Receptor Recognition by the Flexible Peroxisomal Targeting Signal Type 1 of Sterol Carrier Protein 2, Will A. Stanley,[a*] Fabian V. Filipp,[b] Petri Kursula,[a] Dmitri I. Svergun,[a] Michael Sattler[b] and Matthias Wilmanns[a], [a]*EMBL-Hamburg, Germany, and* [b]*EMBL-Heidelberg, Germany*. E-mail: stanley@embl-hamburg.de

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The majority of proteins destined for the peroxisome carry a peroxisomal targeting signal type 1 (PTS1) - a C-terminal tri-peptide with consensus -[S/A/C]-[K/H/R]-[L/M]-CO_2^-. Pex5p is the cytosolic receptor for PTS1 proteins. The C-terminal tetratricopeptide repeat (TPR) domain of Pex5p specifically recognises PTS1 proteins and conducts them to the peroxisomal membrane for subsequent transfer [1]. One intriguing feature of PTS1-mediated import is that folded, liganded or oligomeric proteins can be transferred to the peroxisome lumen [2]. In one case, that of sterol carrier protein 2 (SCP2), it has been speculated that the protein must be loaded with a lipid ligand in order to present its PTS1 for Pex5p recognition [3] - thus, ligand-dependent targeting is proposed, implying a sorting mechanism for folded and functional proteins. We have synergistically used a combination of biophysical and structural biology techniques to demonstrate that recognition of SCP2 by the TPR domain of Pex5p is not ligand-dependent but is ligand-tolerant. The PTS1 of SCP2 displays considerable conformational flexibility to facilitate recognition by the TPR domain. This feature allows different isoforms of SCP2 to interact comparably with the TPR domain while the overall fold of SCP2, and it's fatty acyl CoA binding function, remain intact. A crystal structure of SCP2 in complex with the TPR domain of Pex5p is presented. The structure amply accounts for the tolerant binding mode. Further, we identify novel interactions between non-PTS1 residues in SCP2 and non-TPR residues in Pex5p, with important implications for both peroxisomal targeting and for more generalised interactions between TPR containing proteins and their ligands.

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