Identification of S-nitrosylation targets contributing to pathological aggregation of alpha-synuclein in Parkinson's Disease: a proteomic study

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Parkinson´s disease (PD) is the second most prevalent neurodegenerative disorder and is characterized by motor and non-motor symptoms. PD is classified as a synucleinopathy and is associated with the aggregation of alpha-synuclein (aSyn) and degeneration of dopaminergic neurons. Despite several players involved in aSyn aggregation, early triggers of PD are still unknown. Several proteins interact with aSyn and alter its structural features and its tendency to aggregate. Furthermore, aSyn is a target of several post-translational modifications (PTMs), which also can influence its toxicity. Therefore, identifying the interactome and the PTMs of aSyn are key to providing insights into novel biomarkers and possible therapeutic targets. PD is associated with oxidative and nitrosative stress, which can cause oxidative post-translational modifications in cysteine residues such as S-nitrosylation (SNO). Altough, aSyn lacks cysteine residues in its structure, NO-sensitive proteins that interact with aSyn can be modified by this PTM. This project aims to identify SNO proteome in a neuronal model of PD (SH-SY5Y cells) in nitrosative conditions. Cells were exposed to increasing concentrations of a nitrosating agente, S-nitrosocysteine (CysNO) during 15 minutes and then subjected to different versions of the biotin switch assay to label modified SNO proteins. We found that CysNO was able to oxidize proteins in SH-SY5Y cells, in a concentration-dependent manner, when using a biotin switch assay with DTT. Additionally, a subset of these proteins was identified as being S-nitrosated by CysNO, with the biotin switch assay with ascorbate. These data show that total proteins of SH-SY5Y cells are sensitive to NO and identification of the S-nitrosylated proteins interacting with aSyn will allow us to better understand both the physiological function of aSyn as well as molecular alterations associated with contribute the pathophysiology of PD and related disorders.

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