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Alzheimer's Disease 2007: Mind the Traffic!

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Over the past two decades it has been determined that aggregation of misfolded proteins containing the amyloid β peptides initiates a chain of events inducing oxidative stress and inflammation while also being responsible for neuronal dysfunction and the characteristic clinical and pathological features of Alzheimer's disease. The amyloid β peptide is one of several end products originating from the sequential proteolysis by β and γ secretase cleavage of the transmembrane amyloid precursor protein (APP). The discovery that alterations in the trafficking of APP through intracellular compartments can promote these abnormal amyloid β aggregates indicates that such perturbations in protein transport could play a major role in the pathogenesis of Alzheimer's disease.

In early 2007, Rogaeva et al(1) reported that two sets of SNP clusters at the 3' and 5' ends of the gene *SORL1* on chromosome 11q23.2 were associated with familial and sporadic forms of Alzheimer's disease. She and her colleagues discovered the initial association in a diverse set of families multiply affected by Alzheimer's disease from the Dominican Republic and northern Europe. They subsequently confirmed the association with the same alleles and haplotypes and Alzheimer's disease in three unrelated datasets drawn from ethnically different origins, which proved even more convincing. The authors further suggested that the occurrence of two distinct clusters of SNPs showing association with Alzheimer's disease in multiple datasets was likely due to allelic heterogeneity (i.e. pathogenic variants across multiple domains of the disease gene). They also indicated that the absence of these variants in some datasets might be the result of locus heterogeneity, not unusual in either monogenic or complex traits such as Alzheimer's disease. Subsequent work in clinical and autopsy case-control datasets (2–5) has confirmed the association between Alzheimer's disease and these as well as other SNP clusters located within *SORL1*, and Seshadri et al (6) found relationships between *SORL1* SNPs and age-related cognitive decline in the Framingham cohort.

The mechanism by which inherited variants in *SORL1* alter risk for Alzheimer's disease is not yet clear. *SORL1* (also known as SorLA and LR11) is a glycoprotein expressed mainly in neurons in the cortex, hippocampus, cerebellum and spinal cord, but to a lesser extent in kidney and other organs(7). It is a highly conserved type 1 receptor with a vacuolar sorting (Vps) 10p domain and a low density lipoprotein receptor (LDLR) class A and fibronectin domains as well. The LDLR domain serves as a binding site for APOE and the fibronectin domain may be involved in stability of the neuronal cytoskeleton. *SORL1* is post-translationally glycosylated with an N-linked oligosaccharide in the vacuolar sorting (Vps) 10p domain

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enabling it to mediate the clearance of glycoproteins and influence protein trafficking through the cell (7). In the brain, the SORL1 protein is specifically involved in neuronal transport processes within the trans-Golgi network and endosomes. Endogenous APP and SORL1 physically interact with each other under physiological conditions in cells(1) and SORL1 modulates some parts of the subcellular trafficking of APP(8). The trafficking pathway for APP ends up by producing either amyloidogenic (APPs β plus A β and AICD) or non-amyloidogenic peptides (APPs α plus AICD and p3) depending on the ultimate subcellular disposition of the APP holoprotein via this regulated trafficking system. Recent evidence(8) indicates that SORL1 acts as a regulatory gate keeper for these two pathways determining the ultimate destination for APP. Newly synthesized APP is cleaved by α secretase in a post Golgi compartment or at the plasma membrane producing soluble APP (sAPP α). By the alternate path, some APP is re-internalized from the plasma membrane and subsequently delivered to the late endosome for β -secretase and γ -secretase processing to sAPP β and to amyloid β peptide. When SORL1 effectively binds with APP there is a reduction in of sAPP β and amyloid β . In fact, SORL1 deficient mice produce high levels of sAPP β and A β (9). Thus, SORL1 protects APP from β secretase activity and instead diverts its trafficking along alternative pathways. Consequently, in the absence of SORL1 activity, APP tends to enter the amyloidogenic pathways. It is therefore of note, that Rogaeva et al (2) found that SORL1 expression is reduced in lymphoblasts of carriers of Alzheimer's disease-associated haplotypes in *SORL1*. This observation is consistent with the reports by several groups including, most recently, Sager et al (10), who have found that the expression of SORL1 proteins in neurons is reduced in a subset of patients with late onset Alzheimer's disease or with the amnesic form of mild cognitive impairment (MCI), considered to be an earlier stage of the disease. Sager et al(8) also showed that neuronal expression of the SORL1 protein correlated with global performance on two psychometric measures. However, two further observations reveal that these changes in neuronal SORL1 expression are not simply a consequence of having Alzheimer's disease. First, reduced neuronal SORL1 expression is not a universal feature of all Alzheimer's disease patients. Second, in cases of familial Alzheimer's disease where the disease occurs from a mutation in presenilin 1, the levels of neuronal SORL1 are normal.

In summary, the growing list of reports consistently showing that multiple inherited variants in *SORL1* are associated with Alzheimer's disease are now the basis for the hypothesis that the reduction in SORL1 expression is a primary and pathogenic event. Taken together with the neuropathological observations of reduced SORL1 in a subset of Alzheimer's disease and the with the functional experiments on the effects of reducing SORL1 in vitro and in vivo, these studies would most certainly implicate SORL1 in the pathogenesis of Alzheimer's disease and emphasize the importance of understanding subcellular trafficking of APP. In addition, understanding the various functions of SORL1 may point to a novel therapeutic strategy not yet considered, including potentially the upregulation of SORL1 expression or the function to direct APP processing into non-amyloid-producing pathways.

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