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Commentary

# Unique Role for a DNA Methyltransferase Isoform in Lung Cancer

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Aberrant DNA methylation patterns are one of the most studied epigenetic components in cancer development. In certain cancers, altered expression of DNA methyltransferase (DNMT) family members could potentially cause this DNA methylation re-patterning. Specifically, DNMT3B has over thirty different isoforms with varied expression in tissues (Ostler et al. 2007). Recent studies have shown that DNMT3B is responsible for gene body methylation by recognizing the H3K36me3 modification found in gene bodies, especially gene body remethylation after treatment with a DNA methylation inhibitor (5-Aza-CdR) (Baubec et al. 2015; Yang et al. 2014). The methylated gene bodies showed positive correlations with gene expression and, additionally, hypomethylation of gene bodies could lead to down regulation of gene expression (Yang et al. 2014). Non-small cell lung cancer (NSCLC) is one such disease which has overexpression of DNMT3B, including a specific subfamily which lacks an N-terminal domain (ΔDNMT3B) (Wang et al. 2006). In this issue of *EBioMedicine* the work presented by Ma et al. (Ma et al. 2015), provides exciting developments for NSCLC with findings connecting the aberrant DNA methylation patterns during tumorigenesis with the predominantly expressed DNMT3B isoform: *ΔDNMT3B4-del*, a truncated *DNMT3B* isoform lacking exons 21 and/or 22 which contain the catalytic domain.

DNMTs responsible for DNA methylation establishment include: DNMT1, DNMT3A and DNMT3B, as well as DNMT3L (DNA methyltransferase 3-like). DNMT3A and B are the de novo methyltransferases responsible for developing new methylation patterns in the genome as well as maintenance of stable gene silencing related to key biological processes. Generally, tumorigenesis involves DNA hypermethylation at CpG islands (CGI) as well as global DNA hypomethylation (Jones 2012). Although there are many studies that focus on a specific DNMT and their role during development and cancer, there is still a knowledge gap with respect to how the plethora of DNMT isoforms contributes to DNA methylation alterations.

The work by Ma et al. builds on the foundation that primary NSCLC tumors aberrantly express *ΔDNMT3B* from earlier studies with *ΔDNMT3B4* being the most prevalent isoform (Wang et al. 2007). Additionally, *ΔDNMT3B4* can have a truncated methyltransferase domain (*ΔDNMT3B4-del*) that was shown to facilitate DNA methylation changes in transgenic mice similar to early initiating events in tumorigenesis. Interestingly, approximately half of the NSCLC tumors expressed *DNMT3B-del* variants. Aberrant expression of *ΔDNMT3B4-del* could not fully explain the development of NSCLC however; this finding highlights how DNMT3B isoforms could be potential targets for cancer therapy.

The observed DNA methylation changes could be initiation events for tumorigenesis in NSCLC and is interesting because this shows the impact of one aberrantly expressed DNMT isoform in normal tissue. The transgenic mouse experiments by Ma et al., where *ΔDNMT3B4-del* was exogenously introduced to the genome, resulted in lung specific global hypomethylation, a hallmark of aberrant DNA methylation found during early tumorigenesis (Jones and Baylin 2007). The global hypomethylation could be caused by ΔDNMT3B4-del interacting or preventing interactions between other DNMT family members or the loss of its catalytic domain but requires further in depth functional studies. The functions of ΔDNMT3B4-del is not fully understood, nor are the effects of the induced global hypomethylation during tumorigenesis potentially due to its truncated catalytic domain. Nevertheless, the authors used in vitro model systems to study ΔDNMT3B4-del, finding cells became arrested in the G2/M phase, had increased abnormal DNA content and elevated levels of DNA damage response genes consistent with lung tumorigenesis. Furthermore, the authors show that, although ΔDNMT3B4-del on its own is incapable of inducing tumorigenesis, in combination with carcinogen exposure the transgenic animals develop adenocarcinoma formations. Summarizing these results, it suggests the ΔDNMT3B4-del plays a critical role in promoting genomic instability providing the groundwork for tumor initiation and formation in NSCLC.

These intriguing findings raise multiple new questions. Could other DNMT3B isoform family members provide the first necessary methylome changes resulting in tumor initiation? How do DNMT family members interact with each other when one constituent is over produced? Will targeting specific DNMTs be necessary in cancer treatment and prevention? Answering these questions will be pivotal in providing functional characteristics about DNA methyltransferases and their roles in tumorigenesis. Furthermore it will provide a possible new foundation of how specific genes changing the epigenome can influence more drastic changes leading to tumor evolution.

One problem with targeting DNA methylation is the availability of specific inhibitors for DNMTs. Although 5-azacytidine (5-Aza-CR) and 5-aza-2′-deoxycitidine (5-Aza-CdR) are FDA approved for treatment of myeloid malignances, they lead to the trapping and degradation of DNMTs resulting in passive DNA methylation loss after replication (Ghoshal et al. 2005; Kuo et al. 2007). The best type of therapy would

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be one that targets specific proteins like ΔDNMT3B4-del to restore normal expression of the DNMT family instead of targeting all constitutes and possibly causing off target effects. The identification of drugs that could specifically target one DNA methyltransferase will be an interesting field of research with a potential therapeutic impact on various diseases.

## Conflicts of Interest

The authors declare no conflicts of interest.

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