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Research Highlight

Methylation of FoxO3 regulates neuronal cell death

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Oxidative stress plays an essential role in the development of several neurodegenerative disorders[1]. The evolutionally conserved FoxO (FOX family O class) transcription factors, including FoxO1, FoxO3, FoxO4, and FoxO6 in mammals, induce the expression of downstream pro-apoptotic genes, thus act as critical regulators during the oxidative stress-induced neuronal cell death[2, 3].

FoxO family proteins are regulated by a variety of post-translational modifications, such as phosphorylation, acetylation, ubiquitination and arginine methylation[4]. For instance, serine/threonine kinase PKB/Akt is well known FoxO inhibitor. Phosphorylation of FoxO by Akt at three key residues increases its binding activity to 14-3-3 protein and results in its translocation from nucleus to cytoplasm[5]. One the other hand, phosphorylation of FoxO by Hippo/MST1 kinase dampens its binding to 14-3-3 protein and leads to nuclear accumulation of FoxO1/3[3]. Similar to phosphorylation, acetylation/deacetylation of FoxO proteins dynamically regulates thier biological functions through affecting their DNA-binding activity, stability and interaction with other proteins[6].

Recently, Yuan's group of Institute of Biophysics at Chinese Academy of Sciences identified a novel post-translational modification of FoxO3 transcription factor[7]. They found that a lysine methyltransferase, Set9, methylated FoxO3 at lysine 270 that led to inhibition of DNA binding activity and downregulation of transactivation without affecting Akt-mediated phosphorylation. They showed that lysine methylation of FoxO3 reduced oxidative stress-induced neuronal apoptosis in cerebellar granule neurons through transcriptional downregulation of its pro-apoptotic target, *Bim*. In addition, they observed that the lysine methylation of FoxO3 did not affect its protein stability, Akt-mediated phosphorylation and subcellular localization. Interestingly, they showed that oxidative stress reduced the methylation level of FoxO3, indicating that the methylation of FoxO3 might be dynamically regulated even though they failed to identify the demethylase of FoxO3.

In short, Yuan's group identifies a novel modification of FoxO3 and shows that lysine methylation negatively regulates FoxO3-mediated transcription and neuronal cell death, which implicates a variety of neurodegenerative diseases.

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