Exposure to nicotine during smoking causes a multitude of metabolic changes that are poorly understood. We quantified and analyzed 198 metabolites in 283 serum samples from the human cohort KORA (Cooperative Health Research in the Region of Augsburg). Multivariate analysis of metabolic profiles revealed that the group of smokers could be clearly differentiated from the groups of former smokers and non-smokers. Moreover, 23 lipid metabolites were identified as nicotine-dependent biomarkers. The levels of these biomarkers are all up-regulated in smokers compared to those in former and non-smokers, except for three acyl-alkyl-phosphatidylcholines (e.g. plasmalogens). Consistently significant results were further found for the ratios of plasmalogens to diacyl-phosphatidylcolines, which are reduced in smokers and regulated by the enzyme alkylglycerone phosphate synthase (alkyl-DHAP) in both ether lipid and glycerophospholipid pathways. Notably, our metabolite profiles are consistent with the strong down-regulation of the gene for alkyl-DHAP (AGPS) in smokers that has been found in a study analyzing gene expression in human lung tissues. Our data suggest that smoking is associated with plasmalogen-deficiency disorders, caused by reduced or lack of activity.
of the peroxisomal enzyme alkyl-DHAP. Our findings provide new insight into the pathophysiology of smoking addiction. Activation of the enzyme alkyl-DHAP by small molecules may provide novel routes for therapy.