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Possible use of drugs, used in cystic fibrosis, in neurodegenerative diseases

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Neurodegenerative diseases, including Alzheimer's disease, Parkinson's disease and amyotrophic lateral sclerosis, share a common etiopathogenesis, caused by protein aggregates accumulation in the brain, containing specific misfolded proteins. Correct protein folding is the basis of cellular well-being; misfolded proteins accumulation, inside the endoplasmic reticulum (ER), leads, in fact, to an imbalance of homeostasis, and a ER stress condition. To restore normal physiological conditions, a signal transduction pathway is activated, the unfolded protein response (UPR), controlled by three different proteins resident in the ER: IRE1α, PERK and ATF6, which are kept in an inactive state by binding to the molecular chaperone GRP78/BiP. Misfolded proteins accumulation, in ER lumen, causes a displacement of this chaperone, thus activating the UPR: PERK, after an autophosphorylation, phosphorylates eIF2α, which activates transcription factor ATF4, which, in turn, induces transcription of the pro-apoptotic protein CHOP; ATF6 acts as a transcription factor, activating UPR target genes, including GRP78/BiP; IRE1α, on the other hand, determines an upregulation of ER chaperones expression. UPR consists, therefore, in an adaptive response of the cell to an ER stress condition, which, however, continuing over time, induces permanent damage and apoptosis. The association between reticular stress and programmed death has been highlighted, moreover, also thanks to the Caspase-4discovery, a caspase localized in ER and specifically activated by apoptotic stimuli induced by reticular stress. ER stress is also associated with oxidative stress, caused by high levels of oxygen radical species (ROS), both cytosolic and mitochondrial, which have escaped the enzymatic control of Superoxide Dismutase, whose levels decrease with increasing stress. The aim of my experimental work was to evaluate the corrector Vx-809 (Lumacaftor) activity, a drug used in Cystic Fibrosis, in SH-SY5Y neuronal cells, in which a ER stress condition was mimicked, by Thapsigargin, with the aim of verifying whether this corrector could improve, not only the ΔF508 CFTR folding, but also the other proteins folding, in such a way as to be able to hypothesize its possible therapeutic use in proteinopathies, such as neurodegenerative diseases. Results obtained showed that Vx-809 is involved both in a reduction of proteins expressed under ER stress conditions and in the cytosolic and mitochondrial ROS reduction, as well as in the decrease of the apoptotic pathway activation.

Biography

Michela Pecoraro is a Research Fellow in Biology at University of Salerno. She has published several biological articles and review. She has Ph.D. in Drug Discovery and Development, at the Department of Pharmacy, University of Salerno, with a thesis entitled in "Molecular basis of cardiomyopathy" in March of 2018. In 2016 she was Cooperative researcher in the lab of Prof. Antonio RodriguezSinovas at the Vall d'Hebron Research Institute, Barcelona, Spain.

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