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Neuronal intermediate filament proteins, medium and high molecular weight, (NF-M/H), are aberrantly hyperphosphorylated in the Alzheimer disease

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Aberrant hyperphosphorylation of proline directed serine/threonine (pSer/Thr-Pro and KS/TP) residues in neuronal cytoskeletal proteins is one of the major pathological hallmarks of neurodegenerative disorders such as Alzheimer disease (AD), amyotrophic lateral sclerosis (ALS) and Parkinson's disease (PD). Human NF-M/H comprises a large number of multiple KSP repeats in the carboxy-terminal tail domain. The phosphorylation sites of NF-M/H from AD brains have not been analyzed. Here, we used quantitative phosphoproteomics, iTRAQ (isobaric tag for relative and absolute quantitation) and analyzed the phosphorylation sites of NF-M/H from AD brain. We identified 14 hyperphosphorylated sites of NF-M and 9 Lys-Ser-Pro (KSP) sites; two variant motifs, Glu-Ser-Pro (ESP) Ser^{736} and Leu-Ser-Pro (LSP) Ser^{837}; and 3 non-S/TP motifs, Ser^{783}, Ser^{788} and Thr^{750}. All the Ser/Thr residues were phosphorylated at significantly greater abundance in AD brain compared to normal brain. 11 hyper phosphorylated sites have been identified on C-terminal tail domain of NF-H corresponding to KSP motifs with greater abundance of phosphorylation in AD brain compared to normal brain, including the non-SP site, Thr^{642}. Our data provided the direct evidence that NF-M and NF-H are hyperphosphorylated in AD compared to normal brain and suggested the role of both proline-directed and non proline-directed protein kinases in AD. This study represents the first comprehensive analysis of iTRAQ quantification of phosphorylation sites of human NF-M and NF-H from AD brain and establishes that the aberrant and hyperphosphorylation of neuronal intermediate filament proteins is involved in AD. In addition, the topographic phosphorylation of squid giant axon as a model system was analyzed in detail. This study provided the molecular and cell biological mechanisms associated with this unique novel neurobiological process.

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Nature creates, adapts, protects and sustains life using hydrogen sulfide

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Life emerged on Earth in an anaerobic environment, bathed in noxious gases. Among these gases, the role of hydrogen sulfide is significant since this gas, was required as a building block of life, contributed to abiogenic generation of organic compounds that gave rise to life and drove adaptations of life throughout its entire evolutionary path. During evolution, hydrogen sulfide contributed to sustaining life in face of harsh environmental conditions. Modern cells still utilize hydrogen sulfide as a signaling molecule, in pro and anti-inflammatory responses, for acquisition of tolerance against damage, in directing repair responses, as a source of energy and in modifying their genetic makeup and function to acquire a phenotype reminiscent of early life forms.

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