

# Does epigenetic regulation plays a critical role in acute lung injury?

## Introduction

Acute lung injury and the acute respiratory distress syndrome (ALI/ARDS) are severe respiratory conditions that remain as significant public health concerns, with ARDS mortality as high as 30-40%.<sup>1-4</sup> ALI/ARDS is primarily caused by pneumonia, it is also caused by a variety of other clinical disorders including pulmonary or non-pulmonary sepsis, major trauma, inhalation injury such as aspiration of gastric or oropharyngeal contents, drug over use, and blood products. ALI/ARDS features with widespread damage to the various types of cells in the lung and the structures of alveolar capillary membrane. The pathogenesis of ALI/ARDS involves three major overlapping phases, inflammatory phase, proliferative phase, and fibrotic phase. Pathological stimuli cause cytokine secretion and inflammatory cell infiltration to the injured site followed by the activation of pro-inflammatory mediator cascades. Many pro-inflammatory mediators including pro-inflammatory cytokines and chemokines are involved in the pathogenesis of ALI/ARDS. Increased amount of TNF- $\alpha$ , IL-1 $\beta$ , IL-6, and IL-8 are reported in BAL fluid and plasma of patients with ARDS, orchestrating with the low levels of inflammatory inhibitors such as IL-1 $\alpha$ , IL-4, and IL-10. Inflammation in ALI/ARDS results in cell death, alveolar epithelial membrane leaking, and dysfunction of surfactant secretion. The followed injury repair mediates fibro proliferative response further impaired lung function.

Epigenetic is a rapidly emerging field exploring the processes where gene activity is changed without alteration of the DNA sequence.<sup>5</sup> Epigenetic regulation happens in different layers, it occurs at the chromatin, histone, DNA, RNA, or mRNA levels. Epigenetic studies are well documented at the tone protein levels. Histone proteins are nuclear structural proteins including histone H1, H<sub>2</sub>A, H<sub>2</sub>B, H3 and H4. Among them, two sets of H<sub>2</sub>A, H<sub>2</sub>B, H3 and H4 form a core structure, the protein core is surrounded by ~147 base-pair of genomic DNA to form the basic chromatin structural unit nucleosome. Histone H1 binds to the genomic DNA lined between nucleosomes. Most importantly, his tone NH<sub>2</sub>-terminal tails are not buried into the nucleosome core structure that makes them easy to be accessed by a vast range of post-translational modifiers. Furthermore, the amino acid composition of the primary structure of the his tone NH<sub>2</sub>-terminal tails is vulnerable to a variety of post-translational modifications. Posttranslational modifiers catalyze enzymatic processes that covalently attach various chemical groups to the appropriate amino acid residues in NH<sub>2</sub>-terminal tails. Some of these chemical groups are well studied small chemicals that include the acetyl, methyl, or phosphorus groups. Some of them are small proteins such as ubiquity, or even long chain fatty acid palmitoyl group.<sup>6</sup>

Modification of histone NH<sub>2</sub>-terminal tails by different groups results in the loose or condensation of the chromatin architecture to form heterochromatin or euchromatin that subsequently alters gene promoter accessibility and activity, resulting in transcription activation or repression. Therefore, histone modifiers compromise a variety of epigenetic marks to regulate transcription activity.<sup>7,8</sup> In general, histone acetyltransferases specifically catalyze addition of an acetyl group to the lysine residue of the histone free tail that in general

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loses the chromatin structure to form euchromatin and activates transcription activity. On the other hand, histone methyltransferases attach mono-methyl, di-methyl, or tri-methyl group to the lysine or arginine residues that in general condenses the chromatin to form heterochromatin resulting in transcription repression. It worth to note that within one histone, a range of different modifications happen simultaneously in the susceptible residues. These modifications are temporary and dynamic, can be erased by enzymatic activities that the attached chemical groups are removable by the corresponding enzymes such as deacetylase or demethylase. Furthermore, histone modification interplays with each other. For example, lysine residues are the target of acetylation, methylation, and ubiquitination. One type of histone modification impairs on other types of modification by competition or synergizes the other types of modification for the modified residue may be the pre-request to facilitate another modification enzyme binding. Coordination and orchestration of these epigenetic marks lead to activation or repression of gene transcription.

Ample knowledge has emerged that epigenetics play a central roles in lung cancer, COPD, asthma, iodic pulmonary fibrosis, and pulmonary hypertension.<sup>9</sup> The alteration of epigenetic marks has been well documented in the process of inflammation. Epigenetic alterations have been reported in acute kidney injury, in animal models of sepsis, and in critically ill subjects.<sup>10</sup> Cytokine secretion and inflammatory cell infiltration activity are highly governed by epigenetic regulation in other models.<sup>11</sup> In addition, immune cells such as T-cells are subjected to epigenetic regulation.<sup>12,13</sup> Recent studies, including our own, indicate that histone posttranslational modification is modulated by bacterial infection, and regulates inflammatory gene expression and cytokine secretion.<sup>14,15</sup> While genomic studies have been applied to the pathogenesis of ALI/ARDS, the role of epigenetics in ALI/ARDS pathophysiology remains relatively unexplored. Few studies have investigated epigenetics in ALI, and our understanding in epigenetic regulation in this disorder is very limited.

Epigenetic regulation governs gene transcription, suggesting that epigenetic regulation may be critical to the pro-inflammatory cytokine surge after the pathological stimuli. It has been reported that lipopolysaccharide (LPS) regulates the protein stability of Acyl-

CoA: lysophosphatidylcholine acyltransferase-1 (Lpcat1).<sup>16,17</sup> Lpcat1 is highly expressed in lung epithelial cells and acts as a surfactant synthetic enzyme. Interestingly, LPS treatment and bacterial infection triggers Lpcat1 to migrate into the nucleus. Nuclear Lpcat1 catalyzes a novel histone modification referred to as histone O-palmitoylation that regulates pro-inflammatory gene transcription.<sup>6,15</sup> LPS treatment also results in Histone acetyltransferases binding to origin recognition complex (HBO1) degradation.<sup>18</sup> HBO1 mediated acetylation initiates DNA replication thus modulates cell cycle progression and proliferation through epigenetic mechanisms. As a matter of fact, the protein levels of a diverse of histone modification enzymes are changed after treatment with LPS or infected with bacterial pathogens in lung epithelial cells (unpublished observation). Our recent observation suggested that LPS treatment or bacterial infection may modulate histone modifier enzymatic activity by controlling the molecule homodimerization.<sup>19</sup>

Recent observations from Natajavan's group indicate that LPS treatment epigenetically regulates lung injury via Sphingosine-1-Phosphate (S1P) mediated pathway in lung endothelial cells.<sup>20</sup> They observed that down regulation of Sphingosine-1-Phosphatylase (S1PL) with siRNA blocked LPS-induced IL-6 secretion and partially blocked LPS-induced acetylating of histone H3 and Histone H4 with decreased HBO1 and IL-6 promoter activity and potentiated histone deacetylase (HDAC) 5 expression. They also found that blockade of HDAC activity with histone deacetylase inhibitor Trichostatin A triggered LPS-induced IL-6 secretion while histone Acetyltransferase (HAT) inhibitor Anacardic acid reduced IL-6 production. A more comprehensive study with a mixed deactivation and methylation inhibitors attenuated LPS induced lung injury in mouse models.<sup>20,21</sup> LPS induced acute lung injury was treated with 5-Aza 2-deoxycytidine (Aza) a DNA methyl transferase inhibitor and TSA. TSA+Aza-treatment promoted animal survival and attenuated histopathological damages. Anti-inflammatory cytokine IL-10 levels in blood were noted to be increased.

## Conclusion

The epigenetic study in acute lung injury is still at its infancy. The overall profile of the changes of epigenetic markers in acute lung injury is not yet fully studied. Secondly, the major players among epigenetic markers in acute lung injury are waiting to be clarified. Thirdly, given the fact that gene transcription is the product of a coordinated action of a variety of epigenetic markers, understanding the interplay among these epigenetic markers in acute lung injury is of particular importance. In addition, epigenetic changes in acute lung injury are complicated that may vary depending on the progression of the pathogenesis of the injury. Finally, it is interesting to know what is the feasible pharmacotherapeutic target (s) that may contribute to the control of acute lung injury. The application of histone modifier inhibitors in treatment of acute lung injury needs further test and validation *in vitro* and *in vivo*.

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## Conflict of interest

The author declares no conflict of interest.

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