Cognitive impairment and dementia are major global health problems of the aging human population. It is estimated that about 55 million people were living with dementia in 2019 and this number is expected to triple by 2050. Dementia can result from abnormal structure and function of the brain, and can develop in a variety of conditions including chronic kidney disease (CKD). Recent studies identified new molecular mechanisms of kidney-brain crosstalk including newly identified angiogenic hormones such as the microvascular protein Cellular Communication Network factor 1 (CCN1) produced by the healthy kidney. My hypothesis is that CCN1 helps to maintain the normal structure and function of blood vessels and kidney. In addition, I further hypothesized that reduced CCN1 in CKD may be due to diminished renal production of CCN1 due to kidney disease plays a major role in the development of brain vascular dysfunction.

In this translational project, I measured and found reduced plasma CCN1 levels in patients at the USC’s Alzheimer’s Disease Research Center (ADRC) who exhibited mild cognitive impairment (MCI) compared to those who did not. In addition, plasma CCN1 levels and the density of cell-to-cell junctions in brain endothelial cells were 20% reduced in a mouse model of CKD (5/6 nephrectomy) compared to control healthy mice. In brain endothelial cells cultured in vitro, CCN1 treatment had protective effects on cell proliferation, motility and angiogenesis as confirmed by scratch and tube formation assays. My study helped to improve the mechanistic understanding of CCN1 levels in patients at the USC’s Alzheimer’s Disease Research Center (ADRC) who exhibited mild cognitive impairment (MCI) compared to control healthy mice. In brain endothelial cells cultured in vitro, CCN1 treatment had protective effects on cell proliferation, motility and angiogenesis as confirmed by tube formation assays.

Methods

Mouse studies
• Systolic blood pressure (BP) was measured using the non-invasive tail cuff method.
• Glomerular filtration rate (GFR) was measured using transdermal GFR technology.
• Plasma CCN1 levels were measured using mouse CytoGlo SimpleStep ELISA kits.
• BBB permeability was studied using intravital multiphoton (MPM) microscopy. Fluorescence intensity of the A680 conjugated albumin (70kDa) and the A488 conjugated Dextran (500kDa) was measured in brain interstitium and microvasculature.

Results

Plasma CCN1 levels are reduced in a mouse model of CKD
• No difference in systolic blood pressure.
• Significantly reduced GFR in mice with 5/6 Nx compared to control.
• Significantly reduced plasma CCN1 levels in mice with 5/6 Nx compared to control.

Intravital imaging revealed BBB permeability in a mouse model of CKD
• Increased fluorescence intensity of mid-size plasma proteins (A680 conjugated Albumin 70 kDa) compared to high molecular weight markers (A488 conjugated Dextran 500 kDa) in brain interstitium in 5/6 Nx compared to control.

Figure 1: A: Statistical summary of systolic blood pressure in control and CKD mice. B: Statistical summary of glomerular filtration rate in control and CKD mice. C: Statistical summary of plasma CCN1 levels in control and CKD mice. (n=4 control, and n=5 CKD, ns: not significant, *p<0.05, **p<0.01 using student T test).

Summary and Conclusion

• Plasma CCN1 levels were reduced in patients at the USC’s Alzheimer’s Disease Research Center (ADRC) who exhibited mild cognitive impairment (MCI) compared to those who were cognitively normal.
• Plasma CCN1 levels and the density of cell-to-cell junctions in brain endothelial cells were 20% reduced in a mouse model of CKD (5/6 nephrectomy) compared to control healthy mice.
• In brain endothelial cells cultured in vitro, CCN1 treatment had protective effects on cell proliferation, motility and angiogenesis as confirmed by tube formation assays.

In conclusion, our study helped to improve the mechanistic understanding of the disease process of dementia in CKD and laid the foundation for future novel clinical diagnostic and therapeutic development in this area.