1. No.
   2017T004

2. Title
   Molecular role of smoking-induced DNA damage in the pathogenesis of atherosclerosis

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4. Summary
   Smoking is a known risk factor for atherosclerosis. Since DNA damage is increased in peripheral mononuclear cells of smokers compared to nonsmokers and the relationship between DNA damage and atherosclerosis has recently gained attention, this study examined the mechanism by which the smoking causes vascular inflammation and atherosclerosis, focusing on DNA damage and subsequent cellular responses. Cigarette smoke extract (CSE) was prepared and administered on human umbilical vein endothelial cells. CSE increased nuclear DNA double-strand breaks and oxidative DNA damage in the nucleus and mitochondria, causing mitochondrial dysfunction. Mitochondrial dysfunction reduced the amount of cytoplasmic protein of ICAD, an inhibitor of caspase-activated DNase (CAD) and increased nuclear CAD, which fragments nuclear DNA, suggesting that this is one of the mechanism of nuclear DNA double-strand breaks. DNA fragments were accumulated in the cytoplasm by CSE, and real-time PCR analysis revealed that the DNA fragments were derived from mitochondria as well as the nucleus. We next examined whether DNA accumulated in the cytoplasm activates DNA-sensing pathways in the cytosol, and found that CSE increased the production of cGAMP, a second messenger of cGAS (DNA-sensing receptor) signaling and also activated downstream signaling molecules. IL-6 mRNA expression downstream of the cGAS-STING pathway was increased by CSE, and the increase was suppressed by si-cGAS. These results suggest that sustained exposure to CSE induces DNA damage in the nucleus and mitochondria of endothelial cells, resulting in DNA accumulation in the cytosol and inducing chronic inflammation via the cGAS-STING pathway.