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Pin1 as Super Oncogene Regulator

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Targeted therapy works by blocking a single oncogenic pathway. However, a tumor is never homogeneous and thus have multiple redundant pathway and easily evade the drug pressure. Thus we need to target such oncogene which regulates multiple oncogenic pathway at once.

ATRA is first successful drug for targeted drug therapy in APL approved in late 1995 as differentiation inducing agent. However mechanism of ATRA has so far been not clear. In a novel mechanism based screening, researcher found out that ATRA targets Pin1 in APL. Further study in triple negative breast cancer tumor showed that ATRA mediated Pin1 degradation and inhibited TNBC. Since ATRA is relatively non-toxic with restriction in pregnancy, this study establish Pin1 as novel druggable and safe target. There lacks potent and specific Pin1 inhibitor, this study shows the possibility that discovery of new Pin1 inhibitor might be efficacious in cancer cure.

Introduction

Active Pin1 is a key target of all-*trans* retinoic acid in acute promyelocytic leukemia and breast cancer

Wei S. et., et al., Nature Medicine, 13 April, 2015 (Advance online publication), Harvard Medical School

Abstract

A common key regulator of oncogenic signaling pathways in multiple tumor types is the unique isomerase Pin1. However, available Pin1 inhibitors lack the required specificity and potency for inhibiting Pin1 function *in vivo*. By using mechanism-based screening, here we find that all-*trans* retinoic acid (ATRA)—a therapy for acute promyelocytic leukemia (APL) that is considered the first example of targeted therapy in cancer, but whose drug target remains elusive—inhibits and degrades active Pin1 selectively in cancer cells by directly binding to the substrate phosphate- and proline-binding pockets in the Pin1 active site. ATRA-induced Pin1 ablation degrades the protein encoded by the fusion oncogene *PML–RARA* and treats APL in APL cell and animal models as well as in human patients. ATRA-induced Pin1 ablation also potently inhibits triple-negative breast cancer cell growth in human cells and in animal models by acting on many Pin1 substrate oncogenes and tumor suppressors. Thus, ATRA simultaneously blocks multiple Pin1-regulated cancer-driving pathways, an attractive property for treating aggressive and drug-resistant tumors.