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Web of Science
Page 1 (Records 1 -- 1)

Print

◀ [1] ▶

Record 1 of 1

Title: Presence and utility of intrinsically disordered regions in kinases

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Abstract: Since aberrant cell signaling pathways underlie majority of pathophysiological morbidities, kinase inhibitors are routinely used for pharmacotherapy. However, most kinase inhibitors suffer from adverse off-target effects. Inhibition of one kinase in a pathogenic signaling pathway elicits multiple compensatory feedback signaling loops, reinforcing the pathway rather than inhibiting it, leading to chemoresistance. Thus, development of novel computational strategies providing predictive evidence to inhibit a specific set of kinases to mitigate an aberrant signaling pathway with minimum side-effects is imperative. First, our analyses reveal that many kinases contain intrinsically disordered regions, which may participate in facilitating protein-protein interactions at the kinome level. Second, we employ a kinome-wide approach to identify intrinsic disorder and streamline a methodology that adds to the knowledge of therapeutically targeting kinase cascades to treat diseases. Furthermore, we find that within the kinome network, some kinases with intrinsically disordered regions have a high topological score, likely acting as kinome modulators. Third, using network analysis, we demonstrate that 5 kinases emerge as topologically most significant, forming kinome sub-networks, comprising of other kinases and transcription factors that are known to serve as drivers of disease pathogenesis. To support these findings, we have biologically validated the interplay between kinome modulators SRC and AKT kinases and uncovered their novel function in regulating transcription factors of the SMAD family. Taken together, we identify novel kinome modulators driven by intrinsic disorder, and biologically validate the thesis that therapeutic disruption of the function of kinome modulators engaged in regulatory cross-talk between disparate pathways can lead to reduced oncogenic potential in cancer cells.

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Page 1 (Records 1 -- 1)

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◀ [1] ▶