Jyoti Zack, J Hematol Thrombo Dis 2016, 4:5(Suppl)
http://dx.doi.org/10.4172/2329-8790.C1.003

Effect of RUNX1 mutations on its structural conformation and binding affinity with DNA which constitutively alters the expression of targeted genes

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Runt related transcription factor-1 or RUNX1 regulates the development of hematopoietic system in concert with various transcriptional co-regulators. It is the most common target of chromosomal translocations and mutations in its runt domain and is frequently associated with leukemogenesis. Structural studies of the RUNX1-DNA complexes provide details of the direct contacts formed between the runt domain of RUNX1 and DNA. The amino acid residues, Lys83 and Arg174, of RUNX1 directly interact with its binding site on the promoters. We have used a combined approach i.e., Electrophoretic Mobility Shift Assays (EMSA) and spectroscopic measurements to investigate the structural and functional consequences. CD spectroscopy and tryptophan fluorescence of the wild type and mutant full length purified RUNX1 protein suggested us an altered secondary and tertiary structure of the mutant proteins. The mutant proteins also exhibited decrease in DNA binding as evident by EMSA and binding kinetics using fluorescence spectroscopy. We observed that the DNA binding affinity of the mutated RUNX1 with RUNX3/LAT promoter was about five to seven folds lower than that of wild type RUNX1. These results suggest that both point mutations (Lys83Glu/Arg174Gln) lead to a change in the conformation of full length RUNX1 protein which in turn affects its binding with the DNA. Our patient study also revealed us the altered expression of the targeted genes because of the respective mutation or any other unrevealed mechanism.

Biography

Jyoti Zack has completed her PhD from University of Delhi. After completion of her thesis, she joined as Research Associate and now pursuing her research work in SGPGI, Lucknow, India. She has presented her work in various poster/oral sessions held in national/international conferences and got best poster presentation award too.

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