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   2019T004

2. Title
   Effects of Smoking on Cerebro-Cardiovascular Complications and Cognitive Function in Patients with Metabolic Syndrome through Targeting the Functions of Monocytes/Microglia

3. Period
   2019-2021

4. Summary

[Background] Triggering receptor expressed on myeloid cells 2 (TREM2) expressed in monocytes and microglia, is reported to be associated with the pathogenesis of dementia. The aim is to elucidate the effects of smoking on cognitive impairment in diabetes and obesity, focusing on M1/M2 phenotypes and TREM2 in monocytes/microglia.

[Methods] We performed clinical studies in multicenter cohort of patients with diabetes and/or obesity, to examine the effects of smoking on cognitive impairment (MMSE) and serum sTREM2. In addition, we examined M1/M2 phenotypes and TREM2 of monocytes/microglia in obese mice, and performed the treatment of nicotine in *ob/ob* mice to elucidate the effects of nicotine on microglia activations and TREM2.

[Results] In clinical studies, cross-sectional analysis showed a significant negative correlation between serum sTREM2 and MMSE in 670 patients with diabetes and/or obesity, but no significant association between smoking and serum sTREM2 or MMSE. Longitudinal analysis revealed that baseline sTREM2 was significantly correlated with the decline of MMSE. Smoking status tended to be associated with the changes in serum sTREM2, although it was not associated with the decline of MMSE. In obese mice, systemic inflammation and upregulation of hippocampal M1 marker (TNFα, IL-6) and TREM2 were observed. The nicotine treatment for 2 weeks in *ob/ob* mice significantly increased the expressions of pro-inflammatory cytokines, iNOS and TREM2 in the hippocampus of *ob/ob* mice.

[Conclusions] This study revealed that serum sTREM2 were significantly associated with cognitive decline in obesity and diabetes. We can also suggest that smoking was associated with increase of serum sTREM2 and TREM2 expression and inflammation of microglia, thereby contributing to cognitive impairment in obesity and diabetes.