Abstract

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Drugging MYCN through an allosteric transition in Aurora kinase A.

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Abstract

MYC proteins are major drivers of cancer yet are considered undruggable because their DNA binding domains are composed of two extended alpha helices with no apparent surfaces for small-molecule binding. Proteolytic degradation of MYCN protein is regulated in part by a kinase-independent function of Aurora A. We describe a class of inhibitors that disrupts the native conformation of Aurora A and drives the degradation of MYCN protein across MYCN-driven cancers. Comparison of cocrystal structures with structure-activity relationships across multiple inhibitors and chemotypes, coupled with mechanistic studies and biochemical assays, delineates an Aurora A conformation-specific effect on proteolytic degradation of MYCN, rather than simple nanomolar-level inhibition of Aurora A kinase activity.

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