Functional characterization of Sortilin and SorCS3, members of the Vps10p-domain receptor family

Uffe Bendfeldt Westergaard, MSc

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Official opponents: Professor Bo van Deurs, Professor Daniel Otzen, PhD, and Professor Erik Ilsø Christensen.

Supervisor: Associate Professor Peder Madsen, PhD, and Professor Claus Munck Petersen.

Correspondence: Uffe B. Westergaard, Kirstine Jensens Vej 12, 9240 Nibe, Denmark.

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ABSTRACT

The Vps10p-domain receptors Sortilin, SorLA and SorCS1-3 constitute a family of type-1 transmembrane receptors that are expressed in brain and other neuronal tissue. The N-terminal Vps10p-domain is found in all the receptors and makes up the entire luminal part of Sortilin, the best described family member. The Vps10p-domain features two structural elements, a C-terminal segment with 10 conserved cysteines, designated the 10CC module, and a short N-terminal propeptide, which is cleaved off during receptor processing. Sortilin binds its own propeptide with high affinity, and as the propeptide inhibits binding of all known ligands, the receptor needs propeptide cleavage to gain ligand-binding activity. SorLA exhibits similar features, whereas only weak propeptide interactions are demonstrated for the SorCS1-3 receptors. The work described in this dissertation may be divided into two sections, of which the first concerns a study of the functional organization of the Sortilin Vps10p-domain and the second section involves a functional characterization of the SorCS3 receptor and a discussion of similarities and differences between the Vps10p-domain receptors.

In the first study we mapped binding-significant residues in the Sortilin propeptide, determined the disulphide bridge pattern of Sortilin and established that the 10CC module constitutes the ligandbinding region of the Vps10p-domain. We further showed that Sortilin depends on its propeptide for normal processing. The propeptide is not required for proper receptor folding, but apparently serves to shield and prevent access to the 10CC module and thereby facilitating the passage through the Golgi-apparatus.

The second study demonstrated that SorCS3 is also subject to propeptide cleavage, but in contrast to Sortilin, and SorLA, this receptor does not bind its propeptide. The nerve growth factor precursor, proNGF that binds Sortilin, was also identified as a ligand for SorCS3. SorCS3, however, neither requires propeptide cleavage to acquire ligand-binding capacity, which so far stands as a solitary observation regarding the Vps10p-domain receptor family, nor does the propeptide affect receptor processing. This could indicate redundancy of the propeptides of the SorCS receptors. Finally, we showed that SorCS3 is mainly localized to the cell surface. Like the other family members, SorCS3 undergoes endocytosis but in contrast to Sortilin, it is not implicated in Golgi-to-endosome sorting or in the binding of cytosolic GGA adaptor proteins. Altogether, this indicates that the SorCS3 receptor may have a different and so far undescribed function.