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Trisenox disrupts MDM2-DAXX-HAUSP complex and degradation of MDM2 in acute promyelocytic leukemia cells

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Trisenox (TX) alone or combination with all trans-retinoic acid (ATRA) has been successfully used in the treatment of acute promyelocytic leukemia (APL) patients with highest survival rate. Clinical trials study of TX and their combination with ATRA was shown complete remission in both *de novo* and relapsed APL patients. However, the exact molecular mechanisms of its action through cell cycle arrest and apoptosis are poorly understood. We hypothesized that TX modulates cell cycle and apoptosis through activation of p53 and interaction of death domain-associated protein (DAXX) which disrupted the MDM2-DAXX-HAUSP interaction, MDM2 degradation and their self-ubiquitination. To test the hypothesis, we used western blotting, confocal imaging and other molecular techniques to identify new target of TX action in APL cells. We found that the expression levels of p53 and p21 increased significantly whereas MDM2, DAXX and HAUSP decreased in a dose dependent. Our immunoprecipitation (IP) studies shown that they are well associated each other in cells and TX disrupted their association. After 21 days treatment of TX different doses (1.25, 2.5, 5.0 and 7.5 mg/kg body wt) in transgenic mice we isolated liver tissue and bone marrow cells. We found, p53 was activated in a dose dependent TX treated mice. We conclude that TX disrupts MDM2-DAXX-HAUSP complex, release and degradation of MDM2 expression in APL cells. It leads to accumulation of p53, cell cycle arrest and apoptosis in APL cells. It is novel target for treatment of APL patients by TX and also designing of new drugs.

Biography

Sanjay Kumar has completed his PhD from Jawaharlal Nehru University, New Delhi and Postdoctoral research training at Indiana University, Indianapolis and University of Tennessee Health Science Centre, Memphis, USA, 2008-2012. Currently, he is working as Postdoctoral Research Associate at Jackson State University and his research focused on investigation of new target of Trisenox action in acute promyelocytic leukemia (APL) cells by modulation of cell cycle, p53 signaling and apoptosis using mice model of APL. He has published 16 international research papers and also serving as Editorial Board Member and Reviewer of five reputed journals.

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