Characterisation of host-response heterogeneity in the sepsis transcriptome using two immune axis scores

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Background

Host responses during sepsis are highly heterogeneous, complicating the identification of patients at risk of mortality or those potentially benefitting from targeted therapies. Previous studies have identified transcriptomic endotypes to assist with this challenge, to classify patients into categories. Here we introduce a two-dimensional framework for measuring patients' immune system heterogeneity using two continuous "immune-axis" scores.

Methods

Whole-blood transcriptome was measured in 479 patients with sepsis at ICU admission using microarray (U219). Genes related to the immune system were selected and principal component analysis (PCA) analysis was performed. The first two PC scores are taken as the immune-axes scores. Upon these axes the scatter plot was coloured separately for each of the three existing sepsis endotype systems (Davenport et al., Scicluna et al. and Sweeney et al). Immune system pathway directionality was determined using the centroid of the constituent gene loadings within each Reactome pathway in the "Immune System" domain. A 20-gene signature was developed to enable axis scores to be calculated on different RNA platforms (e.g. RNAseq). Finally the axes scores were calculated for 39 CAP sepsis patients from the placebo arm of an RCT, in which whole-blood transcriptome was measured at multiple time-points (0,1,2,3,7 and 14±2 days after ICU admission) using RNAseq. Individual trajectories were calculated and an average trajectory was estimated using linear mixed modelling, which was then plotted on the axes.

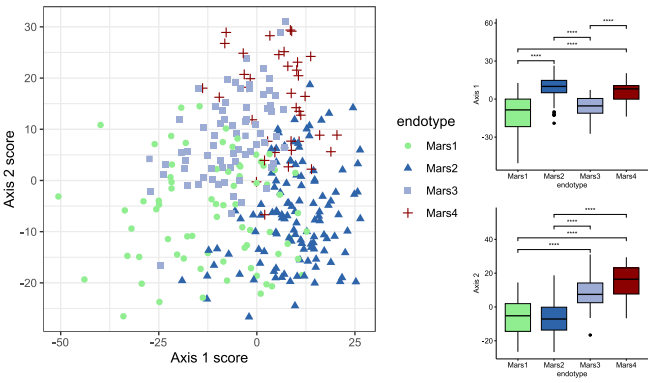

Fig 1. Mars endotypes (Scicluna et al.) are associated with the immune axes

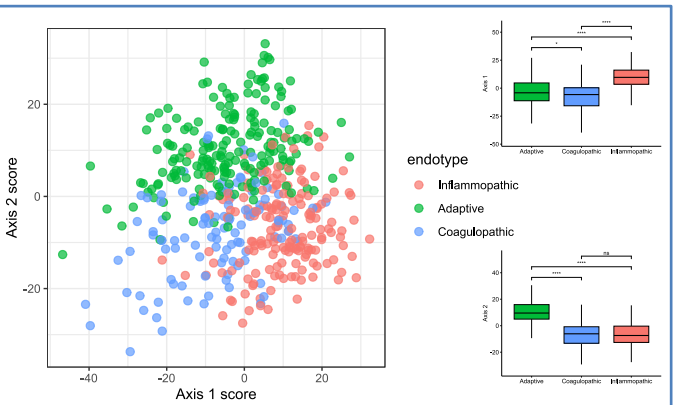

Fig 2. Endotypes of Sweeney et al. are associated with the immune axes

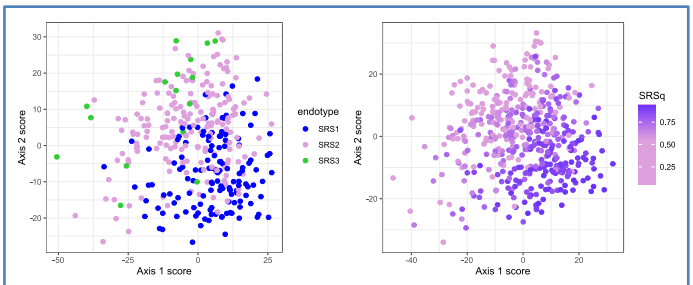

Fig 3. SRS endotypes (Davenport et al.) and the continuous score SRSq (Cano-Gamez et al.) are associated with the two immune axes

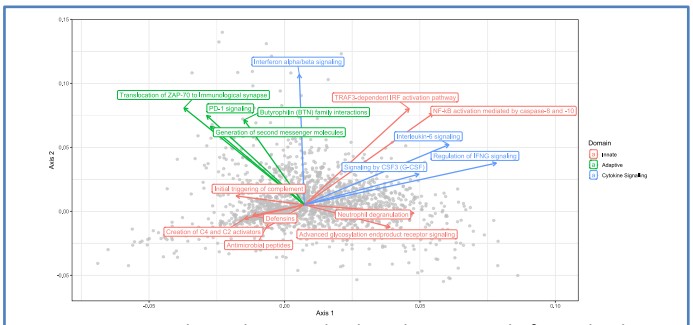

Fig 4. Reactome pathway directionality based on centroid of gene loadings

Predictor	OR (95% CI)	p-value
Immune Axis 1	0.994 (0.979, 1.009)	0.428
Immune Axis 2	0.968 (0.950, 0.985)	**0.00033**

Predictor	OR (95% CI)	p-value
Immune Axis 1	0.992 (0.975, 1.008)	0.311
Immune Axis 2	0.978 (0.960, 0.996)	**0.018**

Table 1. 28-day mortality logistic regression results from an unadjusted model (top) and adjusted model (bottom), where the adjusted model includes APACHE IV severity score.

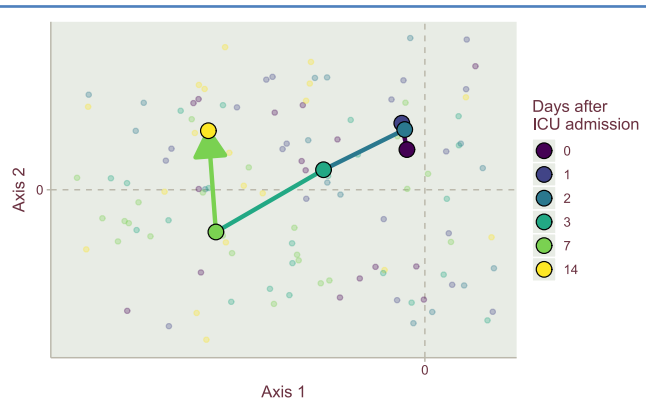

Fig 5. Average trajectory in CAP sepsis calculated using a linear mixed model

Conclusions

- Two axes explain more than 30% of all immune variation observed in the leukocyte transcriptome of patients with sepsis
- Two axes scores are associated with previous endotype systems (SRS, MARS and Sweeney), and give a new way of visually representing them
- Immune Axis 2 is independently associated with 28-day mortality, after adjusting for age and APACHE IV severity score
- Immune Axis 1 is more related to temporal trajectory (first week after admission)

References

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Sweeney TE et al. Unsupervised Analysis of Transcriptomics in Bacterial Sepsis Across Multiple Datasets Reveals Three Robust Clusters. Crit Care Med. 2018
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