Chemical Genetic Discovery of Lamin-binding Ligands (LBLs)

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Nuclear lamins, including lamin A/C, B1, and B2 in humans, form nuclear lamina inside the nucleus to maintain the structure of nucleus. In addition to this traditional view of lamins as nucleoskeleton proteins, they also participate in a variety of nuclear metabolism functions including DNA repair, DNA replication and RNA transcription. Thus, misregulation of lamins has been observed in a variety of diseases ranging from cancer to premature aging (progeria). However, the exact mechanisms that underling these functions are poorly understood. Complicating our understanding of the molecular mechanisms of lamins is the existence of a separate nuclearplasmic pool of lamins, which makes classical genetic strategies inefficient in teasing out such mechanisms. Small molecule regulators of lamins would provide a unique and powerful tool to dissect the molecular mechanisms of lamins' functions. However, there are currently no small molecules known to bind lamins to regulate their functions. In this presentation, we will discuss our discovery of lamin-binding ligands (LBL) from a phenotypic screening of a uniquely synthesized compound library followed by chemical proteomics identification of their binding targets.