

Structure of the VHS Domain of Human Tom1 (Target of Myb 1): Insights into Interactions with Proteins and Membranes

S. Misra, B. Beach, and J. Hurley (Laboratory of Molecular Biology, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health)

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VHS domains are found at the N-termini of select proteins involved in intracellular membrane trafficking. We have determined the crystal structure of the VHS domain of the human Tom1 (target of myb 1) protein to 1.5 Å resolution. The domain consists of eight helices arranged in a superhelix. The surface of the domain has two main features: (1) a basic patch on one side due to several conserved positively charged residues on helix 3 and (2) a negatively charged ridge on the opposite side, formed by residues on helix 2. We compare our structure to the recently obtained structure of tandem VHS-FYVE domains from Hrs [Mao, Y., Nickitenko, A., Duan, X., Lloyd, T.E., Wu, M.N., Bellen, H., and Quioco, F.A. (2000) *Cell* 100, 447-456]. Key features of the interaction surface between the FYVE and VHS domains of Hrs, involving helices 2 and 4 of the VHS domain, are conserved in the VHS domain of Tom1, even though Tom1 does not have a FYVE domain. We also compare the structures of the VHS domains of Tom1 and Hrs to the recently obtained structure of the ENTH domain of epsin-1 [Hyman, J., Chen, H., Di Fiore, P. P., De Camilli, P., and Brünger, A.T. (2000) *J. Cell Biol.* 149, 537-546]. Comparison of the two VHS domains and the ENTH domain reveals a conserved surface, composed of helices 2 and 4, that is utilized for protein-protein interactions. In addition, VHS domain-containing proteins are often localized to membranes. We suggest that the conserved positively charged surface of helix 3 in VHS and ENTH domains plays a role in membrane binding.