

Translating the p53 pathway into drug discovery

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The p53 tumour suppressor is one of the most important proteins that protect humans from the development of cancers. However, p53 in many types of cancers is often deactivated through a concerted action by its abnormally elevated suppressors, such as MDM2, MDMX or SIRT1. SIRT1 is highly expressed due to loss of its repressor HIC-1 via promoter hypermethylation in cancer cells, keeps p53 in a deacetylated status and facilitates its ubiquitylation and degradation by MDM2/MDMX. Thus, reactivation of p53 by targeting these p53 suppressors in p53-containing cancers has become an attractive approach for the development of anti-cancer therapy. Regardless of the intensive endeavor over the past decade, so far none of the known small molecules that target this p53 pathway has yet been developed into a clinically effective therapy. Thus, identifying more effective small molecules that specifically target this pathway in cancer has still remained challenging and exciting. In our initial attempt to screen small molecules that may block MDM2/MDMX-p53 binding, we surprisingly identified a novel small molecule called INZ that effectively activates p53 by inhibiting SIRT1 activity without genotoxicity. Remarkably, INZ suppressed the growth of xenograft tumours derived from p53-containing human lung and colon cancer cells in a p53-dependent fashion. More remarkably, this small molecule was less toxic to normal cells and tissues. Hence, our study as described here unravels INZ as a novel class of small molecules that can activate p53 by inhibiting SIRT1 and repress tumour growth in xenograft tumour models. Identification of INZ as a new class of small molecules that can activate p53 and induce p53-dependent apoptosis and senescence without causing genotoxicity as well as suppress tumour growth with little toxicity to normal cells and tissues offers another golden opportunity in the field of translational cancer research for the development of target-specific anti-cancer therapy either as an individual drug or as a component in combined therapy.

Biography

Hua Lu has completed his Ph.D from Rutgers University/UMDNJ 1993 and postdoctoral studies from Princeton University 1997. He has been working on the field of p53 and cancer biology since 1997. He is now Professor and Chairman of Department of Biochemistry and Molecular Biology and Reynolds and Ryan Families Chair in Transitional Cancer at Tulane Cancer Center, Tulane University School of Medicine, New Orleans, Louisiana, USA.

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