Structural and functional characterization of the Vps10p-domain receptor SorCS2

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ABSTRACT

SorCS2 is a member of the newly identified Vps10p-domain receptor family, which includes Sortilin, SorLA, and SorCS1-3. These type-1 transmembrane receptors are synthesized with a propeptide and consist of an extracellular part, containing an N-terminal Vps10p-domain, a transmembrane segment, and a short cytoplasmic tail comprising different internalization and sorting signals. Sortilin, which is the best described family member, is involved in regulation of neuronal cell death via binding to pro-nerve-growth factor (proNGF) and complex formation with the neurotrophin binding receptor p75 ($p75^{NTR}$).

The aim of this dissertation was to carry out a structural and functional characterization of SorCS2, about which only very little is known,

Generation of SorCS2 deficient mice, in which the SorCS2 gene is inactivated, resulted in apparently normal, fertile mice with no characteristic phenotype.

Biochemical and cell biological studies of SorCS2 were therefore carried out to characterize the structure, potential ligands, and possible function of SorCS2. The results showed that the propeptide is cleaved off during processing, and, surprisingly, that the receptor is cleaved in the C-terminal part of the extracellular domain. In contrast to the other members of the family, SorCS2 is thereby converted into a “two-chain” receptor.

SorCS2 undergoes endocytosis and is found intracellularly as well as on the cell surface. SorCS2 was shown to mediate binding and endocytosis of proNGF. The presence of $p75^{NTR}$ increases the level of endocytosed proNGF. Furthermore, SorCS2 was shown to interact directly with $p75^{NTR}$, and this interaction was strengthened by proNGF. These results indicate that SorCS2, like Sortilin, may be involved in regulation of proNGF-induced neuronal cell death via complex formation with proNGF and $p75^{NTR}$.