FACULTY OF LIFE SCIENCES AND BIOTECHNOLOGY

SOUTH ASIAN UNIVERSITY

GUEST LECTURE SERIES

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Speaker: Dr. Shantanu Sengupta
CSIR-IGIB, New Delhi

Title of the talk: Understanding Cardiovascular Disease in India: An integrative omics approach

Abstract: Cardiovascular diseases are the leading cause of death worldwide. Among the cardiovascular diseases, Coronary artery disease (CAD) account for the largest cause of mortality and morbidity. Although CAD was originally projected to be diseases of the affluent, it is now clear that the incidence of this complex disease is disproportionately increasing in the developing countries. In fact India has the distinction of being the CAD capital of the world and it is estimated that by 2030, 60% of the deaths due to CAD worldwide will be in India. It is therefore imperative to find markers for CAD which could atleast postpone the manifestation of the disease. Currently the markers, including genetic markers available for predicting the risk of CAD does not account for a substantial number of cases. Hence one of the objectives of this study was to identify markers that could increase the predictive accuracy. Since, both environmental (including diet and lifestyle) and genetic factors contribute to the etiology of CAD, we looked at both these aspects in our quest towards identifying risk factors for CAD in Indian population. To identify the variations in genes that could be associated with CAD we embarked on a genome wide association study and genotyped more than 700,000 single nucleotide polymorphisms in about 3000 case control samples in two phases (discovery phase and validation phase). Our analysis revealed several single nucleotide polymorphisms to be associated with CAD which however, could not account for more than 10-15% of the cases. Among the dietary factors, we found low levels of the micronutrient, vitamin B12 and its active fraction holotranscobalamin, to be associated with CAD. Most importantly, we found that low holoTC levels are also significantly associated with low HDL, one of the major risk factors for CAD in India. Further, using a maternal vitamin B12 deficient rat model, we have shown increased levels of triglyceride in the pups born to mothers fed with B12 deficient diet which could be mediated via differential expression of PPAR alpha and gamma. This could be due to an epigenetic phenomenon, since supplementation of vitamin B12 at conception to rat mothers fed with vitamin B12 deficient diet reversed the effect. We thus looked at the whole genome DNA methylation profile of the liver of these rats and found several differentially methylated regions some of which were involved in fatty acid metabolism. To identify proteins or metabolites that may be altered in CAD, we used proteomics and metabolomics approaches and identified several potential markers. We identified four proteins involved in the reverse cholesterol pathway which along with hypertension and diabetes could account for about 88% of CAD cases. Further, using an untargeted LC-MS based metabolomics approach we identified 32 differentially regulated metabolites some of which have been previously reported to be associated with cardiovascular events. We thus believe that a systems biology approach with completely different layers of information (genome, epigenome, proteome and metabolome) is the only way to understand disease progression and complexities associated with it in a holistic manner. This will eventually help in developing a robust, more accurate and precise biomarker panel for screening the population having a higher risk of CAD.