On the modulatory role of phosphorylation and acetylation of the human 3-phosphoglycerate dehydrogenase

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Post-translational modifications (PTMs) are well-known to reversibly activate/inactivate proteins. In the case of 3-phosphoglycerate dehydrogenase (PHGDH), the first enzyme of L-serine (L-Ser) synthesis through the phosphorylated pathway (PP), PTMs have been reported to affect activity, stability and compartmentalization (previously published in: Ma et al. (2021) Nat Metab. 3, 1357-1371). Based on that and the sex-dependent modulation of the serine metabolism during healthy and Alzheimer's disease (AD)-marked aging (previously published in: Maffioli et al. (2022) Cell Rep. 40, 111271), we hypothesized that PTMs of the PP's rate-limiting enzyme could represent a regulatory strategy of the anabolic route, possibly contributing to the neurodegenerative pathophysiology. To this purpose, the endogenous PHGDH was isolated from human hippocampal tissues of both healthy and AD-affected males and females with an ad-hoc optimized immunoprecipitation procedure; the search of the modified residues was conducted via nLC-MS/MS analyses. While the targeted MS/MS approach highlighted the same phosphorylation pattern at five positions among the four categories of subjects, conversely, the selective deacetylation of PHGDH K289 in AD-affected men suggests a distinctive adaptation of males to the decreased L-Ser levels observed in AD. Although not sex-specific or correlated to the pathogenesis, in silico analyses of the modified residues allowed us to propose phosphorylation as a constitutive regulatory mechanism of the enzyme. Accordingly, biochemical studies on PHGDH variants mimicking the phosphorylation state are ongoing. Overall, these studies are paving the way to the elucidation of the processes modulating the PP and L-Ser synthesis in fields other than oncogenesis, the one explored so far. This project was founded by "PRIN-2017 - Dissecting serine metabolism in the brain".