Targeting Intrinsically Disordered Protein p53 Via Rational Drug Design

Content

Intrinsically disordered proteins (IDPs) are highly prevalent in eukaryotes. They were found to be associated with various diseases and have been proposed as promising drug targets. However, conventional structure-based drug design approaches cannot be applied directly in IDPs because of its conformational heterogeneity. In our previous work, we have successfully found several small molecules targeting oncoprotein c-Myc via rational design. Based on the encouraging results on c-Myc, a “multi-conformational-affinity” screening strategy is proposed to target IDPs. We are using this strategy to design small molecules that can bind to the tumor suppressor protein p53 and reduce its in vivo degradation. MDM2 binds the p53 tumor suppressor protein, effectively impairing p53 function. We discovered two compounds binding p53 disordered N-terminal as potent MDM2-p53 interaction inhibitors via rational drug design. The compounds activate the p53 pathway in cancer cells with wild-type p53, leading to cell cycle arrest, apoptosis and growth inhibition.

Primary author(s) : Mr. RUAN, Hao (Peking University)
Presenter(s) : Mr. RUAN, Hao (Peking University)