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Integrated genetic and epigenetic analysis identifies biomarkers of prognostic significance in pediatric acute myeloid leukemia

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Epigenetic mechanisms such as DNA methylation are deregulated in cancer. Aberrant DNA methylation is reported to have clinical significance in acute myeloid leukemia (AML) in adults; however, its impact on pediatric AML is relatively unknown. Our research focuses on integrated genome-wide DNA methylation and gene expression analyses to identify the epigenetic signatures that are associated with gene expression and prognosis in pediatric patients with AML. We developed and applied a novel method that integrates canonical correlation analysis with projection onto the most interesting statistical evidence (CC-PROMISE) to identify genes with methylation and expression values that exhibit a biologically concordant and clinically meaningful pattern of associations' treatment outcome in pediatric AML patients. Our results identified several genes of significant importance in cell growth, proliferation, apoptosis as well as AML biology as top candidates. Of special interest was the gene DNA methyl-transferase gene *DNMT3B*, which has been previously implicated in adult AML, significant methylation-expression correlation and was strongly predictive of poor outcome in pediatric AML. Furthermore, consistent with its biological function, greater *DNMT3B* expression associated with greater genome-wide methylation burden. Collectively, these results indicate that deregulated methylation of the *DNMT3B* locus may modulate *DNMT3B* expression which subsequently alters the methylome, transcriptome, disease progression, and clinical prognosis of childhood AML. Overall understanding epigenetic and transcriptomic landscape of childhood AML can help in better designing the incorporation of epigenetic modifier drugs to standard chemotherapy regimens as well as help in identifying patients that would likely be better candidates to receive such a combination treatment.

Biography

Jatinder Lamba is an Associate Professor in Department of Pharmacotherapy and Translational Research. She completed her PhD in the field of Pharmacogenomics at Postgraduate Institute of Medical Education and Research in Chandigarh, India and Post-doctoral training at St. Jude Children's Research Hospital, Memphis. Her research has been funded from NIH/NCI since 2008 and focuses on Identification, characterization and clinical validation of genomic/epigenomic markers predictive of therapeutic outcome in cancer patient specifically acute myeloid leukemia. Her research spans from preclinical basic research comprising the discovery phase to translational/clinical phase in patient populations from multi-institute clinical trials.

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