1. No.

   2022G037

2. Title

   Effects of Smoking on Cerebrocardiovascular Disease and Cognitive Impairment in Monocyte Function/TREM2-Mediated Diabetes/Obesity — Establishment of an Evaluation System

3. Period

   2022-2025

4. Summary

   We integrated clinical studies based on three cohorts—diabetes/obesity, dementia/MCI, and health checkup cohorts—with basic studies using TREM2-deficient mice and microglia to investigate the mechanisms underlying dementia onset and progression associated with diabetes, obesity, and smoking. In the clinical studies, elevated blood sTREM2 levels were associated with cognitive decline in non-obese patients with diabetes, and this association appeared to be strengthened by smoking. We also identified a biomarker profile of diabetic dementia characterized by decreased sTREM2 and increased pTau without a reduction in Aβ42/40. In the health checkup cohort, we previously observed a tendency toward cognitive decline, particularly memory decline, in current smokers, and also showed that metabolically unhealthy non-obese individuals had a higher risk of cognitive decline. Furthermore, among obese individuals, higher blood leptin levels tended to be associated with preserved cognitive function, whereas smokers showed lower blood leptin levels. In the basic studies, we demonstrated the involvement of TREM2 in impaired glucose metabolism and clarified the anti-inflammatory mechanisms of imeglimin. These findings provide a basis for developing early diagnostic and preventive strategies integrating dementia biomarkers, metabolic markers, and smoking-related factors, and may contribute to identifying high-risk groups and personalized interventions for dementia in patients with diabetes and obesity.