autophagy is a distinct degradation system from the UPS, recent study suggests that there is a cross- talk between the two systems [24]. When one system is impaired (e.g., the UPS), the other is activated. In this regard we address the question if both systems are impaired in the same time as the aberrant proteins aggregate? Given the importance of the two systems, future studies are required to understand their way they function.

6. Future Scope

Our future project is to study the major pathways implicated in the process that eliminate misfolded proteins. The UPS was partially studied (Zouambia et al., 2008). My proposal is to continue these studies by focusing on the UPS escort pathway proteins and the Autophagic Lysosomal Pathway (ALP). Autophagy is defined as the homeostatic delivery of macronutrients and organelles to the lysosome for pH-dependent degradation, and has been shown to play an important role in responding to intracellular energy demands and maintaining energy balance. To date, three major types of autophagy have been described: macroautophagy, whereby bulk cytoplasm and organelles are enclosed within vesicles and are delivered via a series of vesicular fusion events to the lysosome for degradation by lysosomal hydrolases that function optimally at low pH; chaperone mediated autophagy (CMA), whereby proteins with "KFERQ" motifs are selectively shuttled via molecular chaperones including hsc70 to lysosomes, where lysosomal membrane-bound receptors (Lamp2a) selectively internalize these proteins into the lumen of lysosomes for degradation; and microautophagy, a process of direct nutrient uptake by lysosomal membranes. Recent evidence suggests that the degradation of mitochondria by macroautophagy, termed "mitophagy", may be a more selective form of macroautophagy and has been implicated in neurodegenerative disease.

7. Competing Interests

The authors have declared that no competing interests exist.

8. Acknowledgments

The author is greatly indebted to IBRO-UNESCO for a research fellowship 2002. We thank the Netherlands Brain Bank for supplying the human brain tissue.

References

[1] Hershko, A. and Ciechanover, A. (1998) " The ubiquitin system." Annu Rev Biochem 67: 425-79.
[2] Ciechanover A. Proteolysis: From the lysosome to ubiquitin and the proteasome. Nat Rev Mol Cell Biol 2005;6:79-87. [Pubmed: 15688069]
[3] Demartino GN, Gillette TG. Proteasomes: machines for all reasons. Cell 2007; 129:659-662 [PubMed:17512401]
[4] Dick TP, Nussbaum AK, Deeg M, Heinmeyer W, Gr) Contribution of proteasomal beta-subunits to the cleavage of peptide substrates ana lysed yeast mutants. J Biol Chem 273: 25637-25646oll M, et al. (1998).
[5] Kisselev AF, Akopian TN, Castillo V, Goldberg AL. (1999) Proteasome active sites alternatively regulate each other, suggesting a cyclical bite- chew mechanism for protein breakdown. Mol Cell 4: 395-402
[6] DeMartino GN, Slaughter CA (1999) The proteasome, a novel protease regulated by multiple mechanisms J Biol Chem 274: 22123-22126
[7] Rechsteiner M, Hill CP (2005) Mobilizing the proteolytic machine: cell biological roles of proteasome avtivators. Trends Cell Biol 15: 27-33
[8] Fischer, D. F., De Vos, R. A. I., Proper, E. A., Van Dijk, R. et al., Disease accumulation of mutant ubiquitin as a marker for proteasomal dysfunction in the brain. FASEB *J. 2003, 17, 2014-2024*
[9] Bulteau, A., Petropoulos, I, & Friguet, B.(2000) Age-related alteration of proteasome structure and function in aging epidermis. Experimental Gerontology 35,767-777.
[10] Reinheckel, T., Ullrich, O. et al.(2000) Differntial impairment of 20S and 26S proteasome activities in human hematopoietic K562 cells during oxidative stress. Arch Biochem Biophys 377 (1): 65-8.
[11] Keller, J.N., Hanni, K.B., and Markesbery, W.R. (2000). Impaired proteasome function in Alzheimer's disease.J. Neurochem.75,436-439.
[12] Fergusson J, Landon M, Lowe J, Dawson SP, Layfield R, Hanger DP, Mayer RJ (1996) Pathological lesions of Alzheimer's disease and dementia with Levy bodies brains exhibit immunoreactivity to an ATPase that is a regulatory subunit of the 26S proteasome. Neurosc Lett 219:167-170.
[13] Carrard, G., Dieu, M. et al. (2003) Impact of ageing on proteasome structure and function in human lymphocytes. Int J Biochem Cell Biol 35(5): 728-39.
[14] Tonoki, A., Kuranaga, E., Tomioka, T., Hamazaki, J., Murata, S., Tanaka, K. and Miura, M. (2009) Genetic Evidence Linking Age-Dependent Attenuaton of the 26S Proteasome with the Aging Proces Mol & Cell Biol, 29 (4):1095-1106
[15] David DC, Layfield R, Serpell L, Narain Y, Goedert M, Spillantini MG. (2002) Proteasomal degradation of tau protein. J. Neurochem. **83**, 176-185.
[16] Orlowski, M., Wilk, S. (2003) Ubiquitin-independent proteolytic functions of the proteasome. Arch Biochem Biophys; 415: 1-5
[17] Rizzu, P., Hinkle, D. A., Zhukareva, V. et al. (2004) DJ-1 colocalizes with Tau inclusions: a link between Parkinsonism and dementia. Ann Neurol; 55: 113-118
[18] Hasegawa, M., Fujiwara, H., Nonaka, T., Wakabayashi, K., Takahashi, H., Lee, V.M. Trojanowski, J. Q., Mann, D., and Iwatsubo, T. (2002) Phosphorylated alpha-synuclein is ubiquitinated in alpha synucleinopathy lesions. J. Biol. Chem. 277, 49071-49076
[19] Thrower, J. S., Hoffman, L., Rechsteiner, M., Pickart, C. M. (2000) Recognition of the polyubiquitin proteolytic signal. EMBO J; 19: 94-102
[20] Bonifati, V., Rizzu, P., van Baren, M. J. et al. (2003) Mutations in the DJ-1 gene associated with autosomal recessive early-onset Parkinsonism. Science; 299: 256-259
[21] Leroy, E., Boyer, R.,Auburger, G.,Leube, B.,Ulm,G.,Mezey,E.,Harta,G Brownstein, M. J., Jonnalagada, S., Chernova, T., Dehejia, A., Lavedan,

C., Gasser,T., Steinbach, P. J., Wilkinson, K. D., and Polymeropoulos, M. H. (1998) The ubiquitin pathway in parkinson's disease. Nature 395, 451-452

[22] Cuervo A.M: Autophagy in neurons: it is not all about food. *Trends MolMed* 2006, **12:**461-464.

[23] Kruse K. B., Brodsky J. L., McCracken A. A: Characterization of an ERAD gene as VPS30/ATG6 reveals two alternative and fuctionally distinct protein quality control pathways: one for soluble Z variant of human alpha-I proteinase inhibitor (AIPiZ) and another for aggregates of AIPiZ. Mol Biol Cell 2006, **17**:203-212.

[24] Levine B., Yuan J: Autophagy in cell death: an innocent convict? *J Clin Invest* 2005, **115**:2679-2688.

Figures Legend

Figure 1: Immunostaining of beta subunits (20S beta subunits).
(a) Hippocampus from AD patient (#96332) and (c) from DS patient (#25002), note the absence of staining with PW9000, an antibody against beta6 subunit of the 20S core, (b) and (d) Hippocampus from control (#90202), light cytoplasmic staining is shown (arrows).

Figure 2: Immunostaining of alpha5 subunits (20S alpha subunits).
(a) Hippocampus from AD patient (#88252) (b) fromDS patient (#94146), note the nuclear staining with PW8125, an antibody against alpha5 subunits of the 20S proteasome core. (c) Hippocampus from control (#89004). No staining was seen in the control.

Figure 3: Immunostaining of alpha6 subunits (20S alpha subunits).
(a) Hippocampus from AD patient (#89166), some nuclear stainings are visiblewith PW8100 (Arrows), antibody against alpha6 subunit of the 20S core. No staining was obtained in DS patient (#94146H (b) and control (#1126H) (c).
(c) With PW8100.

Figure 4: Immunostaining ATPase S6b subunit (19S regulator)
(a) Hippocampus from AD patient (#99139) and (b) DS patient (#95325) stained with PW8175 (anti-ATPase 6b of the 19S cap). Note the stained NTFs (Arrows). (b) Hippocampus from control (#89004). No staining was showed.
(c) Hippocampus from control (#89004). No staining is visible

Table 1: Antibodies

Antibodies to 19S Regulator ATPase subunits

Specificity	Type	Product Code
Subunit Rpt2	rabbit pAb	PW8160
Subunit Rpt1	rabbit pAb	PW8165
Subunit Rpt5	rabbit pAb	PW8170
Subunit Rpt3	rabbit pAb	PW8175
Subunit Rpt6	rabbit pAb	PW8215
Subunit Rpt4	rabbit pAb	PW8220
Subunit Rpt5	rabbit pAb	PW8245
Subunit Rpt3	rabbit pAb	PW8250
Subunit Rpt1	rabbit pAb	PW8255
Subunit Rpt2	rabbit pAb	PW8260
Subunit Rpt2	rabbit pAb	PW8305
Subunit Rpt5	rabbit pAb	PW8310
Subunit Rpt1	rabbit pAb	PW8315
Subunit Rpt6	rabbit pAb	PW8320
Subunit Rpt5	rabbit pAb	PW8375
Subunit Rpt3	mAb	PW8765
Subunit Rpt5	mAb	PW8770
Subunit Rpt1	mAb	PW8825
Subunit Rpt4	mAb	PW8830
Subunit Rpt6	mAb	PW9265

Antibodies to 19S Regulator non-ATPase subunits

Specificity	Type	Product Code
Subunit Rpn8	sheep pAb	PW8180
Subunit Rpn7	rabbit pAb	PW8225
Subunit Rpn6	rabbit pAb	PW8370
Subunit Rpn12	rabbit pAb	PW8815
Subunit Rpn10	mAb	PW9250
Subunit Rpn12	mAb	PW9260
Subunit Rpn1	mAb	PW9270

Antibodies to 11S Regulator subunits

Specificity	Type	Product Code
Subunit PA28a	rabbit pAb	PW8185
Subunit PA28g	rabbit pAb	PW8190
Subunit PA28b	rabbit pAb	PW8240

Antibodies to 20S Proteasome -subunits

Specificity	Type	Product Code
Subunit a	mAb	PW8100
Subunit a	mAb	PW8105
Subunit a7	mAb	PW8110
Subunit a3	mAb	PW8115
Subunit a4	mAb	PW8120
Subunit al5	mAb	PW8125
Subunit a5/a7, b1, b5, b5i, b7	rabbit pub	PW8155
Subunits a, 2, 3, 5, 6&7	mAb	PW8195
a-subunit (specificity unknown)	mAb	PW8265
Subunit a6	mAb	PW8270
a-subunit (specificity unknown)	mAb	PW8275
a-subunit (specificity unknown)	mAb	PW8280

Antibodies to 20S Proteasome –subunits

Specificity	Type	Product Code
Subunit b3	mAb	PW8130
Subunitb7	mAb	PW8135
Subunit b1	mAb	PW8140
Subunit b2	mAb	PW8145
Subunit b2i	rabbit pAb	PW8150
Subunit a5/a7, b1, b5, b5i, b7	rabbit pAb	PW8155
Subunit b5i	rabbit pAb	PW8200
Subunit b1i	mAb	PW8205
Subunit b2/b2i	rabbit pAb	PW8210
Subunit b1i	rabbit pAb	PW8345
Subunitb2i	rabbit pAb	PW8350
Subunit b5i	rabbit pAb	PW8355
Subunit b1i	mAb	PW8840
Subunit b5i	mAb	PW8845
Subunit b4	rabbit pAb	PW8890
Subunit b5	rabbit pAb	PW8895
Subunitb6	rabbit pAb	PW9000

Note: a= alpha, b = beta and g = gama.

Table 2: Specific localization of Proteasome subunits

Proteasome Complexes	Intracellular Localization	
19S subunits	**nucleus**	**cytoplasm**
ATPase S6b (Rpt3) [a,g]		+++
Non-ATPase (Rpn8) [c]		++
ATPase (Rpt3)		++
ATPase (Rpt5) [c]		+++
11S subunits		
PA28g[c]		+++
PA28b[c]		+++
20Salpha-subunits		
a6-subunit	++	
a5-subunit [b]	+++	
a5/a7,b1, b5, b5i,b7 [c]		+++
a1,2,3,5,6&7 [c]	+++	
20S beta-subunits		
b1-subunit [c]		+++
b2i-subunit [c]		+++
a5/a7,b1, b5,b5i, b7		++
b2/b2i-subunit		++
b6-subunit [c]		+++

++: moderate staining; +++: intense staining ;(a): neurofibrillary tangles, plaque neurites , neuropil threads, Pick bodies and Lewy bodies; (b): staining in patients and old controls; (c): stainings in patients and controls (including young controls).

Note: a = alpha, b = beta and g = gama

Figure 1

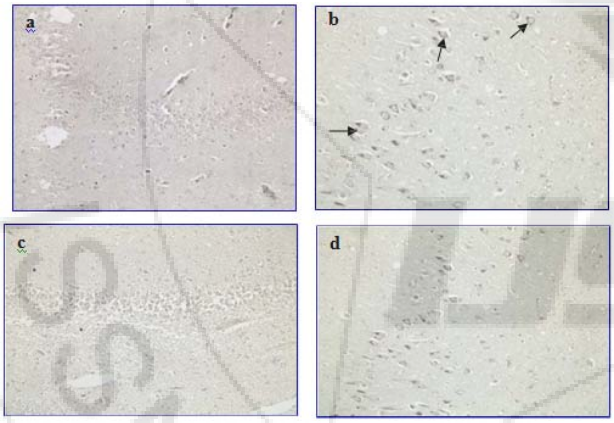


Figure 2

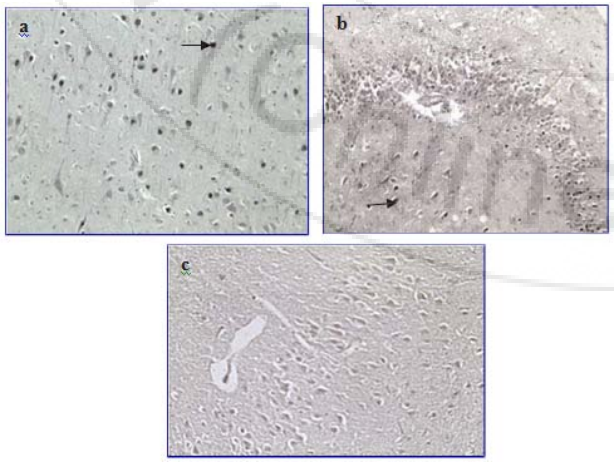


Figure 3

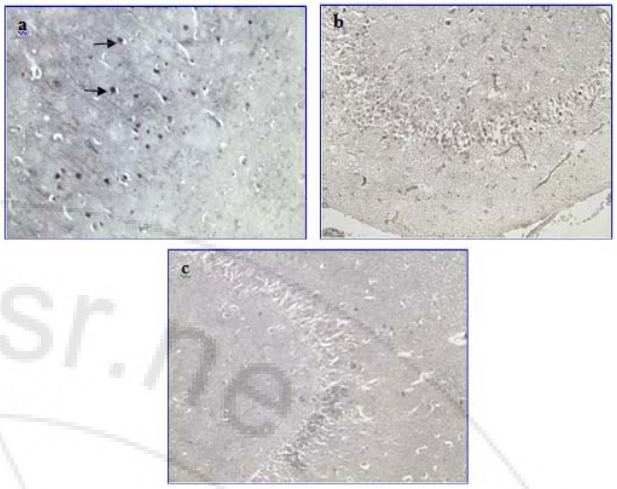
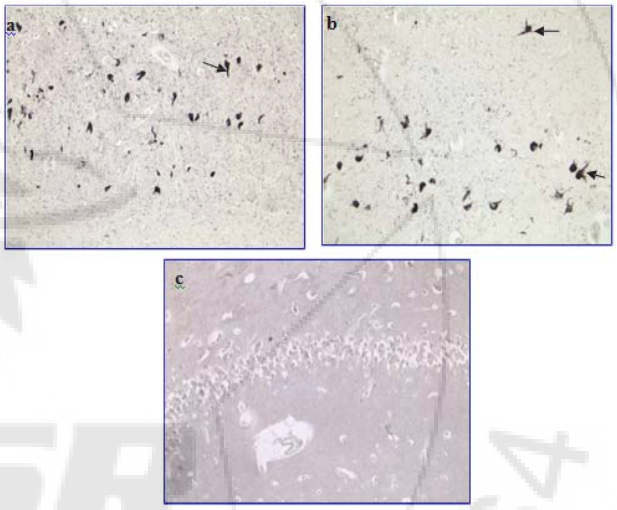


Figure 4



Author Profile

Dr Zouambia Mohamed is a teacher-researcher at the University of Science and technology of Algiers. I have been working in this University since 1981. I got my master degree in 1986 on the following project: Study of the cholinergic system, its implication in water and food intakes. This research work was done in collaboration with a French laboratory. In 2007 I defended my PhD thesis. The field of research was: Study of the neurodegenerative diseases. This research was undertaken in collaboration with "The Netherlands Institute of Neuroscience". At present I have developed a laboratory working on the same project.