Molecular regulation of the forkhead transcription factors by multiple modifications

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Exposure of cells to external signaling causes changes in gene expression for appropriate physiological responses. Once activated on the plasma membrane of cells, the signals initiate a cascade of signals that are transmitted to the nucleus where they switch on and off the expression of target genes by modifying the activity of transcription factors. Targeted modifications of transcription factors, including acetylation, phosphorylation, methylation, and ubiquitination, for rapid alterations in their activities in response to external and internal stimuli have emerged as an important mechanism in the regulation of transcriptional activation of RNA polymerase II-transcribed genes.

In response to insulin, protein kinase B-mediated phosphorylation is shown to modulate the function of the FOXO forkhead transcription family members. The unphosphorylated FOXO factors that localize to the nucleus bind to the insulin response sequence (IRS) within the promoters of the target genes, which control the cell cycle, cell death, oxidative stress, and glucose metabolism. On the other hand, they are phosphorylated by insulin, resulting in promoting their cytoplasmic retention. Although the relevance of FOXO family regulated by multiple modifications to the physiological functions in the transcription-based nuclear action is of significant interest, the fate of FOXO factors in the cells is not yet fully understood. In the present study, I will summarize the recent advance, including our works, upon the regulatory roles for the FOXO factors by multiple modifications.