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2. Title
   Molecular Mechanism Underlying Effects of Nicotine and Its Related Systemic Factors on Dementia Risk

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4. Summary
Epidemiological studies have shown that cigarette smoking increases the risk of Alzheimer disease (AD). However, inconsistent results have been reported regarding the effects of smoking or nicotine on brain amyloid β (Aβ) deposition. In this study, we found that stimulation of the nicotinic acetylcholine receptor (nAChR) increased Aβ production. nAChR activation triggered the MEK/ERK pathway, which then phosphorylated and stabilized nuclear SP1. Upregulated SP1 acted on two recognition motifs in the BACE1 gene to induce its transcription, resulting in enhanced Aβ production. Mouse brain microdialysis revealed that nAChR agonists increased Aβ levels in the cerebral cortex but caused no delay of Aβ clearance. *In vitro* assays indicated that nicotine inhibited Aβ aggregation. Using $App^{NL\text{-}G\text{-}F}$ mice, we found that chronic nicotine treatment increased the Aβ content but did not visibly change the aggregated Aβ deposition in the brain. Thus, nicotine influences brain Aβ deposition in the opposite direction, thereby increasing Aβ production and inhibiting Aβ aggregation. Previous studies indicate that BACE1 expression and activity are significantly increased in the brains of patients with sporadic AD and mild cognitive impairment. In addition, acquired AD risk factors, including several pesticides, synthetic compounds, and metals, are known to induce BACE1 transcription. Accordingly, BACE1 is possibly involved in the molecular pathogenesis of common sporadic AD, and interventional regulation of BACE1 expression is considered a prime strategy for the prevention of sporadic AD. Finally, we also found that the CRISPR/dCAS9 system is useful for suppression of BACE1 expression and Aβ deposition in the brain.