biAb Mediated Restoration of the Linkage between Dystroglycan and Laminin-211 as a Therapeutic Approach for α-Dystroglycanopathies.

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Abstract
Patients with α-dystroglycanopathies, a subgroup of rare congenital muscular dystrophies, present with a spectrum of clinical manifestations that includes muscular dystrophy as well as CNS and ocular abnormalities. Although patients with α-dystroglycanopathies are genetically heterogeneous, they share a common defect of aberrant post-translational glycosylation modification of the dystroglycan alpha-subunit, which renders it defective in binding to several extracellular ligands such as laminin-211 in skeletal muscles, agrin in neuromuscular junctions, neurexin in the CNS, and pikachurin in the eye, leading to various symptoms. The genetic heterogeneity associated with the development of α-dystroglycanopathies poses significant challenges to developing a generalized treatment to address the spectrum of genetic defects. Here, we propose the development of a bispecific antibody (biAb) that functions as a surrogate molecular linker to reconnect laminin-211 and the dystroglycan beta-subunit to ameliorate sarcolemmal fragility, a primary pathology in patients with α-dystroglycan-related muscular dystrophies. We show that the treatment of LARGEmyd-3J mice, an α-dystroglycanopathy model, with the biAb improved muscle function and protected muscles from exercise-induced damage. These results demonstrate the viability of a biAb that binds to laminin-211 and dystroglycan simultaneously as a potential treatment for patients with α-dystroglycanopathy.

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KEYWORDS: LARGE(myd-3J) mice; bispecific antibody; congenital muscular dystrophy; dystrophin-associated glycoprotein complex; laminin-211; limb-girdle muscular dystrophy; surrogate molecular linker; α-dystroglycan; α-dystroglycanopathy; β-dystroglycan