NUS National University of Singapore | Department of Biological Sciences, Faculty of Science

BIOLOGY COLLOQUIUM

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Hosted by A/P Ganesh Anand

Biophysical insights into control mechanisms of NFκB signaling

By **Elizabeth Komives**

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Elizabeth Komives received her SB and SM degrees from MIT in Chemistry and Genetic Toxicology and her PhD degree in Pharmaceutical Chemistry from UCSF. After an NIH postdoctoral fellowship at Harvard, she became an Assistant Professor in Chemistry and Biochemistry at UC San Diego in 1990 and a Full Professor in 2000. Komives pioneered using hydrogen deuterium exchange by MALDI-TOF mass spectrometry (HDX-MS) and was the first to demonstrate that protein interfaces could be mapped by HDX-MS. Combining HDX-MS with NMR and single molecule FRET allowed her to address important but unsolved questions about allosteric regulation of proteins. Her initial discoveries focused on the biophysical behavior of thrombin:thrombomodulin complexes and PKA. Subsequent work on NFkB:IkB signaling established an original paradigm demonstrating kinetic control of transcription factor dynamics. Throughout her career, Komives has integrated biophysical tools to discover new biological principles, which have advanced our fundamental understanding of macromolecular recognition.

The NFκB signalling system receives extracellular signals and turns on hundreds of stress-response genes. The family of NFκB transcription factors is tightly regulated by several inhibitors and exhibits temporal control. Using a combination of biophysical approaches including stopped-flow fluorescence and amide hydrogen/deuterium exchange, we have explored the biophysics of the protein-DNA and protein-protein interactions that govern control of the pathway. Disordered regions containing degron sequences control the intracellular half-life of the key inhibitor, IkBa, which is rapidly degraded unless it is bound to NFkB. The NFkB-IkBa complex is extremely stable, and does not dissociate unless an extracellular signal is received. Once the IkBa is degraded, the NFkB enters the nucleus and activates transcription of hundreds of stress-response genes, including IkBa. The newly synthesized IkBa enters the nucleus and "strips" the NFkB off the DNA achieving rapid and complete cessation of signaling. Thus, the entire pathway is under kinetic rather than thermodynamic control.

Artwork by Ann Nee, DBS, NUS