pLG72 and the modulation of D-aspartate catabolism in human

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D-aspartate (D-Asp) plays important roles in growth, reproduction, and endocrine mediatory functions, but has been mainly investigated as an alternative agonist of N-methyl-D-aspartate receptors (NMDAr). Albeit D-Asp biosynthesis is still obscure, the occurrence of this D-amino acid in the brain is strictly controlled: it is highest during the embryonic phase and drops after the first days of life. Notably, despite its low levels in adult tissues, disruption of D-Asp metabolism was proposed to cause dysfunctions in NMDAr-mediated neurotransmission during the onset of various disorders, among which schizophrenia (as previously published in Nuzzo T et al. NPJ Schizophr. 2017. 3:16)
Here, we focus on the only known enzyme crucially involved in controlling D-Asp brain levels, the peroxisomal FAD-containing flavooxidase D-aspartate oxidase (DASPO) responsible for the selective catabolism of this D-amino acid, and on factors acting in its regulation.
By combining in vitro and cellular studies, we show that human DASPO (hDASPO) interacts with the primate-specific protein pLG72, previously identified as a negative chaperone of the homologous human flavoenzyme D-amino acid oxidase (hDAAO), deputed to the degradation of the NMDAr co-agonist D-Ser. Worthy of note, pLG72 and hDASPO generate a cytosolic complex impairing the enzyme cellular stability: the expression of pLG72 negatively affects hDASPO level by reducing its half-life. We propose that pLG72 binding may represent a protective mechanism, common to hDAAO and hDASPO, aimed at preventing the excessive degradation of their substrates (i.e. the depletion of D-Ser and D-Asp cellular pools). In the case of the highly active hDASPO, this would also allow to avoid cytotoxicity associated to H_2O_2 production, before the final targeting of the enzyme to peroxisomes.

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