



# RESEARCH HIGHLIGHTS

## 1. BASIC STUDIES

### 1.1 Amelioration of neuronal cell death in obese rat model by dietary restriction through modulation of ubiquitin proteasome system

Dietary restriction has been shown to increase longevity, delay onset of aging, reduce DNA damage, oxidative stress and prevent age-related decline of neuronal activity. We previously reported the role of altered ubiquitin proteasome system (UPS) in the neuronal cell death in a spontaneous obese rat model (WNIN/Ob rat). Now we demonstrate the effect of dietary restriction on obesity-induced neuronal cell death in a rat model by feeding the WNIN/Ob rats with either unlimited or restricted (equating to lean rats) diet. Dietary restriction for 6.5 months improved metabolic abnormalities in obese rats. Alterations in UPS, increased ER stress, declined autophagy, increased expression of  $\alpha$ -synuclein, p53 and BAX were observed in obese rats and dietary restriction alleviated these changes in obese rats. Further, diet restriction decreased apoptotic cells. Thus, dietary restriction in obese rats could not only restore the metabolic abnormalities but also preserved neuronal health in the cerebral cortex by preventing alterations in the UPS.

### 1.2 Ubiquitin-Proteasome system and ER stress in the retina of diabetic rats

Diabetic retinopathy (DR) is the most frequently occurring complication of diabetes. Alterations in ubiquitin-proteasome system (UPS) have been associated with several degenerative disorders. In this study, we assessed the role of UPS and ER stress in the retina of diabetic rats. Diabetes was induced in rats and ER stress, UPS, autophagy and apoptosis were investigated after 2- and 4-months of diabetes. Chronic diabetes increased acellular capillaries and pericyte loss in rat retina along with the decreased protein expression of UPS components. Further, increased ER stress in diabetic rats is associated with declined autophagy and apoptosis. Interestingly, treatment of diabetic rats with a chemical chaperone restored the UPS and ameliorated ER stress-induced retinal cell death in diabetic rats. These studies indicate that declined UPS components in the retina of diabetic rats could elicit ER stress, and the prolonged ER stress may trigger CHOP-mediated neuronal apoptosis.

### 1.3 Alzheimer's and Danish Dementia peptides induce cataract and perturb retinal architecture in rats

The familial Danish dementias (FDD) are autosomal dominant neurodegenerative disorders which are associated with visual defects. In some aspects, FDD is similar to Alzheimer's disease (AD). For example, amyloid deposits in FDD and AD are made of short peptides called dementia peptides: amyloid  $\beta$  ( $A\beta$ ) in AD and ADan in FDD. Previously, we demonstrated an interaction between these dementia peptides and  $\alpha$ -crystallin leading to lens opacification in organ culture due to impaired chaperone activity of  $\alpha$ -crystallin. Herein, we provide the evidence for the *in vivo* effects of ADan and  $A\beta$  peptides on the eye. The ADan and  $A\beta$  peptides were injected intravitreally to the rats. The onset of cataract was seen after injection of the peptides, but the cataract matured by 2-5 weeks in the case of ADan peptides and after 6 weeks for of  $A\beta$  peptides. The severity of cataract is associated with insolubilization and alterations in crystallins and loss of chaperone activity of  $\alpha$ -crystallin. Further, disruption of the architecture of retina was evident from a loss of rhodopsin, increased gliosis and the thinning of the retina. These results provided a basis for the visual impairment due to dementia.

## **1.4 Hsp90 regulation of fibroblast activation in pulmonary fibrosis**

Idiopathic pulmonary fibrosis (IPF) is a severe fibrotic lung disease associated with fibroblast activation that includes excessive proliferation, tissue invasiveness, myofibroblast transformation, and extracellular matrix (ECM) production. To develop therapeutic agents, we queried IPF gene signatures against a library of small-molecule-induced gene expression profiles and identified Hsp90 inhibitors as potential therapeutic agents that can suppress fibroblast activation in IPF. In support of this, we found elevated Hsp90 staining in lung biopsies of patients with IPF. Notably, fibroblasts isolated from fibrotic lesions showed heightened Hsp90 ATPase activity compared with normal fibroblasts. 17-*N*-allylamino-17-demethoxygeldanamycin (17-AAG), a small molecule inhibitor of Hsp90 ATPase activity, attenuated fibroblast activation and also fibroblast to myofibroblast transformation. Further, knock-down of the Hsp90 resulted in reduced fibroblast proliferation, myofibroblast transformation, and ECM production. Finally, in vivo therapy with 17-AAG attenuated progression of established and ongoing fibrosis in a mouse model of pulmonary fibrosis, suggesting that targeting Hsp90 represents an effective strategy for the treatment of fibrotic lung disease.

## **1.5 Impact of dietary fatty acids on the progression of nonalcoholic fatty liver disease in fructose induced model of steatosis – Role of adipose tissue insulin sensitivity and secretory function**

Non-alcoholic fatty liver disease (NAFLD) is a chronic liver disease and includes spectrum of liver condition ranging from benign steatosis to non-alcoholic steatohepatitis (NASH), advanced fibrosis and ultimately liver failure. The recent phenomenal increase in prevalence of NAFLD may be associated with significant modification of dietary habits due to westernization of the diet. The changes in dietary habits have made fast food as an important component of today's diet. In addition to providing high calories, several components of the fast food based diets could play a significant role in the pathogenesis of NAFLD. Increased consumption of soft drinks which contain high levels of fructose along with high intake of saturated fat, trans fat, n-6 PUFA and low intake of n-3 PUFA may be the possible cause of increased prevalence of NAFLD. Although the exact cause of the progression from simple steatosis to NASH is not established, lipotoxicity has been suggested to play an important role. Studies were carried out to investigate the impact of specific fatty acids on the progression of NAFLD in the setting of hepatic steatosis. The results showed that fructose: saturated/trans fatty acid combination induced hepatic steatosis. However, compared to fructose: saturated fatty acid combination, fructose: trans fatty acid combination induced NASH as evidenced by increased inflammatory and fibrotic changes suggesting that fructose: trans fatty acids combination is detrimental to the liver. Further, substitution of n-6 PUFA with n-3 PUFA prevented high fructose, high cholesterol induced NASH. The protective effect of n-3 PUFA supplementation on high fructose, high cholesterol induced NASH could be attributed to the suppression of proinflammatory cytokines and oxidative stress by dietary n-3 PUFA. The results of the present study reinforce the current recommendations of restricting the intake of trans fats, moderate the intake of n-6 PUFA and increase the intake of n-3 PUFA for the prevention of diet related chronic diseases including NAFLD.

## **2. EXTENSION AND TRAINING**

### **2.1 Health seeking behaviour, food beliefs and practices among Chenchu women during physiological changes – A gender based approach**

This study was planned to bring awareness on health and nutrition among Chenchus. Data was collected from 16 Chenchu tribal villages in Telangana and Andhra Pradesh. From each state, 4 core villages (2 homogenous villages & 2 heterogeneous villages) and 4 buffer villages (2 homogenous villages & 2

heterogeneous villages) were selected for the research study. a total number of 322 women were interviewed to assess the information relating to food fads, myths and beliefs which are likely to affect the dietary practices during different physiological conditions of Chenchu women.

During lactation (first six months) most of the foods are avoided except rice and spicy chilli powder, leading to malnutrition of both mother and child. No additional food intake is given during pregnancy. Majority of women (79%) gott married before the age of 18 years. Millet acceptability is high but consumption is low due to easy availability of subsidized cereals. Seventy six percent of women used the services of government PHC for health care.

IEC material were developed based on information collected from chenchu tribe these include folders, charts which were distributed among the participants as a source material to educate the women. At the end of the project, a one-day dissemination workshop on “Health and nutrition awareness” was conducted for ICDS & Health functionaries working with Chenchus.

### **3. FOOD AND DRUG TOXICOLOGY RESEARCH CENTRE**

#### **3.1 Differential protein expression in liver tissues in fluoride intoxicated rats by proteomics approach**

There was a significant decrease in body weight in the 50 and 100 ppm F groups compared to control group. There was a significantly higher excretion of fluoride in all the F groups than the control group. There is a significantly increased serum fluoride levels in the 50 and 100 ppm F groups compared to control groups. There was a significant increase in the teeth and bone fluoride levels in the F groups compared to control group. The differential protein expression in the liver of control and 100 ppm fluoride group was observed. 7 spots were identified as differentially expressed proteins by PDQuest software (BIORAD). The proteins highly expressed in control group as compared to fluoride group are glutathione–s-transferase and hemoglobin, alpha 2. The proteins highly expressed in the fluoride groups as compared to control group are dismutase, arginase-1, T-cell receptor beta chain, D-dopachrome decarboxylase.