome (3). To prove that the kinase inhibitors selectively block ERK3 overexpression, but not the induction of other proteasome-controlled proteins, the protein levels of Gadd153 and ATF3 were analyzed by immunoblotting (Fig. 5D). In contrast to ERK3, pre-incubation with the p38 kinase inhibitors did not block induction of Gadd153 and ATF3. To exclude the possibility that the inhibitors of the p38 pathway induce Gadd153 and ATF3 per se, an additional control experiment was performed. As shown by Western blot analysis in Fig. 5E, neither Gadd153 nor ATF3 were induced in MCF-7 cells that had been exposed to p38 inhibitors alone.

**ERK3 Protects Cells from the Antiproliferative Effect of Proteasome Inhibitors**—To investigate the potential role(s) of

![Fig. 6. ERK3 expression and proliferation. Proliferation of MCF-7 cells ectopically expressing ERK3.](image)

![Fig. 7. ERK3 expression, proliferation, and p38 inhibition.](image)
ERK3 induction upon proteasome inhibition, MCF-7 cells were stably transfected with ERK3, producing MCF-7-ERK3 cells, or with a control vector (MCF-7-neo). ERK3 was detected by Western blotting in MCF-7-ERK3 cells but was not present in MCF-7-neo cells (Fig. 5A). Following 40 h of exposure to MG132 or doxorubicin, the proliferation rates of MCF-7-ERK3 and MCF-7-neo were measured (Fig. 6). As shown in Fig. 5A, MCF-7-ERK3 cells were more resistant to the antiproliferative effect of the ERK3 inducer MG132 than to that of doxorubicin, which did not induce ERK3 (Fig. 3B). These results implicate ERK3 in defense mechanisms protecting MCF-7 cells from adverse effects induced by proteasome inhibition.

To further prove this hypothesis, MCF-7 cells were treated for 40 h either with increasing concentrations of the p38-specific kinase inhibitor SB203580 or with combinations of MG132 and SB203580, or rotenone and SB203580, respectively (Fig. 7). The concentrations of MG132, PSI, and rotenone were chosen to yield a half-maximal inhibition (data not shown) of the proliferation rate (0.25 μM MG132, 0.5 μM PSI, and 0.5 μM rotenone). MCF-7 cells treated with MG132 or PSI were sensitive toward increasing concentrations of the ERK3-blocking compound SB203580 and showed a strong SB203580-dependent decrease in the proliferation rate. In contrast, the decrease in the proliferation rate was less pronounced in cells treated with SB203580 alone or in combination with rotenone. Similar results were obtained in MDA MB231, MDA MB468, and DU145 cells, indicating that the protective effect of ERK3 is not restricted to MCF-7 cells.

**Discussion**

A cDNA array hybridization approach as a high throughput screening method for differential gene expression has been applied to develop a comprehensive picture of pathways linked to proteasome inhibition (3). Similar approaches were taken to characterize genotoxic stress patterns (28), transformation-related genes in oral cancer cells (29) and fibroblasts (30), and early steps in immortalization of Burkitt lymphoma (31), to name just a few.

The approach chosen did point toward a large number of pathways affected by the proteasome. In the present study, we focussed on ERK3 because MAP kinases represent key regulators of intracellular signaling pathways. ERK3 regulation seems to involve at least two mechanisms: i) at the transcriptional level, as shown here, and upon ganglioside treatment, as illustrated by Kleines et al. (32), and ii) at the post-translational level, corroborated for instance by Camarillo et al. (33).

ERK3 mRNA induction has been shown to occur as a consequence of proteasome inhibition. The induction was independent of p53, Bcl-2, or caspase 3, all three of them representing important regulatory mechanisms of apoptosis. p38 inhibitors of different chemical structure all abrogated ERK3 induction by proteasome inhibition. ERK3 overexpression occurred downstream of p38 MAPK activation, which was essential for the induction to take place. However, alternative pathways leading to ERK3 overexpression and/or activation by other triggers cannot be excluded.

Activation of p38 typically is accomplished via activation of MEK3/6 (26). Indeed, we were able to confirm this in MCF-7 cells as well. Moreover, we do not see an increase in MEK3/6 protein or p38 protein levels but rather an accumulation of phosphorylated species. At least one component further upstream of MEK3/6 is postulated to be regulated at the expression level. Expression levels of a range of other transducers of the mitogen signal (ERK1, 2, 5, 6, MEK1, and MKP1) all remained unchanged. This putative factor remains to be identified.

A large set of transcription factors including Elk-1, c-Myc, c-Jun, c-Fos, and C/EBP β has been described as being activated by MAP kinases and p38 in particular (34). The nature of the transcription factor that undergoes p38-dependent activation and, as a consequence thereof, induces ERK3 transcription is still elusive. Wang and Ron (35) show that Gadd153 undergoes phosphorylation on two adjacent serine residues, most probably by p38. When considering the kinetics of ERK3 versus Gadd153 induction, we cannot definitely exclude the possibility that phosphorylated Gadd153 indeed regulates ERK3 transcription and that Gadd153 activity is regulated in a dual manner by transcriptional induction and by phosphorylation. This hypothesis, however, is at odds with the notion that Gadd153 overexpression is associated with apoptosis (35, 36). Ectopic overexpression of ERK3, on the other hand, was shown to partially protect cells from growth inhibition by proteasome inhibitor compounds. This protection was not manifested when cells were challenged with other cytotoxic compounds (rotenone and doxorubicin), indicating a divergent mechanism of cell toxicity of those compounds and a very specific mode of protection by ERK3.

Inversely, p38 inhibition specifically sensitized various cells to proteasome inhibitors. We would therefore conclude that ERK3 triggers, or is part of, a rescue mechanism. Combined use of p38 inhibitors with proteasome inhibitors such as PS341, which is in Phase II clinical trials for prostate tumor indications, should represent a successful strategy to treat solid tumors.

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