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The protease fibroblast activation protein is a potential biomarker and therapeutic target in diabetes and fatty liver disease

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Inhibitors of DPP4 enzyme activity are a successful new type 2 diabetes (T2DM) therapy. Non-alcoholic fatty liver disease (NAFLD) is very common in T2DM patients and can progress to involve liver fibrosis. Liver fibrosis is reversible. We are investigating whether the sister protease of DPP4, fibroblast activation protein (FAP), may become a biomarker and therapeutic target in NAFLD. FAP expression by activated fibroblastic cells is predominantly associated with pathological processes including fibrosis severity. Concordantly, natural substrates of FAP include proteins important in fibrinolysis and matrix; alpha2-antiplasmin and collagen. We found that in a diet induced obesity (DIO) model, both DPP4 knockout and FAP knockout mice resist liver damage and have improved glucose tolerance. In T2DM patients, FAP correlated with liver damage markers (ALT, GGT) and liver elastography (FibroScan) score. In obese patients attending hospital for bariatric surgery, FAP correlated with GGT, ALT, AST, iron and ferritin. These associations may reflect FAP shedding from fibroblastic cells in chronic liver injury. Low serum FAP strongly associated with normal elastography scores such that adding FAP to the NAFLD Fibrosis Score algorithm correctly predicted normal elastrography score in two-thirds of T2DM patients. In contrast, serum DPP4, which may be hepatocyte derived, tended to be lower in the T2DM patients and associated with hepatocyte steatosis rather than with fibrosis. FAP is being compared with DPP4, cytokeratin 18 and transferrin in terms of fibrosis prediction. This work may show a new potential clinical application for measuring circulating FAP as a diagnostic and prognostic tool in managing T2DM patients who are at risk of liver fibrosis. FAP assay might also be used to monitor patients following therapeutic intervention. The association of FAP with fibrosis supports the concept that targeting FAP or FAP-expressing cells might be a successful therapeutic in combatting diabetes and alleviating chronic liver diseases.

Biography

Mark D Gorrell is Associate Professor, 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 in the Centenary Institute and the University of Sydney Medical School. He has authored 112 papers and patents, primarily on DPP4 and related proteases DPP8, DPP9 and fibroblast activation protein and on liver disease pathogenesis. His team uncovered mechanisms of protein binding and of enzyme activity in DPP4. He is treasurer of the International Proteolysis Society and is on 3 editorial boards.

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