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The genetic variants control resistin expression through promoter suppression which also leads to the modulation of resistin associated disease pathways

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Genome-wide association studies (GWAS) in the recent past have identified thousands of disease related genetic variants and trait associated polymorphisms. However, translating these associated variants to causality and potential mechanisms of disease have been difficult. Recent advances in high throughput genotyping and gene expression analysis have allowed for an extensive mapping of expressed quantitative trait loci (eQTL). Although many of these eQTL are cell-type specific and also vary between the ethnic groups, they represent a valuable resource for candidate proteins, whose mRNA expression is at least in part are genetically controlled. However, once the priority candidate genes have been identified, it needs to be validated using well designed in vitro, in vivo or ex vivo models using techniques, which go beyond assaying the genome and transcriptome. Additionally, this also requires knowledge on the protein molecule under investigation or pathways identified cell/tissue specificity and functional consequence on the immune system. Hence, there is a need for targeted but yet comprehensive candidate gene based studies looking at various aspects of the potential disease gene from DNA to protein, also in pure populations of immune cells and/or tissues with appropriate stimuli and functional readouts.

We have generated multiple eQTL data sets (whole blood, neutrophils, eosinophils, CD4 and monocytes) which allowed us to explore a number of candidate based eQTLs in Asian population. Here I will present one of the characterized candidate eQTL associated with resistin gene. Using whole blood, cell type specific eQTLs, haplotype promoter reporter analysis, EMSA/supershift, inhibition study, CRISPR/Cas9 editing and targeted bisulphite sequencing, we propose that the suppression of resistin promoter is the underlying mechanisms for genetic regulation of resistin expression in monocytes. Also a genetically defined Cohort based immune-phenotyping and plasma biomarkers analysis showed a significant modulation of immune cells and plasma biomarker which are known to be associated with inflammatory diseases.

Our study provides detailed understanding about the role of resistin associated genetic cis-regulatory variants in the context of inflammatory diseases and also would be helpful for the better identification and design of new therapeutic targets in the field of inflammation.

Biography

Dilip Kumar has his PhD from Ludwig Maximillian's University, Munich, Germany in the area of eukaryotic transcription regulation. After completion of PhD; he moved to Max Planck Institute of Biochemistry, Martinsried where he established BAC (Bacterial artificial chromosome) based mice transgenesis method. Currently, he is working in the field of functional genomics with an emphasis on allergy in Chinese Singaporean population; he is trying to understand the underlying mechanisms for genetic regulation using transcriptomic, genetic, plasma biomarker, immune phenotyping and CAS9 based high-through put gene editing and homology directed recombination. Thousands of genetic pre-disposition markers for different diseases have been defined or are being defined, but most of these genetic markers are poorly understood. Such studies will be helpful to improve our understanding about the genetic predisposition towards specific human diseases, dysregulated biological pathways, and gene-drug interaction for better design of therapeutic intervention.

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