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

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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.

Hepatitis C virus (HCV) infection often involves elevated levels of circulating CXCL10 chemokine, particularly CXCL10 cleaved by DPP4. HCV Pts 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. In T2DM Pts, DPP4 correlated with ALT, GGT, plasma glucose and HbA1c, and liver elastography (FibroScan) score. In NAFLD Pts, both DPP4 and FAP correlated with GGT, ALT, AST, iron and ferritin. 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 DPP4 inhibition as a therapeutic in combatting HCV infection and alleviating other chronic liver diseases. DPP4-driven pathogenesis via IP10 degradation may apply to a broad range of diseases. Patients may benefit from DPP4 assay before prescribing a DPP4 inhibitor.

Biography

Mark D. Gorrell has a Ph.D. 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.

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