Diabetes-2013

OMICS Group Conferences
Accelerating Scientific Discovery

4th World Congress on
Diabetes & Metabolism

August 14-16, 2013 Holiday Inn Chicago-North Shore, USA

Proteases as therapeutic targets and biomarkers in diabetes and its complications and in hepatitis C

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Abstract

Inhibitors of DPP4 enzyme activity are a successful new type 2 diabetes therapy. Current questions include whether DPP4 inhibition can also alleviate diabetes complications such as fatty liver (NAFLD), whether inhibiting the sister protease fibroblast activation protein (FAP) is also a diabetes (T2DM) therapy, and whether either protease may be a biomarker.

FAP expression on fibroblastic cells is predominantly associated with pathological processes including fibrosis severity. FAP increases the activity of a2-antiplasmin. We found that in an obesity model, both DPP4 knockout and FAP knockout mice resist liver damage and have improved glucose tolerance. DPP4 inhibitor in FAP knockout mice showed synergistic enhancement of glucose tolerance.

In T2DM patients, DPP4 correlated with ALT, GGT, plasma glucose and HbA1c, and liver elastography (FibroScan) score. FAP correlated with ALT and liver elastography score. In NAFLD Patients, both DPP4 and FAP correlated with GGT, ALT, AST, iron and ferritin. Hepatitis C (HCV) patients exhibited elevated circulating DPP4 and DPP4 correlated with ALT, AST, ALP, GGT, C-peptide, triglyceride, insulin, ferritin and fibrosis score. FAP correlated with LDL, glucose, BMI, cholesterol, C-peptide, insulin, albumin, bilirubin and INR. These associations might reflect DPP4 shedding from damaged hepatocytes and FAP shedding from fibroblastic cells in liver.

This work may show a new potential clinical application for measurement of serum levels of DPP4 as a prognostic, and possibly for combined FAP and DPP4 inhibition as a therapeutic in combatting diabetes and alleviating chronic liver diseases. Patients may benefit from DPP4 assay before prescribing a DPP4 inhibitor.

Biography

Mark Gorrell has a PhD from Australian National University and conducted postdoctoral studies at University of Melbourne and Johns Hopkins University School of Medicine. He heads a liver disease pathogenesis, dipeptidyl peptidases and diabetes research group. He has authored 109 papers and patents, primarily on DPP4 and related proteases and on liver disease pathogenesis, is treasurer of the International Proteolysis Society and is on 3 editorial boards.