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Characterising the interaction between the COPII component SEC24C and the human serotonin transporter

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Background

The serotonin transporter (SERT) belongs to the SLC6 family of neurotransmitter transporters, which mediate reuptake of previously released neurotransmitters from the synapse. Mutation of C-terminus residues RI607–608 to alanine results in intracellular retention of SERT [1]. We subsequently showed that SERT depends on the COPII component SEC24C for its ER export and proposed RI607–608 as a putative interaction site on SERT for SEC24 proteins [2]. The aim of our current study is to characterise the nature of ER export of monoamine transporters.

Methods

Using siRNAs to knock down SEC24 isoforms A–D in HeLa cells, we screened a series of double and truncation mutants generated along the C-terminus of SERT. HeLa cells were transfected with Sec24 siRNAs and, after 48 h, with YFP-tagged transporter plasmids. Functional effects of SEC24A–D knockdowns were determined by substrate uptake assays.

Results

Export of the IK(609,610)AA-SERT mutant was not sensitive to knockdown of Sec24C. Remarkably, the closely related transporters for dopamine (DAT) and noradrenaline (NET), rely on Sec24D, and not C, for their ER export [2]. Accordingly, we replaced K610 by a tyrosine residue (Y) to switch the SERT export motif to a NET/DAT motif. The resulting K610Y-SERT mutant was more sensitive to the knockdown of SEC24D than of SEC24C. These observations predicted that SLC6 family members with a K-residue at the pertinent position ought to be clients of Sec24C. This prediction was verified by examining mGAT4.

Conclusions

The data imply that residue K610 and the equivalent residues in other transporters specify which SEC24 paralogue is recruited for ER export. These export signals work independently because a concatemer of SERT and GAT-1 is affected by depletion of both SEC24C and SEC24D.

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