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[BioMedical][Molecular Biology] Scientists Show How Phosphorylation Modulates Daxx Selectively Binding to SUMO-1 over Other Paralogs and Its Implications in Stress-induced Apoptosis

[BioMedical][Molecular Biology] Scientists Show How Phosphorylation Modulates Daxx Selectively Binding to SUMO-1 over Other Paralogs and Its Implications in Stress-induced Apoptosis (Chinese Version)

Academia Sinica Newsletter (2011/04/21) The Hsiu-Ming SHIH and Tai-Huang HUANG groups at the Institute of Biomedical Sciences, Academia Sinica, described the structural basis of Daxx SUMO-interacting motif (SIM) in complex with SUMO-1 and the molecular details of how phosphorylation of this SIM motif enhances Daxx selective binding toward SUMO-1 over SUMO-2/3 and its impacts on Daxx SUMO binding, sumoylation, and stress-induced apoptosis. These findings not only provide a previously undescribed paradigm for regulation of protein sumoylation, in which sumoylation is modulated by SIM phosphorylation, but also elucidate a role of Daxx in stress-induced apoptosis via its SIM phosphorylation. The study was published in the leading international journal, Molecular Cell, on April 8, 2011. This paper was highlighted in the journal by a leading expert of the field, Dr. Michael MATUNIS. In addition, the Faculty of 1000 also strongly recommended this paper as a must-read paper on April 18, 2011.

Daxx is a signaling molecule in apoptotic pathway and also acts as a transcriptional corepressor. Dr. SHIH's group has studied Daxx for several years and has discovered a SIM motif within Daxx involved in Daxx sumoylation and interaction with other sumoylated transcription factors, as well as its localization to PML nuclear bodies (POD). Their studies unveiled the molecular mechanism of how sumoylation mediates transcriptional repression. However, important questions of how Daxx sumoylation is regulated by cellular signaling and how Daxx selects SUMO paralogue for binding and conjugation in cells and further contributes to apoptosis remain largely unclear.

In the present study, the team of scientists from Institute of Biomedical Sciences, Institute of Biological Chemistry, and the Genomics Research Center at Academia Sinica determined the structure of Daxx SIM and SUMO-1 complex by NMR spectroscopy and identified the phosphorylation sites of Daxx SIM by mass spectrometry. Further studies proved that CK2 kinase is responsible for Daxx SIM phosphorylation and that phosphorylation enhances Daxx SIM preferentially binding and conjugation by SUMO-1 over SUMO-2/3 in cells. Mutation of the Daxx SIM phosphorylation sites attenuated stress-induced apoptosis. The molecular mechanism that phosphorylation of Daxx SIM mediates Daxx to suppress the antiapoptotic gene expression such as c-FLIP and Bcl-2, sensitizing cells in response to stress-induced apoptosis were subsequently revealed. The discovery provides the molecular basis of SUMO paralog selectivity and also an opportunity to fine-tune the stress-induced apoptosis. Because Daxx has been recently reported to be involved in human cancer formation, the current study could facilitate the development of potential drugs in controlling Daxx activity for anti-cancer agents.

This work was supported by grants from Academia Sinica, the National Science Council, and National Health Research Institutes. The full-text of the study entitled "Structural and functional roles of Daxx SIM phosphorylation in SUMO paralog-selective binding and apoptosis modulation" is available at the Molecular Cell website at: http://www.cell.com/molecular-cell/abstract/S1097-2765(11)00163-8

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Further Information:
Academia Sinica Newsletter 2011/04/21

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