



## COMMENT

## Apoptosis inhibitor of macrophage and diabetic kidney disease

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Dear Editor,

Miyazaki et al. recently reviewed the role of the apoptosis inhibitor of macrophage (AIM) protein, also known as CD5 antigen-like (CD5L), as an apoptosis inhibitor that supports the survival of macrophages and protects against disease when it is in its free 'attacker' form after release from its circulating 'carrier' IgM.<sup>1</sup> In particular, during acute kidney injury (AKI), evidence suggests that AIM is released systemically from the IgM pentamer, resulting in increased urinary excretion of free AIM, which exerts its local scavenging activity.<sup>2</sup> We recently developed a protein biomarker test (PromarkerD) in which human plasma concentrations of AIM, apolipoprotein A-IV (ApoA4) and insulin-like growth factor binding protein 3 (IBP3) are measured using a mass spectrometry (MS) method.<sup>3</sup> The method includes an immunodepletion step that removes IgM-bound AIM and measures only free AIM. As expected,<sup>1</sup> we found that assayed concentrations of bound plus free AIM in whole plasma were 10- to 20-fold increased compared with those after immunodepletion and that free AIM concentrations were highest in young females.

In a cross-sectional analysis of a sample of 963 community-based patients with type 2 diabetes,<sup>4</sup> relative free AIM concentrations (derived from peak area ratios from the MS assay) were 25% increased in individuals with established renal disease (Kidney Disease: Improving Global Outcomes Chronic Kidney Disease Stage  $\geq 1$ )<sup>5</sup> versus those without (geometric mean (SD range) 1.90 (0.87–4.12) versus 1.51 (0.70–3.29)) after adjustment for age, serum HDL-cholesterol and plasma concentrations of the other two biomarkers, APOA4 and IBP3 ( $P < 0.001$ ). This diagnostic finding is consistent with the observation that a substantial amount of free AIM can be found in sera from humans with AKI via immunoblotting.<sup>1</sup> However, the baseline free AIM in serum was also a significant independent but inverse predictor of a subsequent rapid declining eGFR in a subgroup of patients, ~50% of whom had an eGFR  $> 60$  mL/min/1.73 m<sup>2</sup> at baseline, as identified by trajectory analysis.<sup>4</sup>

The fact that lower baseline circulating levels of AIM were observed in our patients whose kidney function then declined rapidly may appear paradoxical. However, as we suggested in our earlier report,<sup>4</sup> it is possible that some patients with type 2 diabetes have a defect in AIM gene expression that predisposes them to the future adverse effects of diabetes on the kidney by consequently reducing plasma concentrations of AIM (total and free). Other possible explanations include altered IgM binding that restricts release of free AIM and thus attenuates its beneficial effects in response to ongoing renal injury, accelerated renal clearance of free AIM (which could reflect a period of hyperfiltration, an adverse prognostic indicator in its own right,<sup>6</sup>) accelerated

AIM metabolism or alternative (non-IgM) binding of circulating free AIM that is not modulated by renal disease.

In the PromarkerD prognostic test, the risk of future rapidly declining function is quantified by plasma concentrations of AIM (inversely), ApoA4 (positively) and IBP3 (inversely) in association with increasing age, reduced serum HDL-cholesterol levels and a reduced estimated glomerular filtration rate. The test has been validated<sup>7</sup> and may serve as a useful addition to the tools available to health care professionals managing patients with type 2 diabetes. In addition, it has been postulated that substances that promote AIM release from its IgM binding sites could prove useful therapeutically,<sup>1</sup> and the PromarkerD test could identify those who could benefit most from this intervention.

**Compliance with ethical standards****ADDITIONAL INFORMATION**

**Conflict of interest:** Proteomics International and the University of Western Australia are owners of patent PCT/AU2011/001212 that relates to biomarkers described in this letter. T.M.E.D. is employed by the University of Western Australia, K.E.P. by Proteomics International, the University of Western Australia and R.J.L. by Proteomics International.

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