Molecular pathogenesis of chronic liver diseases

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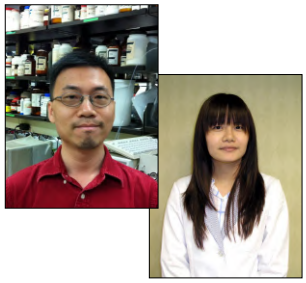


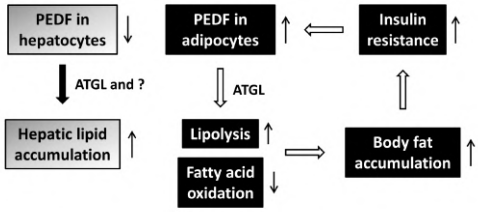
Background

Growing occurrences of non-alcoholic fatty liver disease (NAFLD) have been linked to increased incidence of obesity and other metabolic disorders. NAFLD has become the most common cause of chronic liver diseases in the world, affecting more than 20% of the population. Patients with severe forms of NAFLD are often predisposed to liver fibrosis and cirrhosis. Cirrhosis is characterized by excessive deposition of extracellular matrix, leading to severe architectural/vascular distortion and hepatic dysfunction. Patients with cirrhosis are also at high risk of developing hepatocellular carcinoma (HCC). Therefore, understanding the underlying mechanisms and developing new and effective strategies that prevent progression towards cirrhosis and/or induce regression is strongly encouraged. Our laboratory focuses on molecular factors that are associated with the pathogenesis of NAFLD, liver fibrosis and HCC.

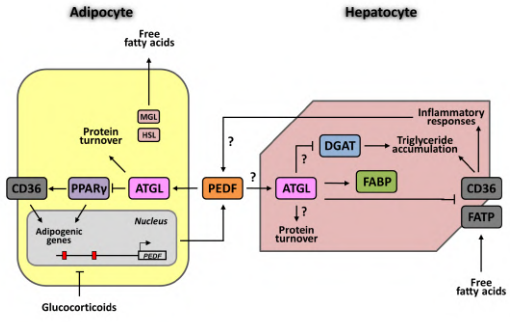
Research Topic I

PEDF in lipid metabolic disorders

Pigment epithelium-derived factor (PEDF) is a secreted glycoprotein first described as a neurotrophic factor. The role of PEDF in lipid metabolism was established when adipose triglyceride lipase (ATGL), a major triglyceride hydrolase, was characterized as its binding partner. We aim to study the role of PEDF in hepatic lipid accumulation and adipocyte function.



Disparate functions of PEDF in lipid metabolic disorders. PEDF exerts its anti-inflammatory and anti-oxidative properties to maintain homeostasis of hepatic lipid accumulation. On the other hand, increased PEDF in adipose tissue has the potential to initiate a cascade of events that may eventually lead to insulin resistance. Huang et al. (2018) *Biomed J*, 41(2): 102-108.



PEDF regulates lipid metabolism through CD36. PEDF inhibits fatty acid uptake by modulating the levels of lipid transport proteins such as CD36. CD36 also plays a direct functional role in adipogenesis. Our goal is to define the regulatory role of PEDF during NAFLD progression and further delineate the contributions of PEDF signaling in the pathogenic activities that lead to advanced disease, including hepatic fatty acid mobilization, adipocyte hypertrophy and inflammatory responses. Adapted from Huang et al. (2018) *Int J Mol Sci*, 19(12): 3992.

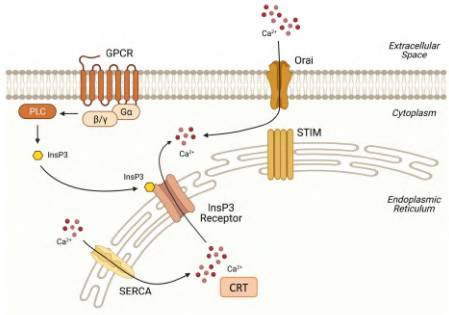
Collaborations

Professor Chao-Long Chen: The role of the antioxidant pathway in hepatic glucose homeostasis and NAFLD.
Dr. King-Wah Chiu: The antiviral mechanisms of vitamin D in living donor liver transplantation.
Dr. Chien-Chih Chen: The immunomodulatory effects of atypical antipsychotics in lipid metabolic abnormalities.

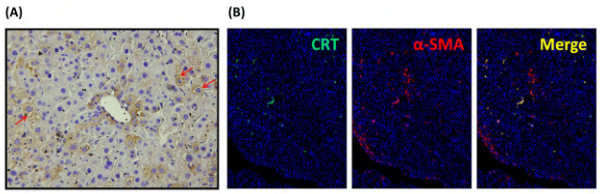
Research Topic II

Calreticulin in the liver fibrogenic process

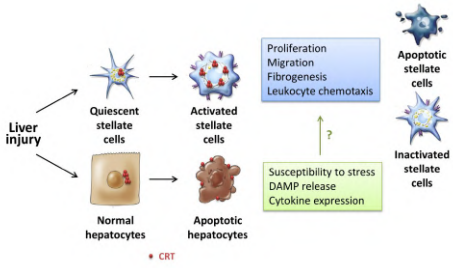
Calreticulin (CRT) is commonly known as a molecular chaperone in the ER, important in protein folding and calcium (Ca^{2+}) homeostasis. CRT has recently gained much attention for its role in the extracellular space, where it directs immunomodulatory activities by appearing as a danger signal for the innate immune system. We are currently investigating its biological functions in liver fibrogenesis.



CRT is a major Ca^{2+}-binding protein in the ER. Upon activation of the cell surface GPCRs, formation of InsP3 triggers Ca^{2+} release from the ER to the cytoplasm. Following Ca^{2+} release, dissociation of Ca^{2+} from the STIM proteins leads to STIM interaction with the plasma membrane Ca^{2+} channel Orai, allowing Ca^{2+} to enter the cell. Conversely, cytoplasmic Ca^{2+} is withdrawn to the ER via SERCA activity. Adapted from Chen et al. (2022) *Int J Mol Sci*, 23(1): 256.



CRT is increased in activated hepatic stellate cells. (A) CRT is increased in dimethylnitrosamine (DMN)-induced fibrotic mouse liver. (B) Immunostaining of liver section from DMN-treated mice shows CRT up-regulation in activated hepatic stellate cells.



Activated hepatic stellate cells are a promising target for developing new therapeutic strategies for liver fibrosis. Our current aims are to define the biological functions of CRT in the ER and in the extracellular space in the liver fibrogenic process.