Thesis title: "Identification of differentially expressed proteins for nonalcoholic fatty liver disease (NAFLD) - a proteomic and genomic approach to understand the disease pathogenesis and progression"

Broad Area of Research: Genomics and Proteomics

Special Field of Research: Molecular mechanisms of NAFLD pathogenesis and progression

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Nonalcoholic fatty liver disease (NAFLD) has emerged as a common health concern globally, and is among the most prevalent chronic liver disorders in the general population of developed and developing countries. Reports suggest that the prevalence of NAFLD in India is similar to western countries (20-40%) but the mechanistic progression of NAFLD in Indian patients is not very well understood. Moreover, in comparison to western populations, Indians differ in their dietary habits, lifestyle and more importantly, genotypic and phenotypic make-up, which may make them vulnerable to NAFLD. To understand the pathophysiology of NAFLD in Indian patients, proteomic and genomic based approaches have been employed in the current work.

* Risk factors such as hyperlipidemia; body mass index (BMI); elevated levels of liver enzymes, alanine transaminase (ALT) and aminotransferase (AST), were found to be associated with the disease progression in Indian patients.

* Adiponectin and leptin are the two major adipocytokines considered as key regulators in NAFLD pathogenesis. Plasma adiponectin and leptin have been evaluated in characterized NAFLD patients.

Significant fall in adiponectin levels and elevation of leptin level in plasma of patients signifies their role in pathophysiology of NAFLD.

* Pro12Ala, the functional variant of PPARγ is significantly associated with NAFLD and higher BMI in patients. Furthermore, we also found two functionally relevant polymorphisms, in the promoter region at -11377 C/G (rs266729) and, in the exon region at +45T/G (rs2241766) of adiponectin gene. These polymorphisms are also associated with severity of liver disease and hypoadiponectemia, respectively, in these patients.

* Six major proteins such as Transthyretin, Apolipoprotein A1, fatty acid binding protein, fibrinogen gamma, human complement component C3 and hepatoglobin alpha were differentially regulated in the NASH patients. FABP levels in the characterized NAFLD patients showed significant association with NAFLD.

* The relative (%) abundance of cysteinylated plasma albumin was significantly higher in NASH patients and could be potentially used as a diagnostic marker.

* Two-dimensional proteomics profile of HF-rat liver revealed expression of more than 300 proteins. Quantitative analysis by Difference gel electrophoresis (DIGE) showed 18 proteins to be significantly differentially expressed in HF-diet rat liver proteome. Protein spots identified by mass spectrometry were arginase 1 (liver specific), glutathione s-transferase-Yb2 (GST-Yb2), regucalcine (SMP30), heat shock protein 60, 70, and 90, ATP synthase, glutamate dehydrogenase and glyceraldehyde dehydrogenase. These differentially expressed proteins were involved in β-oxidation, energy homeostasis and stress response suggesting mitochondrial dysregulation in early stages of the disease pathogenesis.

The research work done in this thesis demonstrates the genetic and non-genetic factors influencing the fatty liver disease pathogenesis and progression.