Primary Cultured Neurons Devoid of Cellular Prion Display Lower Responsiveness to Staurosporine through the Control of p53 at Both Transcriptional and Post-transcriptional Levels*

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We assessed the contribution of the cellular prion protein (PrPc) in the control of neuronal apoptosis by examining cell death in both human cells and murine primary cultured neurons. We first confirmed our previous finding that staurosporine-induced caspase activation is increased by PrPc overexpression in HEK293 cells. We show here that this phenotype is fully dependent on p53 and that the control of p53 activity by PrPc occurs at both transcriptional and post-transcriptional levels in human cells. Of most interest, we demonstrate that neuronal endogenous PrPc also controls a p53-dependent pro-apoptotic phenotype. Thus, DNA fragmentation and TUNEL (terminal deoxynucleotidyltransferase-mediated dUTP nick end-labeling)-positive cells were lower in primary cultured neurons derived from Zrcb-1 mice embryos in which PrPc has been abrogated than in wild-type neurons. PrPc knock-out neurons also displayed drastically diminished caspase-3-like activity and immunoreactivity together with reduced p53 expression and transcriptional activity, a phenotype complemented in part by PrPc transfection. Interestingly, p53 expression was also reduced in the brain of adult Prnp<sup>−/−</sup> mice. Neuronal PrPc likely controls p53 at a post-transcriptional level because the deletion of cellular prion protein is accompanied by a higher Mdm2-like immunoreactivity and reduced phosphorylated p38 MAPK expression. We therefore propose that the physiological function of endogenous cellular prion could be to regulate p53-dependent caspase-3-mediated neuronal cell death. This phenotype likely occurs through up-regulation of p53 promoter transactivation as well as downstream by controlling p53 stability via Mdm2 expression.

Prion-related pathologies are now better understood as diseases that can be of either sporadic or infectious origin but always have a fatal outcome (1, 2). These pathologies are not conventional, first because they appear to be caused mainly by a unique protein that bears the potential of transmissibility in infectious cases of these diseases. It is now widely admitted that transmission occurs independently of any accompanying nucleic acid or viral particles (1, 3). Second, and of most interest, was the demonstration that the scrapie (also called PrP<sup>sc</sup>) is the highly protease-resistant conformer of a ubiquitous protein counterpart referred to as cellular prion protein (PrPc) (4, 5). Another striking aspect is that the host PrP<sup>c</sup> seems to act as a "substratum" for scrapie as demonstrated by the fact that in animals deficient in endogenous PrPc, highly infectious "scrapie-rich" inoculates fail to transmit the disease (6, 7). This observation is not fully understood at a molecular level, and the mechanisms by which PrP<sup>c</sup> is converted into scrapie remain a matter of speculation. Furthermore, this does not explain most of the sporadic cases that are characterized at late stages by spontaneous deposition of PrP<sup>sc</sup> in the absence of exogenous "pathogenic" species.

Some clues to further understand PrP-related pathologies might come from a better knowledge of PrP<sup>c</sup> physiology and putative dysfunctions responsible for the disease. In this respect, an interesting discussion revolving around cell death is ongoing, opening a new field of investigation. It is clear that apoptosis accompanies the late stages of the disease. Following that idea, several groups have set out to investigate the putative role of PrP<sup>c</sup> in the control of cell death. From a theoretical point of view, PrP could be antiapoptotic, and the disease could result in the abolition of this function. Alternatively, PrP<sup>c</sup>-related pathologies could be due to the exacerbation of a pro-apoptotic physiological phenotype associated with PrP<sup>c</sup>. Studies carried out on distinct cell types, with various methodologies and approaches, have led to somewhat opposite conclusions (8–12). Our previous studies have shown that over-expression of PrP<sup>c</sup> in human embryonic kidney cells (HEK293) and TSM1 neurons as well as in an inducible cell line (Rov9) leads to increased susceptibility to apoptotic stimuli, reflected mainly by enhanced caspase-3 activity (13, 14). We further demonstrated that in TSM1 neurons, PrP<sup>c</sup>-induced caspase-3 activation is associated with an up-regulation of p53 expression and transcriptional activity (14). This appears to be due to Mdm2-related post-transcriptional modification of p53 (14).

In the present study, we first establish that in HEK293, PrP<sup>c</sup>-related increased cell death is fully dependent on p53 activity. Moreover, we demonstrate that p53 deletion in fibroblasts fully abolishes both PrP<sup>c</sup>-induced caspase-3 and p53 transcriptional activities. We also show that in addition to our previously described post-transcriptional control of p53 (14),

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1 The abbreviations used are: PrP, prion protein; TUNEL, terminal deoxynucleotidyltransferase-mediated dUTP nick end-labeling; HEK293 cells, human embryonic kidney cells; MAPK, mitogen-activated protein kinase.
PrP\(^c\) also enhances the transactivation of the p53 promoter.

Because our TSM1 neurons stably overexpressed PrP\(^c\), it was also important to confirm the p53-dependent function of endogenous PrP\(^c\). We therefore examined the physiological contribution of cellular PrP\(^c\) to the control of neuronal cell death by comparing primary cultured neurons derived from mice harboring (Prnp\(^{+/+}\)) or devoid (Prnp\(^{-/-}\), Zrch-1 mice (15)) of endogenous PrP\(^c\). We show that neurons derived from Zrch-1 mice embryos are less sensitive to staurosporine and display lower DNA fragmentation, caspase-3 and p53 activities and expression, and higher Mdm2-like immunoreactivity. We demonstrate that endogenous PrP\(^c\) controls neuronal cell death via Mdm2-regulated p53-dependent caspase-3 activation in non-immortalized neurons.

**MATERIALS AND METHODS**

**Primary Cultured Neurons, 3F4-HEK293 Cells, and p53-deficient Fibroblasts—**Primary cultured neurons were prepared from the cerebral hemispheres of 14-day-old PrP\(^{-/-}\) or PrP\(^{+/+}\) mouse embryos as described (16). Briefly, cells were mechanically dissociated with a pipette in Ham’s F12 medium (Invitrogen) supplemented with 10% fetal calf serum and 0.6% glucose. Dissociated cells were then plated at a density of 10\(^5\) cells in 35-mm dishes pre-coated with 10 \(\mu\)g/ml polylysine (Sigma) and grown in a humidified atmosphere of 5% CO\(_2\), 95% air.

**Western Blot Analyses—**Cells were scraped and homogenized in lysis buffer (50 \(\mu\)M Tris-HCl, pH 7.5, 150 \(\mu\)M NaCl, 5 \(\mu\)M EDTA containing 0.5 Triton X-100 and 0.5% sodium deoxycholate). Equal amounts of protein (50 \(\mu\)g) determined by the Bradford method (19) were separated on 12% SDS-PAGE and analyzed for their p53, active caspase-3, Mdm2, phospho-P38, and PrP\(^c\) immunoreactivities by Western blot and hybridization with anti-p53 (mouse monoclonal Pab24, Santa Cruz Biotechnology), anti-active caspase-3 (rabbit polyclonal, RnD Systems), mouse monoclonal anti-Mdm2 (20), anti-phospho-P38 (Promega), and anti-PrP\(^c\) (SAF32 (21), respectively.

**Flow Cytometry and TUNEL Analysis—**Cells were grown in 6-well plates and incubated for 15 h at 37 \(^\circ\)C in the presence or absence of staurosporine (0.5 \(\mu\)M, Sigma) and then rinsed with PBS and suspended with 750 \(\mu\)l of buffer (Tris 20 mm, tri-natrium citrate 0.1%, Triton X-100 0.05%) containing 50 \(\mu\)g/ml propidium iodide. Cells were left overnight at 4 \(^\circ\)C, and then the propidium iodide fluorescence of individual nuclei was measured as described previously (14). For DNA nick-end labeling, cells were fixed for 20 min in 1% paraformaldehyde in phosphate-buffered saline, rinsed in phosphate-buffered saline, left overnight in 70% ethanol, and then processed for the dUTP nick-end labeling TUNEL technique according to manufacturer’s recommendations (kit from Roche Applied Science). Staining was assessed with a peroxidase-conjugated antibody and revealed with a diaminobenzidine substrate.

**Statistical Analysis—**Statistical analysis was performed with Prism software (Graphpad Software, San Diego, CA) using the Newman-Keuls multiple comparison test for one-way analysis of variance and the unpaired Student’s \(t\) test for pairwise comparisons.

**RESULTS**

**PrP\(^c\)-induced Apoptotic Phenotype Is Fully Dependent on p53 in Human Cells and Fibroblasts—**We have established previously that PrP\(^c\) drastically potentiates staurosporine-induced caspase activation in neuronal TSM1 cells (14). This phenotype is antagonized by the depletion of endogenous p53 by using an antisense approach (14). Using a pharmacological approach, we have established here that a very potent and selective p53 inhibitor, pifithrin-\(\alpha\), completely abolishes p53 transcriptional activity in human HEK293 cells (Fig. 1B). Furthermore, pifithrin-\(\alpha\) but not its inactive analog (Fig. 1A) fully inhibits the PrP\(^c\)-dependent increase of staurosporine-induced caspase activation.

We previously documented the fact that PrP\(^c\) increases p38-like immunoreactivity and controls Mdm2-dependent p53 metabolic stability in TSM1 cells (14). Here we show that besides this post-transcriptional effect, PrP\(^c\) also exerts transcriptional control of p53. Thus, 3F4-HEK293 cells display a significantly higher p53 promoter transcription than mock-transfected cells as indicated by the luciferase reporter activity (Fig. 2).

We have previously established a link between p53 and the PrP\(^c\)-induced phenotype using fibroblasts in which the p53 gene harbors a loss-of-function mutation. To confirm this finding and preclude the possibility of a refolding/restoration of p53 activity after the chaperoning of mutated p53 (25), we have now switched to a fibroblastic cell line in which p53 has been invalidated and examined the phenotype triggered by overex-
pression of PrPc. In the absence of p53, there is an important staurosporine-induced caspase-3 activation (Fig. 3B). Interestingly, this p53-independent caspase activity was not enhanced by PrPc (Fig. 3B), whereas the combination of PrPc expression and p53 complementation led to an additional increase of caspase-3 activity (Fig. 3B). Finally, the co-transfection of PrPc with p53 cDNA drastically potentiated the p53 transcriptional activity exhibited by p53 cDNA transfection alone (Fig. 3A).

Altogether, these data, combined with those observed after pifithrin-a inhibition, clearly indicate that the PrPc proapoptotic phenotype is completely dependent on p53 and that the latter is controlled by PrPc at both the transcriptional (Fig. 2) and post-transcriptional (14) levels in human and neuronal cells.

PrPc-/- Primary Cultured Neurons Display Lower Susceptibility to Staurosporine—Our previous statements above were based on several cell lines overexpressing PrPc. It was therefore important to assess the contribution of endogenous PrPc. We thus measured the staurosporine susceptibility of primary cultured neurons from Zrch-1 mice embryos in which the Prnp gene had been disrupted (15). As expected, these neurons do not display any PrPc-like immunoreactivity (Fig. 4A). That PrPc-/- neurons exhibit lower staurosporine-induced responses is evidenced by both TUNEL (Fig. 4, B and C) and DNA fragmentation (Table I) analyses. Clearly, the staurosporine-induced increase in the number of apoptotic nuclei observed in PrPc-/-/neurons is drastically lower in neurons devoid of PrPc (Fig. 4, B and C). This lower staurosporine susceptibility exhibited by PrPc-/- primary cultured neurons is accompanied by lowered caspase-3-like immunoreactivity (Fig. 5A) and activity (Fig. 5B). It is noteworthy that the effect of staurosporine is dose-dependent in both PrPc-/- and PrPc-/- cells, as was another apoptotic effector, ceramide C2 (Fig. 5, C and D). However, the effect triggered by both pharmacological agents always remains lower in PrPc-/- neurons than in PrPc-/- neurons.

PrPc Complementation Partially Restores Staurosporine-induced Caspase-3 Activation in PrPc-/- Primary Cultured Neurons—Transient transfection of PrPc-/- neurons with 3F4MoPrPc cDNA led to enhanced PrPc-like immunoreactivity (Fig. 6A, upper panel). The treatment of mock-transected PrPc-/- neurons with staurosporine increases caspase-3-like immunoreactivity, a phenotype that was drastically enhanced in 3F4MoPrPc-/-transfected primary cultured neurons (Fig. 6A, lower panel). Accordingly, this was accompanied by a consistent elevation of staurosporine-induced caspase activation upon 3F4MoPrPc transfection of PrPc-/- neurons (Fig. 6B). These data indicate that primary cultured neurons were transfectable and that 3F4MoPrPc overexpression in these cells mimics and potentiates the staurosporine-stimulated caspase activation phenotype observed in untransfected primary cultured neurons (see Fig. 5).

We took advantage of this feature to examine whether the lowering of caspase activation observed in PrPc-/- primary cultured neurons could be rescued even partially by 3F4MoPrPc overexpression. Fig. 7A shows that a PrPc-like immunoreactivity was detectable in 3F4MoPrPc-/-transfected PrPc-/- neurons. This was accompanied by a partial but reproducible recovery of the staurosporine-induced caspase activation responsiveness displayed by PrPc-/- neurons (Fig. 7B). Thus, although mock-transfected PrPc-/- display only 54% of the responsiveness of PrPc-/- neurons to staurosporine, three distinct 3F4MoPrPc transfections of PrPc-/- neurons consistently restored the staurosporine-induced caspase-3 activation to about 81% of the control (Fig. 7B). This incomplete rescue is in apparent agreement with the relatively low efficiency of 3F4MoPrPc cDNA transfection illustrated by the expression of exogenous PrPc in PrPc-/- primary cultured neurons and agrees well with all of the data described above.

PrPc-/- Neurons Display Lower p53 Expression and Activity—We examined the putative modulation of the tumor suppressor oncogene p53 by endogenous PrPc. Primary cultured neurons devoid of their endogenous PrPc content display decreased p53 immunoreactivity (Fig. 8A) and transcriptional activity (Fig. 8B), thereby demonstrating that endogenous PrPc controls p53 expression and activity. Of greatest interest was the observation that p53 expression in the 1-month-old mouse brain was drastically lower in PrPc-/- than in wild-type mice (Fig. 8C), indicating that PrPc also controls p53 expression in vivo.

**Fig. 2.** PrPc expression increases p53 promoter transactivation. Transactivation of the p53 promoter was measured as described under “Materials and Methods” in mock-transfected or 3F4-PrPc-expressing HEK293 cells. Bars are the means ± S.E. of luciferase activities (to which control luciferase activity was subtracted) measured in 12 independent determinations. **,** p < 0.001.

**Fig. 3.** Effect of PrPc transfection on caspase-3 and p53 transcriptional activities in p53-deficient fibroblasts. A, p53 transcriptional activity was monitored as described under “Materials and Methods” after transient transfections of p53 knock-out fibroblasts with empty pcDNA3 vector, 3F4MoPrPc (PrPc), or p53 cDNA (p53) alone or in combination (PrPc/p53). In B, caspase-3 activity was measured after identical transient transfection of the indicated cDNA in p53-deficient fibroblasts treated (+) or not (−) with staurosporine. Bars represent the means of six determinations ± S.E. **,** p < 0.05.
under absence (−) or presence (+) of staurosporine in the indicated neurons. Cell death is visualized by black precipitates and quantified (C) as detailed under “Materials and Methods.”

### Table I

**Basal and staurosporine-stimulated propidium iodide incorporation measured in the indicated cell lines by flow cytometry analysis**

|                    | PrP<sup>+/−</sup> | PrP<sup>+/+</sup> |
|--------------------|------------------|------------------|
| **Basal**          | 33.8             | 24.3             |
| **Staurosporine**  | 66.7             | 32.1             |

*The number of apoptotic nuclei is estimated as described under “Materials and Methods.”*

**PrP<sup>+</sup> Controls Post-transcriptional Modulators of p53 Activity**—We searched for post-transcriptional modulators of p53 activity that would be under the control of endogenous PrP in primary cultured neurons. Mdm2 was recently shown to decrease p53 metabolic stability thereby lowering its activity (20). We demonstrate here that Mdm2 immunoreactivity is higher in PrP<sup>−/−</sup> than in wild-type neurons (Fig. 5A), a phenotype completely opposite from that observed for p53 immunoreactivity (see Fig. 5A). As p38 mitogen-activated protein kinase (p38 MAPK) was reported to up-regulate p53 activity via upstream of Mdm2 expression (26), we also examined the endogenous levels of the active, phosphorylated counterpart of p38 MAPK. Active p38 immunoreactivity was higher in wild-type than in PrP<sup>−/−</sup> neurons (Fig. 8E), suggesting that PrP<sup>+</sup> also controls p38 phosphorylation at endogenous levels.

**DISCUSSION**

Spongiform encephalopathies comprise a group of several transmissible diseases known for a long time to affect animals and are always characterized at their later stages by neurodegenerescence and ultimately death (1, 27–30). These pathologies became of higher interest when it appeared that some of these diseases could also affect human beings, leading to the logical suspicion that the human pathology could be transmitteled in man and, therefore, that mankind was facing a novel public health problem with unforeseeable consequences. The boost of interest in this novel and intriguing type of pathology has been focused mainly on a better knowledge of a 33–35 kDa sialoglycosylated and glycosylphosphatidylinositol-anchored polypeptide called prion, which appears to be the main actor in the disease. Interestingly, it was demonstrated that the pathogenic agent (or at least clearly its main component) was a protein called scrapie, or PrP<sup>res</sup>, which has the same primary sequence as its ubiquitous counterpart, cellular prion or PrP<sup>c</sup> (1). However, PrP<sup>res</sup> displays a β-sheet-enriched structure that renders it highly resistant to proteolysis and prone to aggregation (1). How PrP<sup>res</sup> acquires its pathological conformation is not yet established but infectious inoculates “mimicking” the disease require endogenous PrP<sup>c</sup> to propagate, as they are fully innocuous in mice engineered to abrogate their endogenous PrP<sup>c</sup> protein content (6). Also yet not fully understood are the molecular determinants that initiate the pathogenic process in sporadic encephalopathies. A better understanding of these sporadic cases would likely come from a better knowledge of the physiological function of PrP<sup>c</sup> and the putative dysfunction that takes place when these diseases occur.

Few things really are known concerning the physiological function of PrP<sup>c</sup>, but several lines of evidence indicate that PrP<sup>c</sup> could modulate cell death. PrP<sup>c</sup> mutations could trigger caspase activation (31), and murine scrapie appears to be associated with cell death (32). Furthermore, prion infection impairs the cellular response to oxidative stress inducers (33) and triggers apoptosis in a hypothalamic neuronal cell line (34). Altogether, these data suggest the ability of PrP<sup>c</sup> to modulate cell death, but whether this is due to an exacerbation of a proapoptotic function or, alternatively, to the alteration of an antiapoptotic phenotype could both be envisioned. The literature in this field does not really solve the debate, and there are opposing data supporting both possibilities. On one hand, Kuwahara et al. (8) have shown that serum deprivation-induced cell death is exacerbated in hippocampal neurons prepared from Prnp<sup>−/−</sup> mice. On the other hand, PrP<sup>c</sup> also appears to protect human neurons from cell death triggered by overexpression of the proapoptotic oncogene Bax (9). Finally, a recent paper indicates that PrP<sup>c</sup> could be a cellular mediator protecting retinal tissue from anisomycin-induced apoptosis (10). From the above data one should expect a drastic deleterious effect of PrP<sup>c</sup> deletion due to the abrogation of this antiapoptotic phenotype. This seems not to be the case, as PrP<sup>c</sup>-deficient mice are safe, healthy, and apparently develop and behave normally (15). Furthermore, a recent article indicates that post-natal deletion of the PrP<sup>c</sup> alters the excitability of CA1 hippocampal neurons but does not induce neurodegeneration in adulthood (12).

We had previously established that overexpression of PrP<sup>c</sup> enhances staurosporine-induced cell toxicity and DNA fragmentation and activates caspase-3 in stably transfected HEK293, TSM1 neurons, or inducible Rov9 cell lines (13, 14). Furthermore, we showed that PrP<sup>c</sup>-induced caspase-3 activa-
tion is mediated by an Mdm2-regulated p53-dependent pathway in TSM1 neurons (14). These data are fully in agreement with a previous work demonstrating that transgenic mice over-expressing wild-type PrPc could exhibit severe neurodegeneration (11). However, it could be argued that the PrPc-related phenotype could be, in both cases, due to overexpression of the

Fig. 5. Depletion of endogenous PrPc lowers the responsiveness of primary cultured neurons to staurosporine and ceramide C2. Primary cultured neurons were obtained from 14-day-old mouse embryos from wild-type mice (PrP+/+) or Zrch-1 mice in which the Prnp gene had been deleted (PrP−/−) and cultured as described under “Materials and Methods.” Caspase-3-like immunoreactivity (A) and activity (B) were measured in the indicated cell lines in control (−) and staurosporine (Sts)-stimulated (+) conditions. The bars in B correspond to the Ac-DEVD-al-sensitive Ac-DEVD-7AMC hydrolyzing activity and are the means ± S.E. of four experiments (duplicate determinations). C and D, PrP−/− and PrP−/− cultured neurons were incubated with increasing concentrations of staurosporine (C) or ceramide C2 (D), and then caspase-3 was measured as described. The bars show the percent of control corresponding to caspase activity recovered in untreated PrP−/− neurons and represent the means ± S.E. of three independent experiments.

Fig. 6. PrPc cDNA transfection increases staurosporine-induced caspase activity and immunoreactivity in PrP−/− neurons. After transient transfection of wild-type primary cultured neurons (PrP+/+) with 3F4MoPrP cDNA or empty vector (pcDNA3), PrPc- and caspase-3-like (casp.3) immunoreactivities (A) and caspase activity (B) were measured under control (−) and staurosporine-stimulated (+) conditions (see “Materials and Methods” for details). Experiments in B correspond to three independent transfections with 3F4MoPrP cDNA.

Fig. 7. PrPc cDNA transfection partially restores staurosporine-induced caspase activation in PrP−/− neurons. Transient transfection of PrPc cDNA in PrP−/− neurons increases PrPc immunoreactivity (A) and partially restores staurosporine-induced caspase activation (B). Bars correspond to the staurosporine-induced increase of caspase-3 activity expressed as the percent of control corresponding to staurosporine stimulation of wild type PrP+/+ neurons transiently transfected with empty pcDNA3 vector (means of three independent transfections with 3F4MoPrP cDNA).
protein. In line with such an hypothesis, a recent study nicely established that in N2A murine neuroblastoma cells, neurotoxicity and neurodegeneration could be associated with cytotoxic accumulation of PrP\(^{C}\) (35). These data fully agreed with our demonstration that the manipulation of cytotoxic PrP\(^{C}\) concentration could indeed affect cell death. Thus, proteasomal inhibition leads to increased PrP\(^{C}\)-like immunoreactivity accompanied by drastic potentiation of caspase activation in HEK293 cells (13). Conversely, depletion of cellular PrP\(^{C}\) by immunodepletion at the membrane precludes the PrP\(^{C}\)-induced proapoptotic phenotype (13).

The present study first confirms that overexpression of PrP\(^{C}\) enhances staurosporine-stimulated caspase-3 activity and demonstrates for the first time that in HEK293 cells, all PrP\(^{C}\)-related phenotypes are p53-dependent. These data have been fully reinforced by our observation that PrP\(^{C}\) is inactive in p53-deficient fibroblasts. Interestingly, we have established that, besides post-transcriptional modulation of p53, PrP\(^{C}\) also enhances p53 promoter transactivation.

It was most important to establish that the p53-dependent PrP\(^{C}\)-related phenotype was not solely due to an artifactual perturbation of the cell physiology caused by the overexpression of the protein. In this context, we examined the contribution of endogenous PrP\(^{C}\) to apoptotic response by monitoring cell death in primary cultured neurons derived from mice embryos in which the Prnp gene had been ablated (Zrch-1). Our data show that deletion of PrP\(^{C}\) led to a phenotype fully opposite of PrP overexpression. Prnp\(^{-/-}\) neurons are indeed less sensitive to staurosporine as monitored by TUNEL-positive cells, DNA fragmentation, and caspase activity and immunoreactivity. Furthermore, this phenotype appears linked to a drastic reduction of p53 activity and immunoreactivity. Finally, the p53 activator (p38 MAPK) and inhibitor (Mdm2) immunoreactivities are reduced. This indicates that PrP\(^{C}\) likely controls p53, at least in part, at a post-transcriptional level, as we demonstrated in TMS1 neurons by an overexpression approach (13). Therefore, our current study further demonstrates that PrP\(^{C}\) controls caspase activity through a p53-dependent and Mdm2-regulated process and that this proapoptotic phenotype is not caused artifically by overexpression of the protein.

We recently established that in Alzheimer's disease, presenilin-2, a protein that when mutated mainly contributes to Alzheimer's disease-related pathologies, also controls cell death response to staurosporine by an identical p53-dependent mechanism (36). This observation, together with our demonstration that similar proteolytic dysfunctions occur in both Alzheimer's and prion diseases, suggests that several common features could link apparently distinct neurodegenerative diseases (37). This is also true when one considers Parkinson's disease pathology in which an \(\alpha\)-synuclein anti-apoptotic physiological phenotype (22) is associated to p53 down-regulation, which is abolished by 60F-dopa, a toxin associated with this pathology (38). Altogether, these observations suggest envisioning p53 as a molecular target for therapeutic strategies in various neurodegenerative pathologies.

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