Post-translational modification of SLC3A2 plays a crucial role in the membrane trafficking of some amino acid transporters belonging to the SLC7 family.

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L. Console[I], M. Scalise[I], S. Salerno[II], C. Indiveri[I,III]

[I]Department of Biology, Ecology and Earth Sciences (DiBEST), University of Calabria, Via P. Bucci 4c, 87036, Arcavacata di Rende, Italy, [II]CNR Institute on Membrane Technology, National Research Council of Italy (CNR-ITM), Via P. Bucci, cubo 17/C, 87036,, Arcavacata di Rende, Italy, [III]CNR Institute of Biomembranes, Bioenergetics and Molecular Biotechnologies (IBIOM), Via Amendola 122/O, 70126, Bari, Italy

Human proteome complexity is not only due to genetic processes, such as alternative mRNA splicing, but it's also enriched by post-translational modifications (PTM), pushing the total number of proteoforms to at least several millions. Moreover, PTM can profoundly affect different protein aspects, such as function regulation, stability, and cellular localization, playing a crucial role in cell homeostasis and disease development. Among other PTM, N-glycosylation of some membrane proteins was found to be critical for their trafficking and stability. However, some amino acid transporters of the SLC7 family do not have N-glycosylation sites. These transporters need ancillary proteins such as SLC3A2, also known as CD98, to reach the plasma membrane. In this scenario, the role of the four N-glycosylation sites of SLC3A2, a single-pass membrane protein that can form heterodimers with SLC7 members but has no transport function, was investigated. A combined approach that includes bioinformatics, site-directed mutagenesis, and cell biology was used. Single or multiple mutants of the four glycosylated sites were used to evaluate the stability and the trafficking of SLC3A2 to the plasma membrane by a biotinylation assay and a brefeldin assay. Results highlighted that the ablation of all the glycosylation sites severely affected the stability and the abundance of SLC3A2 at the plasma membrane. The impairment of SLC3A2 trafficking correlated with a lower presence of its interactions, belonging to the SLC7 family, at the cell surface. SLC7 members, such as SLC7A5, are considered hot targets for cancer therapy. Hence, targeting SLC3A2 may act synergistically for potential anticancer treatment.