O-GlcNAcylation-mediated degradation of FBXL2 stabilizes FOXM1 oncogenic transcription factor to promote cancer progression

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O-GlcNAcylation is a dynamic and reversible post-translational modification of cytonuclear molecules and critical for intracellular signaling. The modification is regulated by only two enzymes, OGT and OGA, which add and remove a glucose metabolite, UDP-GlcNAc, respectively. Elevated *O*-GlcNAcylation is a hallmark of cancer and contributes to cancer malignancy. However, the molecular mechanism is not fully understood. Recently, we showed that FOXM1, which is a critical oncogenic transcription factor and wildly overexpressed in solid tumors, was elevated in a human cancer cell line by an OGA inhibitor, Thiamet G (TMG), inducing augmented *O*-GlcNAcylation. In this study, we identified FBXL2 E3 ligase as a new target of *O*-GlcNAcylation. The FOXM1 expression was increased accompanying with decreased its ubiquitination and degradation by TMG treatment. FBXL2 ubiquitinated FOXM1, and the ubiquitination of FOXM1 was reduced by TMG treatment. FBXL2 was ubiquitinated, which was promoted by TMG. Moreover, FBXL2 induction using the Tet-on system showed that FOXM1 expression and cell proliferation were reduced in NUGC-3 cells, and the reductions were attenuated by TMG. Taken together, we found that FOXM1 was stabilized by the *O*-GlcNAcylation-mediated degradation of FBXL2. These data suggest that elevated *O*-GlcNAcylation might contribute to cancer progression via the suppression of FBXL2-mediated degradation of FOXM1.