Recent advancements in understanding mammalian O-mannosylation.

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Abstract

The post-translational glycosylation of select proteins by O-linked mannose (O-mannose or O-man) is a conserved modification from yeast to humans and has been shown to be necessary for proper development and growth. The most well studied O-mannosylated mammalian protein is α-dystroglycan (α-DG). Hypoglycosylation of α-DG results in varying severities of congenital muscular dystrophies, cancer progression and metastasis, and inhibited entry and infection of certain arenaviruses. Defects in the gene products responsible for post-translational modification of α-DG, primarily glycosyltransferases, are the basis for these diseases. The multitude of clinical phenotypes resulting from defective O-mannosylation highlights the biomedical significance of this unique modification. Elucidation of the various O-mannose biosynthetic pathways is imperative to understanding a broad range of human diseases and for the development of novel therapeutics. In this review, we will focus on recent discoveries delineating the various enzymes, structures and functions associated with O-mannose-initiated glycoproteins. Additionally, we discuss current gaps in our knowledge of mammalian O-mannosylation, discuss the evolution of this pathway, and illustrate the utility and limitations of model systems to study functions of O-mannosylation.

KEYWORDS: O-mannosylation; congenital muscular dystrophy; dystroglycan; glycosylation

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