Selective inhibition of the kinase DYRK1A by targeting its folding process

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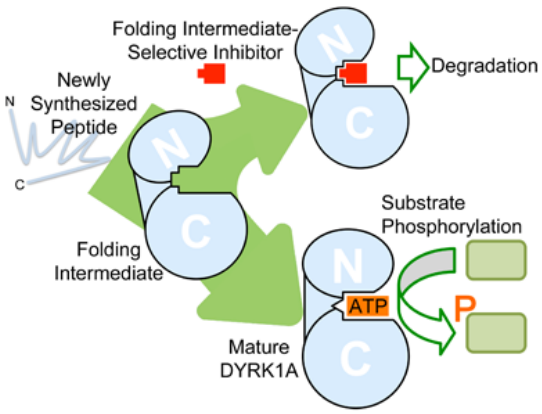
Autophosphorylation of amino-acid residues is part of the folding process of various protein kinases. Conventional chemical screening of mature kinases has missed inhibitors that selectively interfere with the folding process. Here we report a cell-based assay that evaluates inhibition of a kinase at a transitional state during the folding process and identify a folding intermediate-selective inhibitor of dual-specificity tyrosine-phosphorylation-regulated kinase 1A (DYRK1A), which we refer to as FINDY. FINDY suppresses intramolecular autophosphorylation of Ser97 in DYRK1A in cultured cells, leading to its degradation, but does not inhibit substrate phosphorylation catalysed by the mature kinase. FINDY also suppresses Ser97 autophosphorylation of recombinant DYRK1A, suggesting direct inhibition, and shows high selectivity for DYRK1A over other DYRK family members. In addition, FINDY rescues DYRK1A-induced developmental malformations in *Xenopus laevis* embryos. Our study demonstrates that transitional folding intermediates of protein kinases can be targeted by small molecules, and paves the way for developing novel types of kinase inhibitors.



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