Novel Mechanisms and Further Refined Phenotypes of Elderly Asthma

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Elderly asthma (EA) usually refers to asthma in people aged 65 years and over. Aging is accompanied with changes in respiratory physiology, and immunology (Figure 1). There are specific issues associated with the management of EA, such as adherence to therapy, increased side effects, and decreased responsiveness to medication. However, phenotypes of EA have not been clearly delineated so far. This presentation aims to characterize the phenotype of EA.

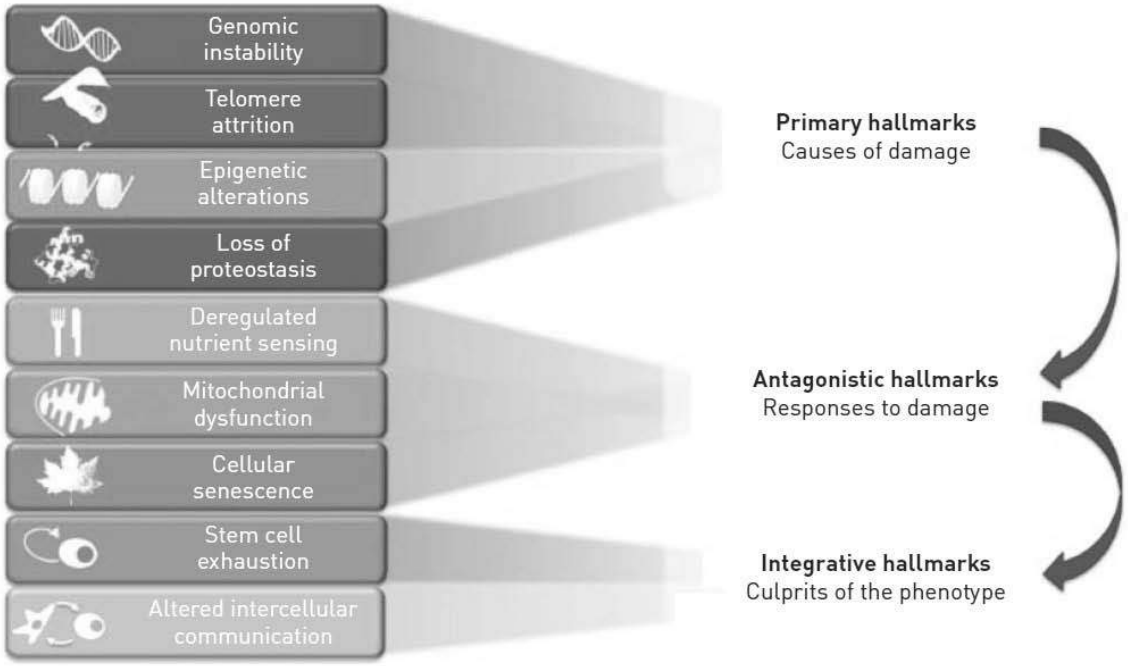

Figure 1. Hallmarks of ageing categorized into primary causes of cellular damage (top), compensatory or antagonistic responses (middle), and those ultimately responsible for the functional decline associated with ageing (bottom). Compensatory responses initially mitigate damage, but eventually, if chronic or exacerbated, they may become deleterious themselves [from Ref. 1].

Elderly and non-elderly asthma: similar outside but dissimilar inside

Currently, we have no clinical measurements specific to EA when we assess, diagnose and treat patients with EA. However, we reported that EA and non-elderly asthma (NEA) have different compositional patterns underlying their clinical variables by performing principal component analysis using 434 patients with EA and 1,633 patients with NEA (Figure 2).

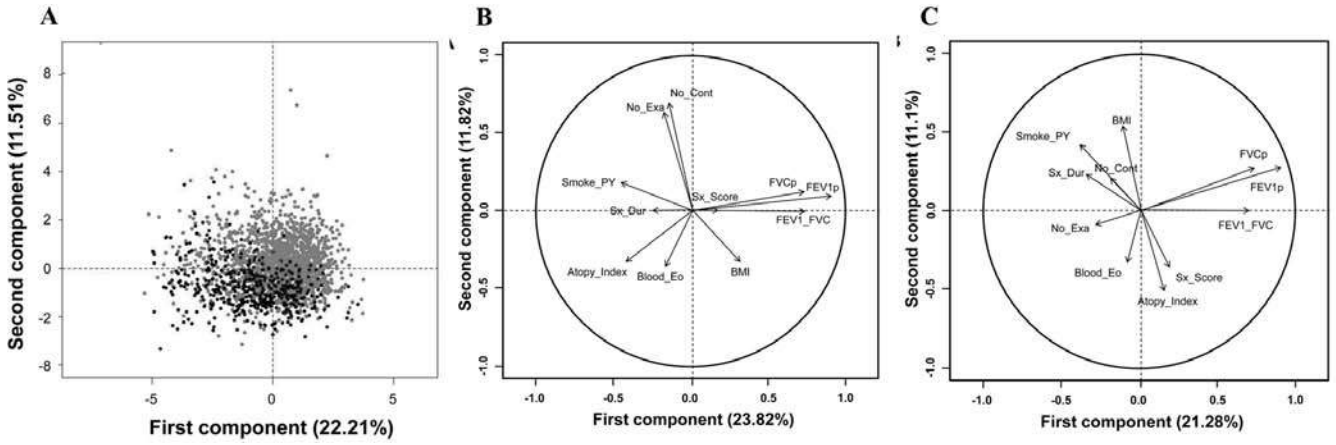

Figure 2. (A) PCA of all asthmatics showed that EA and NEA were distinctly separated by the first and second principal component on the plot of individual asthmatics according to their scores. A plot of individual asthmatics according to their scores of the first and second principal component. Black dots represent NA and grey dots represent non-elderly asthma, (B) A circle of correlations and loadings of clinical variables for the first and second principal component for EA, (C) A circle of correlations and loadings of clinical variables for the first and second principal component for NEA [Abbreviations are: FVCp, predicted % forced vital capacity; FEV1p, predicted % of FEV1; FEV1_FVC, post-bronchodilator FEV1/FVC ratio; Sx_Score, symptom score; Atopy_Index, atopy index; Blood_Eo, number of eosinophils in peripheral blood; No_Exa, number of exacerbation; No_Cont, number of controller medications; Sx_Dur, symptom duration; Smoke_PY, smoking pack year; BMI, body mass index] [from Ref. 2].

Recent findings that serum IL-33 and IL-31 levels were significantly lower in EA, while no differences were found in the serum level of IL-8, eotaxin-2, TGF-β1 or periostin compared to NEA suggest that age-related changes of epithelial cell-derived cytokines may affect clinical phenotypes and severity of elderly asthma. In addition, based on the observation from a prospective cohort of EA consisted of 1,382 patients, we found that fixed airway obstruction was the most important factor predicting acute exacerbations in patients with EA, whereas, in patients with NEA, eosinophil count was the strongest predictor of exacerbation (Figure 3). It suggests that different strategies are needed to prevent exacerbation in EA versus NEA.

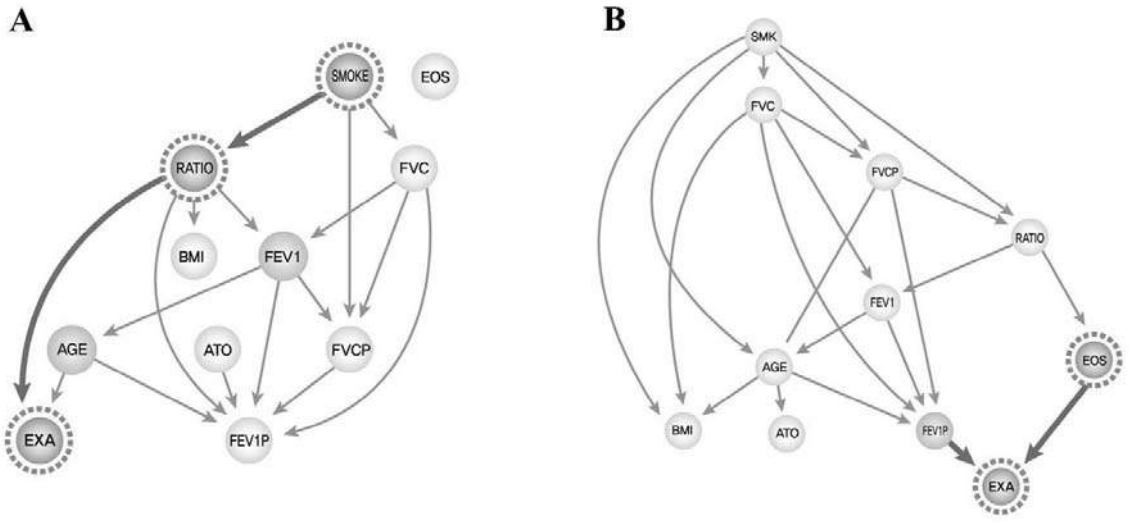

Figure 3. (A) Bayesian network analysis showed that FEV1/FVC ratio and age were directly connected to acute exacerbation events in EA, (B) In contrast, FEV1% predicted and blood eosinophil count were directly connected to acute exacerbation in NEA. ([Abbreviations are: EXA, exacerbation; ATO, atopy; BMI, body mass index; SMOKE, 10 pack year smoking; Ratio, FEV1/FVC; EOS, blood eosinophil count] [unpublished data]

How to appraise heterogeneity of EA phenotype and underlying pathophysiologic mechanisms?

Xenon ventilation computed tomography

Xenon ventilation computed tomography (CT) has shown potential in assessing the regional ventilation status in patients with EA (Figure 4).

We evaluated a total of 30 patients with EA. The severity of dyspnoea measured by the visual analogue scale showed a significant correlation with the total number of areas of xenon gas trapping (XT) on the xenon ventilation CT taken in the pre-bronchodilator wash-out phase. The total number of areas of XT significantly decreased after bronchodilator inhalation, and differences in the total number of areas of XT (between the pre- and post-bronchodilator wash-out phases) at baseline showed significant correlations with the per cent increases in forced expiratory volume in 1 s after subsequent anti-asthma treatment. These findings suggest that Xenon ventilation CT may be an objective and promising tool in the measurement of dyspnea and prediction of the treatment response in patients with EA.

	Case 1 66-yr, female	Case 2 65-yr, female
At baseline		
PC_{20} (mg/ml)	1.29	5.19
FEV1 % predicted	65	66
% increase in FEV1 after BD inhalation	5	-1
After 12-wk treatment		
FEV1 % predicted	116	78
% increase in FEV1 after treatment	78	18

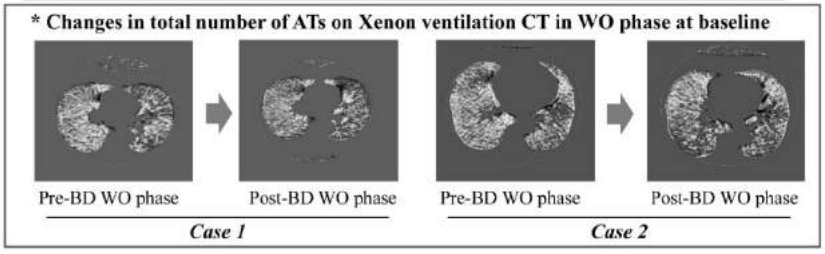

Figure 4. Case examples. On the color-coded maps, areas normally enhanced by xenon in the wash-in phase appeared as yellow to green. Areas that were blue, indigo or violet in the wash-in phase were interpreted as a ventilation defect. In the wash-out (WO) phase, normal areas exhibited no or minimal enhancement of xenon and were colored blue because the subjects exhaled almost all of the xenon. Thus, xenon gas trapping was defined as a red, orange or yellow area. Both case 1 and case 2 shared similar clinical features and also exhibited negative bronchodilator (BD) responses (per cent increase in FEV1 after BD inhalation; less than 12%) at baseline. However, a relatively greater decrease in the total number of areas of XT on xenon ventilation computed tomography in WO phase after BD inhalation was found only in case 1 compared with case 2. These variations were associated with greatly different responses in per cent increases in FEV1 (78% versus 18%) after anti-asthma treatment [from Ref. 3].

Machine learning

Clustering, or unsupervised learning, is a form of exploratory data analysis that divides data into groups (clusters) that are meaningful, useful, or both. We applied k-means cluster to 872 elderly asthmatics aged 65 years or older in a prospective, observational, and multi-centered cohort. Acute asthma exacerbation data collected over the prospective follow-up of two-year was used to evaluate clinical trajectories of these clusters. Four clusters of elderly asthmatics were identified: (i) long symptom duration and marked airway obstruction; (ii) female dominance and normal lung function; (iii) smoking male dominance and reduced lung function; and (iv) obese and borderline lung function. Cluster grouping was strongly predictive of time to first acute asthma exacerbation (Figure 5).

Genomics

By hierarchical clustering of 3,156 gene expression profiles in sputum cells from patients with EA, we identified two distinct clusters. Cluster 1 showed a lower eosinophil proportion in sputum and less severe airway obstruction

A

	Cluster 1	Cluster 2	Cluster 3	Cluster 4	P value
	N = 145	N = 237	N = 182	N = 308	
Male, n (%)	95 (65.5)	41 (17.3)	175 (96.2)	101 (32.8)	<0.001
BMI (Kg/m^2)	23.1±3.6	24.6±3.3	23.5±3.2	25.2±3.4	<0.001
Asthma symptom duration (year)	16.0±7.4	3.9±5.3	4.9±6.3	8.8±5.3	<0.001
Atopy, n (%)	28 (19.3)	37 (15.6)	48 (26.4)	52 (16.9)	0.028
CRS, n (%)	41 (28.3)	99 (41.8)	53 (29.1)	133 (43.2)	0.001
Pack year	7.7±12.2	1.9±6.9	55.7±46.1	2.7±7.6	<0.001
Previous exacerbation*, n (%)	24 (16.6)	18 (7.6)	27 (14.8)	38 (12.3)	0.039
Post-BD FEV1 %Pred.	49.0±11.3	106.9±12.7	66.8±18.1	77.8±10.1	<0.001
Post-BD FEV1/FVC ratio	55.0±12.1	79.5±10.0	62.6±12.6	73.2±10.5	<0.001

B

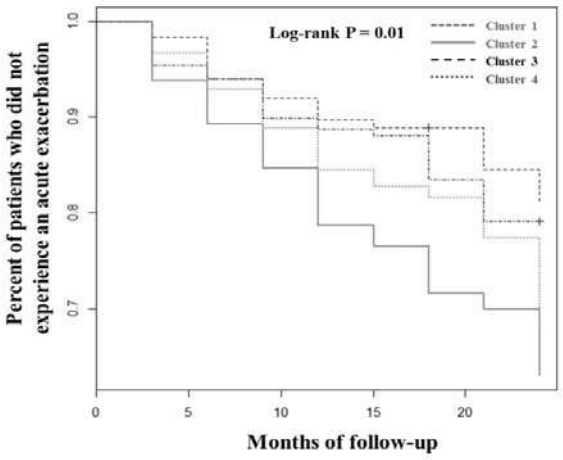

Figure 5. (A) Four clusters of elderly asthmatics were identified, (B) Kaplan–Meier plots by cluster of the cumulative probability of a first acute asthma exacerbation. [Abbreviations are: BMI, Body mass index; CRS, Chronic rhinosinusitis; BD, Bronchodilator; FEV1 Pred.%, % of predicted value of a forced expiratory volume in 1 second; FVC, Forced expiratory capacity] [from Ref. 4].

compared to cluster 2. Gene set enrichment analysis revealed the significant enrichment of 5 gene sets in cluster 1 (OXIDATIVE_PHOSPHORYLATION [OXPHOS], UNFOLDED_PROTEIN_RESPONSE [UPR], MYC_TARGETS_V1, DNA_REPAIR, and ADIPOGENESIS) and 3 gene sets in cluster 2 (EPITHELIAL_MESENCHYMAL_TRANSITION [EMT], MYOGENESIS, and KRAS_SIGNALING_DN). GSEA results and Fig. 2) revealed the significant enrichment of 5 gene sets in cluster 1 (OXIDATIVE_PHOSPHORYLATION [OXPHOS], UNFOLDED_PROTEIN_RESPONSE [UPR], MYC_TARGETS_V1, DNA_REPAIR, and ADIPOGENESIS) and 3 gene sets in cluster 2 (EPITHELIAL_MESENCHYMAL_TRANSITION [EMT], MYOGENESIS, and KRAS_SIGNALING_DN) (Figure 6).

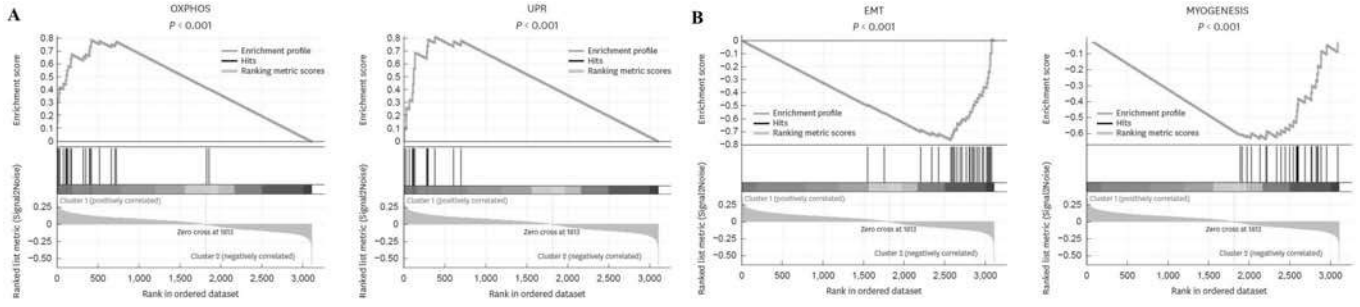

Figure 6. Gene sets enriched in each cluster identified in the discovery dataset with FDR P values less than 0.001. (A) Cluster 1, (B) Cluster 2. [Abbreviations are: OXPHOS, OXIDATIVE_PHOSPHORYLATION; UPR, UNFOLDED_PROTEIN_RESPONSE, EMT, EPITHELIAL_MESENCHYMAL_TRANSITION] [from Ref. 5].

Future direction

So far, there has been limited information on the phenotype of EA. For the better understanding, a comprehensive approach is necessary. A new field of research, known as systems biology if applied to model systems, or network medicine if applied to human beings, has emerged over the past decade or so, to address biological complexity in a holistic, integrated way. It offers, therefore, great potential to improve our understanding of multi morbidity and age related respiratory diseases, such as asthma (Figure 7).

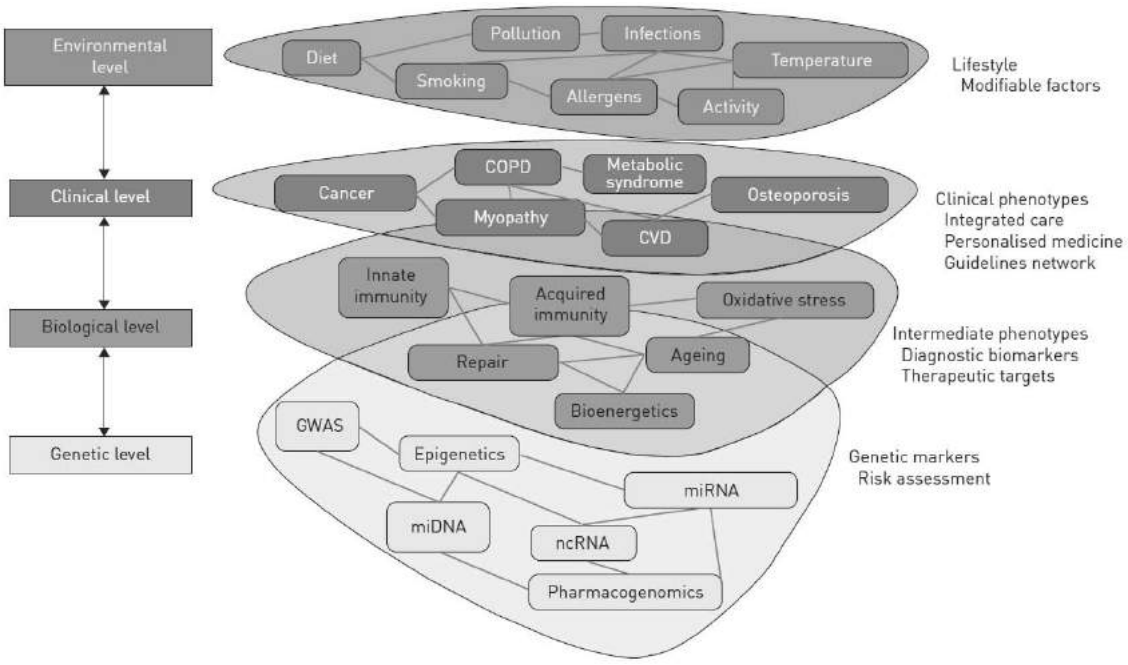

Figure 7. Diagram illustrating the different levels of complexity of chronic geriatric disease and the outcomes of potential clinical relevance (right-hand column). [Abbreviations are: CVD, cardiovascular disease; GWAS, genome-wide association studies; miDNA, mitochondrial DNA; miRNA, microRNA; ncRNA, noncoding RNA] [from Ref. 1].

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