OMICS Group Conferences
Accelerating Scientific Discovery

3rd World Congress on
Cancer Science & Therapy

October 21-23, 2013 DoubleTree by Hilton Hotel San Francisco Airport, USA

The unique proline isomerase Pin1: A novel drug target acting on numerous key cancer-driving pathways

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Abstract

Many cancer patients do not respond or become resistant to molecularly targeted drugs because multiple pathways drive cancer growth simultaneously, especially in aggressive and drug-resistant cancers. This lecture will address how to identify and develop reagents against the common signaling mechanisms in cell proliferation and transformation. A central signaling mechanism is proline-directed serine or threonine phosphorylation, which directly or indirectly controls numerous oncogenes and tumor suppressors. We have previously shown that such phosphorylation signaling is further regulated by a unique prolyl isomerase, Pin1, via *cis/trans* conformational changes after phosphorylation, which can now be detected by proline isomer-specific antibodies. Importantly, Pin1 is often overexpressed in human cancers and thereby activates and inactivates over 30 oncogenes and tumor suppressors, respectively, contributing to poor clinical outcome. Furthermore, whereas transgenic Pin1 overexpression induces tumorigenesis, Pin1 knockout or knockdown effectively prevents cancer development induced by oncogenes in vitro and in mice. Moreover, we have recently found that Pin1 activity and oncogenic function are normally inhibited by post-translational modifications, including phosphorylation in the catalytic active site by the known tumor suppressor DAPK1. These results indicate that the Pin1 isomerase activity is essential for its function in tumorigenesis and suggest that Pin1 inhibitors might have the desired effects to suppress numerous key cancer-driving pathways. Indeed, we have developed high-through screens for identifying Pin1 inhibitors and successfully developed small molecular compounds that effectively block tumor growth in vitro and in vivo. Further development of these novel Pin1 inhibitors might lead to new potent drugs for treating aggressive and drug-resistant cancers.

Biography

Professor Lu has discovered Pin1 and shown that Pin1-catalyzed cis-trans isomerization after phosphorylation catalyzed is a pivotal novel signaling mechanism in diverse cellular processes. Moreover, Dr. Lu has uncovered the unexpected and opposite effects of Pin1 deregulation on the development of cancer and Alzheimer's disease, which has not only provided the first link between these major diseases that were rarely studied together before, but also offered a promising new paradigm for their diagnosis and treatment. Dr. Lu has served on editorial boards of numerous journals and review committees for the NIH and many other foundations.