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Functional significance of O-GlcNAcylation of ICln in the regulation of cellular volume

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Abstract

O-GlcNacylation (O-GlcNAc) is a post-translational modification of serine or threonine residues of nuclear and cytoplasmic proteins and occurs *via* conjugation to a single monosaccharide, the N-acetylglucosamine. O-GlcNAc modification intervenes in a wide variety of physiological and pathological processes, and negatively affects the regulation of cellular volume with a molecular mechanism still unknown. Recently, the protein ICln, crucial in the activation of a chloride conductance (ICl_{swell}) after anisosmotic cell swelling, has been found to be O-GlcNacylated. Mass spectrometry and bioinformatics show multiple O-GlcNAc modification sites, of which the impact on ICln function is unknown. To explore the functional significance of O-GlcNAc modification of ICln, the wild type and different mutant forms of ICln have been expressed in a heterologous system and characterized by whole-cell patch-clamp in the presence of normal or elevated O-GlcNAc levels. The results show that: I) O-GlcNAc elevation suppresses the ICln-induced current; II) IClnT223A is functional and sensitive to O-GlcNAc elevation; III) IClnS193X loses most of its activity, though the residual current is sensitive to O-GlcNAc elevation; IV) IClnS67A is functional but insensitive to O-GlcNAc elevation; V) the IClnS67T-induced current is lower compared to the wild type, and is no longer responsive to O-GlcNAc elevation. Overall, the evidence obtained indicates that O-GlcNAcylation of ICln at the level of Serine 67 leads to suppression of the ICln-induced current and may disclose the mechanism by which O-GlcNAc elevation alters the regulation of cellular volume. We suggest that the protein ICln may represent a novel target in the prevention or treatment of pathological states characterized by chronically elevated O-GlcNAcylation levels

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