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Protein O-mannosylation is found in yeast and metazoans, and a family of conserved orthologous protein O-mannosyltransferases is believed to initiate this important post-translational modification. We recently discovered that the cadherin superfamily carries O-linked mannose (O-Man) glycans at highly conserved residues in specific extracellular cadherin domains, and it was suggested that the function of E-cadherin was dependent on the O-Man glycans. Deficiencies in enzymes catalyzing O-Man biosynthesis, including the two human protein O-mannosyltransferases, POMT1 and POMT2, underlie a subgroup of congenital muscular dystrophies designated alpha-dystroglycanopathies, because deficient O-Man glycosylation of alpha-dystroglycan disrupts laminin interaction with alpha-dystroglycan and the extracellular matrix. To explore the functions of O-Man glycans on cadherins and protocadherins, we used a combinatorial gene-editing strategy in multiple cell lines to evaluate the role of the two POMTs initiating O-Man glycosylation and the major enzyme elongating O-Man glycans, the protein O-mannose alpha-1,2-N-acetylglucosaminyltransferase, POMGnT1. Surprisingly, O-mannosylation of cadherins and protocadherins does not require POMT1 and/or POMT2 in contrast to alpha-dystroglycan, and moreover, the O-Man glycans on cadherins are not elongated. Thus, the classical and evolutionarily conserved POMT O-mannosylation pathway is essentially dedicated to alpha-dystroglycan and a few other proteins, whereas a novel O-mannosylation process in mammalian cells is predicted to serve the large cadherin superfamily and other proteins.

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