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DIAGNOSTIC AND THERAPEUTIC IMPACTS OF AIM ON END-STAGE KIDNEY DISEASE

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Background and Aims: End-stage kidney disease (ESKD) is life-threating, and indispensably requires dialysis which however imposes huge burdens on patients' QOL and medical expense. No therapies to prevent CKD progression to the end-stage have reached clinic to date. Patients undergoing dialysis exhibit a high mortality mainly due to cardiovascular diseases (CVDs), but no biomarkers are available to predict the patients' death and the incidence of cardiovascular disease (CVD), the major cause of death, before initiation of dialysis. AIM is a macrophage-derived circulating protein present in blood at relatively high levels (∼5 μg/mL). We initially identified AIM as a supporter of macrophage survival, and it is now known as a facilitator of repair in many diseases. In healthy state, AIM associates with IgM pentamer through disulfide-bond formation and charge-based interaction with IgM-Fc, using the solitary cysteine residue and the positively charged-amino acid cluster present at the carboxyl-terminus. During various diseases including acute kidney injury, hepatocellular carcinoma and peritonitis, AIM dissociates from IgM and binds to the body-derived types of inflammatory elements using the identical sites necessary for binding to IgM, thereby promoting their phagocytic removal by phagocytes.

Method: In 561 CKD patients of all stages and 310 dialysis patients, we analyzed the serum AIM and the serum solute profiles, and thereby assessed their efficacy in predicting survival and CVD risk after dialysis induction. Additionally, a therapeutic efficacy of recombinant AIM (rAIM) in preventing CKD progression to end-stage was addressed in house cats, that are highly susceptible to CKD and show a similar disease course to humans.

Results: AIM dissociated from IgM pentamer along CKD progression. Dialytic patients showing low levels of AIM dissociation before initiation of dialysis harbored less serum detrimental solutes, exhibited lower risk of CVD and had better survival than those with high grades of AIM dissociation, suggesting that the IgM-free AIM represents the state of serum toxic solutes, and predicts patients' prognosis before initiation of dialysis. In addition, treatment of pre-uremic (late IRIS stage 3) cats, 50% of which died of severe uremia within 196 days after diagnosis, with recombinant AIM prevented aggravation of renal function and inflammation, as well as serum toxic solute profile, thereby improving the cats' survival dramatically. Importantly, the same serum toxin/inflammatory solutes regulatable by rAIM in cats influenced dialysis patients' prognosis.

Conclusion: There results promise the effects of AIM treatment in humans, reducing the need for dialysis. Our findings could be a platform for new CKD therapies and predictive diagnoses to improve the prognosis of patients with ESKD.