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2. Title
   Genomic alterations through EZH2-mediated chromatin modification as polycomb group proteins in early-staged lung cancer in smokers

3. Period
   2019-2023

4. Summary
   In the present study, we tried to elucidate a novel mechanism underlying the development of smoking-related lung cancer associated with enhancer of zeste homolog 2 (EZH2), the Polycomb group protein, using whole-genome sequencing (WGS). Lung cancer, particularly small cell lung cancer, showed high EZH2 expressions, which were inversely correlated with E-cadherin expressions, an epithelial-mesenchymal transition marker, suggesting that EZH2 induces EMT. The comparison of WGS results based on EZH2 expressions identified ubiquitination-related genes in smoking early staged lung cancer and *MUC3A* missense mutations in almost all non-smoking early staged lung cancer. Copy number variant (CNV) analysis demonstrated higher proportions of CNVs in smokers with low EZH2 expressions and non-smokers with high EZH2 expressions. The database for annotation, visualization and integrated discovery (DAVID) for genes with CNVs identified DNA-methylation-related molecules, including S-adenosyl-L-methionine (SAM). Immunohistochemistry for early staged lung cancer demonstrated that EZH2, SAM, and MUC3A expressions were associated with tumor diameter, smoker, and neve-smokers, respectively. Furthermore, both univariate and multivariate analyses showed mutual associations between EZH2 and SAM expressions independently. Each EZH2 and SAM expression group tended to have more prolonged survival, although not statistically significant. As with smokers, each EZH2 and SAM expression group tended to have more prolonged survival, although not statistically significant. The findings of the study suggest that SAM and MUC3A may have contributed to the development of smoking-related and non-smoking-related lung cancer, respectively.