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# The protease fibroblast activation protein as a biomarker and therapeutic target in cancer and chronic liver injury

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Humans have more than 400 proteases, many of which have potential uses in medicine. The main advantages of exploiting proteases are that assays are rapid and cheap and a chemical compound can target a specific proteasefar less expensively than an antibody. The most successful example is inhibitors of DPP4 protease activity for type 2 diabetes (T2DM). T2DM frequently associates with non-alcoholic fatty liver disease (NAFLD), which can progress to inflammation and fibrosis. Fibrosisis reversible but sometimesinstead progresses to liver failure or cancer. The potential of the sister protease of DPP4, fibroblast activation protein (FAP),to become a biomarker and therapeutic target in T2DM and NAFLD as well as cancer are investigated. FAP expression byactivated fibroblastic cells is predominantly associated with pathological processes in tumors, arthritis and fibrosis. It is found that in a diet induced obesity model, both DPP4 knockout and FAP knockout mice resist liver damage and have improved glucose tolerance and less insulin resistance. We developed a novel specific sensitive quantitative assay for FAP enzyme activity. FAP was dramatically increased in tissue samples from cirrhotic liver and tumors. However, in assays ofpatients' era, FAPlevels rose above controls only in patients with severe liver fibrosis, as assessed by biopsy or elastography score. These associations may reflect the shedding of FAP from fibroblastic cells in chronic liver injury and the large mass of the liver. Low serum FAP was strongly associated with normal elastography scores such that adding FAP to the NAFLD Fibrosis Score algorithm correctly predicted normal elastography score in two-thirds of T2DM patients, thereby correctly diagnosing as non-fibrotic about half of the patients who now receive an uncertain diagnosis and are then shown to be non-fibrotic by elastography. In contrast, serum DPP4, which is probably mainly hepatocyte derived, was lower in the T2DM patients and associated with hepatocyte steatosis rather than with fibrosis. 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 liver fibrosis 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.

**Conclusions**: FAP has an important role in glucose and lipid metabolism and in fibrosis. Adding an FAP measurement to the existing clinical NFS algorithm appears to greatly increase the accuracy of this diagnostic.

## Biography

Mark D Gorrell has a PhD from the Australian National University and conducted postdoctoral studies at the 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 115 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, sits on the Australian Gastroenterological Society research committee and is on four editorial boards.

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