1. No.
   2022G020

2. Title
   Elucidation of the Effects Caused by Cigarette Smoking on Intestinal Inflammation due to Crohn's Disease-Susceptibility Genes

3. Period
   2022-2024

4. Summary
   Cigarette smoking increases and decreases the sensitivity to Crohn's disease (CD) and ulcerative colitis (UC), respectively. Cigarette smoke induces activation of toll-like receptor 9 (TLR9), activation of which induces production of type I IFNs. Mutation in nucleotide-binding oligomerization domain 2 (NOD2) is the strongest risk factor for CD. In this study, we explored molecular interaction between cigarette smoke-induced TLR9 and NOD2. We found that colonic mucosa of mice displaying dextran sodium sulfate (DSS)-induced colitis and of patients with active CD and UC were characterized by enhanced activation of TLR9-induced type I IFN signaling pathways. Importantly, NOD2 activation negatively regulates TLR9-induced colitogenic type I IFN responses through induction of deubiquitinating enzyme A expression. Thus, these studies partially explain molecular mechanisms regarding the interaction between CD-associated NOD2 mutations and cigarette smoking. Cigarette smoking is a risk factor for obesity. We addressed whether obesity associated with cigarette smoking increases or decreases the sensitivity to DSS colitis. Unexpectedly, obesity protected mice from DSS colitis regardless of NOD2 gene status. Collectively, our data suggest that cigarette smoking increases the sensitivity to CD via activation of TLR9 whereas cigarette smoking-induced obesity protects against UC.