Cholesterol Biosynthesis Is Required for Cell Death in Response to G9A Inhibitor in Lung Cancer (P05-010-19)

Ha Eun Kim, Seo Yoon Choi, and Yoon Jung Park

Ewha Womans University

Objectives: G9A is a eukaryotic histone methyltransferase that contributes to transcriptional silencing of tumor suppressor genes by modulating histone 3 lysine 9 methylation (H3K9m). It has been recently suggested as a promising therapeutic target for breast cancer and neuroblastoma. This study was aimed to investigate the effect of G9A inhibition and its cellular metabolic mechanisms.

Methods: Using Oncomine^{TM}, G9A overexpression in lung cancer was assessed. Cell viability upon treatment of G9A inhibitor (BIX01294, BIX) and siG9A was measured by MTT and IncuCyte^{R} assays. Additionally, apoptosis and autophagy were analyzed through western blots. In order to identify targets, transcriptomes using RNA sequencing was conducted upon BIX treatment. Further functional relevance of targets was validated using Chromatin IP and recovery tests.

Results: BIX-mediated inhibition of G9A reduced cell viability of lung cancer cells via induction of autophagy. Through RNA sequencing, we found that G9A inhibition mainly affected cholesterol biosynthesis pathway. BIX directly induced the expression of *SREBF2* gene, by lowering H3K9me1 and H3K9me2 at the promoter. A cholesterol biosynthesis inhibitor, 25-HC, partially recovered BIX-induced cell death by attenuating autophagy. Our data suggests that cholesterol metabolism can be a potential therapeutic target by G9A inhibition and its induction of autophagic cell death.

Conclusions: Our data suggests that cholesterol metabolism can be a potential therapeutic target by G9A inhibition and its induction of autophagic cell death.

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