Sputum Cytokine Profile in Rheumatoid Arthritis-Associated Interstitial Lung Disease and Correlation with the *MUC5B* Promotor Variant

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Background

- Rheumatoid Arthritis-associated interstitial lung disease (RA-ILD) develops in 10% of patients and contributes significantly to morbidity and mortality[1-2].
- A variant within the promotor region of *MUC5B* is one of the strongest risk factors for developing ILD in RA[3] (Figure 1).
- Mechanisms driving the association between RA-ILD and *MUC5B* promotor variant remain poorly understood.
- Identifying lung-based biomarkers using induced sputum may be more informative in characterizing pathogenesis of RA-ILD

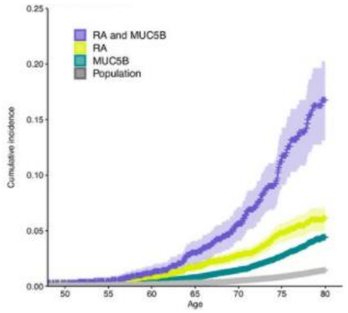
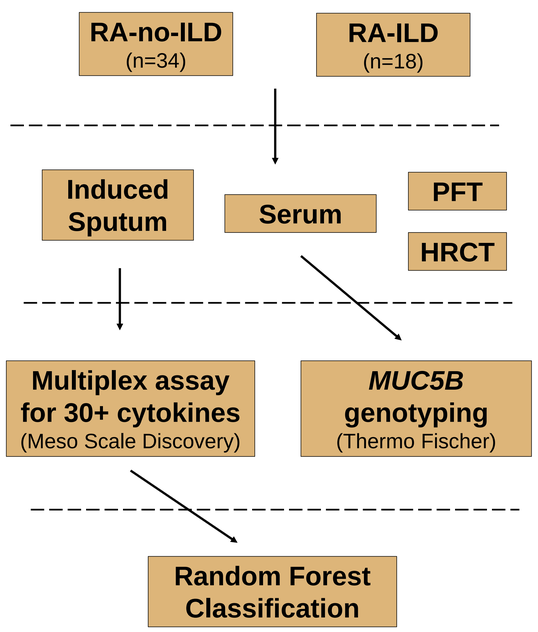


Figure 1. Cumulative incident risk of ILD in RA based on *MUC5B status*

Methods



Results

Table 1. Clinical characteristics of subject cohort

	RA-no-ILD* (n=34)	RA-ILD* (n=18)	P-value**
Age	51 ± 15	68 ± 8	<0.001
Female	31 (91)	9 (50)	0.002
Ever smoker	11 (32)	10 (56)	NS
Smoking pack years	5 ± 10	23 ± 36	NS
% predicted FVC	104 ± 16	82 ± 16	0.001
% Predicted DLCO	95 ± 22	73 ± 19	0.01
MUC5B genotype***			
GG	22 (92)	11 (69)	NS
GT or TT	2 (8)	5 (31)	

*Values displayed as mean ± SD or n (%).
**Based on Chi-square or t-test where appropriate, NS = not significant, P>0.05.
***Serum available for 24 of 34 RA-no-ILD and 16 of 18 RA-ILD subjects

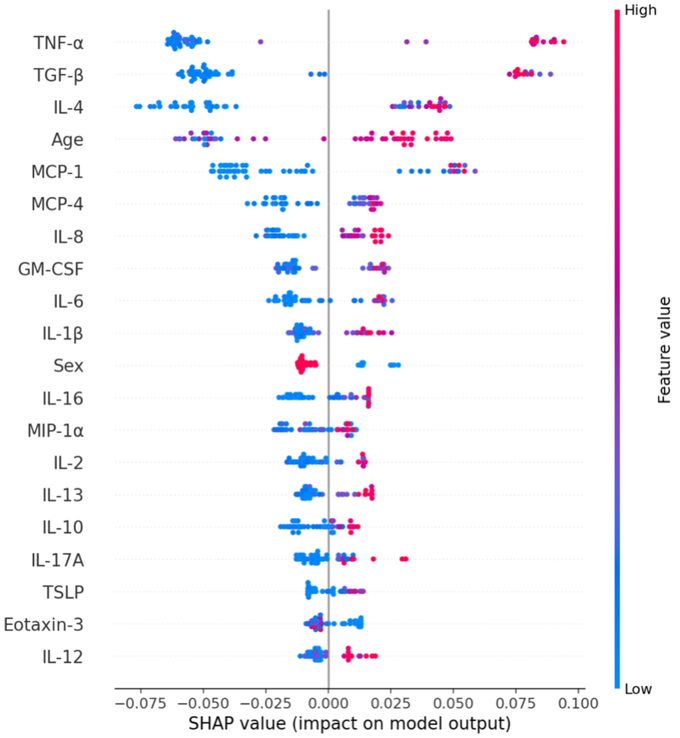


Figure 2. Top 20 cytokines/chemokines ranked from most (top) to least (bottom) impactful in predicting whether a subject is RA-no-ILD vs RA-ILD . Each data point represents one subject. Shapley Additive Explanation (SHAP) value depicts the probability of the impact on the model's prediction. The feature value depicts whether a variable has a low, medium or high value.

TNF-α, TGF-β1, IL-4 and MCP1 are significantly increased in RA-ILD

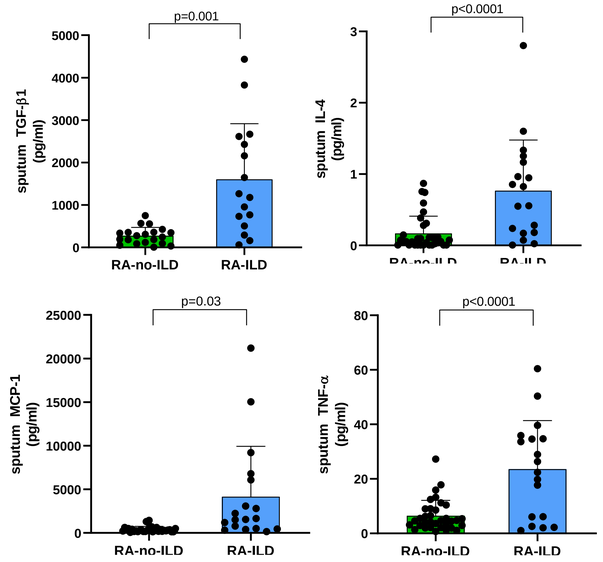


Figure 3. Significant sputum cytokine levels in RA-ILD. After RF modeling, sputum levels of most influential cytokines in predicting RA-no-ILD (n=34) vs RA-ILD (n=18). P-value based on logistic regression model controlling for co-variates (Age, sex, smoking status).

In RA-ILD, cytokine levels are increased in those with *MUC5B* promotor variant

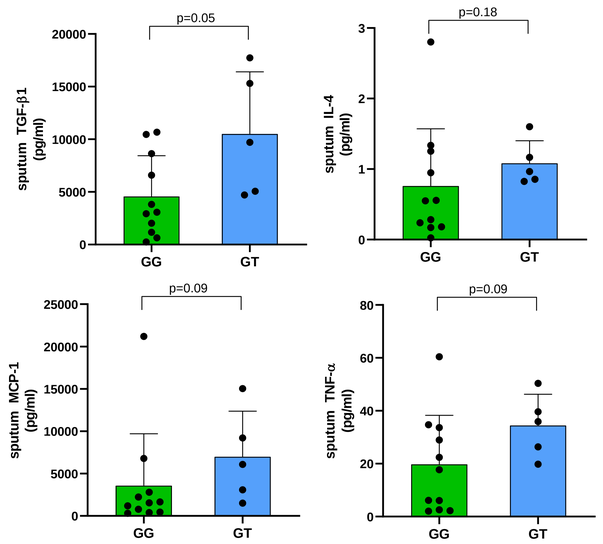


Figure 4. *MUC5B* genotype (GG or GT) correlated with sputum cytokine levels in RA-ILD subjects (n=16). P-value based on nonparametric Mann-Whitney U testing.

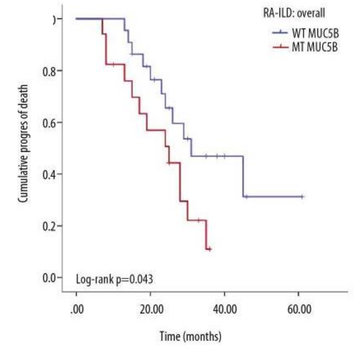
Conclusion

- We show that sputum levels of TGF-β1, TNF-α, MCP-1, and IL-4 were significantly elevated in RA patients with ILD compared to those without evidence of ILD.
- There was a trend of higher cytokine levels in those with the *MUC5B* promotor variant.

Implications

- *MUC5B* status has recently associated with decreased survival in a small cohort of RA-ILD subjects[4] (Figure 5).

Figure 5



- Future studies are needed to better understand the influence of the *MUC5B* promotor variant on cytokine generation in the lung in RA-ILD and overall mortality.

References

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