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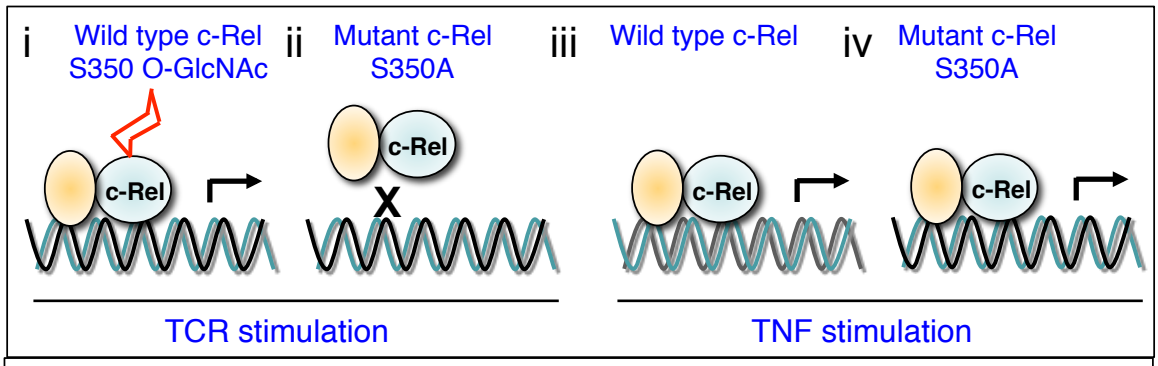
Abstract

The transcription factor nuclear factor kappaB (NF-kB) rapidly reprograms gene expression in response to various stimuli, and its activity is regulated by several posttranslational modifications, including phosphorylation, methylation, and acetylation. The addition of O-linked beta-*N*-acetylglucosamine (a process known as O-GlcNAcylation) is an abundant posttranslational modification that is enhanced in conditions such as hyperglycemia and cellular stress. We report that the NF-kB subunit c-Rel is modified and activated by O-GlcNAcylation. We identified serine 350 as the site of O-GlcNAcylation, which was required for the DNA binding and transactivation functions of c-Rel. Blocking the O-GlcNAcylation of this residue abrogated c-Rel–mediated expression of the cytokine-encoding genes IL2, IFNG, and CSF2 in response to T cell receptor (TCR) activation, whereas increasing the extent of O-GlcNAcylation of cellular proteins enhanced the expression of these genes. TCR- or tumor necrosis factor (TNF)–induced expression of other NF-kB target genes, such as NFKBIA (which encodes IkBa) and TNFAIP3 (which encodes A20), occurred independently of the O-GlcNAcylation of c-Rel. Our findings suggest a stimulus-specific role for hyperglycemia-induced O-GlcNAcylation of c-Rel in promoting T cell–mediated autoimmunity in conditions such as type 1 diabetes by enhancing the production of T helper cell cytokines.



Schematic models of the regulation of the DNA binding and transactivation functions of c-Rel by O-GlcNAcylation. (i) Stimulation of the TCR induces the O-GlcNAcylation of c-Rel at Ser350, the binding of c-Rel to target DNA, and the induction of gene expression. (ii) The S350A mutation blocks the TCR-induced binding of c-Rel to DNA and inhibits gene expression. (iii and iv) The S350A mutation of c-Rel has no effect on TNF-induced gene expression.