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Using VBIM technique to identify histone lysine demethylase FBXL11 as a negative regulator of NFκB

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Abstract

The activation of NFκB, a central coordinator of immune responses, is tightly regulated in order to achieve its normal transient activation in response to stress. In cancer, NFκB is activated abnormally, contributing to oncogenesis and progression. The regulation of transient activation is complex, and we are still learning the details of how the essential fine control is achieved. Here, we uncover a novel regulatory pathway for NFκB that is driven by cycles of lysine methylation and demethylation. Using a novel lentiviral Validation-Based Insertional Mutagenesis (VBIM) method, we identified the F-box leucine repeat rich protein 11 (FBXL11), a known histone H3 lysine 36 (H3K36) demethylase, as a potent negative regulator of NFκB. Deletion of the demethylase domain of FBXL11 abolishes this activity. Knocking the expression of FBXL11 down activates NFκB, as does over-expression of the corresponding histone H3K36 methylase, NSD1. The p65 subunit of NFκB binds to NSD1 and FBXL11, and significant methylation of K218 and K221 of p65 was detected in cells with constitutively active NFκB or upon cytokine stimulation. Importantly, FBXL11 is transcribed in response to NFκB activation and thus, like the well known inhibitor IκB, FBXL11 participates in an auto-regulatory negative feedback loop. We show that lysine methylation is an important regulatory post-translational modification of NFκB that is mediated by the FBXL11-NSD1 enzyme pair. Furthermore, we demonstrate that the VBIM technique is a powerful tool for gene discovery that has broad applications in many different systems.

Biography

Tao Lu is a tenure-track Assistant Professor and principle investigator at Department of Pharmacology and Toxicology and Department of Biochemistry and Molecular Biology, as well as a member of Experimental and Developmental Therapeutics Research Program at Simon Cancer Center at Indiana University School of Medicine. Dr. Lu obtained her Ph.D. degree from University of Toledo, School of Medicine. She then did her postdoctoral training with the world renowned scientist Dr. George R. Stark at Cleveland Clinic, Ohio. Dr. Lu has been working on discovery of novel regulators of NFκB, and is particular interested in epigenetic regulation of transcription factors and their role in cancer. Dr. Lu has won several international awards, including the First Place Prize of Young Investigator Award at Tri-Society [Society of Leukocyte Biology (SLB) & International Cytokine Society (ICS) & International Society of Interferon and Cytokine Research (ISICR)] conference and Seymour and Vivian Milstein Young Investigator Award at ISICR&ICS International conference.