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The kidney-gut-brain axis : Effect of restoring gut microbiome on the longterm development of dementia following AKI

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Objectives: Although epidemiological studies suggest that longterm survivors of dialysis requiring AKI had increased risk of dementia, its mechanisms remain uncertain. Based on recent data showing kidney-gut crosstalk mediated by immune modulation in AKI, we hypothesized that gut dysbiosis and aberrant gut immune response contribute to the cognitive dysfunction following AKI.

Methods: In mouse longterm AKI survival model, we determined functional and structural alterations of brain, changes in gut microenvironment including dysbiosis and immune cell activation. For better insight about the causal relationship in kidney-gut-brain axis, we also tested the effect of FMT and cohousing on brain in longterm AKI mouse model.

Results: One year after IRI, mice showed abnormal behaviors in open field test compared to sham control. Whole transcriptosome of hippocampus demonstrated more than 120 differentially regulated genes including those involved in angiogenesis/immune and inflammatory response. We found structural brain injury including disruption of BBB, neuroinflammation as well as accumulation of hyperphosphorylated tau proteins, suggesting the development of Alzheimer like dementia long after AKI. Gut microbiota structure 1yr after IRI was also clearly distinguished from that of control and it was associated with increased ratio of Th17/Tregs balance, decreased immune modulatory $Ly6c^{+}$ $CX_3CR_1^{high}$, resident macrophages showing the persistence of gut dysbiosis and aberrant gut mucosal immune response long after AKI. Both cohousing and FMT partially restored the gut mucosal inflammation and this also led to improved cognitive function as well as neuroinflammation and tauopathy.

Conclusions: This is the first animal study showed that AKI can lead to Alzheimer like neurodegeneration. Gut dysbiosis and aberrant mucosal immune response is thought to contribute to the development of tauopathy/neuroinflammation and cognitive dysfunction long after AKI. Our data provide insights into "kidney-gut-brain" axis in AKI and suggest that gut might be a new therapeutic target for the prevention of long-term complications in AKI patients.