1. No.
   2018G006

2. Title
   Molecular Mechanism Underlying Regulation of Muscular Quality Control by Smoking and Its Application for the Risk Reduction of Cardiovascular Diseases

3. Period
   2018-2022

4. Summary
   While smoking has some positive aspects such as mental relaxation, exposure to high-dose sidestream smoke has harmful effects on the body. We found that exposure to cigarette sidestream smoke (CSS) causes a membrane protein complex between transient receptor potential canonical (TRPC) 3 channel protein and reactive oxygen species (NADPH oxidase 2 (Nox2)), as well as anticancer drug administration and hyperglycemic stress. We revealed that the activation of Nox2-mediated redox signaling through TRPC3-Nox2 interactions leads to myocardial atrophy in rodents. In addition, we identified several compounds that can inhibit TRPC3-Nox2 complex formation from 1,270 approved drugs, and demonstrated that ibudilast, which has the highest inhibitory activity, suppresses myocardial and skeletal muscle atrophy caused by doxorubicin treatment. We noticed that the risk factors for cardiac atrophy are also the risk factors for the aggravation of COVID-19. We found that the expression level of myocardial ACE2 was dependent on TRPC3-Nox2 complex formation due to exposure to CSS. Furthermore, we succeeded in identifying clomipramine, a tricyclic antidepressant, which can also suppress the SARS-CoV-2 entry to host cells, providing a repurposing of this drug for the breakthrough treatment of COVID-19.