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   2019G005

2. Title
   Novel mechanism for DNA damage formation and cancer due to the DNA repair intermediate caused by smoking

3. Period
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4. Summary
   Tobacco smoking has been associated with many types of human cancer. Among the various carcinogenic substances present in tobacco smokes, benzo[a]pyrene is the major cause of lung cancer. Benzo[a]pyrene forms a bulky adduct after metabolic activation. This adduct is removed by nucleotide excision repair (NER). We have previously found that in a quiescent state, NER process induces different types of DNA damage, ssDNAs and DSBs. These secondary DNA lesions activate the members of PI-3-kinase-related kinases such as ATM, DNA-PKcs, and ATR. However, it is unknown whether benzo[a]pyrene also induces secondary DNA damage. Moreover, the mechanism of secondary DNA damage formation and their biological meanings are unclear.

   We revealed that BPDE treatment activates DNA damage response pathways in an NER-dependent manner as well as UV-irradiation. Exo1, the processing enzyme for ssDNA gap intermediates, is also found to be required for BPDE-induced H2AX phosphorylation, suggesting ssDNA gap intermediates would be enlarged. We also showed that the secondary DNA damage indeed causes the mutations and chromosome aberrations. These results suggest that benzo[a]pyrene in tobacco smokes induces secondary DNA damage as a potentially another cause of carcinogenesis. Furthermore, we found that at least two endonucleases are required for the activation of ATM as well as DNA-PKcs. Several endonucleases may act on ssDNA gap intermediates for producing DSBs.