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Editorial

The Variations of MER Receptor Tyrosine Kinase and the Development of Chronic Obstructive Pulmonary Disease

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▸ See the article "Association between Genetic Variations of *MERTK* and Chronic Obstructive Pulmonary Disease in Koreans" in volume 33, e56.

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Chronic obstructive pulmonary disease (COPD) is an acquired disease and is caused by significant exposure to noxious particles and gases, mainly by smoking. Meanwhile, it is also apparent that there are susceptible smokers who are prone to develop COPD and "non-susceptible" smokers who never develop clinically significant airflow limitation. In fact, only a small proportion (about 15%–50%) of smokers suffer from the clinically relevant disease,[1] which suggests that genetic susceptibility may also affect the development of the disease. In the early 2000s, a cohort study showed the significant risk of airflow limitation in smoking siblings of patients with severe COPD,[2] which supports the importance of genetic susceptibility in the development of COPD. At that time, however, the causable genetic variations were not evident except alpha-1 anti-trypsin and some single nucleotide polymorphisms. After a decade, with the progression in methodology, the genome wide association study elucidated many susceptible genes including cholinergic nicotine receptor alpha 3/5 (*CHRNA3/5*), iron regulatory binding protein 2 (*IREB2*), hedgehog-interacting protein (*HHIP*), family with sequence similarity 13, member A (*FAM13A*), and advanced glycosylation end product-specific receptor (*AGER*),[3] which have been validated in various cohorts. Despite these progressions in genetics, our understanding of the genetic variations in COPD is still insufficient and more studies are required to fully understand their role in the pathogenesis of COPD.

MER receptor tyrosine kinase (MERTK) is a member of Tyro3/Axl/MER (TAM) receptor kinase family and is known to play a pivotal role in the engulfment of the apoptotic cells by phagocytes, called "efferocytosis".[4] The activation of MERTK enhances the clearance of the apoptotic cells and inhibits the consequent inflammatory process which is caused by the release of 'damage associated molecular patterns (DAMPs)' from apoptotic cells.[5] Considering reports that the impaired efferocytosis and the accumulation of apoptotic cells are observed in the lungs of patients with COPD,[4,5] it is meaningful to investigate the possible link between the variations of MERTK and the development of the disease.

Kim and Lee[3] investigated the variations of *MERTK* and compared the frequency of each variation or haplotype between patients with COPD and healthy controls. Although the frequencies were comparable between the groups, it is worthy of note that the study raised the issue of undiscovered variations of *MERTK*. The authors found 10 variations of *MERTK*

including 4 variations that have never been reported previously. Given the small number of subjects from a homogeneous ethnic background in this study, there might be more *MERTK* variants that have not yet been discovered. Large-scale following studies are required to identify undiscovered variations of *MERTK* that might contribute to the development of COPD. The authors also performed in vitro assays, but none of the variations including 3 promoter-, 4 nonsynonymous-, and 3 synonymous-variations showed an effect on the promoter activity or the expression of MERTK. However, it needs to be interpreted with caution because the function of proteins such as enzymes, transporters, and receptors can be impaired even when their expression remains unaffected.[6] Moreover, considering that the TAM receptor tyrosine kinase family, which encompasses MERTK, requires the bridging molecules such as protein S or growth-arrest-specific gene 6 (Gas6) for activation,[5] the variations that affect binding sites for the bridging molecules may cause impairment of the receptor function without obvious influence on the genetic expressions. Therefore, to clarify the effect of the *MERTK* variants found in this study, functional evaluation should be performed in following studies.

In summary, despite of the recent progress in genetics, the role of genetic variations in the pathogenesis of COPD is still unclear. The variations of *MERTK* which play an important role in the clearance of apoptotic cells and in the inhibition of inflammation might contribute to the development of COPD. Large-scale functional studies should be conducted to identify the candidate genetic variations and their role in the pathogenesis of COPD.

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