The human metabolic assembly for L-serine biosynthesis

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L-Serine (L-Ser) is the precursor of the neuroactive signaling molecules D-serine (D-Ser) and glycine, which modulate the activity of N-methyl-D-aspartate receptors. L-Ser biosynthesis in the mammalian brain proceeds through the phosphorylated pathway (PP) involving 3-phosphoglycerate dehydrogenase (PHGDH), phosphoserine aminotransferase (PSAT) and phosphoserine phosphatase (PSP), expressed in astrocytes. L-Ser plays a major role in the development and function of the human CNS: various severe, infantile, neurological disorders have been linked to its deficiency.

Using the proximity ligation assay and confocal microscopy, we demonstrated that in iPSC-derived differentiated human astrocytes the three enzymes of the PP co-localise in cytoplasmic clusters, which size is similar to the one reported for other metabolons (i.e. the purinosome). Kinetic studies of the in vitro reconstituted pathway generated using the recombinant human PHGDH, PSAT and PSP (at physiological enzymes and substrates concentrations) supported the production of an enzymatic agglomerate: PHGDH catalyzes the rate-limiting step and PSP reaction is the driving force for the whole pathway.

We propose that human PHGDH, PSAT and PSP can cluster in a transient metabolic assembly, the putative “serinosome” (previously published in: Rabattoni V. et al. (2023) FEBS J. 290(15), 3977-3895), providing a channeling solution for the pathway intermediates and delivering a relevant level of sophistication to the control of L-Ser biosynthesis. Its modulation by known pathological SNPs of the three proteins, by metabolites and interacting partners in physiological and pathological conditions is under investigation.

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