Human serine racemase: structural flexibility and interaction with protein partners

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Human serine racemase (hSR) is a pyridoxal-5'-phosphate (PLP)-dependent enzyme involved in the production of D-serine, a co-agonist of N-methyl-D-aspartate receptors (NMDARs). Given its role in the regulation of excitatory glutamatergic neurotransmission, hSR is involved in the pathophysiology of different brain disorders, such as Alzheimer's and Parkinson's disease or schizophrenia (previously reviewed in Raboni S et al. (2019) Front Mol Biosci 5, 112). hSR is a dimer able to catalyze the formation of D-serine from L-serine, as well as the dehydration of both L- and D-serine to form pyruvate and ammonia. The activity of hSR is regulated by Mg^{2+}, small molecules such as ATP, glycine or malonate and by the interaction with protein partners. To evaluate the structural flexibility of hSR upon ligand binding and expand the knowledge on its interactome, we exploited PLP ^{31}P-NMR and limited proteolysis to study the binding of small-molecule interactors and assessed the binding of the third PDZ domain of PSD-95, a protein involved in trafficking and localization of glutamate receptors. Although some preliminary measurements suggested the presence of an interaction between hSR and PSD-95 PDZ3, NMR and ITC indicated that the two proteins bind only weakly (previously published in Giaccari R et al. (2022) Int J Mol Sci 23(9):4959). The dehydratase activity of hSR was not significantly affected by PSD-95 PDZ3 in the presence of ATP, while a moderate increase of the activity was observed in the absence of ATP. Moreover, our results show that the presence of ATP and malonate shifts hSR towards a closed conformation, in agreement with crystallographic data reported in the literature.