Commentary

Association between hypomethylation of specific smoking-related CpG sites and lung cancer

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DNA hypermethylation and hypomethylation have been reported to play important roles in carcinogenesis (1). However, lung cancer was not known to be related to DNA methylation until Fasanelli *et al*. first reported it (2). DNA methylation is not a rare process and is correlated with normal cell development, differentiation, and a number of key physiologic processes, such as genomic imprinting, X-chromosome inactivation, repression of repetitive elements, and aging (3). Therefore, DNA methylation is not associated with carcinogenesis, but with normal physiological processes.

The correlation between DNA methylation and smoking has recently become well-known (4,5). Fasanelli *et al*. previously reported that a study on 1,000 healthy subjects from the EPIC and Norwegian Women and Cancer (NOWAC) cohorts indicated that smokers had a lower rate of methylation at the AHRR CpG site cg05575921 compared with never-smokers. Furthermore, former smokers had a gradual reversal of methylation rates to the level of never-smokers and that other smoking-related CpG methylation marker sites remained stable for more than 30 years after quitting smoking

In the recent publication, Fasanelli *et al*. aimed to investigate the correlation between smoking-related hypomethylation CpG sites on the AHRR and F2RL3 genes and lung cancer risk based on the NORWAC data (discovery set). The validation sets, which comprised cohorts from the Melbourne Collaborative Cohort Study (MCCS), Northern Sweden Health and Disease Study (NSHDS), and the EPIC Heidelberg Study (EPIC HD), were likewise investigated for the correlation between smoking-related hypomethylation in AHRR and R2RL3 genes with lung cancer risk, after strict adjustment for smoking (2).

In the discovery sets, the odds ratio (OR) for lung cancer was 7.38 for former and current smokers [95% confidence interval (CI), 3.99–15.13]. Furthermore, in a genome-wide methylation analysis to evaluate the importance epigenetic alterations in peripheral blood DNA to lung cancer etiology, the methylation rates of CpGs in the AHRR (OR 0.37; 95% CI, 0.31–0.54; $P=1.36\times10^{-5}$ by Bonferroni) and F2RL (OR 0.40; 95% CI, 0.31–0.56; $P=1.58\times10^{-4}$ by Bonferroni) genes were inversely associated with lung cancer risk. These results implied hypomethylation in lung cancer cases.

Using the validation sets, the lung cancer risk associated with the methylation rates in the following genes showed: (I) AHRR (OR 0.39; 95% CI, 0.24–0.61; $P=2.55\times10^{-5}$ by Bonferroni) and F2RL3 (OR 0.51; 95% CI, 0.35–0.73; $P=4.10\times10^{-4}$ by Bonferroni) for NOWAC data; (II) AHRR (OR 0.62; 95% CI, 0.50–0.78; $P=2.91\times10^{-5}$ by Bonferroni) and F2RL3 (OR 0.70; 95% CI, 0.58–0.85; $P=2.21\times10^{-4}$ by Bonferroni) for MCSS data; (III) AHRR (OR 0.42; 95% CI, 0.30–0.58; $P=2.06\times10^{-7}$ by Bonferroni) and F2RL3 (OR 0.61; 95% CI, 0.47–0.79; $P=1.56\times10^{-4}$ by Bonferroni) for NSHDS data; and (IV) AHRR (OR 0.45; 95% CI, 0.22–0.92; $P=2.95\times10^{-2}$ by Bonferroni) and F2RL3 (OR 0.62; 95% CI, 0.38–1.04; $P=7.02\times10^{-2}$ by Bonferroni) for EPIC-HD data.

Furthermore, in the NOWAC cohort, the authors evaluated the association between smoking cessation and

methylation rates in the AHRR and F2RL3 genes. After smoking cessation, methylation rates increased at 10 years after quitting and appeared to approach the methylation rates in never-smokers. These findings correspondent to the risk of lung cancer decreased substantially after smoking cessation. Mediation analysis showed that hypomethylation of the AHRR and F2RL3 genes were not confounding factors for lung cancer and approximately one-third of the increased risk was induced by tobacco exposure.

Recent study by Fasanelli *et al.* is the first to demonstrate evidence on the association between hypomethylation of specific smoking-related CpG sites and lung cancer risk in prospective cohort studies.

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Footnote

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References

1. Jones PA, Baylin SB. The epigenomics of cancer. Cell 2007;128:683-92.
2. Fasanelli F, Baglietto L, Ponzi E, et al. Hypomethylation of smoking-related genes is associated with future lung cancer in four prospective cohorts. Nat Commun 2015;6:10192.
3. Jaenisch R, Bird A. Epigenetic regulation of gene expression: how the genome integrates intrinsic and environmental signals. Nat Genet 2003;33 Suppl:245-54.
4. Guida F, Sandanger TM, Castagné R, et al. Dynamics of smoking-induced genome-wide methylation changes with time since smoking cessation. Hum Mol Genet 2015;24:2349-59.
5. Zeilinger S, Kühnel B, Klopp N, et al. Tobacco smoking leads to extensive genome-wide changes in DNA methylation. PLoS One 2013;8:e63812.

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