CFTR Modulates Acute Lung Injury: Evidence from A Genetic Association Study

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Cystic fibrosis transmembrane conductance regulator (CFTR) is a well-known component since it was found that some specific mutations of CFTR gene can cause cystic fibrosis and congenital bilateral absence of vas deferens (1, 2). Interestingly, more and more studies demonstrate that CFTR also modulates acute lung injury (ALI) (3-8), a devastating inflammatory lung syndrome characterized by diffuse alveolar infiltration, hypoxemia, respiratory failure and even death due to multiorgan dysfunction. Every year in the USA alone there are 150,000-200,000 ALI cases with 34 to 58% mortality (9).

How does CFTR modulate ALI? CFTR plays an active role in both impaired lung edema clearance and abnormal lung inflammation, two of the hallmark features for the patients with ALI. As an ABC transporter-class ion channel, CFTR transports chloride and thiocyanate ions across epithelial cell membranes, and thus regulates lung alveolar fluid transport and epithelial sodium channels (8). In terms of lung inflammation, CFTR is a negative regulator of NF-κB mediated inflammatory responses. Expression of wild-type CFTR has been shown to suppress NF-κB driven inflammatory signaling (5). Dysfunctional CFTR in the airways is associated with elevated levels of NF-κB mediated IL-8 signaling leading to neutrophil chemotaxis and chronic lung inflammation in cystic fibrosis (4). Furthermore, lack of functional CFTR in neutrophils can promote LPS-induced acute lung injury (6).

Theoretically, genetic mutations of CFTR may affect CFTR activity, and further influence its functions in lung injuries. Currently, up to 1700 CFTR genetic mutations have been identified. Some of them can change CFTR functions, and could modulate ALI. Dr. Mary Dahmer and colleagues in this issue of Critical Care Medicine showed that high risk (TG)m(T)n alleles located in intron 8 of the CFTR gene were significantly associated with the need for mechanical ventilation and ALI development in African American children with community-acquired pneumonia (CAP), which is one of the common

causes of ALI. However, this association was not found in Caucasian children with ALI. The same high risk (TG)m(T)n alleles are assumed to have the same effect on CFTR RNA splicing in African Americans and Caucasians. Why were high risk (TG)m(T)n alleles of the CFTR gene significantly associated with ALI in African Americans, but not in Caucasians? One possibility is that the intracellular levels of specific regulatory splicing factors could be different between African Americans and Caucasians (8). There may be two other possible answers: one is that high risk (TG)m(T)n alleles may have significant linkage-disequlibrium with other single nucleotide polymorphisms (SNPs), especially in CFTR coding regions including the M470V locus within exon 10. These SNPs may differ between the two races and thus differentially affect CFTR activity. The dense CFTR SNP genotyping in larger African American and Caucasian CAP cohorts is necessary to identify specific and differential CFTR haplotypes with high risk (TG)m(T)n alleles. These specific haplotypes may have distinct effects on the NF-κB signaling pathway and thus induce differential inflammatory responses in African American and Caucasian patients with CAP. The other possible explanation is variability in the genetic structure and composition between African Americans and Caucasians, which may have differential inflammatory responses under pathophysiological conditions. A SNP (rs2814778) from Duffy is a case in point. Duffy was originally defined as a malaria parasite receptor expressed in human red blood cells (RBCs) and endothelial cells. In general, people of African descent are more likely to be Duffy negative than Caucasians due to historical evolutionary advantage when living in malaria prone environment. Interestingly, Duffy is also called Duffy antigen receptor for chemokine (DARC), with which RBCs seem to be a reservoir for CC and CXC chemokines including IL8 (10). Theoretically, Duffy negative people with pneumonia are likely to produce more neutrophil-specific chemokines, have more transendothelial neutrophils migrate to the inflammation sites, and thus exaggerate lung injury. An epidemiological study (10) has shown that the DARC rs2814778 SNP is associated with worse outcomes among African Americans with ALI. In fact, it is also reported that African American ethnicity is an independent risk factor for exaggerated inflammation, oxidative stress and cardiovascular diseases (11, 12).

To further understand the role of CFTR genetic polymorphisms in ALI, we need large-scale CFTR genotyping in larger cohorts of African American and Caucasian patients with ALI. In addition, a clinical trial could be designed to isolate peripheral blood mononuclear cells (PBMCs) from the people with different CFTR haplotypes. An in vitro stimulation with heat-inactivated *Streptococcus pneumoniae* could then be conducted to measure cytokines and chemokines in the cell culture media and cells. African Americans with specific CFTR haplotypes, including high risk (TG)m(T)n alleles, may produce more inflammatory responses than Caucasians.

A better understanding of how CFTR genetic polymorphisms influence ALI is important for the development of novel and personalized therapies for the patients with ALI according to their specific CFTR haplotypes.

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