Extracellular vesicles in sarcoidosis: unlocking molecular signatures for precision therapy

Sahil Pandya and Scott M. Matson

University of Kansas Medical Center, Division of Pulmonary, Critical Care and Sleep Medicine, Kansas City, KS, USA.

Corresponding author: Scott Matson (smatson@kumc.edu)

Shareable abstract (@ERSpublications)
Extracellular vesicles and proteomics make a powerful combination for treatment prediction in sarcoidosis https://bit.ly/3Uw5lB7

Cite this article as: Pandya S, Matson SM. Extracellular vesicles in sarcoidosis: unlocking molecular signatures for precision therapy. *ERJ Open Res* 2025; 11: 01028-2024 [DOI: 10.1183/23120541.01028-2024].

Received: 9 Oct 2024
Accepted: 18 Oct 2024

Sarcoidosis develops within a web of interconnected "insults" (environmental exposures) in genetically vulnerable hosts to create a dysregulated immune response. Epidemiologically, sarcoidosis impacts patients variably, with Black and female patients often exhibiting the most severe presentations [1, 2]. The varied clinical manifestations of sarcoidosis hint at significant underlying molecular heterogeneity [3, 4], yet current treatment strategies often regard the disease as a monolith rather than a spectrum of distinct biological subtypes. Despite advances in precision medicine for many diseases, sarcoidosis management still relies heavily on a "trial and error" approach when it comes to therapy selection [5]. This gap in our understanding has contributed to inconsistent treatment responses as clinical decisions are rarely guided by molecular insights, and makes the balance of treatment-emergent side-effects and benefit difficult to predict.

There are promising systems biology methods that offer the potential to uncover the molecular traits that inform molecular heterogeneity, and can be leveraged to identify markers of driving pathways to better inform treatment decisions. In this issue of ERJ Open Research, Kraaijvanger *et al*. [6] take a meaningful step forward by utilising proteomics of extracellular vesicles (EVs) isolated from blood to identify biomarkers that predict treatment response in pulmonary sarcoidosis.

For pulmonary diseases such as pulmonary sarcoidosis, EVs offer a potential method to access important cell–cell signals *via* biologic envelopes carried in blood that either originate in the lung or are destined for the lung, with important biologic consequences [7–9]. By leveraging this biologically informative component of blood samples researchers can gain access to important lung-based biosample material without the need for more invasive procedures such as biopsy or bronchoalveolar lavage fluid to obtain lung samples [10]. EVs carry proteins, RNAs and other molecules; this EV cargo can then be isolated, labelled and quantified to offer a snapshot of phenotype states and cellular communication pathways of the host.

The authors used a targeted proteomics approach *via* the OLINK platform, measuring 92 proteins in peripheral blood EVs of patients with sarcoidosis. By focusing on a cohort stratified by response to either prednisone or methotrexate (MTX), two commonly used sarcoidosis therapies, they identified differentially expressed proteins between responders and non-responders. This analysis revealed key proteins, such as CHI3L1 and CPA1, which showed potential in predicting treatment response to prednisone and MTX, respectively. These findings were further validated through ELISA (enzyme-linked immunosorbent assay) in a larger cohort, moving beyond hypothesis generation and demonstrating the clinical potential of these proteins as biomarkers.

Although targeted proteomics, like the OLINK platform, provides absolute quantification and easier clinical translation, it inherently limits the scope of discovery to pre-selected proteins, leaving other potentially relevant proteins and pathways unexplored. Further, by limiting the analysis to only those

available proteins detected in circulating EVs, the pathway analyses presented in this work are hypothesis-generating but are only based on a small snapshot of the available biomaterial.

The majority of patients studied in this cohort represent those of European descent, leaving questions unanswered around differences in more diverse cohorts. Additionally, "responders" were defined as showing forced vital capacity improvement of >5% or diffusing capacity for carbon monoxide improvement of >10%, which though they are reproducible measures of pulmonary function may not linearly correlate with patient perception of improvement [11]. Despite these limitations, the approach is powerful for its potential in advancing precision medicine, particularly when coupled with validation efforts in larger cohorts, as shown in this study.

The results of the study are promising: CHI3L1 had a sensitivity and specificity of 0.72 and 0.70 for predicting response to steroids, while CPA1 predicted MTX response with a sensitivity of 0.78 and specificity of 0.70 – metrics that improve further when combined with other proteins, such as uPA. This may add to the shared decision making that occurs between physician and patient to better weigh the benefits and risks of immunomodulatory therapy. These test characteristics are crucial for future prospective studies aimed at refining sarcoidosis treatment based on molecular profiles.

This stepwise approach, starting with broad proteomic analyses followed by targeted validation in sarcoidosis, could be expanded to other clinical questions such as identifying immunosuppressive responders, distinguishing remission from recurrence, or differentiating systemic manifestations of the disease. As the cost and accessibility of proteomics platforms continue to improve, we may be on the verge of transforming sarcoidosis care through molecularly informed, personalised treatment strategies.

Provenance: Commissioned article, peer reviewed.

Conflict of interest: All the authors have nothing to disclose.

Support statement: S.M. Matson is funded *via* p20GM130423.

References

1 Sharp M, Eakin MN, Drent M. Socioeconomic determinants and disparities in sarcoidosis. *Curr Opin Pulm Med* 2020; 26: 568–573.
2 Hena KM. Sarcoidosis epidemiology: race matters. *Front Immunol* 2020; 11: 537382.
3 Lin NW, Arbet J, Mroz MM, *et al.* Clinical phenotyping in sarcoidosis using cluster analysis. *Respir Res* 2022; 23: 88.
4 Konigsberg IR, Lin NW, Liao SY, *et al.* Multi-omic signatures of sarcoidosis and progression in bronchoalveolar lavage cells. *Respir Res* 2024; 25: 289.
5 Baughman RP, Valeyre D, Korsten P, *et al.* ERS clinical practice guidelines on treatment of sarcoidosis. *Eur Respir J* 2021; 58: 2004079.
6 Kraaijvanger R, Janssen Bonás M, Paspali I, *et al.* Targeted proteomics in extracellular vesicles identifies biomarkers predictive for therapeutic response in sarcoidosis. *ERJ Open Res* 2025; 11: 00672-2024.
7 Yáñez-Mó M, Siljander PR-M, Andreu Z, *et al.* Biological properties of extracellular vesicles and their physiological functions. *J Extracell Vesicles* 2015; 4: 27066.
8 Mathieu M, Martin-Jaular L, Lavieu G, *et al.* Specificities of secretion and uptake of exosomes and other extracellular vesicles for cell-to-cell communication. *Nat Cell Biol* 2019; 21: 9–17.
9 O'Brien K, Breyne K, Ughetto S, *et al.* RNA delivery by extracellular vesicles in mammalian cells and its applications. *Nat Rev Mol Cell Biol* 2020; 21: 585–606.
10 Ngo LT, Rekowski MJ, Koestler DC, *et al.* Proteomic profiling of bronchoalveolar lavage fluid uncovers protein clusters linked to survival in idiopathic forms of interstitial lung disease. *ERJ Open Res* 2024; 10: 00192-2024.
11 Judson MA. The symptoms of pulmonary sarcoidosis. *J Clin Med* 2023; 12: 6088.