1. No.
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2. Title
   Molecular mechanisms of STAT3 activation by tabacco carcinogen

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4. Summary
   STAT3 acts as a signal transducer of IL-6 family cytokines and transcriptionally activates specific target genes. STAT3 has been shown to act as an oncoprotein. Cigarette smoke contains diverse harmful chemicals including nicotine and benzo[a]pyrene. Some of these chemicals cause cancer. This study aims to clarify the effects of these tobacco-related chemicals on STAT3-related signaling. Cells were stimulated with nicotine or benzo[a]pyrene in the presence or absence of IL-6. Western blot analysis to detect phosphorylation levels of STAT3 in cell lysates was performed. Luciferase activities of cells transfected with STAT-LUC, in which the α2-macroglobulin promoter drives expression of a luciferase reporter gene, were measured. Total RNA was prepared and used for qPCR analyses of gene transcripts. siRNA-mediated gene knockdown was performed. The effect of benzo[a]pyrene on IκB-ζ 3'-UTR-mediated mRNA stability regulation was evaluated by a luciferase reporter. In a lung cancer cell line A549, nicotine but not benzo[a]pyrene augmented IL-6-induced phosphorylation of STAT3. In A549 cells, benzo[a]pyrene enhanced the transcription of IκB-ζ, a transcriptional target of STAT3, without influencing STAT3 phosphorylation. Furthermore, benzo[a]pyrene suppressed Regnase-1’s function by a decrease of Regnase-1 expression, resulting in the increased mRNA stability of IκB-ζ. Benzo[a]pyrene enhanced the expression of IκB-ζ by repressing Regnase-1’s function in A549 cells.