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Insights on the molecular and structural basis of human dystroglycanopathies

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Dystroglycanopathies are neuromuscular disorders associated with abnormal neuronal migration and muscular dystrophy. Clinical manifestations are extremely variable, and include a wide spectrum of phenotypic severity. Dystroglycanopathies are mainly due to abnormal glycosylation of dystroglycan (DG) which is a cell-surface glycoprotein that links the cytoskeleton with the extracellular matrix acting as a receptor for extracellular matrix proteins containing laminin-G domains. Dystroglycan is composed of two subunits: the extracellular highly glycosylated α-DG and the transmembrane β-DG. A multistep glycosylation process is necessary to decorate the α-DG subunit with complex glycans that are crucial for its interaction with the extracellular matrix proteins, such as laminins. Most of the dystroglycanopathies are due to an impaired functional state of the enzymes involved in α-DG maturation. Nevertheless, a set of missense mutations has been recently identified on the N-terminal region of α-DG (a.a. 50-313 in mouse) that determine the hypoglycosylation of the DG complex, due to the impairment of a key step in α-DG glycosylation operated by the bifunctional glycosyltransferase LARGE1.
With the aim of elucidating the molecular and structural implications of the pathological mutations leading to dystroglycanopathies, we have undertaken a multi-technique study, including synchrotron radiation approaches to gain insight on the molecular structure of a recently discovered α-DG point pathological mutant (L84F) in both crystals and solution. Indeed, we determined the high-resolution molecular structure of L84F mutant by X-ray crystallography. Moreover, Small Angle X-ray Scattering (SAXS) has been employed as a complementary approach to get low resolution information on the flexibility, conformation and the structural organization of this α DG mutant at near-physiological conditions. The results of the synchrotron radiation-based experiments, combined with biochemical, cellular and microscopic data, allowed us to shed light on the molecular and structural basis of dystroglycanopathies.

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