Dag1

Other names
Dystroglycan, 156 dystrophin-associated glycoprotein (DAG), 43 DAG, SL156, cranin

Gene symbol
Dag1

Accession number
MGI: 101864

Area of impact
Development

General description

Dystroglycan was first identified as an integral membrane component of the dystrophin–glycoprotein complex in skeletal muscle. A number of components of this complex, though not dystroglycan itself, are genetically involved in various forms of muscular dystrophy. Dystroglycan consists of α and β subunits which are the post-translationally derived products of a single gene. In muscle, α dystroglycan binds to laminin in the extracellular matrix and β dystroglycan binds to dystrophin in the cytoskeleton, thereby linking the outside with the inside of the cell. Dystroglycan is expressed in a wide variety of non-muscle cell types and tissues where it is also postulated to mediate cell–extracellular matrix interactions.

KO strain construction

The *Dag1* gene was isolated from a lambda FIXII 129Sv genomic library. From the *Dag1* sequence, regions of *Dag1* homology were cloned flanking the *neo* gene in the targeting vector pPNT. A 5 kb *Not* I/*Hin*dIII fragment carrying the 3′ portion of exon 2 and a 1.9 kb *Eco*RI fragment of intronic sequence was used for 5′ homology. The vector was electroporated into R1 ES cells derived from strain 129Sv and the chimeric mice were bred with C57BL/6 mice to test for germ line transmission. The homozygous deletion of *Dag1* was confirmed by immunostaining early embryos with C-terminal dystroglycan antibody.

Phenotype

Heterozygous $Dag1^{+/-}$ mice appeared normal, but the homozygous $Dag1^{-/-}$ mutation was embryonic lethal. In homozygous $Dag1^{-/-}$ mice development was apparently normal up to the egg cylinder stage, around E5.5. $Dag1^{-/-}$ embryos failed to progress beyond the egg cylinder stage and did not gastrulate. Beginning around E5.5, maternal red blood cells were evident in the yolk sac cavity, although other features of the embryo were normal for that stage. Maternal red blood cells in the yolk sac cavity suggested a breakdown in the barrier function of Reichert's membrane. Dystroglycan protein was localized in apposition to Reichert's membrane in normal egg cylinder stage embryos. In the $Dag1^{-/-}$ mutant embryos, key structural proteins comprising Reichert's

membrane, laminin and collagen IV were drastically disrupted, explaining the breakdown in the barrier to maternal blood. Parietal endoderm cells were present at the appropriate locations in the Dag1$^{-/-}$ embryos, indicating that the disruption of Reichert's membrane is not secondary to an absence of the cells which synthesize that structure.

Comments

The phenotype of Dag1 KO mice indicate that dystroglycan is required for the development of Reichert's membrane, a basement membrane structure. The details of the Dag1-null phenotype suggest that dystroglycan acts by anchoring laminin to the cell surface and/or by facilitating the assembly of laminin networks within the basement membrane structure. This function for dystroglycan may extend to other tissues in which it is expressed. The embryonic lethality of the Dag1-null mutation probably explains the present lack of such mutations associated with muscular dystrophy.

Acknowledgements
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Reference

1 Williamson, R.A. et al. (1997). Human Mol. Genet. 6, 831–841.