Fatum Inexorabile: Do Monocytes Predict the Fate of Interstitial Lung Abnormalities?

Recently, the Fleischner society defined the incidental finding of nondependent radiological abnormalities in asymptomatic individuals in whom interstitial lung disease (ILD) is not suspected as interstitial lung abnormalities (ILAs). Studies suggest that ILAs can be found in up to 10% of older adults aged 60 years and older (1). Risk factors for the development of ILAs include age, smoking, lifetime exposure to air pollution, and distinct comorbidities such as gastroesophageal reflux (2–4). Genetic polymorphisms including the MUC5B promoter variant rs35705950 (5) have also been described as risk factors. The finding of ILAs carries an appreciable risk (up to 75% in some studies) of progression into clinically overt ILD, with the associated poor outcomes that this group of conditions convey (6). Risk factors for ILA progression match the risk factors for ILA (e.g., age, smoking, and genetic polymorphisms); in addition, radiological pattern is also a predictor of progression (reviewed in Reference 2). Although some biomarkers have been reported to be related to the presence of ILAs, such as SP-D, matrix metalloproteases (3), or aging-related biomarkers such as growth differentiation factor-15 (7), no biomarker, to our knowledge, has yet been described to predict progression of ILAs. A simple, clinic-ready biomarker predictive of ILA progression would be of huge benefit in aiding risk stratification and identification of individuals at greatest risk of progression for whom close surveillance, invasive diagnostic assessment, or early treatment might be appropriate.

Recent progress has been made in establishing potential candidate biomarkers across various ILDs, particularly idiopathic pulmonary fibrosis (IPF) (8). Among these, absolute blood monocyte count seems to be one of the most promising; in individuals with IPF, monocyte counts are associated with risk of disease progression and death. Importantly, when it comes to clinical translation of this finding, monocyte count is already easily and cheaply accessible to clinicians as part of a complete blood count (9–11). With this in mind, in this issue of the *Journal*, Kim and colleagues (pp. 795–805) examined the role of monocytes as potential predictors of the occurrence of ILAs and of subsequent ILA progression (12). For this, the authors analyzed participants in whom monocyte counts and chest computed tomography imaging were available, from four large cohorts in which the clinical significance of ILAs have been described before: MESA (Multi-Ethnic Study of Atherosclerosis), AGES-Reykjavik (Age/Gene Environment Susceptibility Study), COPDGene (Genetic Epidemiology of COPD), and ECLIPSE (Evaluation of COPD Longitudinally to Identify Predictive Surrogate Endpoints). Kim and colleagues found that higher blood monocyte counts correlated with the occurrence and progression of ILAs and with lower FVC. The association of other leukocyte subsets with ILAs was less consistent. A number of conclusions can be drawn from the data presented. The data reported are methodologically sound, with the authors having made strenuous efforts to incorporate multiple well-described validation cohorts. The authors highlight a mechanistic role for monocytes in ILA progression, having demonstrated monocyte activation in one of the cohorts. Furthermore, these data lend further support to recent reports on the role of monocytes as predictive biomarkers in IPF (9–11). For these efforts and their important findings, the investigators should be applauded.

The study does, however, leave several open questions. Although Kim and colleagues did not find a clear effect of smoking status, sex, or age on the relationship between monocytes and risk of ILA or ILA progression, all four cohorts comprised elderly individuals enriched for relevant risk factors for ILAs/ILDs. Furthermore, the majority of participants in the four cohorts were White; only one cohort included a significant Asian population. The composition of the cohorts could therefore have biased the reported outcomes, and this leaves open the question of whether monocytes are valuable biomarkers for early identification of ILAs in the general population rather than just in preselected high-risk populations. It also remains to be shown whether monocyte counts provide additional information on risk in other selected populations such as non-White ethnic groups or younger patients or those without a smoking history.

There remains a major unmet need for simple, minimally invasive biomarkers that provide information regarding risk of development and/or progression of ILD and that measure treatment response in individuals at high risk of developing ILD (e.g., those with systemic autoimmune disease such as systemic sclerosis [13] or those with a family history of ILD). The data by Kim and colleagues support the further analysis of monocytes in this context. However, there are also some missed opportunities. The role played by genetic polymorphisms in the development of ILD and pulmonary fibrosis is increasingly understood, and genotyping is increasingly being used to inform risk predictions in healthy individuals. Polymorphisms related to IPF have previously been shown to predict risk of ILA in several of the cohorts included in the current study; however, the additive value of integrating genetic and monocyte count data was not explored in the current study. Another challenge presented by the work of Kim and colleagues is the translation of their findings into clinical practice. Unlike many putative biomarkers reported in the ILD literature, monocyte count is readily available to clinicians in day-to-day practice. Although the authors clearly demonstrate that rising monocyte counts are associated with risk of ILA and

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illustrate this by showing differences in ILA occurrence by tertile of monocyte count, they fail to identify a reliable threshold of monocyte count above which clinicians might initiate a more careful search for ILAs. In the absence of a clear threshold or a simplified algorithm, the data presented lack immediate clinical utility.

Taken together, the work presented by Kim and colleagues adds support to the notion that monocytes have the potential to be important biomarkers for aiding detection of individuals with ILAs and early ILD and for predicting progression of ILAs and other fibrotic lung diseases. Furthermore, the association between monocytes and ILAs/ILD hints at an important mechanistic role for these cells in the development of fibrotic lung disease. However, considerable further work is needed to translate these findings into clinical practice and to establish whether these cells might be potential therapeutic targets for preventing progression of ILAs to clinically overt ILD. ■

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