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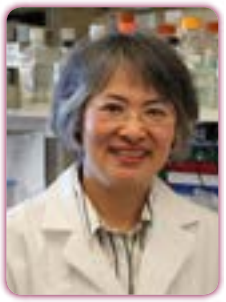

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Pin1-catalyzed conformational regulation as a common oncogenic signaling mechanism and a unique drug target

It has become evident that the activation of multiple interactive/redundant oncogenic pathways and the presence of cancer stem cells are two major sources of drug resistance in modern cancer therapy. Pin1 is a unique phosphorylation-specific proline isomerase that functions as a master regulator of oncogenic signaling networks. It simultaneously activates at least 43 oncoproteins and inactivates over 20 tumor suppressors and global miRNAs to activate multiple oncogenic pathways and expand cancer stem cells in various cancers. However, Pin1 inhibitors are lacking. Our recent mechanism-based high throughput screens have led to the unexpected discovery that all-*trans* retinoic acid (ATRA) is a Pin1 inhibitor. The combination of ATRA with arsenic trioxide (ATO) has transformed acute promyelocytic leukemia (APL) from being highly fatal to highly curable, but their mechanisms of action and efficacy aren't fully understood. We have shown that ATRA inhibits APL, acute myeloid leukemia, breast and liver cancer by directly binds to and induces Pin1 degradation. We have further shown that ATO also inhibits and degrades Pin1, and suppresses its oncogenic function by noncovalent binding to Pin1's active site. ATO's anticancer activity is potentiated by ATRA, which increases cellular ATO uptake through upregulating aquaporin-9. ATO and ATRA, at clinically safe doses, cooperatively ablate Pin1 to block numerous. Cancer-driving pathways and inhibit the growth of triple-negative breast cancer cells and cancer stem cells in cell and animal models including patient-derived orthotopic xenografts, like Pin1 knockout, which is substantiated by comprehensive protein and microRNA analyses. These results not only identify Pin1 as the elusive drug target for ATO and ATRA, but also establish a proof-of-concept that targeting of Pin1 by ATO and ATRA or other more potent and specific Pin1 inhibitors offers an attractive approach to combating breast and many other cancers.

Biography

Xiao Zhen Zhou, MD, is an Assistant Professor at Beth Israel Deaconess Medical Center, Harvard Medical School. She received her medical training from Suzhou Medical College and passed The United States Medical Licensing Examinations and obtained Educational Commission for Foreign Medical Graduates Certification. She started her research career in the Shirish Shenolikar laboratory at Duke University and then in the James Hoch laboratory at Scripps Research Institute, working on phosphorylation signaling in mammals and bacteria, respectively. After joining the Kun Ping Lu's laboratory at Harvard, she has established the fundamental principle of Pin1-catalyzed signaling mechanism and also identified several Pin2/TRF1-interacting proteins, including PinX1, the first mammalian endogenous telomerase inhibitor and a major tumor suppressor.

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