From gene to function: conditional knockout of four splice variants of the murine SorCS1 gene

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ABSTRACT

The PhD dissertation was carried out at the Institute of Medical Biochemistry, University of Aarhus in connection with the characterization of the Vps10p-domain receptor family, which comprises Sortilin, SorLA, and SorCS1-3.

They are all type-1 transmembrane receptors sharing the characteristic structural feature of an N-terminal Vps10p-domain with high homology to Vps10p, a sorting protein in yeast. At present the physiological role(s) of the receptor family is not clarified, but recent findings indicate that both Sortilin and SorLA play a crucial role as regulator of neuronal survival and death. As opposed to the other members of the family, murine SorCC1 is unique because it exists in four different splice variants which encode an identical extracellular and transmembrane part, but a cytoplasmic domain that differ in length and sequence. Their physiological role(s) are unknown; however, the existence of several SorSC1 splice variants indicates that they might possess diverse physiological functions.

The aim of this PhD dissertation has been to unravel the biological function of SorCS1, and in particular the role of each isoform, by generating transgenic mouse models lacking expression of one, more or all splice variants of SorCS1. Furthermore cellular functionality studies have been conducted to elucidate the function of the different isoforms. These studies showed that the isoforms exhibit diverse distribution and different subcellular expression indicating that each splice variant is implicated in different biological activities.

Alternative splicing is used extensively as a way of increasing proteomic diversity, but despite numerous gene targeting approaches no studies have to the best of our knowledge reported the inactivation of one or more specific splice variants of a gene in a conditional manner. In this dissertation we have generated a conditional knockout lacking all splice variants of SorCS1 and successfully developed a new targeting strategy using FLP recombination and an insertion technique called “recombinase-mediated cassette exchange” (RMCE) to produce conditional knockouts lacking expression of only one of the receptor splice variants. Surprisingly, the SorCS1 (-/-) knockout mice showed no gross abnormalities, they were fertile, exhibited normal life span, and displayed no apparent signs of changed behaviour. Future phenotypic characterization is required to unravel the physiological function of SorCS1 and its specific splice variants.