Can YKL-40 be used as a biomarker and therapeutic target for adult asthma?

To the Editor:

We read with great interest the article by Gomez *et al.* [1] on the role of YKL-40 in the different asthma phenotypes in adults. They found that the serum and sputum YKL-40 levels in C3 and C4 groups were significantly higher than those in C1 and C2 groups by clustering analyses, and the increased serum YKL-40 levels were associated with severe exacerbations and worse airflow obstruction in patients with asthma. Moreover, the paper suggested that YKL-40 may be a non-type 2 (T2) asthma biomarker. Here, we take the opportunity to report a meta-analysis and systematic review that we recently performed, and to discuss further whether YKL-40 can be used as a potential biomarker and therapeutic target for adult asthma.

In our study, we carried out a systematic literature search in several databases and on commercial Internet search engines to identify studies published in English. A total of 16 eligible articles were included in our study. Firstly, the overall meta-analysis results indicated that serum YKL-40 levels in patients with asthma were significantly higher than those in healthy controls (standardised mean difference (SMD) 0.66, 95% CI 0.43–0.90; p<0.001). In a subgroup analysis of disease status, the results demonstrated that serum YKL-40 levels were statistically different between the exacerbation group and the stable group in patients with asthma (SMD 0.75, 95% CI 0.08–1.42; p<0.001). We also performed a subgroup analysis by severity of disease in asthmatic patients, and found that the serum YKL-40 levels were statistically different between the severe asthma group and the nonsevere asthma group (SMD 0.57, 95% CI 0.35–0.78; p<0.001). Secondly, our study further indicated that the levels of sputum YKL-40 in patients with asthma were significantly higher than those in healthy controls (SMD 0.48, 95% CI 0.09–0.86; p=0.015) by pooled analysis of four original studies. Finally, and most interestingly, we analysed the correlations between serum YKL-40 levels and clinical parameters in asthmatic patients. The meta-analysis results suggested that elevated serum YKL-40 levels were negatively correlated with lung function (forced expiratory volume in 1 s (FEV_1): pooled r=−0.25, Z=−0.26, p=0.027; FEV_1 % predicted: pooled r=−0.28, Z=−0.29, p<0.001), while they were not correlated with blood IgE concentrations (pooled r=0.05, Z=0.05, p=0.534) or blood eosinophil counts (pooled r=0.20, Z=0.20, p=0.123).

Our conclusions were consistent with those of Gomez *et al.* [1] but we want to highlight some more important issues here. To begin with, there were limited studies reporting whether the serum YKL-40 levels in patients with asthma would change after appropriate treatment. Lai *et al.* [2] found serum YKL-40 levels to be reduced in asthmatic patients after inhaled corticosteroid treatment. However, another study suggested that YKL-40 levels did not change significantly after 2 weeks of corticosteroid therapy in patients with asthma [3]. Moreover, previous studies, along with the article by Gomez *et al.* [1], were mainly of a case–control or cross-sectional nature. Just as Gomez *et al.* [1] mentioned, further prospective studies were needed to better explore the interaction of YKL-40 with asthma. Secondly, the findings of Gomez *et al.* [1] demonstrated that the YKL-40 could be used as a non-T2 inflammation biomarker, while one previous study showed that the YKL-40 was involved in the initiation and effector phases of T2 inflammation in animal knockout models [4]. In addition, some studies found that YKL-40 levels were increased not only in asthma but also in other chronic respiratory inflammatory disease, including chronic obstructive pulmonary disease (COPD) and asthma–COPD overlap syndrome [3, 5]. These studies indicated that the YKL-40 might be involved in these diseases with different mechanisms. Thirdly, Gomez *et al.* [1] found that the clusters with high serum YKL-40 demonstrated high sputum YKL-40 protein levels. However, Hinks *et al.* [6] suggested that there was only moderate correlation between the sputum and serum YKL-40 values. Another study showed that with high-dose allergen challenge, sputum YKL-40

@ERSpublications
The YKL-40 may be used as a potential biomarker and therapeutic target for adult asthma http://ow.ly/fgAw30h99Nt

Cite this article as: Tong X, Wang D, Liu S, *et al.* Can YKL-40 be used as a biomarker and therapeutic target for adult asthma? *Eur Respir J* 2018; 51: 1702194 [https://doi.org/10.1183/13993003.02194-2017].

levels increased significantly while plasma YKL-40 did not change significantly [3]. Until now, it is not clear whether the sputum YKL-40 is correlated with the serum YKL-40, as well as the correlation between the sputum YKL-40 and clinical characteristics. Finally, a series of studies have found that the genetic variants in the *CHI3L1* gene were associated with asthma, and serum YKL-40 levels were strongly affected by variations in the *CHI3L1* gene [3, 7]. Recently, an interesting study found that the *CHI3L1* genetic variation could influence blood YKL-40 levels by partly mediating its gene's methylation profiles [8]. Therefore, we think that YKL-40 could be used as a potential target for treatment.

Taken together, we think that YKL-40 is not only potentially useful for identification of individuals with severe or exacerbation-prone asthma, but also a potential therapeutic target. Further research is needed to better evaluate the association between YKL-40 and asthma, and to assess whether monitoring its levels could optimise its medical management and facilitate successful clinical decisions.

Xiang Tong[1,3], Dongguang Wang[1,3], Sitong Liu[1], Yao Ma[2] and Hong Fan[1]
[1]Dept of Respiratory and Critical Care Medicine, West China Hospital/West China School of Medicine, Sichuan University, Chengdu, China. [2]The Center of Gerontology and Geriatrics, West China Hospital/West China School of Medicine, Sichuan University, Chengdu, China. [3]These authors contributed equally to this work.

Correspondence: Hong Fan, Dept of Respiratory and Critical Care Medicine, West China Hospital/West China School of Medicine, Sichuan University, Guoxuexiang 37, Chengdu, Sichuan, 610041, China. E-mail: fanhongfan@qq.com

Received: Oct 25 2017 | Accepted: Oct 27 2017

Conflict of interest: None declared.

References

1 Gomez JL, Yan X, Holm CT, *et al.* Characterisation of asthma subgroups associated with circulating YKL-40 levels. *Eur Respir J* 2017; 50: 1700800.
2 Lai T, Chen M, Deng Z, *et al.* YKL-40 is correlated with FEV1 and the asthma control test (ACT) in asthmatic patients: influence of treatment. *BMC Pulm Med* 2015; 15: 1.
3 James AJ, Reinius LE, Verhoek M, *et al.* Increased YKL-40 and chitotriosidase in asthma and chronic obstructive pulmonary disease. *Am J Respir Crit Care Med* 2016; 193: 131–142.
4 Lee CG, Hartl D, Lee GR, *et al.* Role of breast regression protein 39 (BRP-39)/chitinase 3-like-1 in Th2 and IL-13-induced tissue responses and apoptosis. *J Exp Med* 2009; 206: 1149–1166.
5 Gao J, Iwamoto H, Koskela J, *et al.* Characterization of sputum biomarkers for asthma–COPD overlap syndrome. *Int J Chron Obstruct Pulmon Dis* 2016; 11: 2457–2465.
6 Hinks TS, Brown T, Lau LC, *et al.* Multidimensional endotyping in patients with severe asthma reveals inflammatory heterogeneity in matrix metalloproteinases and chitinase 3-like protein 1. *J Allergy Clin Immunol* 2016; 138: 61–75.
7 Gomez JL, Crisafi GM, Holm CT, *et al.* Genetic variation in chitinase 3-like 1 (*CHI3L1*) contributes to asthma severity and airway expression of YKL-40. *J Allergy Clin Immunol* 2015; 136: 51–58.e10.
8 Guerra S, Melen E, Sunyer J, *et al.* Genetic and epigenetic regulation of YKL-40 in childhood. *J Allergy Clin Immunol* 2017; in press [https://doi.org/10.1016/j.jaci.2017.06.030].